O1 – 002
CORRELATION BETWEEN THE EFFECTS OF FIRST-LINE CHEMOTHERAPY AND SURVIVAL TIME FROM SECOND-LINE CHEMOTHERAPY IN PATIENTS WITH ADVANCED GASTRIC CANCER

H. Tabuse1, H. Yasui1, T. Furukoshi1, S. Hamauchi1, T. Tsushima1, H. Taniguchi1, A. Todaka1, T. Yokota1, N. Machida1, K. Yamashita1, A. Fukumori1, Y. Onozawa2, N. Boku2
1Divisions of Gastrointestinal Oncology and, 2Clinical Oncology, Shizuoka Cancer Center, 3Department of Clinical Oncology, St Marianna University School of Medicine

Background: In advanced gastric cancer (AGC), several prognostic factors for survival time in first-line chemotherapy (1st-CTX) have been reported. However, there are few reports about the relationship between the effects of 1st-CTX and survival time after 2nd-CTX. Univariate and multivariate analyses were carried out to examine the correlation between 2nd-MST and the efficacy of SP therapy (+ progression free survival: 1st-PFS, best tumor response rate: best-RR, time to best response) and other prognostic factors.

Objectives: To evaluate between the effects of S-1 + CDDP (SP) therapy as 1st-CTX and 2nd-MST in patients with AGC.

Patients and methods: The subjects were 32 patients who were treated with SP therapy as 1st-CTX between October 2002 and December 2010 at our institute. The main selection criteria were as follows: with measurable lesions, treated with Irinotecan (CPT-11) or weekly Paclitaxel (wTXL) as 2nd-CTX. Univariate and multivariate analyses were carried out to examine the correlation between 2nd-MST and the efficacy of SP therapy (+ progression free survival: 1st-PFS, best tumor response rate: best-RR, time to best response) and other prognostic factors.

Results: The median survival time (1st-MST) and 1st-PFS was 425 and 206 days, respectively. The RR in SP therapy was 66% (PR 21 patients). Best-RR was 30 – 50/51 – 70/ > 71, %:4/4/3/8/2 patients, respectively. The median to best response time was 73 days. The patient characteristics at the start of 2nd-CTX were as follows: median age, 58 years; PS: 0/1/2: 9/13/10, histology: intestinal type/ diffusive type; 19/13, number of organs with metastases; 1/2/ > 3: 3/6/16/10, lymph node metastases; yes/no: 20/12, peritoneal dissemination; yes/no: 15/17, 2nd-CTX; CPT/ wTXL: 18/14. The 2nd-MST was 173 days. The following factors were correlated with longer 2nd-MST by univariate analyses; age (< 65 years), intestinal type, no lymph node metastasis, best-RR over 50% and median time to best response (< 73 days). However, there is no significant factor by multivariate analyses.

Conclusions: The effect of SP therapy as 1st-CTX is not prognostic factor of 2nd-MST.

O1 – 003
PRELIMINARY SAFETY DATA FROM RANDOMIZED PHASE II STUDY COMPARING DOSE-ESCALATED WEEKLY PACLITAXEL VERSUS STANDARD-DOSE WEEKLY PACLITAXEL FOR PATIENTS WITH PREVIOUSLY TREATED ADVANCED GASTRIC CANCER

1Departments of Gastroenterology of Sapporo City General Hospital, 2Clinical Oncology of Aichi Cancer Center Hospital, 3Gastroenterology of Hokkaido University Hospital, 4Clinical Oncology of Saint Marianna University School of Medicine, 5Cancer Chemotherapy Center, Osaka Medical College, 6Department of Medical Oncology of KKR Sapporo Medical Center Tahan Hospital, 7Division of Gastroenterology of Kyoto Prefectural University of Medicine, 8Department of Gastroenterology and Hematology of University of Toyama, 9Division of Epidemiology and Prevention of Aichi Cancer Center Research Institute

Background: Neutropenia during chemotherapy has been reported to be a predictor of better survival in patients with several types of cancers including gastric cancer. Therefore, we conduct a multi-institutional, randomized phase II trial comparing dose-escalated weekly paclitaxel dose adjustments determined by degree of

O1 – 004
ABSENCE OF LIVER METASTASIS, LYMPH NODE METASTASIS AND PERITONEAL METASTASIS PREDICT LONGER PROGRESSION FREE SURVIVAL BY S-1 PLUS CIPLATIN TREATMENT IN ADVANCED GASTRIC CANCER

D. Ioue1, K. Chin1, K. Ohsara1, K. Takagi2, M. Ozaka2, M. Ogura1, M. Suenaga1, E. Shinozaki1, S. Matsusaka1, N. Mizunuma1, K. Hatake1
1Cancer Institute Hospital and 2Clinical Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research

Background: Some reports have shown long-term survival cases in advanced gastric cancer (AGC). In our institute, some patients with AGC have had complete response (CR) with cisplatin plus S1 (SI) treatment, and some of them had stopped their chemotherapy. The purpose of this study was to evaluate clinicopathological backgrounds of long-term responder and to find out features of cases that can stop their chemotherapy.

Patients and methods: From 2007 to 2009, 142 patients treated with SP as first-line chemotherapy in Cancer Institute Hospital of JFCR. We regarded patients whose progression-free survival (PFS) was above 500 days as long-term responders (group A), and others as control group (group B). We evaluated clinicopathological features of them, and univariate and multivariate analyses were carried out on the baseline factors before starting chemotherapy.

Results: Of 142 patients, 24 patients were categorized group A. Patients characteristics were as follows (group A versus B): median age, 58.2 versus 58.0 (years); gender (male), 62.5% versus 72.9%; ECOG performance status 0, 91.7% versus 80.0%; previous gastrectomy, 75.0% versus 11.0%; histological type (intestinal), 29.2% versus 25.4%; metastatic site (liver 12.5% versus 44.1%, lymph node 20.8% versus 78.0%, peritoneum 4.2% versus 44.9%). Of patients in group A, 16 patients have had CR. Four of them quit SP treatment (median length of treatment was 53.5 months) and only one patient had PD in 2 months after discontinuance of treatment. In univariate analysis, the absence of measurable lesion (P < 0.0001), recent gastrectomy (P < 0.0001), absence of metastatic site of liver (P = 0.004), lymph node (P = 0.001), peritoneum (P < 0.0001) predicted long-term disease control. Multivariate analysis showed three limiting factor predicted long-term survival; absence of metastatic site of liver (P = 0.004), lymph node (P = 0.001), peritoneum (P = 0.001). Histological type, ECOG performance status, tumor marker did not show statistical significance.

Conclusion: Absence of liver, lymph node, and peritoneal metastasis predicted longer PFS, and there were tendency that the absence of measurable lesion and recent gastrectomy predict long-term disease control.
The median MASCC score of admitted patients was 21 (range 14–21) and the thirty-day mortality rate was 0%. Two patients were admitted to ICU. The median age was 58 years (range 38–81).

**Background:** After the result of ToGA study, trastuzumab was introduced in Japan, which is the first molecular targeting therapy in the era of gastric cancer.

**Aims:** To investigate HER2 overexpression in advanced gastric cancer (stage 4) by immunohistochemistry using endoscopic biopsy samples. To discuss the feasibility and problems of trastuzumab plus capecitabine/caisplatin (HXP) therapy.

**Methods:** We investigated HER2 overexpression in 35 patients of advanced gastric cancer from March 2011 to December 2011. Among these, 12 patients revealed HER2 positive by endoscopic biopsy, and 9 patients were introduced HXP. As a rule, we investigated the overexpression of HER2 protein in all cases of unresectable gastric cancer by immunohistochemistry. Basically, we carried out endoscopic biopsy from different sections (if possible six sites) of the main tumor, considering the heterogeneity of HER2 overexpression.

**Results:** We introduced HXP for five males and four females. Median age was 67. Tumor location: body/antrum/cardia = 6/2/1. Histology: well/moderately/poorly = 1/5/3. In four cases, HXP was carried out as the first-line chemotherapy, whereas the others had been received previous chemotherapy such as S1 plus cisplatin (SP) therapy. Effect evaluation: CR/PD/SD/PD/NE = 0/2/3/2/2. Remarkable adverse events due to trastuzumab were seen in only one case; fever and chills considered as infusion reaction. On the other hand, six cases showed renal dysfunction. No one showed serious adverse events regarded as grade 3/4.

**Discussion:** Trastuzumab was well tolerated without significant adverse events in our clinical experience. Trastuzumab seems to be safe for elderly patients. Due to renal dysfunction, whenever necessary we reduced or interrupted cisplatin administration and continued trastuzumab. There is no evidence for the efficacy of trastuzumab beyond second-line therapy and there remains a question whether it is effective to continue trastuzumab beyond PD. Therefore, future clinical trials can be expected in this regard.

**Oral Session 2: Palliative and supportive care 3**

**O1 – 006 EARLY CLINICAL EXPERIENCE OF TRASTUZUMAB PLUS CAPECITABINE/CISPLATIN (HXP) THERAPY FOR PATIENTS WITH UNRESECTABLE ADVANCED GASTRIC CANCER**

H. Takeda1, T. Tsumura1, A. Sekikawa1, E. Iguchi1, T. Kanesaka1, S. Saito2, A. Natsu1, H. Nishikawa1, R. Kita1, T. Maruno1, Y. Okabe1, T. Kimura1, Y. Osaki1, T. Wakahai2

1The Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, 2The Department of Pathology, Osaka Red Cross Hospital

**Background:** After the result of ToGA study, trastuzumab was introduced in Japan, which is the first molecular targeting therapy in the era of gastric cancer.

**Aims:** To investigate HER2 overexpression in advanced gastric cancer (stage 4) by immunohistochemistry using endoscopic biopsy samples. To discuss the feasibility and problems of trastuzumab plus capecitabine/caisplatin (HXP) therapy.

**Methods:** We investigated HER2 overexpression in 35 patients of advanced gastric cancer from March 2011 to December 2011. Among these, 12 patients revealed HER2 positive by endoscopic biopsy, and 9 patients were introduced HXP. As a rule, we investigated the overexpression of HER2 protein in all cases of unresectable gastric cancer by immunohistochemistry. Basically, we carried out endoscopic biopsy from different sections (if possible six sites) of the main tumor, considering the heterogeneity of HER2 overexpression.

**Results:** We introduced HXP for five males and four females. Median age was 67. Tumor location: body/antrum/cardia = 6/2/1. Histology: well/moderately/poorly = 1/5/3. In four cases, HXP was carried out as the first-line chemotherapy, whereas the others had been received previous chemotherapy such as S1 plus cisplatin (SP) therapy. Effect evaluation: CR/PD/SD/PD/NE = 0/2/3/2/2. Remarkable adverse events due to trastuzumab were seen in only one case; fever and chills considered as infusion reaction. On the other hand, six cases showed renal dysfunction. No one showed serious adverse events regarded as grade 3/4.

**Discussion:** Trastuzumab was well tolerated without significant adverse events in our clinical experience. Trastuzumab seems to be safe for elderly patients. Due to renal dysfunction, whenever necessary we reduced or interrupted cisplatin administration and continued trastuzumab. There is no evidence for the efficacy of trastuzumab beyond second-line therapy and there remains a question whether it is effective to continue trastuzumab beyond PD. Therefore, future clinical trials can be expected in this regard.

**Conclusions:** In areas with limited resources, self-assessment of FN can be an alternative option, although that should be applied to young and literate patients educated by skilled medical team.
multicenter clinical trial, JOCG1018, a subset of PRO-CTCAE items related to the expected adverse events in this trial, will be administered. An electronic-based system will be developed to provide interfaces to investigators, clinicians, and patients to collect and report patient-reported symptom data.

**Oral Session 3: Palliative and supportive care 4**

**O1 – 012**

**THE EFFICACY OF R-THROMBOMODULIN IN COMPARISON WITH DALTEPARIN NA IN 26 PATIENTS WITH HEMATOLOGIC MALIGNANCY COMPLICATED BY DIC**

T. Morishita1, S. Sakuragi1, K. Miyao1, T. Saito1, H. Sakumura2, K. Watanabe1, K. Nira1, Y. Oto1, M. Sawa1
1Department of Hematology & Oncology, Anjo Kosei Hospital, 2Department of Hematology & Oncology, Nagoya Daini Red Cross Hospital

**Introduction:** Hematological malignancy is often complicated by many critical diseases including DIC. The resolution of DIC safety is one of the most important aspects in getting over hematological malignancy. We would like to report our comparative review of the administration of Recombinant Thrombomodulin (Recomodulin) versus Dalteparin Na (Fragmin) and this time, we would also report the possibility of reducing blood products such as fresh frozen plasma (FFP).

**Patient:** Thirteen patients (mean age 57.0 years, men/women 8/5, AML 6, APL 4, ALL 3) were administered Dalteparin Na.

**Result:** The average of FDP, Fib, and JMHW DIC score has improved in both therapies. On prophylaxis of fluorouracil-induced oral mucositis.

**Conclusion:** Our study demonstrated that irsogladine maleate was effective for reducing blood products such as fresh frozen plasma (FFP).

**O1 – 013**

**IRSOGLADINE MALEATE REDUCES THE INCIDENCE OF ORAL MUCOSITIS IN PATIENTS RECEIVING FLUOROURACIL-BASED CHEMOTHERAPY: A PILOT STUDY**

M. Nomura, M. Kamata, H. Koijma, K. Hayashi, S. Sawada
Department of Radiology of Kansai Med University

**Background:** 5-Fluorouracil (5-FU) is the most effective and frequently used agent for gastrointestinal cancer, and that is well known for causing mucositis. Irsogladine maleate (IM), an anti-ulcer drug, reinforces gap junction and accelerated intercellular communication in the oral and gastric mucosa. The objective of the present study was to evaluate irsogladine maleate in the prophylaxis of fluorouracil-induced oral mucositis.

**Methods:** We retrospectively analyzed 34 cancer patients undergoing fluorouracil and platinum chemotherapy as primary treatment between August 2011 and November 2011. The chemotherapy regimens consist of continuous infusion of 5-FU 700 mg/m² on day 1–4 and cisplatin 70 mg/m² on day 1 (FP), or continuous infusion of 5-FU 700 mg/m² on day 1–5 and nedaplatin 130 mg/m² on day 6 (FN), repeated every 4 weeks. Patients were randomly assigned to IM group (given 4 mg/day IM on day 1–14) or non-IM group. Oral mucositis were graded according to World Health Organization criteria.

**Results:** The incidence of 5-FU associated oral mucositis (WHO grade 1 or above) in which four patients (23.5%) in IM group (1 patient with grade 2 and 2 patients with grade 1) and 13 patients (76.5%) in non-IM group (four patients with grade 2 and 7 patients with grade 1) were observed (x² test: odds ratio, 5.96; 95% confidence interval, 1.33–26.66; P = 0.015). No patient with grade 3 or above oral mucositis was observed in both groups.

**Conclusion:** Our study demonstrated that irsogladine maleate was effective for prophylaxis of fluorouracil-induced oral mucositis.

**O1 – 015**

**CORRELATION BETWEEN DOXETAXEL-INDUCED SKIN TOXICITY AND THE USE OF STEROIDS AND H2 BLOCKERS: A MULTI-INSTITUTION SURVEY**

K. Kawaguchi1, H. Ishiguro1, S. Mota1, S. Nakamura1, S. Ohno1, N. Masudari1, H. Iwata1, K. Aogi1, K. Kuroi1, M. Toy1
1Department of Breast Surgery, Kyoto University Hospital, 2Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, 3Breast Center, Shova University Hospital, 4Division of Breast Oncology, National Kyushu Cancer Center, 5Department of Surgery, Breast Oncology, Osaka National Hospital, 6Department of Breast Oncology, Aichi Cancer Center Hospital, 7Department of Breast Oncology, National Hospital Organization Shikoku Cancer Center, 8Department of Surgery, Division of Clinical Trials and Research, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

**Background:** Steroids and H2 blockers are commonly used as supportive care for taxane-containing chemotherapy, but they also affect docetaxel’s primary metabolizer, cytochrome P450 3A4. This retrospective observational study was carried out to better understand the effects of the compounds on docetaxel-induced skin toxic effects, specifically hand-foot syndrome (HFS) and facial erythema (FE), a relationship that is currently poorly understood.

**Methods:** Member institutions of the Japan Breast Cancer Research Group were invited to complete a questionnaire on the occurrence of grade 2 or higher HFS and FE among patients treated between April 2007 and March 2008 with docetaxel as an adjuvant or neoadjuvant chemotherapeutic treatment of breast cancer.

**Results:** We obtained data of 993 patients from 20 institutions. Twenty percent received H2 blockers, and all patients received dexamethasone. Univariate and multivariate analyses revealed that H2 blockers are associated with a significantly higher incidence of both HFS and FE. The incidence of FE was significantly higher for the docetaxel and cyclophosphamide (TC) regimen than for non-TC regimens combined. Dexamethasone usage did not affect the incidence of either HFS or FE.

**Conclusion:** In conclusion, the use of H2 blockers as premedication in breast cancer patients receiving docetaxel significantly increases the risk of both HFS and FE.

**Oral Session 4: Palliative and supportive care 5**

**O1 – 019**

**PROSPECTIVE STUDY OF SWITCH FROM ORAL MEDICINE OF TRAMADOL TO FENTANYL STICKING MEDICINE IN THORACIC MALIGNANCY WITH THE PAIN OF THE THORACIC MALIGNANCY:**

M. Tanita1, T. Hirashima1, M. Kobayashi1, S. Morita1, O. Morimura1, T. Shiyomiya1, K. Okatuli1, Y. Matsuura1, N. Morishita1, H. Suzuki1, K. Iwata1, N. Ryota1, H. Hino2, N. Okamoto1, I. Kawase1
1Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Thoracic Malignancy, 2Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Nursing

**Background:** Tramadol is a weak agonist actions at the μ-opioid receptors, and acting on neurotransmission of SNRI. Fentanyl is a potent synthetic narcotic analgesic with a rapid onset and short duration of action. It is a strong agonist at μ-opioid receptors. Both tramadol and fentanyl patches are used for the carcinomatous pain in clinical.

**Method:** Efficacy and the safety when switching from the tramadol to fentanyl sticking medicine in the third where the conversion chart based on 500:1 compared with general conversion is used in foreign countries are examined prospectively. All patients were required to provide written informed consent.

**Results:** This study included 14 patients (12 men and 2 women), including 12 with adenocarcinoma, 1 with squamous cell carcinoma, 1 with mesothelioma. We examined control of pain, nausea, vomiting, constipation, sleepiness, and PS at the time of registration, a fentanyl patch change from tramadol, a first fentanyl patch change, a second fentanyl patch change, and a fourth fentanyl patch change. Furthermore, we examined degree of satisfaction about this trial and the change from tramadol to fentanyl patch, and the wish of whether to like to continue a fentanyl patch.

**Conclusion:** We collect 15 patients of target in this study and report the details of a result.
**Oral Session 5: Lung cancer basic**

**O1 – 023 SENSITIVITY OF MICROARRAY ARRAY SYSTEM FOR CIRCULATING TUMOR CELLS IN LUNG CANCER PATIENTS**

H. Kenmotu1, M. Hosokawa2, Y. Koh3, T. Yoshino2, T. Yoshikawa2, T. Naito1, T. Takahashi1, H. Murakami1, R. Watanabe4, S. Ono1, Y. Kikuhara1, H. Kanbara1, T. Matsunaga2, N. Yamamoto1

1 Division of Thoracic Oncology, Shizuoka Cancer Center Research Institute, 2Institute of Engineering, Tohoku University of Agriculture and Technology, 3Drug Discovery and Development Division, Shizuoka Cancer Center Research Institute, 4Division of Diagnostic Pathology, Shizuoka Cancer Center, 5Hitachi Chemical Co., Ltd.

**Background:** Epithelial cell adhesion molecule (EpCAM)-based enumeration of circulating tumor cells (CTCs) has a prognostic value in solid tumors such as advanced breast, colon and prostate cancers. However, poor sensitivity has been reported in non-small-cell lung cancer (NSCLC). We have developed a microarray system (MCA) integrated with a microfluidic device for recovery and enumeration of CTCs, regardless of EpCAM expression level. This system can isolate tumor cells on the basis of differences in size and deformability between tumor and hematologic cells.

**Methods:** Paired peripheral blood samples were collected from metastatic lung cancer patients. CTCs were enumerated by EpCAM-based immunomagnetic capture (CellSearch, Veridex) and by the MCA system. In the MCA system, trapped cells were stained with Hoechst 33342, FITC-labeled anti-pan cytokeratin antibodies and PE-labeled anti-CD45 antibodies for subsequent imaging analysis. CTCs were defined as cells with round to oval morphology, a visible nucleus, positive staining for pan-cytokeratin and negative staining for CD45. We evaluated the sensitivity of the MCA system for detecting CTCs in lung cancer patients compared with the CellSearch system.

**Results:** Twenty-two metastatic NSCLC patients and 13 small-cell lung cancer (SCLC) patients were enrolled into this study between April 2011 and January 2012. CTCs were detected using the MCA system in 17 of 22 NSCLC patients (count > 1 per 7.5 ml) compared with 9 of 22 patients using CellSearch (P = 0.013). On the other hand, CTCs were detected using MCA in all 13 SCLC patients compared with just 9 of 13 patients using CellSearch (P = 0.012). More CTCs from NSCLC patients were detected by the MCA system (median 13, range 0–313 cells/7.5 ml) than by the CellSearch system (median 0, range 0–37 cells/7.5 ml) demonstrating statistical superiority (P = 0.002, Wilcoxon test).

**Conclusion:** Our results suggest that the MCA system is potentially superior to the CellSearch system for detecting CTCs in lung cancer patients and further clinical development should be considered.

**O1 – 025 CHARACTERIZATION OF A LUNG CANCER GROWTH FACTOR, LASEP1 AS A SEROLOGICAL AND PROGNOSTIC BIOMARKER AND A THERAPEUTIC TARGET**

A. Takano1, Y. Nakamura2, Y. Daigo1,2

1 Department of Medical Oncology, Shiga University of Medical Science, 2Human Genome Center, Institute of Medical Science, University of Tokyo

**Identification of early cancer detection and prognostic biomarkers is urgently required to improve the clinical outcome. We have screened cancer biomarkers using a strategy as follows: (a) to identify up-regulated genes in non-small-cell lung cancers (NSCLC) using the cDNA microarray representing 27, 648 genes and 120 lung cancers, (b) to verify the candidate genes for their no or low expression in 23 normal tissues by northern blot analysis, (c) to validate clinicopathological significance of their protein expression by using NSCLCs tissue microarray, (d) to verify whether they are essential for the growth of cancer cells by siRNA assay, and (e) to measure their protein expression by Western blotting using NSCLCs tissue microarray.**

**Characterization of LASEP1:** LASEP1 showed LASEP1 protein was frequently over-expressed in lung cancers; positive staining of LASEP1 was observed in 210 (56.1%) of 374 NSCLC. Strong LASEP1 staining of LASEP1 was observed in 210 (56.1%) of 374 NSCLC. Strong LASEP1 staining of LASEP1 was observed in 210 (56.1%) of 374 NSCLC. Strong LASEP1 staining of LASEP1 was observed in 210 (56.1%) of 374 NSCLC. Strong LASEP1 staining of LASEP1 was observed in 210 (56.1%) of 374 NSCLC.

**Conclusion:** Our target analysis demonstrated that LASEP1 was over-expressed in lung cancers compared with normal tissues. Furthermore, LASEP1 knock-down by siRNA significantly suppressed tumor growth in vitro and in vivo using EMT6 cells. Using GeneChip and lung cancer cell lines transfected with siRNAs for LASEP1, we identified several downstream genes of LASEP1 that were related to carcinogenesis. LASEP1 is a potential target for the development of diagnostic and prognostic biomarkers for lung cancer.

**O1 – 026 CYTOKERATIN (CK) 8 EXPRESSION IN NON-SMALL-CELL LUNG CANCER (NSCLC) AND ITS RELATION TO TUMOR INVASIVENESS AND PATIENT SURVIVAL**

A. Kubo1, N. Kanaji2, S. Bando1, T. Ishii1, J. Fujiita1, T. Matsunaga2, E. Yamaguchi1

1 Division of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine, 2Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, 3Department of Infectious, Respiratory and Digestive Medicine, University of Ryukyu

**Purpose:** Type II intermediate filament protein CK8 is highly expressed in NSCLC. The role of CKs in tumor invasiveness is controversial. While circulating CKs have been used as tumor markers, the significance of circulating CK8 in NSCLC is undetermined. The significance of CK8 in NSCLC was assessed using cell lines and clinical samples.

**Methods:** We quantitatively evaluated expression of type I CK 18/19/20, type II CK 7/8, type III vimentin, and type V laminas among 12 NSCLC, 7 SCLC and 10 non-LLC lines. Highly invasive NSCLC sublines were selected from two adenocarcinoma cell lines, A549 and H1107, using a membrane invasion chamber system (MICS), and were assessed for CK 7/8/18/19 expression. Expression CK18 was induced by transfection, and endogenous CK 8/18/19 were knocked down by RNA interference (RNAi), followed by invasion assay using MICS. Circulating CK8 was assessed using sera from 60 NSCLC and 10 SCLC patients and ELISA.

**Results and discussion:** CK 8/18 were expressed in all NSCLC lines and CK8 was the dominant type II CK. The invasive sublines of A549 and H1107 showed lower expression levels of CKs compared with their parental cells. Suppression of either CK8 or CK18 by RNAi led to a decrease in the total CK amount and increased invasiveness of both H1107 and A549 cells. On the other hand, serum levels of CK8 in NSCLC patients correlated with progressing tumor clinical stage, and inversely correlated with survival in patients with NSCLC. Apparently contradictory results in the roles of CK8 as a negative regulator of tumor invasion and its prognostic impact on poor survival in NSCLC may suggest that circulating CK8 may reflect tumor burden rather than invasiveness of individual tumors.

**O1 – 027 MINICHROMOSOME MAINTENANCE PROTEIN 7 PLAYS ESSENTIAL ROLES IN CANCER CELL GROWTH AND IS A POTENTIAL THERAPEUTIC TARGET IN HUMAN CANCER**

G. Toyokawa1, R. Hamamoto2, K. Sugio1, Y. Ichinose1, Y. Nakamura2

1Department of Thoracic Oncology, National Kyushu Cancer Center, 2Human Genome Center, Institute of Medical Science, University of Tokyo

**Background:** The research emphasis in anti-cancer drug discovery has always been to search for a drug with the greatest antitumor potential but fewest side-effects. This can only be achieved if the drug used is against a specific target located in the tumor cells. In this study, we evaluated Minichromosome Maintenance Protein 7 (MCM7) as a novel therapeutic target in cancer.

**Results:** Immunohistochemical analysis showed that MCM7 was positively stained in 196 of 331 non-small-cell lung cancer (NSCLC), 21 of 29 bladder tumor and 25 of 70 liver tumor cases whereas no significant staining was observed in various normal tissues. We also found an elevated expression of MCM7 to be associated with poor prognosis for patients with NSCLC. qRT-PCR revealed a higher expression of MCM7 in clinical bladder cancer tissues than in corresponding non-neoplastic tissues, and we confirmed that a wide range of cancers also overexpressed MCM7 by cDNA microarray analysis. Suppression of MCM7 using specific siRNAs inhibited incorporation of BrdU in lung and bladder cancer cells overexpressing MCM7, and suppressed the growth of those cells more efficiently than that of normal cell strains expressing lower levels of MCM7.

**Conclusions:** Since MCM7 expression was generally low in a number of normal tissues we examined, MCM7 has the characteristics of an ideal candidate for molecular targeted cancer therapy in various tumors and also as a good prognostic biomarker for NSCLC patients.

**O1 – 028 ASP3026, A SELECTIVE ALK INHIBITOR, INDUCES TUMOR REGRESSION AGAINST CRIZOTINIB RESISTANT EML4-ALK-DEPENDENT TUMOR MODELS IN MICE**


EML4-ALK translocation has been validated as a therapeutic target in a subset of non-small-cell lung cancer (NSCLC) patients. In clinical settings, crizotinib has shown promising response rates in patients with EML4-ALK-positive NSCLC. However, disease relapse has been observed after an initial favorable response and...
several resistance mechanisms, including the gatekeeper L1196M mutation, have been reported to date.

We have discovered ASP3026, a selective inhibitor for the ALK kinase. ASP3026 potentially inhibited ALK kinase activity with an IC_{50} value of 3.5 nmol/L and showed more selective inhibition in a Tyr-kinase panel than crizotinib. Using NCI-H2228, a human NSCLC cell line endogenously expressing EML4-ALK, we determined the anti-proliferative effect of ASP3026. ASP3026 inhibited the in vitro proliferation with an IC_{50} value of 64.1 nmol/L and induced dose-dependent anti-tumor effect starting at 1 mg/kg with marked regression at 10, 30, and 100 mg/kg in a subcutaneous tumor model. Body weights were unaffected. ASP3026 at 100 mg/kg also showed tumor regression against EML4-ALK-driven tumor model with gatekeeper mutation while crizotinib at 100 mg/kg was ineffective. In an NCI-H2228 orthotopic lung model, ASP3026 at 30 mg/kg induced sustained tumor regression during the experimental period. In contrast, crizotinib at 30 mg/kg induced initial regression during the first 7 days but regrowth of the tumor was observed despite continuous crizotinib administration. After tumor regrowth was established in crizotinib-treated mice, substantial tumor regression was achieved by subsequent administration of ASP3026 at 30 mg/kg.

Taken together, these results suggest that ASP3026 in the non-clinical setting shows superior efficacy to crizotinib in crizotinib-resistant models.
feasibility study of S-1 and carboplatin combination for patients with advanced or ineligible for other treatment modality of NSCLC patients.

Methods: Patients with histologically or cytologically confirmed NSCLC, clinically diagnosed pulmonary fibrosis, aged 80 years old or younger, performance status 0–2 and chemo-naïve were eligible for the study. Carboplatin (AUC 5) was administered on day 1 and S-1 (80 mg/m²/day) on day 1 to 4 for six cycles. End points were response rate, common safety profiles and effect to PF.

Results: From March 2009 to December 2011, 21 patients (19 males/2 females, median age 67 years old, ranged 55 to 77, 10 adenocarcinoma, 10 squamous, 1 adenosquamous, stage IIA: 1, IIA: 3, IIIA: 9, IV: 4, recurrence: 4) were enrolled. All patients had moderate or severe PF. Treatment delivery: 1 cycle: 3 patients, 2: 3 patients, 3: 3 patients, 4: 10 patients, 5: 1 patient, 6: 1 patients. Partial responses were observed in 5 patients (23%). The median progression-free survival duration was 4.0 months, and the median overall survival duration in 10.4 months. During the treatment, two patients experienced moderate deterioration of pulmonary fibrosis, one experienced infectious pneumonia—all three patients recovered from the event. There was no treatment related death. Besides pulmonary toxicity, most common adverse events were myelotoxicities.

Conclusions: This is the first trial of S-1 and carboplatin combination for patients with PF and NSCLC. The study revealed S-1 and carboplatin combination was feasible and active even in patients with PF and NSCLC who are usually excluded from cancer clinical trials.

O1 – 038 ACUTE EXACERBATION OF PRE-EXISTING INTERSTITIAL LUNG DISEASE (ILD) IN PATIENTS WITH LUNG CANCER UNDER VARIOUS TREATMENTS

Y. Nishigaki1, H. Asakawa1, S. Ozumi2, Y. Fujita3, K. Takamura1, M. Yamamoto2, S. Fuku4, T. Kojima1, T. Harada1, Y. Kawas1, S. Sasaki1, K. Kinoshiba1, H. Akita2, M. Nishimura1

1Department of Respiratory Medicine, National Hospital Organization Asahikawa Medical Center, 2First Department of Medicine, Hokkaido University School of Medicine, 3First Department of Medicine, Obihiro-Kosei General Hospital, 4Department of Medical Oncology and Respiratory Medicine, KKR Sapporo Medical Center, 5Center for Respiratory Disease, Hokkaido Social Insurance Hospital, 6Department of Respiratory Medicine, Oji General Hospital, 7Respiratory Center, Asahikawa Medical University, 8Department of Medical Oncology, Hokkaido University Graduate School of Medicine

Background: Acute deterioration of ILD for unknown causes, sometimes called as acute exacerbation (AE), can occur at any point in the course of ILD. However, little is known about its incidence and prognostic significance in lung cancer patients with pre-existing ILD who receive various treatments. Methods: A total of 242 subjects (6.9% of all) were retrospectively identified to have pre-existing ILD by computed tomography (CT) from a sum of 3524 patients at 8 institutions during 2004 to 2009. All CT images were centrally reviewed. Uni- and multivariate analyses were carried out using a Cox proportional hazard model to examine the potential role of any prognostic factors for overall survival (OS) from the initial lung cancer diagnosis.

Results: Patient characteristics were: male/female = 217/25; median age (range) = 73 (42–98) years; smoking status: ever/never = 223/19; PS: 0/1/2/3/4 = 74/121/23/19/5; stage I/II/III/IV = 48/10/36/8; histology: Ad/Sq/La/NOS/Sm = 90/75/6/19/52; CT pattern: usual interstitial pneumonitis (UIP)/non-UIP = 118/124; extent of normal lung on baseline CT: 10%–50%/60%–90% = 154/88; pre-existing emphysema: yes/no = 178/64. AE occurred in 71 of 242 patients (29%) overall; 56 of 147 patients (38%) with chemotherapy (Chx), 6 of 38 patients (16%) with surgery, 2 of 17 patients (12%) with palliative radiotherapy, and 5 of 36 patients (14%) with BSC alone, and Cx was an independent risk factor for the occurrence of AE (P < 0.001). When separated by histology, in NSCLC, multivariate analysis revealed that age (≥70 years, hazard ratio [HR]: 1.84, 95% CI: 1.25–2.71, P = 0.002), PS (2–5; HR: 2.96, 95% CI: 1.80–4.68, P < 0.001), stage (≥3; HR: 4.03, 95% CI: 2.42–6.71, P < 0.001), and AE (HR: 1.84, 95% CI: 1.26–2.69, P = 0.002) were significantly associated with OS, while in SCLC, AE was the only significant prognostic factor (HR: 2.26, 95% CI: 1.08–4.73, P = 0.032).

Conclusions: The occurrence of AE is not rare in the lung cancer treatment and it is a factor for poor prognosis in patients with pre-existing ILD.

O1 – 039 EFFICACY OF FEXOFENADINE IN PREVENTING TYROSINE KINASE INHIBITOR (TKI)-INDUCED INTERSTITIAL LUNG DISEASE

R. Ko1, S. Sasaki1, Y. Nambara1, A. Ishimori1, M. Yoshio1, Y. Yoshio1, S. Tominaga1, K. Takahashi2

1Department of Respiratory Medicine, Juntendo University Urayasu Hospital, 2Department of Respiratory Medicine, Juntendo University School of Medicine

Background: Tyrosine kinase inhibitors (TKIs); gefitinib and erlotinib are widely indicated in NSCLC patients, especially those harboring an active mutation of EGFR, and have shown excellent efficacy. However, severe interstitial lung disease (ILD) can occur as an adverse event with TKIs, and is sometimes fatal. Fexofenadine has been used to prevent TKI-induced skin rash in all patients, who received EGFR-TKIs, since April 2009 in our hospital, and seems to reduce the incidence of ILD. Therefore, we retrospectively analyzed the efficacy of fexofenadine in preventing TKI-induced ILD.

Methods: 145 NSCLC patients, in whom TKIs were administered, were analyzed in the study, comprising 54 and 91 patients with and without concomitant administration of fexofenadine, respectively. Univariate and multivariate analyses with logistic regression model were used to investigate whether fexofenadine could prevent EGFR-TKIs-induced ILD or not.

Results: ILD occurred in 21 patients (14.5%), and was fatal in 5 (3.4%). The number of ILD patients with/without fexofenadine was 4 out of 54 (7.4%)/17 out of 91 (18.7%), and the mortality was 1 out of 54 patients (1.9%)/4 out of 91 (4.4%), respectively (P = 0.006). Interestingly, severe ILD events (grades 2, 3, 4, or 5) were significantly reduced in patients with fexofenadine compared with patients without fexofenadine (P = 0.031). Although the administration of fexofenadine was not independent predictive factor for EGFR-TKIs-induced ILD according to multivariate analysis, it seems to reduce the ILD events (P = 0.061).

Conclusions: Our data suggest that fexofenadine seem to reduce the incidence of TKI-induced ILD. However, the prospective study needs to be carried out to confirm our result.

O1 – 035 ASSOCIATION OF SECOND PRIMARY MALIGNANCIES WITH PAST AND FAMILY HISTORY OF MALIGNANCY IN PATIENTS WITH SMALL CELL LUNG CANCER


Division of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan

Background: Based on recent development in the treatment of small-cell lung cancer (SCLC) such as chemotherapy and radiotherapy, long-term survivors are frequently observed. Meanwhile, etoposide and radiotherapy, which are key treatments for SCLC, are also known as methods to set up late complication including carcinogenicity. There have been few reports of second primary malignancies (SPM) in patients with SCLC, and risk factor for SPM has not become evident other than smoking continuation.

Methods: From July 1992 to December 2009, 900 patients with SCLC were treated in National Cancer Center Hospital East. Medical records of all patients were retrospectively reviewed, and the incidence and risk factor for SPM were investigated.

Results: Demographics of all patients with SCLC were as follows: male/female, 738/162; median age, 66 years (range 22–87); smoking pack-year (PY) <30/30 ≥< 155/745; limited/extension, 468/432. Median follow-up time was 4.5 years. Three and 5-year overall survival rates were 16.4% and 11.6%, respectively. Twenty-seven patients (3.0%) developed SPM, 15 patients (54%) of whom died due to SPM. Thoracic cancer occupied 52% of them (lung, 11; trachea, 1; esophagus, 4; breast, 4); breast. Three and 5-year cumulative incidence rates (CIR) of SPM were 2.5% and 11.8%, respectively. Although there was no significant risk factor for SPM, the groups having past history of malignant disease and heavy smoker (PY ≥30) tended to develop SPM (P = 0.13 and 0.07). Using etoposide containing regimen and thoracic irradiation were not significant risk factors for the incidence of SPM (P = 0.84 and 0.24). Neither serum level of CEA, NSE nor ProGRP were risk factors of incidence of SPM (P = 0.51, 0.09 and 0.21). Within over 2-year survivors, there was a significant correlation between family history of cancer within first-degree relatives and CIR of SPM (P < 0.01).

Conclusions: Five-year CIR of SPM was 11.6%, and secondary thoracic cancer accounted for a large portion of them. It was concluded that cumulative smoking amount, past history of malignant disease, and positive family history of cancer within first-degree relatives were risk factors for SPM.

O1 – 036 RETROSPECTIVE ANALYSIS OF THE CHEMOTHERAPY FOR PATIENTS OF EXTENSIVE SMALL CELL LUNG CANCER WITH POOR PERFORMANCE STATES

M. Yomota, K. Sekihara, Y. Nakahara, Y. Ookuma, Y. Takagi, Y. Hosomi, M. Igarashi, T. Okamura, M. Shibuya

Tokyo Metropolitan Komagome Hospital

Background: Small cell lung cancer is recognized as a malignant tumor with high sensitivity to anticancer drug, and it is recommended strongly to carry out the systematic chemotherapy for patients in small cell lung cancer with enough general condition. However, there are few evidence of the efficiency and toxicity of the chemotherapy for cases presenting poor PS.
Background: Extranasal NK/T-cell lymphoma-associated hematopathologic syndrome (NK/T-LAHS) is a rare life-threatening disorder, which has been mainly reported in Asia countries. It progresses rapidly, and the prognosis is usually poor. However, the pathogenesis and prognostic factors of NK/T-LAHS are not fully understood. To find out more about the disease, we conducted a retrospective study on the NK/T-LAHS.

Methods: We reviewed medical charts of patients with extensive small-cell lung cancer with poor PS (ECOG/3.4) treated by systemic chemotherapy from April 2002 to January 2012 at Metropolitan Komagome Hospital.

Results: The characteristics of the 16 cases were median age 74.5 years, 12 cases with PS 3, 4 cases with PS 4. All cases carried out at least one cycle of chemotherapy including platinum drug.

Results and conclusions: Previously, the medium survival time for patients of extensive small-cell lung cancer with only best supportive care is reported to be 1–2 months. Our investigation suggested that systemic chemotherapy contributes to the extension of survival time even among cases with poor PS; therefore, chemotherapy can be considered for patients who wish life prolongation.

Background: AMR, a new anthracycline agent, has achieved some promising results for advanced SCLC both in the first-line and the second-line setting. However, the efficacy of AMR alone against refractory relapsed SCLC was relatively low in previous studies. This study was conducted to evaluate the safety and efficacy of the combination of AMR–CBDCA in patients with refractory relapsed SCLC.

Methods: Patients with advanced SCLC who relapsed within 90 days after the completion of first-line chemotherapy received AMR (30 mg/m², day 1–3) and CBDCA (AUC 4.0, day 1) every 3 weeks. The primary endpoint of this study was overall response rate (ORR), and secondary end points were progression-free survival (PFS), overall survival, and toxicity profile. Assuming that ORR of 45% in eligible patients would indicate potential usefulness while ORR of 20% would be the lower limit of interest, with alpha = 0.10 and beta = 0.10, at least 24 patients were required.

Results: From September 2008 to May 2011, 30 patients were enrolled from 10 institutions. One patient was excluded because of ineligible histology. Patient characteristics were male/female 26/3; median age 67 (range 50–79) years; and performance status 0/1/2 9/1/0. The median number of treatment cycles was 4 (range 1–7). The objective response rates evaluated by RECIST were CR 0, PR 10, SD 14, and PD 6. The ORR was 34% and the disease control rate was 83%. The median PFS was 3.5 months and the median survival time was 7.3 months. Grade 3–4 neutropenia was observed in 23 patients (79%) and grade 3–4 thrombocytopenia was observed in 7 patients (24%). One patient (3%) suffered from grade 3 to 4 leucopenia neutropenia. Other grade 3 non-hematological toxic effects such as infection, neutropenia was observed in 23 patients (79%) and grade 3–4 neutropenia was observed in 23 patients (79%).

Conclusions: This is the first prospective study of AMR combined with CBDCA for refractory relapsed SCLC, which was effective and well tolerated. Further investigation of this treatment is warranted.

Background: We evaluated the prognostic significance of apoptosis-related proteins in DLBCL patients treated with cyclophosphamide/doxorubicin/vincristine/ prednisone (CHOP)-based chemotherapy. We evaluated the association between apoptosis-related proteins and clinical features, laboratory findings, treatments and prognosis of these patients were collected and analyzed.

Results: Of the 23 NK/T-LAHS patients, the median age was 45 years old and 15 (65.2%) were male. 11(47.8%) had an Ann Arbor stage of I/II/III/IV: 19(82.6%) cases originate from colon, cervix, or skin. LDH levels were elevated in all 23 cases at the time of diagnosis, and 10(43.5%) cases showed elevated LDH levels of more than 1000 IU/L. At the onset of HPS, which predicted a poor prognosis, NK/T-LAHS was characterized by fever, pancytopenia, liver dysfunction, and hypokalemia, where only 9 cases (39.1%) were found lymphohematopoiesis in bone marrow. The median OS was 8.5 months from the diagnosis of NK/T cell lymphoma, and the median LAHS survival duration was 14 days. Chemotherapy and high-dose glucocorticoids were not so effective to NK/T-LAHS that almost 100% cases died soon.

Conclusions: NK/T-LAHS usually occurs in the nasal type of NK/T cell lymphoma, but the prognosis is poorer for the extranasal type. The rate of its definite diagnosis at the early stage is most. Most of the patients were died of multorgan failure, infection, and bleeding. Thus, the clinical lesion and LDH level may be prognostic factors. There was no effective treatment for NK/T-LAHS that it remains a challenge.

Background: Our earlier study showed that certain proportion of early-stage H. pylori (HP)-positive gastric diffuse large B-cell lymphoma (DLBCL) with features of mucosa-associated lymphoid tissue (MALT), DLBCL(MALT), could achieve long-term complete pathological remission (pCR) after frontline HP eradication therapy (HPE). In this retrospective, explorative study, we evaluate the efficacy of HPE on early-stage gastric DLBCL without features of MALT, the pure (de novo) DLBCL, in comparison with its efficacy on high-grade transformed gastric MALT lymphoma, the DLBCL(MALT).

Methods: A total of 50 patients of stage IE/II/IIE1, HP-positive gastric DLBCL with frontline HPE treatment were included. Of them, 16 patients with pure (de novo) DLBCL were retrospectively identified from medical/pathologic review and 34 patients with DLBCL(MALT) were an expanded cohort of one previously reported multicenter prospective study. pCR was defined as regression of DLBCL to Wooterspoon grade 2 or less in all histologic sections of follow-up endoscopic biopsies.

Results: HP infection was successfully eradicated in 100% (16/16) of the pure (de novo) DLBCL and 94.1% (32/34) of the DLBCL(MALT) patients. A total of 68.8% (11/16) of pure (de novo) DLBCL and 56.3% (18/32) of DLBCL(MALT) patients achieved pCR after HPE. The median time-to-pCR was 2.1 months (95% CI, 0.6–3.7) months for pure (de novo) DLBCL and 5.0 months (95% CI, 2.8–7.5) months for DLBCL(MALT) (P = 0.024). At a median follow-up of 7.7 years (95% CI, 4.5–10.9), all patients with pCR after HPE were alive and free of lymphoma, except one patient with pure (de novo) DLBCL died of lung cancer.

Conclusions: Similar to DLBCL(MALT), a substantial portion of early-stage, HP-positive gastric pure (de novo) DLBCL remains HP-dependent and respondsto antibiotic treatment. Prospective studies to validate the findings are warranted.

Background: We evaluated the prognostic significance of apoptosis-related proteins in DLBCL patients treated with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) chemotherapy with or without rituximab. Methods: Pretreatment tumor biopsy specimens from 111 patients (stage I: 15, II: 29, III: 34, IV: 33 patients) with DLBCL were analyzed for Bcl-2, Bcl-6, Topoisomerase-II (Topo-II), β-tubulin and p53 proteins expression by immunohistochemistry. Thirty-nine patients were treated with CHOP regimen, while 72 patients with R-CHOP.

Methods: We reviewed medical charts of patients of extensive small-cell lung cancer with only best supportive care is reported to be 1–2 months. Our investigation suggested that systemic chemotherapy contributes to the extension of survival time even among cases with poor PS; therefore, chemotherapy can be considered for patients who wish life prolongation.

Background: Extranasal NK/T-cell lymphoma-associated hematopathologic syndrome (NK/T-LAHS) is a rare life-threatening disorder, which has been mainly reported in Asia countries. It progresses rapidly, and the prognosis is usually poor. However, the pathogenesis and prognostic factors of NK/T-LAHS are not fully understood. To find out more about the disease, we conducted a retrospective study on the NK/T-LAHS.

Methods: 23 NK/T-LAHS patients diagnosed between July 2006 and September 2011 in Fudan University Shanghai Cancer Center were included. The information of clinical features, laboratory findings, treatments and prognosis of these patients were collected and analyzed.

Results: Of the 23 NK/T-LAHS patients, the median age was 45 years old and 15 (65.2%) were male. 11(47.8%) had an Ann Arbor stage of I/II/III/IV: 19(82.6%) cases originate from colon, cervix, or skin. LDH levels were elevated in all 23 cases at the time of diagnosis, and 10(43.5%) cases showed elevated LDH levels of more than 1000 IU/L. At the onset of HPS, which predicted a poor prognosis, NK/T-LAHS was characterized by fever, pancytopenia, liver dysfunction, and hypokalemia, where only 9 cases (39.1%) were found lymphohematopoiesis in bone marrow. The median OS was 8.5 months from the diagnosis of NK/T cell lymphoma, and the median LAHS survival duration was 14 days. Chemotherapy and high-dose glucocorticoids were not so effective to NK/T-LAHS that almost 100% cases died soon.

Conclusions: NK/T-LAHS usually occurs in the nasal type of NK/T cell lymphoma, but the prognosis is poorer for the extranasal type. The rate of its definite diagnosis at the early stage is most. Most of the patients were died of multorgan failure, infection, and bleeding. Thus, the clinical lesion and LDH level may be prognostic factors. There was no effective treatment for NK/T-LAHS that it remains a challenge.

Background: We evaluated the prognostic significance of apoptosis-related proteins in DLBCL patients treated with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) chemotherapy with or without rituximab. Methods: Pretreatment tumor biopsy specimens from 111 patients (stage I: 15, II: 29, III: 34, IV: 33 patients) with DLBCL were analyzed for Bcl-2, Bcl-6, Topoisomerase-II (Topo-II), β-tubulin and p53 proteins expression by immunohistochemistry. Thirty-nine patients were treated with CHOP regimen, while 72 patients with R-CHOP.
Background: Bendamustine (Benda) has been recently approved in Japan. Not only Benda itself has the favorable toxicity profile, but also Benda in combination with Rituximab (BR) seems to be superior because of synergy of the two drugs. We retrospectively analyzed the results of the treatment consisting of Benda with BR (BR) for the patients with relapsed or refractory low-grade B-cell lymphoma.

Methods and patients: Nineteen relapsed or refractory patients with follicular lymphoma (FL) (n = 11; 2 of which have transformed to diffuse large B-cell lymphoma), mantle cell lymphoma (MCL) (n = 5); marginal zone lymphoma (MZL) (n = 1), lymphoplasmacytic lymphoma [LPL] (n = 1), small lymphocytic lymphoma [SLL] (n = 1), received BR therapy (at most six cycles of Benda [120:90:60 mg/m2 ON1:1:1], and rituximab). The best response, adverse events and immunological parameters after therapy were evaluated.

Results: The median age was 66 (52–84) years, and number of previous therapy was 1–7 (M = 2) regimen, that included R (19), Zevalin (7) and nucleoside analogues (4), respectively. The evaluable overall response rate was 89% (16/18, FL 9, MCL 4, MZL 1, LPL 1, SLL 1) with 28% (5/18, FL 2, MCL 2, MZL 1) complete response. Hematological toxic effects were prominent but manageable, including grade 3/4 neutropenia, anemia and thrombocytopenia which were demonstrated in 38%, 11%, 16% of the patients, respectively. Non-hematological grade 3/4 toxic effects were observed, such as pneumonia, empyema and hiccup in one patient, respectively, and vasculitis in three patients. Majority of the evaluable patients revealed a considerable reduction of peripheral CD4+ T-lymphocyte number and immunoglobulin level, and two patients showed cytomegalovirus antigenemia, at various time points after therapy.

Conclusions: The results of our study suggest that BR therapy may play a promising role as a salvage therapy for low-grade B-cell lymphoma, not only for FL, but also for other types such as MCL, MZL, LPL and SLL. This therapy was well tolerated even in patients previously received radio-immunotherapy (Zevalin) or nucleoside analogues. Appropriate anti-infectious precautions seem to be necessary because of substantial immune-suppression.


Clinical outcome of radioimmunotherapy with asct (Z-leed) for relapsed and refractory B-cell lymphoma

Department of Hematology and Rheumatology, Kinki University Faculty of Medicine

Background: Raritumomimunotherapy (RIT) with 90-ytrrium ibritumomab tuxetan (90Y-IT) is known to be an effective approach for treatment of NHL, because lymphoma is highly radiosensitive, however, 3-year progression-free survival in our department is 39.1% (overall survival is 79.9%), which is not sufficient considering the cost-effectiveness. Consolodation therapy with RT is another attractive approach; however, bone marrow supression is a major and life-threatening issue for especially aged patients. In view of these findings, we employed RIT (90Y-IT) followed by HDT (LEED) in patients with relapsed and refractory B-cell lymphoma. In this report, we tried to evaluate the safety and efficacy of RIT using ibritumomab tuxetan (Zevalin) combined with high-dose LEED chemotherapy and ASCT (Z-LEED) in refractory/relapsed B-cell lymphoma.

Patients and methods: Eight patients with relapsed or refractory B-cell lymphoma (three mantle cell lymphoma patients and five grade III FL/DLBCL patients) were treated with Z-LEED. After PBSC mobilization and harvesting, the minimum target dose of CD34+ cells (2 × 10^6/kg) was stored. Patients were 11 in ibritumomab tuxetan (185 MBq IV) on day 1, followed by 90Y-IT (14.8 MBq/kg IV) administration on day 8 after rituximab. Then high-dose chemotherapy was delivered using the LEED (500 mg/m² etoposide on day 4, 3, and 2; 60 mg/m² cyclophosphamide on day 4 and 3; 130 mg/m² melphalan on day 1; and 40 mg/m² dexamethasone on day 4, 3, 2 and 1).

Results: Two patients had received more than three prior treatments, and three had chemotherapy-resistant disease. There were no therapy-related deaths. While one patient with conventionally measurable disease at the time of treatment, the respective complete and overall response rates were 100%. Seven patients remain CR at 2–27 months from transplantation and 8–102 months from diagnosis. One patient relapsed after 4 months from transplantation.

Conclusion: Rituximab tuxetan combined with LEED high-dose chemotherapy is safe and possibly effective as a conditioning regimen for ASCT.

Oral Session 9: Malignant lymphoma prognostic factor

A prognostic index for acute and lymphoma type adults T-cell leukemia/lymphoma


1Research Center for Innovative Oncology, National Cancer Center Hospital East, 2Department of Medicine, Division of Medical Oncology, Hematology and Infectious Diseases, School of Medicine, Fukukia University, 3Department of Hematology, Imamura Bun-in Hospital, 4Department of Hematology, Kagoshima Medical Center, 5Department of Hematology, Hannamnachi Medical Center, 6Department of Hematology, Sasebo City General Hospital, 7Department of Hematology, Oita Prefectural Hospital, 8Department of Internal Medicine, Karatsu Red Cross Hospital, 9Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, 10Department of Hematology, Nagasaki Medical College, 11Cancer Center, Shiane University

Purpose: The prognosis of acute and lymphoma type adult T-cell leukemia/lymphoma (ATL) has remained very poor, but there is a marked diversity in survival outcomes. The aim of this study was to develop a prognostic index (PI) for acute and lymphoma type ATL (ATL-PI). Patients and methods: In a retrospective review, data from 807 patients newly diagnosed with acute and lymphoma type ATL between January 2000 and May 2009 were evaluated. We randomly divided subjects into training (n = 404) and validation
EVALUATION OF A CARBOPLATIN (CBDCA) DOSING METHOD IN DEVIC CHEMOTHERAPY


1Department of Pharmacy, Fujita Health University Hospital, 2Department of Hematology and Medical Oncology, Fujita Health University Hospital

Background: In DeVIC chemotherapy (dexamethasone, etoposide, ifosfamide, carboplatin), a salvage chemotherapy for non-Hodgkin’s lymphoma (NHL), a dosage of CBDCA is determined based on body surface area (BSA). We investigated the accuracy of this dosing method.

Subject and methods: Forty-three cases treated by DeVIC chemotherapy at Fujita Health University Hospital between January 2005 and December 2011 were included in this study. CBDCA was dosed based on BSA (300 mg/m²), and the area under the plasma concentration time curve (AUC) was calculated based on a given dosage using a Calvert formula.

Results: In 24 cases with 1.3–1.8 m² of BSA and 60–120 ml/min of the estimated glomerular filtration rate (eGFR), AUC calculated based on a given dosage was 3.1–5.7 (median 3.9). The data showed that the calculated AUC was within appropriate and safe level as targeted AUC in chemotherapies for solid tumors. Adverse drug reactions (especially thrombocytopenia) with this AUC level were tolerable. In 14 of the 19 cases with <1.3 m² of BSA or <60 ml/min of eGFR, there was a great variation in the calculated AUC with the result of 2.8–7.8 (median 4.1). Five cases with over 120 ml/min of eGFR were excluded from the analysis.

Discussion: In phase II studies for NHL, it was demonstrated that there was no difference in a response rate with 200–400 mg/m² of CBDCA stratified dose. 63% of response rate and 38% of complete remission rate (CR) with a dosage of CBDCA 300 mg/m² for relapsed/refractory NHL. It was reported in DeVIC clinical study for relapsed/refractory NHL. It is suggested that this CBDCA dosing method based on BSA in DeVIC chemotherapy is appropriate for cases with the general BSA and renal function; however, dose evaluation should be required in cases with lower BSA or moderate/severe renal impairment.

EFFECTIVITY AND SAFETY OF DOSE-ADJUSTED EPOCH FOR RELAPSED AND REFRACTORY NON-HODGKIN LYMPHOMA (NHL)

T. Suzuki, Y. Harada, E. Matsubara, T. Aoki, T. Oyama, M. Kasai, T. Uchida, M. Oghara

Department of Hematology and Oncology Nagoya Daini Red Cross Hospital

Introduction: Since prognosis of patients with relapsed or refractory NHL is very poor, an effective salvage regimen is required to be investigated. We retrospectively evaluated the efficacy and the safety of dose-adjusted EPOCH (DA-EPOCH) reported by Wilson et al. for relapsed or refractory NHL in our institute.

Patients and methods: Patients with relapsed or refractory NHL selected based on practical clinical situation were treated with DA-EPOCH. The starting dose was as follows: doxorubicin 10 mg/m², etoposide 50 mg/m² and vincristine 0.4 mg/m² as a continuous infusion on days 1–4, cyclophosphamide 750 mg/m² intravenously on day 5 and oral prednisone 60 mg twice a day on days 1–5. CSF was started on day 6 until neutrophil recovered to more than 5000/µL. The dose was adjusted according to hematologic toxic effects. Patients with CD20-positive B-cell NHL (B-NHL) received DA-EPOCH with rituximab (DA-EPOCH-R). Response was evaluated in patients who received three cycles or more, and toxicity was evaluated in all patients.

Results: A total of 22 patients (male/female = 13/9) were treated with DA-EPOCH (11 patients with T-cell NHL) or DA-EPOCH-R (11 patients with B-NHL). Median age was 61 years (range 44–81), and median number of prior therapy was 2 (range 1–4). The median dose level of DA-EPOCH was 100% (range 80–100%). The treatment was discontinued in nine patients, due to disease progression in four patients and prolonged toxic effects in five patients. Seven patients achieved CR and two patients achieved PR (40.9% of ORR). The most frequent toxicity was grade 4 neutropenia observed in 20 patients (91.0%). Grade 3 febrile neutropenia was observed in seven patients (31.8%). Dose reduction was required in 6 of 13 patients who received at least three cycles. No treatment-related death was observed.

Conclusion: DA-EPOCH-R regimen is effective and well tolerated, even in heavily pretreated patients with relapsed or refractory NHL. Further prospective large scaled study is warranted in Japan.

TRYPTOPHAN CATABOLISM IS ASSOCIATED WITH THE PROGNOSIS OF PATIENTS WITH DE NOVO ACUTE MYELOID LEUKEMIA


First Department of Internal Medicine, Gifu University Graduate School of Medicine

Background: Indoleamine 2,3-dioxygenase (IDO) exerts immunomodulatory effects due to enzymatic activities catalyzing the essential amino acid L-tryptophan. IDO activity might play an important role in regulating immune responses exerted by antigen-presenting cells. We have recently been able to clarify the utility of either serum kynurenine or tissue IDO expression as prognostic factors for DLBCL patients treated using R-CHOP. In addition, blasts of patients with acute myeloid leukemia (AML) were shown to express IDO. In the present study, we investigated the tryptophan catabolism in AML.

Patients and methods: The study protocol comprised a retrospective, consecutive entry design that was approved by our Institutional Review Board. We investigated 61 patients between December 1994 and March 2011 who were diagnosed with AML. We measured serum kynurenine by high-performance liquid chromatography. IDO mRNA expression in leukemic blasts of patients with AML were measured by rTCA.

Results: The median serum kynurenine level was 1.79 µM (range 0.78–5.19). The 5-year overall survival (OS) rates for patients with kynurenine <2.0 and >2.9 µM were 68% and 11%, respectively (P < 0.05). Thirty-four patients were analyzed for the expression of IDO by reverse transcriptase PCR. We confirmed that 15 patients with IDO mRNA expression and 19 patients were without IDO mRNA expression. The 5-year OS rates for patients with IDO mRNA expression and without IDO mRNA expression were 29% and 60%, respectively (P < 0.05).

Conclusion: Serum kynurenine and IDO mRNA expression might be novel prognostic factors to determine the treatment outcome of AML. Inhibition of IDO expressed by AML blasts may result in breaking immune tolerance and offers new therapeutic options for patients with AML. AML IDO might thus represent a candidate therapeutic target for AML patients who show resistance to chemotherapy. Since these results are based on a small sized retrospective analysis, further investigation is required.
leukemia (Ph(-) ALL), the impact of the donor source, particularly the position of cord blood (CB) transplantation, is still uncertain. Methods: We retrospectively analyzed 1726 adult Ph(-) ALL patients transplanted at the first time between 1998 and 2009 with myeloablative preparatory regimens who were registered in the Japan Society for Hematopoietic Cell Transplantation database. Two hundred and thirty-three received CB transplantation [first complete remission (CR1); 95, subsequent CR; 53, non-CR; 85], 898 received allo-SCT from unrelated donor (URD) [CR1; 434, subsequent CR; 158, non-CR; 271], and 684 received allo-SCT from related donor (RD) [CR1; 388, subsequent CR; 89, non-CR; 207]. Results: Overall survival (OS) in patients after CB transplantation in CR1 was comparable with that after allo-SCT from URD or RD (P = 0.726 and 0.413, P = 0.20 at 4 years, respectively). Donor source was not a significant risk factor for OS in multivariate analysis. Although URD was a favorable factor for relapse and an unfavorable factor for non-relapse mortality (NRM), CB was not a significant factor for them [relapse: 22% in CB, 17% in URD, and 24% in RD at 3 years, respectively (P = 0.02); NRM: 27% in CB, 23% in URD, and 13% in RD at 3 years, respectively (P = 0.0001)]. Similarly, OS was not different by donor source in subsequent CR or non-CR [subsequent CR: 48% in CB, 39% in URD and 48% in RD, P = 0.03; non-CR: 18% in CB, 21% in URD, and 15% in RD, P = 0.20 at 4 years, respectively]. Conclusions: CB-SCT using CB led to similar outcomes as either RD or URD in any disease status. CB transplantation is a good alternative for adult Ph(-) ALL patients without a suitable RD or URD.

O1 – 054 THE EFFECT OF DECREASED-DOSE IDARUBICIN FOR ELDERLY PATIENTS WITH ACUTE MYELOID LEUKEMIA

M. Ichikawa, T. Kobayashi, Y. Nannya, M. Kurokawa
Department of Hematology and Oncology, the University of Tokyo Hospital

Recent studies show that anthracycline dose intensification improves survival of patients with acute myeloid leukemia (AML). However, elderly patients often do not tolerate the life-threatening side-effects of standard chemotherapy, and anthracycline doses are reduced in these patients although its efficacy is not well documented. Therefore, we evaluated whether reduced-dose chemotherapy consisting of two daily doses of idarubicin (IDR, 12 mg/m2) and 5 days of continuous injection of cytarabine (Ara-C, 100 mg/m2) (2 + 5) for patients aged 65–74 is effective by retrospectively comparing the results with those of younger patients (aged 55–64) who are treated with the standard 3 + 7 chemotherapy. Between 1999 and 2009, we treated 20 patients aged 65–74 with the 2 + 5 regimen, and 23 patients aged 55–64 with the standard 3 + 7 regimen. Two-year overall survival rates were 55.9% for patients treated with 2 + 5, and 32.3% for patients treated with 3 + 7; 2-year rates of relapse-free survival were 15.7% and 36.5%, respectively. The differences in both overall and relapse-free survival were not statistically significant (P = 0.726 and 0.413, respectively). Despite the importance of age as a prognostic factor, the treatment results of 2 + 5 therapy for ages 65 and above were not significantly worse than those of 3 + 7 for slightly younger patients. Therefore, if treated with IDR + Ara-C, elderly patients who do not tolerate standard 3 + 7 chemotherapy should still benefit from the decreased 2 + 5 chemotherapy.

O1 – 056 CLINICAL ANALYSIS AND TREATMENT OUTCOME OF AIDS-RELATED BURKITT LYMPHOMA IN JAPAN

1Department of Hematology, National Hospital Organization Nagoya Medical Center, 2Department of Hematology, National Center for Global Health and Medicine, 3Department of Infectious Disease, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 4Division of Gastroenterology and Hematology, Department of Internal Medicine, Faculty of Medicine, Miyazaki University, 5AIDS Clinical Center, National Center for Global Health and Medicine, 6Department of Infectious Diseases, National Hospital Organization Osaka Medical Center, 7Center for AIDS Research, Kumamoto University

Background: With the widespread use of highly active antiretroviral therapy (HAART), the prognosis of HIV infected subjects has been improved, even if with AIDS-related lymphoma. Burkitt lymphoma progresses very rapidly, but highly intensive chemotherapy (e.g.CODOX-M/IVAC, hyper-CVAD/MA) has been shown to be a promising strategy. In this time, AIDS-related lymphoma is treated with similarly to non-AIDS lymphoma; nevertheless, it is not clear whether the highly intensive regimens are feasible and beneficial for AIDS-related Burkitt or not. We conducted nationwide retrospective survey to clarify the clinical outcomes of AIDS-related Burkitt lymphoma.

Materials and methods: All AIDS-related Burkitt lymphoma newly diagnosed at center hospitals for HIV/AIDS in Japan during the period 2002–2010 were serially registered.

Results: We identified 33 patients; the median age was 41 (range, 26–70 years) and the male gender accounted for 97% of the patients (32/33). Twenty-three patients (79%) had history of AIDS and the median CD4 count was 205/mm3 (range, 3–488/mm3). Twenty-nine (88%) were diagnosed in advanced stage (III/IV), with bone marrow involvement in 16 (48%) and central nervous system infiltration in 7 (21%). Nineteen (58%) were treated with rituximab-contain regimen and 14 (42%) were not. As chemotherapy regimen, 6 (18%) were treated with CODOX-M/IVAC, 22 (67%) with hyper-CVAD/MA and 5 (15%) with other regimens. Of 19 patients treated with rituximab-contain regimen, none were treated with CODOX-M/IVAC. Response to the end of treatment among 32 assessable patients was as follows: CR: 24 (73%); PR: 2 (6%); SD: 1 (3%); PD: 5 (15%). The median follow-up was 17 months. Two-year OS of total patients was 68.1%. There was no significant difference between chemotherapy regimens with/without rituximab (P = 0.367). Two-year OS was 66.7% in CODOX-M/IVAC and 71.0% in hyper-CVAD/MA (P = 0.724). There were a few patients with treatment-related death.

Conclusions: The favorable overall outcomes of AIDS-related Burkitt lymphoma were shown in this study. The addition of rituximab to highly intensive chemotherapy has not shown to be beneficial for AIDS-related Burkitt lymphoma. We now conduct prospective a clinical trial to optimize the treatment strategy for AIDS-related Burkitt lymphoma.
Conclusions: Repeated dosing of palonosetron on days 1 and 3 was safe and well tolerated for the prevention of nausea and vomiting induced by high or moderate emetogenic chemotherapy. This study was reviewed and approved by the Fukuoka University Ethics Committee and Institutional Review Board of Fukuoka University Hospital. All patients provided written informed consent.

**O1 – 061 SIGNIFICANCE OF THE INSTITUTIONAL ANTIEMETIC GUIDELINES FOR CHEMOTHERAPY INDUCED NAUSEA AND VOMITING: EVALUATION OF EFFICACY AND COSTS**

Y. Sato¹, R. Tatsuta¹, R. Nakahara¹, S. Otsubo², H. Itoh³, R. Morinaga³, K. Shirao⁴
¹Department of Pharmacy of Oita University Hospital, ²Department of Medical Oncology of Oita University, Faculty of Medicine

**Purpose:** Chemotherapy-induced nausea and vomiting (CINV) is one of the major adverse events in patients receiving cancer chemotherapy. Preventing CINV is the key to maintaining a patient’s quality of life. At Oita University Hospital, the antiemetic regimen was standardized based on the antiemetic guidelines for CINV published by the Japanese of Society Clinical Oncology (JSCO) in May 2010. In the present study, we retrospectively evaluated the clinical and economic effects of standardizing the antiemetic regimen.

**Methods:** Palonosetron, dexamethasone, aprepitant, was administered as antiemetics according to the newly standardized regimen. The efficacy and costs of antiemetic treatment of chemotherapy before and after standardization of the antiemetic regimen between July 2010 and December 2010 were compared between patients receiving high-grade emetogenic chemotherapy (HEC) and those receiving moderate-grade emetogenic chemotherapy (MEC) and that the recommended doses were 360 mg bid for CYP2C19 extensive metabolizers (EMs), 240 mg bid for CYP2C19 intermediate metabolizers (IMs) and 240 mg bid for poor metabolizers (PMs). Nonclinical studies demonstrated that the dose-limiting toxicity (DLT) of ARQ 197 was neutropenia, and that the recommended doses were 360 mg bid for patients with newly diagnosed cancer and randomly selected 164720 non-cancer controls which matched with age and sex (case-control ratio = 4:1) in 2005–2008. This study used multivariate logistic regression analysis to calculated odds ratios (ORs) and 95% confidence intervals (CIs) of mental disorders associated with cancer risk adjusted for sociodemographic factors and co-existing diseases.

**Results:** The prevalence of mental disorders for cancer patients and controls were 18.7% and 24.8%, respectively. People with mental disorders had higher risk of cancer compared with people without mental disorders (OR: 1.38, 95% CI: 1.34–1.41). Liver cirrhosis was associated with cancer risk (OR: 2.80, 95% CI: 2.59–3.03). Experienced emergency care or inpatient care for mental disorders were significant factors associated with cancer risk. The increased risk of cancer was associated with higher number of outpatient visits for psychiatric care.

**Conclusions:** Mental disorders could be considered as a risk factor for cancer. The severity-dependent effect exists in the association between mental disorders and cancer risk.

**O1 – 066 MENTAL DISORDERS AS A RISK FACTOR FOR CANCER: A POPULATION-BASED CASE–CONTROL STUDY**

Y.-C. Chou¹, T.-L. Chen², C.-C. Liao³
¹Department of Physical Medicine and Rehabilitation, China Medical University Hospital, ²Department of Anesthesiology, Taipei Medical University Hospital

**Background:** Previous studies reported controversial results in the association between depression and risk of cancer. The purpose of this study is to investigate mental disorders and risk of cancer in a population-based-case–control study.

**Methods:** We used insurance claims data from the National Health Insurance Research Database, a universal insurance program with a coverage rate of more than 99% of the population in Taiwan. We identified 41 191 patients with newly diagnosed cancer and randomly selected 164 720 non-cancer controls which matched with age and sex (case-control ratio = 4:1) in 2005–2008. This study used multivariate logistic regression analysis to calculated odds ratios (ORs) and 95% confidence intervals (CIs) of mental disorders associated with cancer risk adjusted for sociodemographic factors and co-existing diseases.

**Results:** The prevalence of mental disorders for cancer patients and controls were 18.7% and 24.8%, respectively. People with mental disorders had higher risk of cancer compared with people without mental disorders (OR: 1.38, 95% CI: 1.34–1.41). Liver cirrhosis was associated with cancer risk (OR: 2.80, 95% CI: 2.59–3.03). Experienced emergency care or inpatient care for mental disorders were significant factors associated with cancer risk. The increased risk of cancer was associated with higher number of outpatient visits for psychiatric care.

**Conclusions:** Mental disorders could be considered as a risk factor for cancer. The severity-dependent effect exists in the association between mental disorders and cancer risk.

**O1 – 070 PHASE I TRIALS OF A C-MET INHIBITOR ARQ 197 IN COMBINATION WITH AN EGFR INHIBITOR ERLOTINIB IN ADVANCED/METASTATIC NON-SMALL CELL LUNG CARCINOMA (ARQ 197-003/005 TRIAL)**

Y. Fujisaka¹, N. Yamamoto², T. Hirashima³, K. Takeda⁴, K. Sugido⁵, M. Satouchi⁶, K. Nagagawa⁷
¹Department of Medical Oncology, Kei University Faculty of Medicine, ²Thoracic Oncology Division, Shizuoka Cancer Center, ³Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, ⁴Department of Clinical Oncology, Osaka City General Hospital, ⁵Institute for Clinical Research, National Kyushu Cancer Center, ⁶Department of Pulmonary Medicine, Hyogo Cancer Center

**Background:** ARQ 197 (also known as Tivantinib) is a selective, oral, non-ATP-competitive, small molecule inhibitor of c-MET, and is mainly metabolized by CYP3A4. A Japanese phase I study evaluating ARQ 197 as a single agent demonstrated that the dose-limiting toxicity (DLT) of ARQ 197 was neutropenia, and that the recommended doses were 360 mg bid for CYP3A4 extensive metabolizers (EMs) and 240 mg bid for poor metabolizers (PMs). Nonclinical studies have shown synergism of c-MET ligand HGF with EGF. In addition, a Western phase 2 study demonstrated prolonged progression-free survival in metastatic non-small-cell lung cancer (NSCLC) patients treated with ARQ 197 in combination with an EGFR inhibitor Erlotinib. In this study, the safety and tolerability of ARQ 197 in combination with Erlotinib were evaluated in Japanese patients.

**Methods:** Advanced or metastatic NSCLC patients received ARQ 197 as a single agent for single-dose analysis on day 1, and thereafter, started a repeating dose of ARQ 197 and Erlotinib combination for 29 days. ARQ 197 was administered at 300/360 mg bid for EMs (n = 4 and 12, respectively), and 120/240 mg bid for PMs (n = 3 and 6, respectively), whereas Erlotinib was administered at 150 mg/day for all patients. DLT observation period was defined from the first dose to the end of the 29 days of the combinational treatments.

**Results:** No DLT was observed in the enrolled 25 patients (16 EMs, 9 PMs). Rash, dry skin, diarrhea, leukopenia, mucositis oral and nausea were the treatment emergent adverse events observed in >20% of the enrolled patients, including both EMs and PMs during the DLT observation period. Those adverse events were well manageable. Drug–drug interaction was not clearly observed in ARQ 197 metabolism in combination with Erlotinib. Of 25 patients evaluable for response, three patients (two EMs, one PMs) achieved a partial response and 10 patients maintained stable disease.

**Conclusion:** ARQ 197, when combined with Erlotinib, was well tolerated up to 360 mg bid for EMs and 240 mg bid for PMs. A randomized, placebo-controlled, double-blind phase 3 trial is currently underway in Asian countries to evaluate the efficacy of ARQ 197 plus Erlotinib treatment over Erlotinib alone, on OS prolongation in non-squamous NSCLC with wild-type EGFR.

**Oral Session 13: Novel anti-cancer drug 1**

**O1 – 064 CANCER PATIENTS ON TWITTER: THE NOVEL COMMUNITIES ON SOCIAL MEDIA**

H. Narimatsu¹, Y. Sugawara², A. Fukao³
¹Advanced Molecular Epidemiology Research Institute, Faculty of Medicine, Yamagata University, ²Department of Medical Informatics, Major of Environmental Life Science, Graduate School of Medical Science, Yamagata University

**Background:** Twitter is an interactive and real-time media. It is considered to be able to play an important role in modern social community of cancer patients.

**Methods:** Descriptive characteristics were extracted from the public profile pages on Twitter of self-identified cancer patients. The relationship between cancer patients on Twitter and the contents of tweets were therefore investigated using Web tools.

**Results:** Fifty-two users accounts with 500 or more followers were extracted. The three types of cancer were breast cancer (n = 14), malignant lymphoma (n = 10) and leukemia (n = 5). After excluding the user account of a famous entertainer with cancer, the relationships between cancer patients were then analyzed based on the data of account User 0 with breast cancer who had the largest number of followers (2463 followers). User 0 exchanged tweets with breast cancer patients (n = 3), with patients suffering from cancer of the uterus (n = 1) and a patient with cancer of unidentified origin (n = 1). Among the patients with a direct relationship to User 0, the patients with the largest number of tweets was 120/240 mg bid for PMs (n = 3 and 6, respectively), whereas Erlotinib was administered at 150 mg/day for all patients. DLT observation period was defined from the first dose to the end of the 29 days of the combinational treatments.

**Conclusion:** The Twitter networks of cancer patients centered on active users were demonstrated, which could provide psychological supports for cancer patients.
PHASE I STUDY OF OMBRABULIN IN COMBINATION WITH CISPLATIN (CDDP) ADMINISTERED EVERY 3 WEEKS TO JAPANESE PATIENTS WITH ADVANCED SOLID TUMORS

S. Takahashi1, T. Ura1, K. Nakano1, K. Chin1, M. Yokoyama1, K. Hatake1, T. Yokota1, K. Shtara2, K. Muru1, T. Aoyama3

1Department of Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 2Department of Clinical Oncology, Aichi Cancer Center Hospital, 3Oncology Business Unit, Sanofi-aventis Japan

Background: Ombrabulin, an analog of Combretastatin A4, is a vascular disrupting agent that destroys established tumor vasculature, causing blood perfusion shutdown and tumor necrosis. Ombrabulin in combination with platinum derivatives has shown synergistic antitumor activity in animal models. In non-Japanese patients, the recommended dose (RD) of this combination was established at 25 mg/m² for ombrabulin and 75 mg/m² for CDDP, given every 3 weeks. A phase III study using this combined therapy in advanced soft tissue sarcoma is ongoing.

Methods: This was an open-label, sequential cohort, dose escalation study of ombrabulin (15.5 and 25 mg/m²) administered immediately following a CDDP (75 mg/m²; fixed dose) every 3 weeks. DLTs were to be evaluated during the first treatment cycle only. RD was defined as the highest ombrabulin dose at which <33% of all evaluable patients experienced DLTs. PK of ombrabulin, its active metabolite RPR258063 and total/free CDDP were evaluated at cycle 1.

Results: A total of 10 patients (M/F, 5/5; median age, 49.5 [31–67]), including three breast cancer and two esophagus cancer patients, were treated. The median number of cycles was 4.0 (range 1–6). The RD for the combination was 25 mg/m² ombrabulin and 75 mg/m² CDDP. No DLT or severe cardiovascular adverse events (AE) were observed. No grade 3/4 AE were observed at RD other than neutropenia, which occurred in three of the six patients. The most frequent related AEs at RD in five of the six were neutropenia, decreased appetite, nausea, hiccups, constipation and fatigue. One patient (unknown primary origin) at RD had a partial response (PR) and 5 of the 10 patients had a stable disease (SD) as per RECIST. Preliminary PK parameters were in the range of those observed in non-Japanese patients.

Conclusions: Ombrabulin in combination with CDDP in Japanese patients was well tolerated. The RD for Japanese patients was defined as 25 mg/m² of ombrabulin and 75 mg/m² of CDDP, identical to the one in non-Japanese patients. Tumor responses (PR and SD) were observed in different tumor types and at different ombrabulin doses.

PHASE I STUDY OF OMBRABULIN, A VASCULAR DISRUPTING AGENT (VDA), ADMINISTERED EVERY 3 WEEKS TO JAPANESE PATIENTS WITH ADVANCED SOLID TUMORS

T. Kurata1, H. Murakami2, Y. Fujisaka1, H. Kiyota1, H. Hayashi1, K. Tanaka1, K. Nakagawa1, Y. Onzawa1, J. Watanabe1, N. Yamamoto1, T. Aoyama3

1Department of Medical Oncology, Kanagawa University Faculty of Medicine, 2Division of Thoracic Oncology, Shizuoka Cancer Center, 3Oncology Business Unit, Sanofi-Aventis Japan

Background: Ombrabulin, an analog of Combretastatin A4, is a vascular disrupting agent that destroys established tumor vasculature, causing blood perfusion shutdown and tumor necrosis. In non-Japanese patients, the recommended dose (RD) for ombrabulin single agent was established at 50 mg/m² given every 3 weeks. A phase I study of ombrabulin as a single agent administered to Japanese patients with advanced solid tumors was carried out.

Methods: The primary objective of the study was to determine the maximum tolerated dose (MTD) of ombrabulin and RD in Japanese patients. Secondary objectives were the assessment of the overall safety profile, the pharmacokinetic (PK) profile and preliminary anti-tumor activity.

Results: A total of 13 patients were enrolled (eight males and five females; age range 73 years), and received treatment at doses 0.25 mg BID (n = 4), 0.50 mg BID (n = 3), 0.75 mg BID (n = 3), and 1.0 mg BID (n = 3). DLTs were observed in one patient treated at 0.75 mg/m². No DLTs were observed at doses 0.25, 0.50 and 0.75 mg/m², one of six patients treated at 1.0 mg/m² experienced DLTs grade 2 hypertension and grade 3 diarrhea. RD/MTD was then determined at 50 mg/m². The most frequent related adverse events at RD were diarrhea (83.3%), nausea (83.3%) and hypertension (66.7%). Neither severe myelotoxicity nor abnormal elevation in cardiac markers was observed. Of 15 patients, 5 (33.3%) had stable disease (SD) as per RECIST. Preliminary PK parameters were in the range of those observed in non-Japanese patients.

Conclusions: Treatment with ombrabulin given every 3 weeks in patients with advanced solid tumors was well tolerated with limited cardiovascular toxicity events; 33.3% of patients had SD. Results from this study in Japanese patients indicate that the ombrabulin RD is 50 mg/m², the same as in non-Japanese patients.

PHASE I AND PHARMACOKINETICS/ PHARMACODYNAMICS (PK/PD) STUDY OF RO5126766, A FIRST-IN-CLASS DUAL RAF/MEK INHIBITOR, IN JAPANESE PATIENTS WITH ADVANCED SOLID TUMORS

K. Honda1, N. Yamamoto1, H. Nokihara1, Y. Yamada1, T. Yamura1, H. Aasahina1, S. Suzuki1, N. Yamazaki1, Y. Ogit1, W. Hasegawa2, M. Matsuoka2, T. Tamura3

1Division of Internal Medicine and Thoracic Oncology, 2Division of Internal Medicine and Gastrointestinal Oncology, 3Department of Dermatology and, 4Division of Oncopharmacology, National Cancer Center Hospital, Japan, 5Chugai Pharmaceutical Co., Ltd.

Background: RO5126766, a highly selective dual Raf and MEK inhibitor, is a first-in-class tandem MAPK signaling pathway inhibitor. The objectives of this phase I study were to determine MTD and to evaluate safety, PK, PD and anti-tumor activity in Japanese patients with advanced solid tumors.

Methods: 72–144 hours after oral single dose administration of RO51266 (0.8, 1.2, 1.8 and 2.25 mg/day), patients received oral RO51266 administered on a continuous once daily dosing (QD) in 28-day cycles. The +3 dose-escalation design was used. PD was evaluated by pERK and pMEK inhibition in peripheral blood mononuclear cells (PBMC).

Results: Twelve patients were enrolled in cohort of 0.8, 1.2, 1.8 and 2.25 mg/day. Considering 2.25 mg/day had been defined as the MTD on the QD oral dosing regimen in another phase I study conducted in Europe, higher dose than 2.25 mg/day was not administered in this study. In the dose range tested, no DLT was observed and the MTD has not been defined. Main adverse events (AE) included dermatitis acnesiform, creatine phosphokinase (CPK) elevation and eye disorders. The plasma exposures of RO51266 appeared to increase dose-linearly with long plasma half-life (1/2) of 45.8–93.7 h. After multiple dose administration, steady-state conditions were reached by cycle 1 day 8 (240 h). The inhibitory effects of RO51266 in both pERK and pMEK in PBMCs were increased in a dose-dependent manner. Five of 12 patients achieved stable diseases including a case of melanoma with over 20% shrinkage.

Conclusions: RO5126766 has a manageable safety profile up to 2.25 mg/day once daily with a favorable PK/PD profile in Japanese patients with advanced tumors.

FINAL REPORT ON PHASE 1 CLINICAL TRIAL OF ORAL PPARI AGONIST EFATUTAZONE (CS-7017) IN JAPANESE PATIENTS WITH METASTATIC SOLID TUMORS


1Department of Medical Oncology, Shizuoka Cancer Center, Shizuoka, 2Department of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, 3Department of GI Oncology, Shizuoka Cancer Center, Shizuoka, 4Clinical Development Department, Daiichi Sankyo Tokyo

Background: Peroxisome proliferator-activated receptor gamma (PPARγ) agonists are potent antitumor agents in preclinical models. Efaturazone is a novel, third-generation thiazolidinedione (TZD) showing higher potency over second-generation TZDs, such as pioglitazone. Now, phase 2 clinical trials of efaturazone in patients with metastatic non-small-cell lung cancer and colorectal cancer at doses of 0.50 mg twice-daily (BID) are ongoing in the USA and Europe.

Methods: This phase 1 dose-escalation study using a 3 + 3 design was initiated in Japanese patients with metastatic solid tumors. Patients with preexisting severe fluid retention were excluded. Efaturazone was administered orally BID starting at a dose of 0.25 mg. Pharmacodynamic (PD) and pharmacokinetic (PK) samples were collected on days 1 and 2. Archived tumor specimens were used for immunohistochemistry (IHC). Primary objectives of this study were to assess safety profile and PK. All subjects provided written informed consent.

Results: A total of 13 patients were enrolled (eight males and five females; age range 45–73 years), and received treatment at doses 0.25 mg BID (n = 4), 0.50 mg BID (n = 6) and 0.75 mg BID (n = 3). Efaturazone was tolerated. Dose-limiting toxicity (DUT) was not observed, but one grade 3 edema, unresponsive to therapy, occurred after the DLT evaluation period (day 27). The maximum tolerated dose (MTD) was not reached. Observed common adverse events were edema (85%), weight increase (85%), hemoglobin decrease (54%) and creatinine increase (54%). All patients were
evaluable for response. One subject with thymic cancer achieved a partial response (treatment duration >365 days as of 19 January 2012). In addition, 3 out of 13 patients showed stable disease. Elatuzumab increased plasma adiponectin levels. Plasma concentration of elatuzumab and adiponectin had a tendency to be saturated in the 0.50 mg cohort. Results of IHC showed no clear correlation between the immunostaining intensity of PPARy and the efficacy of elatuzumab.

Conclusions: Elatuzumab is a novel anticancer therapy, which is tolerated and demonstrates evidence of antitumor activity and disease stabilization. Although the MTD was not reached, 0.50 mg BID, corresponding to the global recommended dose, was selected as the recommended phase 2 dose.

**O1 – 075**

**LINIFANIB PLUS CARBOPLATIN/PACLITAXEL IN JAPANESE PATIENTS WITH ADVANCED/METASTATIC NON-SMALL-CELL LUNG CANCER**

M. Terashima1, K. Nakagawa1, T. Okae1, H. Kaneda1, N. Yamamoto2, H. Nokihara2, H. Horinouchi2, T. Horai3, M. Nishio3, F. Ohyanagi3, A. Horiike3, M. McKee4, D. Carlson4, H. Xiong4, T. Tamura2
1Department of Medical Oncology, Kinki University, Faculty of Medicine, Osaka, Japan. 2Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan. 3Thoracic Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan. 4Abbott Laboratories, Abbott Park, IL, USA

**Background:** Linifanib (ABT-896), a potent and selective inhibitor of VEGF and PDGF receptor tyrosine kinases, potentiates the action of carboplatin/paclitaxel (CP) in preclinical tumor models including NSCLC. This study assessed safety and tolerability of linifanib plus CP pharmacokinetics (PK), and preliminary anti-tumor activity in Japanese NSCLC patients.

**Methods:** Adult patients with ECOG PS score ≤1 and no prior chemotherapy for NSCLC received standard CP [C area under the concentration–time curve 6 mg/ml/min; P 200 mg/m2 on day (d) 1 of every 21-day cycle (c)] and oral linifanib 7.5 mg daily (c). Patients were treated sequentially in 3 dose cohorts: 5 mg/m2 (n = 6), 7.5 mg/m2 (n = 6), and 10 mg/m2 (n = 6) linifanib daily (c). The primary study objectives were to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), and pharmacokinetics (PK) of linifanib with CP. Patients were enrolled in a 2:1 ratio of CP alone to CP plus linifanib.

**Results:** Enrollment was 6 patients at 7.5 mg linifanib and 6 patients at 12.5 mg. One patient in each cohort had a serious AE of febrile neutropenia at ≤2. Most common AEs leading to treatment interruption were neutropenia (9), anaemia (5), leucopenia (4), febrile neutropenia (3), hand and foot syndrome (2) and oral ulceration (2). One patient treated with linifanib 10 mg/m2 had grade 3/4 continuous neutropenia and thrombocytopenia, grade 3 hypertension, grade 2 hand and foot syndrome, and grade 2 vomiting. From cycle 6 of treatment, 3 patients discontinued treatment at least partially due to neutropenia (2), anaemia (1), or dose reduction (2). The MTD was not reached at 10 mg/m2 linifanib daily (c). The median time from start of treatment to the first DLT was 8 days (range 2–28 days). The median PK parameters were AUC0–24h = 160 μg·h/ml (range 126–213 μg·h/ml), Cmax = 3.5 μg/ml (range 1.0–7.1 μg/ml), and CL = 0.16 μg·h/ml/min (range 0.03–0.45 μg·h/ml/min).

**Conclusions:** Preliminary findings suggest that CP with daily linifanib is tolerable in Japanese patients with advanced/metastatic NSCLC. PKs have been observed. These data will be reviewed in the context of an ongoing global study in a similar population receiving similar treatments.

**Oral Session 14: Novel anti-cancer drug 2**

**O1 – 076**

**MET KINASE INHIBITOR E7050 REVERSES THREE DIFFERENT MECHANISMS OF HEPATOCYTE GROWTH FACTOR-INDUCED TYROSINE KINASE INHIBITOR RESISTANCE IN EGFR MUTANT LUNG CANCER**

T. Nakagawa, S. Takeuchi, T. Yamada, S. Yano
Division of Medical Oncology, Cancer Research Institute, Kanazawa University

**Purpose:** Hepatocyte growth factor (HGF) induces resistance to reversible and irreversible epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in EGFR mutant lung cancer cells by activating Met and the downstream PI3K/Akt pathway. Moreover, continuous exposure of HGF accelerates emergence of EGFR-TKI-resistant clones. The present study was carried out to determine whether a new Met kinase inhibitor, E7050, reverses three different mechanisms of resistance to EGFR-TKIs.

**Experimental design:** The effects of E7050 on HGF-induced resistance to reversible (gefitinib), irreversible (BIBW2992) and mutant-selective (WZ4002) EGFR-TKIs were determined using the EGFR-mutant human lung cancer cell lines PC-9 and HCC827 with exon 19 deletion, and H1975 with T790M secondary mutation. As an in vivo model, E7050 combined with gefitinib-induced marked regression of tumor growth associated with inhibition of Akt phosphorylation in cancer cells.

**Results:** A new Met kinase inhibitor, E7050, reverses three different mechanisms of gefitinib resistance induced by HGF, suggesting the usefulness of E7050 for overcoming HGF-induced resistance to gefitinib and next-generation EGFR-TKIs.

**O1 – 077**

**CANCER VACCINATION TRIAL WITH NOVEL MULTIPLE PEPTIDES IN PREVIOUSLY TREATED ADVANCED NON-SMALL-CELL LUNG CANCER**

T. Hirose1, H. Noda2, K. Okudaira1, S. Abe1, Y. Otwa2, Y. Kusumoto1, T. Sugiyama1, H. Ishida1, T. Shirai2, M. Nakashima1, T. Yamaoka2, T. Ohshita2, Y. Yamasaki3, M. Adachi3
1Division of Respiratory Medicine and Allergology, Showa University of Medicine, 2Department of Pharmacy, Showa University of Medicine, 3Institute of Molecular Oncology, Showa University of Medicine, 4Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Sciences, University of Tokyo

**Background:** Cell division cycle associated gene 1 (CDCA1) and insulin-like growth factor II mRNA binding protein 3 (IMP-3) are novel cancer-testis antigen overexpressed in non-small-cell lung cancer (NSCLC). The aim of this study was to evaluate the safety, efficacy and immunological response of a novel peptide vaccination therapy, CDCA1 and IMP-3, in patients with previously treated advanced NSCLC.

**Patients and methods:** Human histocompatibility leukocyte antigen (HLA)-A2402-positive advanced NSCLC patients who failed to standard therapy were enrolled if they had a performance status of three or less, were ≥80 years or younger and had adequate organ function. The cocktail of two peptides was subcutaneously injected with 1 ml of incomplete Freunds adjuvant to axillary or inguinal regions weekly. Immunological response was evaluated with enzyme-linked immunospot assay before and after vaccinations every 4 weeks.

**Results:** From November 2009 to November 2011, 20 patients (13 men and 7 women; median age: 65 years; range, 36–78 years) were enrolled. CDCA1 and IMP-3 specific cytotoxic T lymphocyte responses were observed after vaccinations in 60% and 73% of patients, respectively. The overall response rate was 5% (95% CI, 0.1–24.9%) and stable disease rate was 55% (95% CI, 31.5–76.9%). The median survival time from the start of vaccination therapy was 7 months (range 1–26 months). The median progression-free survival time was 3 months (range 1–15 months). One patient with interstitial lung disease (ILD) had acute exacerbation of ILD during vaccination therapy. The other 19 patients did not have any grade 3 or 4 adverse events.

**Conclusion:** This vaccination therapy was effective and well tolerated in patients with NSCLC who failed to standard therapy, and therefore warrants further clinical studies.

**O1 – 079**

**PHASE 1 DOSE-ESCALATING STUDY OF BMS-754807 IN JAPANESE PATIENTS WITH ADVANCED SOLID TUMORS**

Y. Tamura1, H. Nokihara1, N. Yamamoto1, H. Waku1, K. Honda1, H. Asahina1, Y. Yamada1, T. Komaba1, T. Tamura1
1Division of Internal Medicine, National Cancer Center Hospital, 2Bristol-Myers K. K

**Background:** The type I insulin-like growth factor receptor (IGF-IR) is an important growth factor receptor in cancer cells and is an attractive target for cancer therapy. IGF-IR is a receptor tyrosine kinase closely related to the insulin receptor (IR). BMS-754807 is a potent and reversible tyrosine kinase inhibitor of IGF-1R and IR intended for oral administration. This study was conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of BMS-754807 in Japanese patients with advanced solid tumors.

**Methods:** BMS-754807 was administered orally on a once-daily schedule. The dose levels were 20, 30, 50 and 100 mg/day. Dose limiting toxicity (DLT) was evaluated from the first dose to day 29 in the first cycle.

**Results:** Fifteen patients (female/male: 11/4; median age: 59 years; ECOG PS 0/1: 9/6, tumor type: 8 sarcoma, 2 colon, 1 gastric, 1 lung and 3 others) were enrolled and treated three patients each at 20, 30 and 50 mg/day and 6 at 100 mg/day. DLT was observed in one patient at 100 mg/day. This patient required 14 days interruption of dosing due to thrombocytopenia (<100 000/μl). The most common drug-related adverse events were hyperglycemia (n = 8), nausea (n = 6), hypoglycemia, anorexia and diarrhea (n = 4, each). Hyperglycemia was reversible and manageable with drug
interrupted and/or oral administration of metformin. Hypoglycemia was also well managed by oral glucose and close monitoring. No objective response was observed, and four patients had stable disease (unconfirmed). BMS-754867 was rapidly absorbed with maximum drug concentration (Cmax) observed within from 1 to 4 h after dosing and the steady-state exposure was achieved in day 8 with no unexpected accumulation. The mean Cmax and AUC of BMS-754867 appeared to be dose dependent, but not proportional.

Conclusions: BMS-754867 was well tolerable up to 100 mg/day in Japanese patients with solid tumors, and was warranted for further clinical evaluation.

C01 – 040

**P**HASE I AND D**O**SE FINDING STUDY OF U3-1287, A HUMAN MONOCLONAL ANTIBODY TARGETING HER3, IN JAPANESE PATIENTS WITH ADVANCED SOLID TUMORS

H. Waku1, N. Yamamoto1, S. Nakamichi2, Y. Tamura2, H. Nokihara3, Y. Yanarda2, T. Tamura4

1Department of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, 2Department of Internal Medicine and Gastrointestinal Oncology, National Cancer Center Hospital

Background: HER3 is a key dimerization partner for HER-family members that activates oncogenic signaling pathways leading to cell survival and proliferation. U3-1287 is a fully human anti-HER3 monoclonal antibody that has demonstrated antitumor activity in preclinical models. In a preceding US phase I study, the tolerability of U3-1287 was evaluated up to the dose of 20 mg/kg without dose-limiting toxic effects (DLT). In this study, we evaluated the tolerability, pharmacokinetics (PK) and potential antitumor activities of U3-1287 in Japanese patients with solid tumors up to the dose of 18 mg/kg.

Methods: Patients with advanced solid tumors that were well known to express HER3 were eligible (e.g. lung, breast, colorectal, cervical, esophageal and sarcoma). Patients received U3-1287 9 or 18 mg/kg intravenously every 3 weeks (q3w). The incidence of anti-U3-1287 antibodies (HAAH), tumor response and U3-1287 related biomarkers were also evaluated.

Results: Nine patients, three at 9 mg/kg and six at 18 mg/kg, were enrolled. Five patients were male, all patients had ECOG PS 0 and median (range) age was 67 (50-69) years. Primary tumor types were lung (2), colorectal (2), esophageal (2), breast (1), cervical (1) and sarcoma (1). U3-1287-related AEIs reported in 2 patients were AIT increase (3 patients), platelet count decrease, diarrhea, stomatitis, chilblains, rash maculo-papular and AST increase (2 each). No DLTs were observed. Plasma disappearance of U3-1287 was bi-phasic and terminal half-life at the dose of 18 mg/kg was approximately 9 days. The PK profile was similar to the US phase I study. Four patients had a best response of stable disease. All patients tested negative for HAA formation.

Conclusions: U3-1287 was well tolerated up to 18 mg/kg in Japanese patients with solid tumors. These data support a dosing regimen of 18 mg/kg q3w in future studies.

C02 – 002

**O**VEREXPRESSION OF FOXQ1 IS IMPORTANT FACTOR IN TUMORIGENICITY AND TUMOR GROWTH


1Department of Medical Oncology and 2Department of Genome Biology, Kinki University School of Medicine, 3National Cancer Center Hospital

Forkhead Box Q1 (Foxq1) is a member of the forkhead transcription factor family, and it has recently been proposed to participate in gastric acid secretion and mucin gene expression in mice. However, the role of Foxq1 in humans and especially in cancer cells remains unknown. We found that FOXQ1 mRNA is overexpressed in clinical specimens of colorectal cancer (28-fold/dilucin mucosa). A microarray analysis revealed that the knockdown of FOXQ1 using siRNA resulted in a decrease in p115(2p) expression, and a reporter assay and Chromatin immunoprecipitation assay showed that p21 was one of the target genes of FOXQ1. Stable FOXQ1-overexpressing cells (H1299/Foxq1) exhibited elevated levels of p21 expression and inhibition of apoptosis induced by doxorubicin or camptothecin. Although cellular proliferation was decreased in H1299/Foxq1 cells in vitro, H1299/Foxq1 cells significantly increased tumorigenicity (EGFP: 2/15, Foxq1: 7/15) and enhanced tumor growth (437 ± 301 versus 1735 ± 769 mm3, P < 0.001) in vivo. Moreover, stable p21 knockdown in H1299/Foxq1 cells increased tumor growth, suggesting that FOXQ1 promotes tumor growth independent of p21. Microarray analysis of H1129/EGFP and H1299/Foxq1 revealed that FOXQ1-overexpression upregulated several genes that have positive roles for tumor growth including VEGFA, WNT3A, RSP02, and 80 to 100 fold (80 to 100 fold) by microarray analysis and chemoresistance using these stable FOXQ1 transfectants. Changes by microarray analysis and chemoresistance using these stable FOXQ1 transfectants.
Conclusions: These data imply the potential of our detection system for clinical application.

**O2 - 006**

**PROGNOSTIC SIGNIFICANCE OF L-TYPE AMINO ACID TRANSPORTER 1 EXPRESSION IN COMPLETELY RESECTED PanCREATIC CANCER**

K. Kai1, Y. Sunose1, K. Arakawa1, N. Sunaga1, Y. Iwasaki1, M. Mori1, T. Oyama1, I. Takeyoshi1
1Department of Medicine and Molecular Science, University of Gunma, 2Department of Thoracic and Visceral Surgery, 3Department of Surgery, Maebashi Red Cross Hospital, 4Department of Diagnostic Pathology, University of Gunma

**Purpose:** The expression of L-type amino acid transporter 1 (LAT1) is tumor-specific and has been shown to play essential roles in cell growth and survival. However, little is known about the clinical significance of the role of LAT1 expression in pancreatic cancer. This study was conducted to determine prognostic significance according to the expression of LAT1 after curative surgery.

**Experimental design:** A total of 97 consecutive patients with completely resected pathologic stage I–IV pancreatic ductal adenocarcinoma were retrospectively reviewed. Tumor sections were stained by immunohistochemistry for LAT1, CD98, Ki-67, vascular endothelial growth factor (VEGF), microvesSEL density determined by CD34 and p53. The expression of these biomarkers were correlated with resected pancreatic benign lesions (n = 18). **Results:** LAT1 and CD98 was highly expressed in 52.6% (51/97) and 56.7% (55/97), respectively (P = 0.568). For 18 patients with pancreatic benign diseases, a high LAT1 expression was observed in 0% (0/18). The expression of LAT1 within pancreatic cancer cells was significantly associated with distant recurrence, tumor size, tumor pathological stage, lymph node, tumor portal vein, and CD34, cell cycle regular (p53) and CD98 expression. LAT1 expression was confirmed as a significant prognostic factor for predicting poor overall survival (OS) and progression-free survival (PFS) by multivariate analysis. In a combining analysis, patients with high LAT1/high Ki-67 tumor had a significantly shorter PFS and OS than patients with high LAT1/low Ki-67 tumor. **Conclusion:** LAT1 expression is a promising pathological marker to predict the outcome in patients with resectable pancreatic cancer.

**Oral Session 16: Lung cancer NSCLC chemotherapy 1**

**O2 - 008**

**PHASE II STUDY OF AMRUBICIN (AMR) FOR PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) AS THIRD-LINE OR FOURTH-LINE CHEMOTHERAPY: HOKKAIDO LUNG CANCER CLINICAL STUDY GROUP TRIAL (HOT) 0901**

K. Itoh1,2, T. Harada1,2, K. Takenamura1,2, E. Kuwachi1,2, S. Ohiwara1,2, S. Sugawara1,2, M. Maemondo1,2, Y. Fujita1,2, K. Kinoshita1,2, A. Housui1,2, F. Hommura1,2, Y. Katsura1,2, H. Dosaka-Akita1,2, H. Ishobe1,2, M. Nishimura1,2
1Obihiro-Kosei General Hospital, 2Hokkaido Social Insurance Hospital, 3Hokkaido University School of Medicine. 4Sendai Kousei Hospital. 5Miyagi Hospital, 6Asahikawa Medical Center, 7Hokkaido University Graduate Hospital, 8Hokkaido Cancer Center, 9Department of Medical Oncology, KKR Sapporo Medical Center, 10First Department of Medicine, Hokkaido University School of Medicine, 11Department of Respiratory Medicine, National Hospital Organization, Asahikawa Medical Center, 12Department of Respiratory Medicine, National Hospital Organization, Hokkaido Cancer Center

**Background:** Although an increasing number of NSCLC patients receive third-line chemotherapy, the role of cytotoxic agent in this setting has not yet been well defined prospectively. AMR, third-generation synthetic anthracycline agent, has found favorable clinical activity and acceptable toxicity for NSCLC as well as small cell lung cancer. This prospective trial was conducted to evaluate the efficacy and safety of AMR for NSCLC patients as third-line or fourth-line chemotherapy.

**Method:** Eligible patients had a performance status 0 to 2, failure of second-line or third-line chemotherapy and adequate organ function. Patients received AMR 35 mg/m² intravenously on days 1–3 every 3 weeks. The primary end point was disease control rate (DCR; CR + PR + SD). Secondary end points were overall survival (OS), progression-free survival (PFS), response rate (RR) and toxicity profile.

**Results:** From August 2009 to May 2011, 41 patients were enrolled from 10 institutions. Patient characteristics were: male/female, 29/12; median age 66 (range 20 to 74 years), chemotherapy-naïve stage IIIB/IV non-squamous non-small cell lung carcinoma (NSCLC), and adequate organ function. Patients received CBDCA at a dose the median survival time was not reached. Grade 3/4 hematological toxic effects were neutropenia (68%), anemia (12%), thrombocytopenia (12%) and febrile neutropenia (17%). Grade 3/4 non-hematological toxic effects were anorexia (12%), nausea (10%) and vomiting (2%). No treatment-related death was observed.

**Conclusions:** AMR shows significant clinical activity with acceptable toxic effects as third-line or fourth-line chemotherapy for advanced NSCLC.

**O2 - 012**

**PHASE II TRIAL OF CARBOPLATIN AND PEMETREXED AS FIRST-LINE CHEMOTHERAPY FOR NON-SQUAMOUS NON-SMALL CELL LUNG CANCER AND CORRELATION BETWEEN THE EFFICACY/TOXICITY AND SINGLE NUCLEOTIDE POLYMORPHISMS ASSOCIATED WITH PEMETREXED METABOLISM: HOKKAIDO LUNG CANCER CLINICAL STUDY GROUP TRIAL (HOT) 0902**

K. Kanazawa1, T. Ishida1, Y. Fujita2, S. Fujisaki1, T. Harada3, M. Harada1, K. Takenamura1, I. Kinoshita1, Y. Katsura1, O. Hono1, T. Kojima1, S. Oizumi1, H. Ito1, M. Munakata1, M. Nishimura10
1Obihiro-Kosei General Hospital, 2Hokkaido Social Insurance Hospital, 3Hokkaido University School of Medicine, 4Sendai Kousei Hospital, 5Miyagi Hospital, 6Asahikawa Medical Center, 7Hokkaido University Graduate Hospital, 8Hokkaido Cancer Center, 9Department of Medical Oncology, KKR Sapporo Medical Center, 10First Department of Medicine, Hokkaido University School of Medicine

**Background:** The importance of biomarkers is increasing in individualized treatment strategy for cancer patients. We evaluated the efficacy and safety of carboplatin (CBDCA) and pemetrexed (PEM) in Japanese patients, and single nucleotide polymorphisms (SNPs) associated with PEM metabolism were also analyzed to investigate their relationship with efficacy or toxicity.

**Patients and methods:** Eligible patients had a performance status 0 or 1, aged from 20 to 74 years, chemotherapy-naïve stage III/IV non-squamous non-small cell lung cancer (NSCLC), and adequate organ function. Patients received CBDCA at a dose...
targeting an area under the concentration-time curve of 5 and 500 mg/m² PEM every 3 weeks. More than three cycles was considered as completion of treatment. Peripheral blood was drawn for SNP analyses of thymidylate synthase (TS) and methylenetetrahydrofolate reductase (MTHFR) genes in patients with consent for the biomarker study.

Results: Forty-one patients (28 men, 13 women; median age 63 years, range 43–73), with 39 adenocarcinomas and 2 large cell carcinomas, were enrolled and SNP analyses were performed in 37 patients. The median follow-up time was 12.9 months and the median number of treatment cycle was 4 (range 1–6). The completion rate was 80.5% (33 patients). All patients were assessable for response; the overall response rate (RR) was 36.6% and disease control rate (DCR) was 85.4%. Median progression-free survival (PFS) and overall survival (OS) were 4.6 months (95% CI 3.6–5.6 months) and 16.1 months (95% CI 8.0–24.2 months), respectively. Grade 3 or 4 hematologic toxic effects included anemia (34.1%), neutropenia (29.3%), leukopenia (19.5%) and thrombocytopenia (17.1%). Grade 3 or 4 non-hematologic toxic effects included anorexia (7.3%) and nausea (4.9%). No treatment-related death was observed. Although the SNP analyses did not have any relation to PFS, OS, RR nor hematologic toxicity, the variable number of tandem repeat (VNTR) of the TS gene significantly correlated with anemia (P = 0.047) and thrombocytopenia (P = 0.038).

Conclusions: The efficacy of this regimen seems even better than previously reported, and with acceptable toxic effects. VNTR of the TS gene has the possibility of being a predictive factor of anemia and thrombocytopenia for this regimen.

**Oral Session 17: Lung cancer NSCLC chemotherapy 2**

**C02 – 014 THE FEASIBILITY STUDY OF CDDP PLUS DOCETAXEL FOLLOWED BY TS-1 MAINTENANCE AS POST OPERATIVE ADJUVANT CHEMOTHERAPY FOR COMPLETELY RESECTED PATHOLOGICAL STAGE II TO IIIA NSCLC PATIENT**


1Saitama Cancer Center, Department of Thoracic Oncology, 2Juntendo University School of Medicine, Department of General Thoracic Surgery, 3National Cancer Research Center Hospital East Thoracic Oncology Division, 4Tokyo Medical University First Department of Surgery, 5Tokorozawa Prefectural Central Hospital Department of Respiratory Disease, 6Nagita Cancer Center Hospital Division of Chest Surgery, 7Gunma Prefectural Cancer Center Department of Respiratory Medicine, 8Kanagawa Cardiovascular and Respiratory Center Department of Respiratory Medicine, 9Yokohama Municipal Citizen’s Hospital Department of Respiratory Medicine, 10National Kyushu Cancer Center Department of Thoracic Oncology, 11Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital Department of Respiratory Medicine, 12Kanagawa Cancer Center Division of Thoracic Surgery, 13Non Profit Organization Thoracic Oncology Research Group

Background: Maintenance chemotherapy could prolong overall and/or progression-free survival in advanced NSCLC. S-1 is an oral antitumor agent comprised of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate. The TORG 0809 study was conducted to evaluate the feasibility and efficacy of maintenance chemotherapy of S-1 following DOC + CDDP in patients with curatively resected stage II and IIIA NSCLC.

Methods: Patients received three cycles of DOC (60 mg/m² d1) plus CDDP (80 mg/m² d1), q3-wk, and subsequently S-1 at 40 mg/m² twice a day for 14 consecutive days, q8w, for more than 6 months (max 1 year). The primary end point was determination of feasibility, which was defined as the proportion of patients who had completed maintenance for 8 cycles of S-1 or more. If the lower confidence interval (CI) of this proportion was 50% or more, the feasibility of the treatment was considered confirmed. The sample size was set to be 125.

Results: Between June 2009 and November 2010, 131 patients were enrolled, of whom 129 patients were eligible and assessable. The median age was 63 (23–74) years, PS 0: 107, 1: 22; p-stage IIa: 19, IIb: 30, IIIA: 80; adenocarcinoma: 99, non-adeno: 30. Of 129 patients, 109 patients (84.5%) completed three cycles of DOC + CDDP. One hundred and six patients initiated the maintenance S-1 at 50–100 mg/body per day in an outpatient setting. The primary end point of this trial was the completion rate of eight cycles. Results: From July 2009 to July 2011, 25 patients were enrolled in the study. However, one patient withdrew the consent before administration of S-1. Patient characteristics: male/female = 16/9, median age = 76 (range 71–85). ECOG PS 0/1 = 17/8, pathological stage IB/IIA/IIIB/II = 10/6/3/5/1, and adenocarcinoma (Ad) non-Ad = 17/8. Toxicity was generally mild. Only one patient experienced grade 3 anorexia. No hematologic toxic effects ≥grade 3 occurred. The completion rate of eight cycles was 70.8% (90% confidence interval (CI), 52.1% to 85.4%). The reasons for incomplete cycles were patient refusal in four patients, anorexia in two and thrombocytopenia in one.

Conclusions: Adjuvant chemotherapy with S-1 in the reduced doses and schedule was found to be a feasible treatment of Japanese elderly patients following surgical resection for NSCLC.

**C02 – 016 PHASE I TRIAL OF COMBINATION CHEMOTHERAPY OF PEMTREXED (PEM) PLUS CISPLATIN (CDDP) AND CONCURRENT THORACIC RADIOThERAPY (TRT) FOLLOWED BY PEM CONSOLIDATION THERAPY IN PATIENTS WITH LOCALLY ADVANCED NON-SQUAMOUS (NON-SQ) NON-SMALL-CELL LUNG CANCER (NSCLC): POST-HOC ANALYSIS FOR PROGRESSION-FREE SURVIVAL (PFS) AND RECURRENT SITES**


1Division of Thoracic Oncology, National Cancer Center Hospital East, 2Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, 3Division of Radiology Oncology, National Cancer Center Hospital East, 4Division of Radiation Oncology, National Cancer Center Hospital, 5Department of Medical Oncology, Graduate School of Medicine, Chiba University, 6Department of Internal Medicine, Division of Pulmonary Medicine, Infectious Diseases, and Oncology, Nippon Medical School

Background: Combination chemotherapy of PEM plus CDDP is established as a standard treatment of advanced non-Sq NSCLC. PEM has radiosensitizing potential when evaluated in vitro in combination with platinum-containing compounds and radiation. Our previous phase 1 trial demonstrated that combination chemotherapy of PEM plus CDDP with concurrent TRT at a total dose of 66 Gy was well tolerated in patients with locally advanced non-Sq NSCLC, and the response rate was 83% (The European Multidisciplinary Cancer Congress 2011, #9060). We conducted a post-hoc analysis of PFS and recurrent sites in those patients who were enrolled in the phase 1 trial.

Methods: Patients received PEM 500 mg/m² plus CDDP 75 mg/m² on day 1 of a 21-day interval for three cycles and concurrent TRT of 60 Gy (n = 6) or 66 Gy (n = 12) followed by consolidation PEM 500 mg/m² of a 21-day interval for three cycles. We reviewed the medical records to collect data on progression, recurrent sites, late toxicity and survival.

Results: Between November 2008 and December 2010, 20 patients were enrolled in this study, and 18 patients received the protocol treatment. No late radiation morbidity was observed. Twelve patients had progressed, and recurrence included distant metastases (7 cases; n = 7), local (n = 7) (in the radiation field (n = 6), out of the radiation field (n = 2) and both (n = 1)), and local plus distant sites (n = 2). Median
A PHASE II STUDY OF CISPLATIN (P), S-1 (S) AND CONCURRENT THORACIC RADIOThERAPY (TRT) FOR LOCALy ADVANCED NON-SMALL-CELL LUNG CANCER (LA-NSCLC): OKAYAMA LUNG CANCER STUDY GROUP TRIAL G0501

S. Harita2,4, S. Kuyama2,5, S. Hosokawa2,6, K. Gemba2,7, M. Takemoto2,8, I. Kawase3, A. Kumanogoh1

Methods: The primary objective is to assess the efficacy and safety of S plus P with concurrent TRT for LA-NSCLC. Although the median survival time (MST: 26.3 months) was excellent, grade 3 or greater toxicities (10%) and neutropenia (14%) were observed and treatment-related death was 3%. Thus, further improvement in the safety as well as efficacy is strongly warranted. S, an oral fluoropyrimidine, is a new alternative treatment option, carboplatin plus pemetrexed followed by maintenance therapy with pemetrexed, for patients with elderly (75 years old or more) advanced non-small-cell lung cancer (NSCLC) patients. Treatment consists of up to four cycles of induction therapy followed by maintenance therapy until disease progression or treatment discontinuation in 3-6 patients/cobert (Phase I), and 34 patients (phase II). The primary end points of the present study are to determine the recommended dose (RD) and maximum tolerance dose (MTD) of carboplatin plus pemetrexed in elderly patients (Phase I). In phase II, the efficacy objectives are to assess the 1-year survival rate, the overall survival (OS), response rates, progression-free survival (PFS). In addition, safety will be investigated in phase II study. If the primary objective (recommended dose and 1-year survival rate) is achieved, this study will provide robust results on an alternative treatment option, carboplatin plus pemetrexed followed by maintenance therapy with pemetrexed, for patients with elderly (75 years old or more) advanced non-squamous NSCLC.

Background: We previously reported an efficacy and safety of fractionated schedule of P and docetaxel (D) days 1, 8, 29 and 36, each and concurrent TRT (DP-TRT) for LA-NSCLC (JCO 2010). Although the median survival time (MST: 26.3 months) was excellent, grade 3 or greater toxicities (10%) and neutropenia (14%) were observed and treatment-related death was 3%. Thus, further improvement in the safety as well as efficacy is strongly warranted. S, an oral fluoropyrimidine, is a new active agent possessing a radio-sensitizing effect. Additionally, combining S and P offered an active and safe regimen for metastatic NSCLC. The objective of this study was to assess the efficacy and safety of S plus P with concurrent TRT for LA-NSCLC.

Methods: Patients with stage IIA/IIIB, aged under 76 years and PS 0-1, and without any prior chemotherapy were eligible for this study. Patients were treated with P (40 mg/m2 on day 1, 8, 29 and 36) and S (40 mg/m2/dose b.i.d. on days 1-14 and 29-42) and TRT (60 Gy/30 Fr over 6 weeks starting on day 1). Primary end point was response rate (RR), and required sample size was 48 patients.

Results: Between 2006 and 2009, 48 patients were enrolled (37 men; median age, 66 years; PS 0/1, 36/14; sq/non-sq, 22/26). Partial response was observed in 37 patients (77%, 95% confidence interval: 63–88%). The response rate was higher in older patients (65 years or older) than younger ones (under 66 years) (89% versus 64%, P = 0.041). At a median follow-up of 40 months, median progression-free survival and MST were 9.3 and 31.3 months, respectively. No difference in efficacy (response and survival) was observed stratified by histology (sq versus non-sq). Toxic effects were generally mild, including G3/4 neutropenia (44%), G3/4 thrombocytopenia (13%), G3 febrile neutropenia (8%) and G3 pneumonitis (4%). No one developed G3/4 esophagitis. No toxic deaths occurred.

Conclusions: This chemoradiotherapy regimen yielded a favorable overall survival data. It was also well-tolerated in patients with LA-NSCLC as compared with concurrent DP-TRT therapy especially in term of TRT-related toxic effects. A phase III trial of this regimen versus DP-TRT is now planning.
**Methods:** The primary end point was an objective response rate. Secondary end points included disease control rate, overall survival, safety and a biomarker finding. Advanced NSCLC patients without EGFR gene mutation who had received one to three prior chemotherapy regimens and who had never smoked or light smoked (smoking index <200) were eligible in this study. The EGFR gene status was evaluated by the PNA-LNA PCR clamp method. Erlotinib was administered daily (150 mg/day) until disease progression or unacceptable toxic effects.

**Results:** Forty-one patients were enrolled between March 2010 and November 2011. One patient was excluded for evaluation because having mutation of EGFR. Efficacy and safety were evaluated among 46 patients. Best responses were: PR 7 (15.2%), SD 22 (26.1%), PD 26 (46.4%), NE 1 (2.2%). Response rate and disease control rate were 15.2% (95% CI: 4.9–25.5%) and 41.3 % (95% CI: 27.1–55.5%), respectively. Grade 3 or 4 adverse events were anorexia (4), skin rash (2), neutropenia (1), leukopenia (1), anemia (2), elevation of AST/ALT (1), rectal ulcer (1) and cerebral infarction (1). Two patients suffered grade 3 interstitial lung disease.

**Conclusion:** This is the first report to evaluate Erlotinib efficacy in selected NSCLC who do not possess EGFR gene mutation. Erlotinib showed significant anti-tumor activity in pretreated never or light smoked Japanese NSCLC patients without EGFR gene mutation.

**O2 - 026**

**HP70 CAUSES EGFR-TKIS RESISTANCE IN A MUTANT EGFR EXPRESSED NON-SMALL-CELL LUNG CANCER**

T. Ohmori¹, T. Yamaoka¹, Y. Ichihashi¹, T. Hirose², N. Saijo³

¹Institute of Molecular Oncology, Showa University, ²Division of Allergology and Respiratory Medicine, Department Internal Medicine, Showa University School of Medicine, ³Department Medical Oncology, Kinki University School of Medicine

**Purpose:** Non-small-cell lung cancer (NSCLC) cells that expressed mutant EGFR are more sensitive to EGFR-tyrosine kinase inhibitors (EGFR-TKIs) than that expressed wild-type EGFR. Recent clinical trials revealed that more than 70% NSCLC patients that expressed mutant EGFR showed sensitivity to EGFR-TKIs, such as gefitinib and erlotinib. To elucidate the mechanism of this hypersensitivity, we explored the difference of EGFR-binding proteins between wild-type EGFR and 15 bp deletion mutant EGFR using respective stable transfectants.

**Methods:** Wild-type EGFR and a 15-bp deletion mutant EGFR plasmids were transfected into HEK293 cells. The stably transfectant cells were established, and were designated 293_pEGFR and 293_pΔ15, respectively. Cell lysate was prepared by centrifugation and the supernatant was mixed with a polyclonal EGFR antibody for 1 h and EGFR was immunoprecipitated by Protein A-Sepharose. After adequate washing, coprecipitated proteins that bound to EGFR were eluted and separated by 2D-PAGE (Immobiline DryStrip (pH 3-10 NL, 7 cm) and 10% SDS-PAGE). Proteins were visualized by silver staining and identified by LC-MS/MS. HP70 siRNA was transfected into the cells by lipofection method. Sensitivity to gefitinib was measured by the MTT assay. EGFR binding affinity to gefitinib was measured using [14C] gefitinib.

**Results and discussion:** We detected several EGFR-binding proteins. Among these proteins, one candidate (lesser binding to wild-type EGFR than the mutant EGFR) was identified as HSP 70 by LC-MS/MS. The total amount of HSP70 protein was not different between 293_pEGFR and 293_pΔ15, respectively. Cell lysate was prepared by centrifugation and the supernatant was mixed with a polyclonal EGFR antibody for 1 h and EGFR was immunoprecipitated by Protein A-Sepharose. After adequate washing, coprecipitated proteins that bound to EGFR were eluted and separated by 2D-PAGE (Immobiline DryStrip (pH 3-10 NL, 7 cm) and 10% SDS-PAGE). Proteins were visualized by silver staining and identified by LC-MS/MS. HP70 siRNA was transfected into the cells by lipofection method. Sensitivity to gefitinib was measured by the MTT assay. EGFR binding affinity to gefitinib was measured using [14C] gefitinib.

**Results and discussion:** We detected several EGFR-binding proteins. Among these proteins, one candidate (lesser binding to wild-type EGFR than the mutant EGFR) was identified as HSP 70 by LC-MS/MS. The total amount of HSP70 protein was not different between 293_pEGFR and 293_pΔ15, respectively. Cell lysate was prepared by centrifugation and the supernatant was mixed with a polyclonal EGFR antibody for 1 h and EGFR was immunoprecipitated by Protein A-Sepharose. After adequate washing, coprecipitated proteins that bound to EGFR were eluted and separated by 2D-PAGE (Immobiline DryStrip (pH 3-10 NL, 7 cm) and 10% SDS-PAGE). Proteins were visualized by silver staining and identified by LC-MS/MS. HP70 siRNA was transfected into the cells by lipofection method. Sensitivity to gefitinib was measured by the MTT assay. EGFR binding affinity to gefitinib was measured using [14C] gefitinib.

**Conclusions:** In patients with advanced EGFR mutation-positive NSCLC, prior EGFR TKIs therapy status is not significantly associated with efficacy of bevacizumab with carboplatin plus paclitaxel.
Methods: The expression of mutant EGFR proteins was quantified by immunohistochemical analysis with mutation-specific antibodies in tumor specimens from 47 NSCLC patients with postoperative recurrent disease who harbored activating EGFR mutations. The expression score was determined from both the staining intensity and the proportion of tumor tissue expressing the mutant EGFR.

Results: The median PFS after the start of gefitinib treatment was significantly longer in patients with a high score for mutant EGFR expression than in those with a low score, whereas no significant difference in median PFS was observed between the two groups. This association between the expression score for mutant EGFR and PFS was apparent both in patients with deletions in exon 19 of EGFR and in those with the L858R mutation in exon 21.

Conclusions: Quantitative analysis of mutant EGFR expression by immunohistochemical analysis with mutation-specific antibodies may predict the efficacy of gefitinib treatment of EGFR mutation positive NSCLC.

DIFFERENCE IN INCIDENCE AND PATTERN OF SALVAGE TREATMENT AFTER FAILURE TO 1ST-LINE EGFR-TKI THERAPY AND STANDARD CYTOTOXIC CHEMOTHERAPY IN PATIENTS WITH EGFR-MUTANT ADVANCED NSCLC: OKAYAMA LUNG CANCER STUDY GROUP EXPERIENCE

Y. Kato1,2, E. Ichihara2, K. Hotta2, A. Hisamoto2,2, N. Takigawa1,2, N. Nogami1,2, T. Kozuki2, K. Kudo1,2, M. Tabata2,2, T. Shinjikai2,2, M. Tanimoto2,2, K. Kubo2,2
1 Okayama University Hospital, 2 Okayama Lung Cancer Study Group, 3 Shikoku Cancer Center

Background: EGFR-TKI (E) therapy yielded a better PFS than standard cytotoxic chemotherapy (C) therapy and a comparable OS in untreated patients with EGFR-mutant tumors, suggesting that each of the treatments is now crucial for such patients. But, it has not been fully evaluated yet which of each should be initiated first, and to what degree both of two are actually administered in early line setting in the treatment course. We here investigated a potential difference in incidence and pattern of delivery of subsequent crossover therapy after failure to each of the treatments in patients with EGFR-mutant tumors.

Methods: Consecutive 79 patients with advanced EGFR-mutant NSCLC were retrospectively assessed who underwent E therapy (n = 39) or C therapy (n = 40) in the 1st-line setting between 2007 and 2011.

Results: In the E group, 16 (41%) of 39 patients were still on 1st-line E therapy. Nine (36%) of the remaining 23 could not receive standard C therapy after failure to E therapy due to symptomatic CNS metastasis (mets) in six, skeletal events in two, and patient refusal in one, whilst in C group only one (3%) of 40 failed to receive C therapy due to symptomatic CNS metastasis (mets) in six, skeletal events in two, and patient refusal in one.

Conclusions: In patients with EGFR-mutant tumors who were treated with 1st-line C, there were limitations in the opportunity to receive post-progression E therapy than those treated with 1st-line E. Difficulty in adequate delivery of subsequent C therapy, possibly due to the difference in PFS deterioration rate and relapse pattern.

Oral Session 20: Gastrointestinal cancer translational 1

O2 – 332 COMPREHENSIVE ANALYSIS OF GENETIC POLYMORPHISMS AND IRINOTECAN-INDUCED ADVERSE EVENTS IN JAPANESE GASTROINTESTINAL CANCER PATIENTS: A DMET MICROARRAY PROFILING STUDY

H. Kuramochi1, H. Kann1, T. Uchiyama2, G. Nakajima1, K. Saito1, K. Hayashi1
1 Department of Chemotherapy and Palliative Care, Tokyo Women’s Medical University, 2 Division of Genomic Medicine, Department of Advanced Biomedical Engineering and Science, Graduate School of Medicine, Tokyo Women’s Medical University

Background: Irinotecan is a key drug in the treatment of colorectal and gastric cancer, which may occasionally cause severe adverse events (AEs), especially neutropenia and diarrhea. Although UDP-glucuronosyltransferase (UGT)1A1 polymorphisms are used as biomarkers for predicting AEs, the effect of UGT1A1 in
clinical use is limited, suggesting that there is a possibility of the existence of other, unknown biomarkers.

**Methods:** Fourteen gastrointestinal cancer (five gastric, nine colorectal) patients who had undergone irinotecan-based chemotherapy were enrolled. DNA extracted from peripheral blood cells was genotyped by the DMET Plus microarray system, and 1931 gene polymorphisms were investigated. The relationship between AEs and polymorphisms was analyzed statistically.

**Results:** Eleven polymorphisms showed the P-value of <0.05 with grade 3, 4 neutropenia, but no statistically significant polymorphisms were found after the correction of multiple comparisons. With respect to the association with diarrhea, 12 polymorphisms showed P < 0.05, and even after the correction of multiple comparisons, CYP2F1_96G > A(P32P) showed a significant relationship (P < 0.00001). With respect to the relationship between UGT1A1*6, *28 polymorphisms and AEs, *6 polymorphisms showed significant (P = 0.044) association with grade 4 neutropenia.

**Conclusions:** CYP2F1_96G > A polymorphism showed significant association with diarrhea. The association of UGT1A1*6 polymorphism and neutropenia was confirmed, as in previous reports.

**O2 – 033**

**ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY OF CETUXIMAB AGAINST COLORECTAL CANCER CELL LINES WITH WILD-TYPE AND MUTANT KRAS**

Y. Nakadate1, Y. Kitamura1, T. Tamura1, F. Koizumi2

1Shien-Lab., National Cancer Center Hospital, 2Department of Thoracic Oncology, National Cancer Center Hospital

Cetuximab is a chimeric IgG1 monoclonal antibody (mAb) that targets the epidermal growth factor receptor (EGFR). In addition to direct EGFR inhibition, antibody-dependent cellular cytotoxicity (ADCC) is considered to be an important mechanism of action of cetuximab. Recently, KRAS mutations in tumors have been shown to be a negative predictive factor for response to cetuximab treatment of colorectal cancer (CRC). KRAS mutations potentially contribute to the resistance to the direct inhibitory effect of cetuximab. However, the influence of KRAS mutations on cetuximab-induced ADCC is not fully understood. In this study, we investigated cetuximab-mediated ADCC against human CRC lines, HCT116 and DLD-1, which carry mutated KRAS, and their derivative cell lines, HBx2 and DKO-4, respectively, in which the mutated KRAS allele was deleted by targeted disruption (KRAS wild-type). Peripheral blood mononuclear cells (PBMCs) from healthy volunteers and NK92, a natural killer cell line, exogenously expressing FcγR IIIA (CD16a) were used as effector cells. We first determined the growth-inhibitory effect of cetuximab alone. Growth inhibition was observed only in KRAS wild-type cell lines, but its effect was only slight. In a standard short-term (4 h) ADCC assay that mainly evaluate lytic activity via perforin/granzyme, ADCC activities were exhibited to a similar extent against CRC cell lines regardless of the KRAS mutation status. We also examined a long-term (24 h) ADCC assay under the perforin-inhibited condition to evaluate the death receptor ligand-induced apoptosis, which is another major mechanism of ADCC. In this assay, cetuximab-mediated ADCC was induced in wild-type but not mutated KRAS cell lines. Similar to the previous report, HBx2 and DKO-4 displayed a higher sensitivity to recombiant human Fas ligand (FasL) and TRAIL than did HCT116 and DLD-1, respectively. Furthermore, blocking experiments with neutralizing antibodies revealed that induction of apoptosis via Fas-FasL interaction is involved in perforin-independent cetuximab-mediated ADCC against KRAS wild-type cells. In conclusion, these results suggest that mutated KRAS may contribute to the resistance to the antitumor effects of cetuximab not only through direct receptor inhibition but also through ADCC mediated by Fas-FasL interaction.

**O2 – 034**

**DETECTION AND HER2 EXPRESSION OF CIRCULATING TUMOR CELLS IN ADVANCED GASTRIC CANCER PATIENTS**

S. Matsusaka1,2, K. Chih1-2, M. Ogun1, E. Shinozaki1,2, M. Sugaya1,2, M. Mizumura1,2, T. Sano1, T. Yamaguchi1, K. Hatake1

1Department of Gastroenterology, Gastroenterology Center, Cancer Institute Hospital, 2Division of Gastroenterological Surgery, Gastroenterology Center, Cancer Institute Hospital

**Purpose:** This study was aimed at detecting and HER2-expressing circulating tumor cells (CTC) in peripheral blood of chemo-naive or chemo-resistant patients with advanced gastric cancer.

**Materials and methods:** All patients were enrolled using institutional review board-approved protocols at the Cancer Institute Hospital in the Japanese Foundation for Cancer Research and provided informed consent. The study population consisted of patients of aged 18 years or older with histologically proven advanced gastric cancer. A total of 140 patients with advanced gastric cancer were enrolled into a prospective study. We used CellSearch system for the detection and HER2 expression for CTC.

**Results:** We detected more than or equal to 1 CTC/7.5 ml in 80 of 140 patients (57.1%). HER2-positive CTC were observed in 19 of 80 CTC-positive patients (23.8%), including six patients with HR2-negative primary tumors. Twenty-one patients with HER2-positive primary tumors administered trastuzumab in combination with chemotherapy (Xeloda + cisplatin; 15, weekly paclitaxel; 5). We detected more than or equal to 1 CTC/7.5 ml at the baseline in 11 of 20 patients with trastuzumab treatment. HER2-positive CTCs were observed in 6 of 11 CTC-positive patients (54.5%). Patients with HER2-positive CTC at the baseline were shorter PFS than those with HER2-negative CTC at the baseline.

**Conclusion:** HER2 expression on CTC was associated with chemoresistance. Information on the HER2 status of CTC might be helpful for stratification of HER2-directed therapies.

**O2 – 035**

**RECURSIVE PARTITIONING FOR NEW CLASSIFICATION OF PATIENTS WITH ESOPHAGEAL CANCER TREATED WITH CHEMORADIOThERAPY**

M. Nomura1-3, K. Shiota1, T. Kodaira1, C. Kondoh1, D. Takahari2, T. Ura1, H. Kojima1, M. Kamata1, K. Muro1, S. Sawada3

1Department of Radiology, Kansai Medical University, 2Department of Clinical Oncology, Aichi Cancer Center Hospital, 3Department of Radiation Oncology, Aichi Cancer Center Hospital

**Background:** The 7th edition of the American Joint Committee on Cancer staging system does not include lymph node size in the guidelines for staging patients with esophageal cancer. The objectives of this study were to determine the prognostic impact of the largest lymph node diameter (ND) on survival and to validate and develop a new staging system for patients with esophageal squamous cell cancer who were treated with definitive chemoradiotherapy (CRT).

**Methods:** Information on 402 patients with esophageal cancer undergoing CRT at two institutions was reviewed. Univariate and multivariate analyses of data from one institution were used to assess the impact of clinical factors on survival, and recursive partitioning analysis was carried out to develop the new staging classification. To assess its clinical utility, the new staging system was validated using data from the second institution.

**Results:** According to RPA, ND stages were best when classified as ND0 (the absence of lymph node metastases), ND1 (<2.7 cm), and ND2 (>2.8 cm). By multivariate analysis, gender, T, N, and ND stages were independently and significantly associated with survival (P < 0.05). The resulting new staging classification showed the following: T1-2N0 (group I); T3-4N0 and T1-2N1 as group II; T3-4ND1 as group III; and T4N2D2 as group IV. The four new stages led to good separation of survival curves in both the developmental and validation datasets (P < 0.005).

**Conclusions:** Our results showed that the lymph node size is a strong independent prognostic factor and that the new staging system, which incorporated lymph node size, provided good prognostic power and discriminated effectively for patients with esophageal cancer undergoing CRT.

**O2 – 036**

**INITIAL STANDARDIZED UPTAKE VALUE (ISUV) OF 18F-FLUORODEOXYGLUCOSE PET CAN CUSTOMIZE TREATMENT OF ESOPHAGEAL ADENOCARCINOMA (EAC) PATIENTS WHO ACHIEVE CLINICAL COMPLETE RESPONSE (CCR) AFTER CHEMORADIATION**

A. Suzuki1,8, L. Xiao1, T. Taketsu1, M. Blum1, J. Welsh1, S. Lin1, M. Bhutani4, J. Lee1, D. Rice1, D. Maru1, J. Erasmus5, W. Hofstetter6, S. Stephen1,7, H. Onodera1, A. Ajiara1

1Departments of1GI Medical Oncology, 2Statistics, 3Radiation Oncology, 4Gastroenterology, 5Thoracic Surgery, 6Pathology, and, 7Radiology, University of Texas, MD Anderson Cancer Center, 8GI Surgery, St. Luke’s International Hospital

**Background:** Patients with localized esophageal adenocarcinoma (EAC) receive preoperative chemoradiation followed by surgery (triamodality [TM] therapy) or definitive chemoradiotherapy (bimodality [BM] therapy) based on comorbidities and tumor geography. However, we cannot individualize recommendations beyond these parameters. We hypothesized that ISUV could customize therapy.

**Methods:** Data source was our prospective database of fully staged EAC patients (2002–2010). All patients had a cCR (post-chemoradiation negative biopsy and post-chemoradiation physiologic uptake on PET). ISUV cut-point was derived by recursive partitioning.

**Results:** For 323 cCR patients, the median follow-up was 40.8 months. 206 (63.8%) patients had TM and 117 (36.2%) had BM therapy. Median OS of TM patients and
BM patients were 94.8 months (95% CI; NA-NA) and 36.5 months (95% CI; 30.5–42.4; P < 0.001), respectively. Similar differences were observed in RFS (P < 0.001). The median iSUV was 9.4 (range, 0–58.0). Intriguingly, TM patients with iSUV of ≥6 had a better OS (94.8 months; 95% CI; 39.1–150.5) and RFS (94.8 months; 95% CI; 18.2–171.4) compared with BM patients with iSUV of <6 OS (31.4 months; 95% CI; 21.0–41.9; P < 0.001) and RFS (17.2 months; 95% CI; 14.5–19.8; P < 0.001). However, the prognosis of TM and BM cCR patients with iSUV <6 was similar (OS, P = 0.62 and RFS, P = 0.46). The pathological CR (pathCR) rate in TM patients was similar irrespective of iSUV of ≥6 (27.1%) versus iSUV <6 (28.6%; P = 0.85).

Conclusion: Our unique data provide an insight into the fate of cCR EAC patients by iSUV. Patient with iSUV ≥6 dramatically benefit from surgery and TM therapy is encouraged. iSUV and pathCR do not correlate. iSUV can customize therapy of localized EAC patients.

O2 – 008

MUTATIONS IN NRAS CODON 61 AND KRAS CODON 146 ARE POOR PROGNOSTIC FACTORS IN PATIENTS WHO RECEIVED ANTI-EGFR MONOCLONAL ANTIBODY FOR METASTATIC COLORECTAL CANCER

N. Takahashi1, Y. Yamada1, H. Taniguchi2, K. Akiyoshi1, Y. Homma1, S. Isawa1, K. Kato1, T. Hamaguchi1, Y. Shimada1

1Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, Japan.
2Division of Pathology, National Cancer Center Hospital, Tokyo, Japan.

Background: Previous studies showed that gene mutations (NRAS, BRAF, PIK3CA) are associated with a poor prognosis or resistance to anti-EGFR antibody in metastatic colorectal cancer (mCRC) patients with wild-type (WT) of KRAS codon 12/13 (KRAS-WT). However, the significance of these biomarkers has not been clarified. In addition, EGFR immunohistochemistry (IHC) and EGFR gene amplification to evaluate the efficacy of anti-EGFR antibody treatment have not been reported for mCRC.

Method: We evaluated tumor response and survival in patients who received anti-EGFR antibody by mutation analysis of KRAS, NRAS, BRAF, and PIK3CA in KRAS-WT mCRC patients. Tumor samples are obtained from patients treated in our hospital with anti-EGFR antibody between August 2008 and August 2011.

Results: A total of 117 patients were enrolled in this analysis, including 100 KRAS-WT patients. Seventy-one patients (67.0%) were all WT for KRAS, NRAS, BRAF, and PIK3CA, and 46 patients (39.3%) had at least one mutation or had insufficient DNA samples to analyze. Mutations of KRAS codon 61 (2 patients), KRAS codon 146 (5), BRAF V600E (2), PIK3CA exon9 (8), NRAS codon 12/13 (2), and NRAS codon 61 (5) were detected. No patients had a mutation of PIK3CA exon 20. Patients with at least one mutation had no response. Mutations of KRAS codon 146, NRAS codon 61, and BRAF V600E were associated with a shorter progression-free survival (PFS) compared with all WT patients (P = 0.049, P = 0.004, P = 0.036, respectively). Twelve patients (12% of KRAS-WT patients) with a mutation of KRAS codon 146, BRAF V600E, NRAS codon 61 had poor prognostic compared with the other KRAS-WT patients (PFS: 6.4 versus 2.0 months, P < 0.001; overall survival (OS), 13.7 versus 7.9 months, P = 0.012). In all WT patients, moderate to strong EGFR IHC was associated with a better response rate than negative and weak IHC (P = 0.046).

Conclusion: Mutations of KRAS codon 146, NRAS codon 61, and BRAF V600E could be a strong prognostic factor of anti-EGFR antibody in patients with mCRC. Combination of IHC and DISH of EGFR could identify patients with a tumor response to anti-EGFR antibody in patients that are all wild type for KRAS, NRAS, BRAF, and PIK3CA.

O2 – 009

PROSPECTIVE TRIAL OF CETUXIMAB PLUS IRINOJECT CANCER CHEMOTHERAPY-REFRACTORY PATIENTS ADVANCED AND/OR METASTATIC COLORECTAL CANCER, EVALUATION OF THE Efficacy AND SAFETY BASED ON Mutation STATUS of the EGFR RELATED GENES

H. Shimodairai1, 2, H. Soeda1, 2, M. Gamoh3, H. Andoh4, T. Yamaguchi5, K. Kato1, T. Hamaguchi1, Y. Shimada1

1Department of Clinical Oncology, National Cancer Center Hospital East, 2Department of Clinical Oncology, Osaki Citizen Hospital, 3Akita University Graduate School of Medicine.
4Department of Medical Statistics, National Cancer Center Hospital, Tokyo, 5Department of Pathology, Tohoku University, 6Yamagata Pref. Central Hospital.

Background: Activating mutation of the KRAS gene is a predictive biomarker for the loss of efficacy to Anti-EGFR antibody therapy. However, this was mainly established by the evidences of Caucasian studies. Then, this prospective study investigated the role of KRAS and other EGFR-related gene mutations on efficacy and safety to cetuximab plus irinotecan in Japanese patients with metastatic colorectal cancer (mCRC).

Method: We conducted a prospective study to analyze objective response to cetuximab plus irinotecan in molecularly defined KRAS wild-type (WT) or mutant subgroups of chemotherapy-refractory mCRC. KRAS mutations were detected by direct sequencing on DNA from formalin-fixed, paraffin-embedded tissue of patients treated in 11 centers in Japan. Additional EGFR-related genes such as BRAF, PIK3CA, NRAS and AKT1 were examined.

Results: Forty-three patients were enrolled. KRAS mutations were found in 31.9% of 41 eligible patients. Response rate (RR) to cetuximab plus irinotecan for the primary end point of the study, was 17.9% and 0% for the WT KRAS patients and mutant KRAS patients, respectively. Progression-free survivals were 3.7 months versus 1.6 months (P = 0.0039); overall survivals were 7.7 months versus 4.4 months (P = 0.0005) for the WT KRAS patients and mutant KRAS patients, respectively. No significant differences in toxicity were observed between the WT and mutant KRAS groups. The combination of five genes analysis made the difference of clinical outcomes wider between all WT group and any mutant group.

Conclusion: We confirmed that the KRAS status is a useful predictive maker for the efficacy and intention plus combination of tumor therapy in Japanese KRAS-WT patients even though the response rate in the KRAS WT group was lower than expected. The combination of analysis in EGFR-related genes possibly contributes to the better prediction of the response.

O2 – 040

NEW CLASSIFICATION BASED ON ATOH1 EXPRESSION IN COLON CANCER MIGHT BE USEFUL AS BIOMARKER

Y. Kano, K. Tsuchiya, M. Watanabe

Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University.

Background and aims: The transcription factor Atoh1 plays crucial roles in the differentiation of the secretory intestinal epithelium cells. Although we have reported that Atoh1 protein was degraded in colon cancer, the Atoh1 expression and function in various cancers are still controversial. Moreover, it remains unknown whether Atoh1 contributes to cancer stemness. We therefore aim to investigate the Atoh1 function in colon cancer.

Methods: Mutated Atoh1 protein combined with mIHC (SSA-Atoh1) was generated and stably expressed in colon cancer cells. SSA-Atoh1 cells were analyzed for differentiation and cancer stem cell phenotype expression by RT-PCR, immunofluorescent staining and reporter assay. Cell proliferation and chemoresistance were analyzed by MTS assay. Fucci system with timelapse live imaging and measurement of Atoh1 expression after induction of chemotherapy.

Results: Mutated Atoh1 protein was stably expressed in cancer cells, resulting in the acquisition of not only the differentiated form but also cancer stemness. Atoh1 protein stabilization induced the expression of Wnt target genes by enhancement of the Wnt signal. Moreover, cell cycle arrest in G0/G1 phase was induced by the Atoh1 protein stabilization, resulting in the acceleration of cell survival and chemoresistance. Furthermore, oxalaplatin was found to inactivate GSK3 kinase, resulting in the stabilization of Atoh1 protein in wild-type Atoh1 gene-positive cancer. Subsequently, Atoh1-positive cancer acquired chemoresistance in vivo.

Conclusion: The Atoh1 protein regulates the cancer stemness rather than differentiation phenotype in colon cancer, suggesting the mechanism of which vicious cancer resists chemotherapy. Moreover, measurement of Atoh1/ protein expression in colon cancer might be useful to predict the effect of chemotherapy.

O2 – 041

CLINICAL OUTCOME OF CETUXIMAB FOR METASTATIC COLORECTAL CANCER PATIENTS HARBORING KRAS CODON61, KRAS CODON146, BRAF, NRAS OR PIK3CA MUTATIONS

K. Yamazaki1, K. Bando2, E. Shinozaki3, T. Nishina4, S. Kadowaki5, S. Yuki6, S. Kajura7, K. Tsuchihara7, K. Fuji8, Y. Yamakawa9, T. Yoshino2

1Division of Gastroenterological Oncology, Shizuoka Cancer Center, 2Department of Gastroenterology and Oncology, Chiba City Hospital, 3Department of Gastroenterology, Hokkaido University Graduate School of Medicine, 4The Third Department of Internal Medicine, University of Toyama, 5Cancer Physiological Project, Research Center for Innovative Oncology, National Cancer Center Hospital East, 6Division of Gastroenterological Oncology, Shizuoka Cancer Center, 7Department of Gastroenterology, Saitama Cancer Center, 8Division of Gastroenterological Oncology, Shichizuka Cancer Center, 9Division of Gastroenterology and Hematology, Tokyo Medical and Dental University.

Background: Retrospective pooled analyses have identified KRAS, BRAF, NRAS, and PIK3CA mutations as potentially negative predictive factors for colorectal cancer patients treated with Cetuximab (Cmb). We developed a novel kit that applies Luminex technology for the detection of mutations in KRAS codon 61, KRAS codon 146, BRAF, NRAS, and PIK3CA in a single reaction (GENOSEARCH Mu-PACK).

Method: Clinical Outcome of Cetuximab for metastatic colorectal cancer patients harboring KRAS codon 61, KRAS codon 146, BRAF, NRAS or PIK3CA mutations
Methods: Formalin-fixed paraffin-embedded tumor samples and clinical data of colorectal cancer patients treated with Cmb-containing regimens were collected from seven Japanese centers. KRAS, BRAF, NRAS, and PIK3CA gene statuses were determined, both by our kit and by direct-sequencing (DS). Objective response, progression-free survival (PFS), and overall survival (OS) were evaluated in subgroups determined by the mutation status.

Results: A total of 82 samples were collected. The concordance rate between our kit and DS data was 98.7%. Our kit results identified 21 samples with mutations in KRAS codon 12, 13 (25.6%), 3 in KRAS codon 61 (3.7%), 2 in KRAS codon 146 (2.4%), 4 in BRAF (4.9%), 2 in NRAS (2.4%), and in PIK3CA (4.9%). All of these mutations, except for PIK3CA, were mutually exclusive. The response rate for all patients in the study was 25.6%, whereas the response rate for the group of patients with all wild-type tumors was 42.0%. The median PFS values of patients with all wild-type tumors (n = 50), with KRAS codon 12, 13 mutation (n = 20), and with any of KRAS codon 61, KRAS codon 146, BRAF, NRAS, or PIK3CA mutations (n = 12) were, respectively, 6.4 months (95% CI: 3.1, 9.8), 2.1 months (95% CI: 0.8–3.5), and 1.6 months (95% CI: 1.5, 1.7) (log-rank test, P = 0.0001). The median OS values were, respectively, 15.6 months (95% CI: 11.1, 20.2), 7.9 months (95% CI: 4.8, 10.9), and 6.3 months (95% CI: 1.9, 10.7) (log-rank test, P = 0.0001).

Conclusions: Patients with KRAS codon 61, KRAS codon 146, BRAF, NRAS, and PIK3CA mutations may not derive clinical benefits from Cmb, nor would patients with KRAS codon 12, 13 mutations. This newly developed detection kit is robust and practical for examining a patient’s KRAS codon 61, codon 146, BRAF, NRAS, and PIK3CA gene status.

Oral Session 22: Oncology team 1

C02 – 046

AIZAWA COMPREHENSIVE CANCER CENTER CONSISTS OF FOUR INDIVIDUAL DEPARTMENTS, AND CASE CORENCES

M. Nakamura1, T. Onikubo1, K. Nakamura1, K. Oda1, Y. Nishida2, K. Tauchi1,2

1Aiwa Hospital Aizawa Comprehensive Cancer Center, 2Aiwa Hospital Department of Surgery

New drugs including molecular therapy prolong the prognosis of cancer patients. On the other side, there are many problems including various toxic effects, supportive care, cancer survivorship, palliative care and psychological support. Appropriate and excellent oncology team is needed to coordinate and resolve these problems. Aizawa Comprehensive Cancer Center consists four individual cancer-related departments, 20 chemotherapy bed, mixing room, IMRT, patient and family center and cancer registration. Four departments are department of chemotherapy, radiotherapy, palliative care and psycho-oncology. That makes easy to construct comprehensive cancer therapy such as chemo-radiotherapy, palliative care and psychological approach during the cancer therapy. We discussed about all the patients by all staff every day. In the discussion, doctors, nurses, pharmacist and CRC state their opinion equally, and determine the treatment plan concerning disease spread, adverse event, quality of life, and social, economic situations. To be a better oncology team, professionalism, ambition, responsibility, honor, pleasure and respect to each other in each staff are needed.

Oral Session 23: Oncology team 2

C02 – 048

CURRENT PRACTICES AND FUTURE PROSPECTS OF A MEDICAL TEAM IN CANCER CHEMOTHERAPY IN TERMS OF THE ROLE OF A BOARD-CERTIFIED SPECIALIST ONCOLOGY PHARMACIST

Y. Konodou1, T. Hirasima1, N. Okamoto1, N. Ryouta1, K. Shimura1, Y. Nakamura1, M. Sando1, H. Suzuki1, M. Tamaya1, N. Morishita1, T. Shiroyama1, M. Saijo1, Y. Oomori1, K. Kita1, I. Kawase1

1Department of Pharmacy of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, 2Department of Thoracic Malignancy of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, 3Department of Outpatient Treatment of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, 4Department of Palliative Care of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, 5Department of Nursing of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases

Background: With the recent remarkable developments in anti-cancer agents such as targeted molecular therapies, treating patients with malignancies while keeping a balance among effect, safety, and QOL has become complicated.

Methods: From the perspective of the role of a board-certified specialist oncology pharmacist, we analyzed the future prospects of medical teams in cancer chemotherapy by examining the current practices of the medical team at our hospital.

Results: In 2011, our hospital became an authorized base hospital for lung cancer therapy in Osaka Prefecture. The medical team for cancer chemotherapy and supportive therapy at this hospital consists of two medical oncologists, two oncology pharmacists, one certified specialist cancer nurse, one certified cancer chemotherapy nurse, two certified palliative care nurses, and one psychologist. Three departments—thoracic oncology, outpatient chemotherapy, and gynecology—perform cancer chemotherapy. The total number of cancer chemotherapies carried out in 2011 was1433 (thoracic malignancies: 88.4%; breast cancer: 51.1%; gastrointestinal cancer: 6.5%) in outpatients and 1572 (thoracic malignancies: 83.3%; gynecological cancer: 11.8%; gastrointestinal cancer: 4.3%; breast cancer: 0.6%) in inpatients. In 2011, the oncology pharmacist carried out the following important functions in medical team: (i) sitting on a review board four times a year for approval of cancer chemotherapy; (ii) daily management of the ordering system for cancer chemotherapeutic agents; (iii) holding meetings four times a year to educate other specialists about new regimens or anti-cancer agents; (iv) monitoring the dose, schedule and patient’s information about cancer chemotherapy to prevent severe toxic effects or treatment death; (v) each day, instructing patients who are receiving cancer chemotherapy; and (vi) consulting daily about side-effects and supportive therapy.

Conclusions: The oncology pharmacist currently plays an important role in the medical team and will become more important in the future.
Background: In Japan, transarterial infusion chemotherapy (TAI) with cisplatin (CDDP) is used for advanced hepatocellular carcinoma (HCC) patients, and the response rate (RR) was 33.8% in previous phase (P) II study. S-1, oral systemic chemotherapy, is also promised for advanced HCC patients, and achieved 23.1% RR in previous P-II study. The clinical feasibility and efficacy of CDDP for TAI plus S-1 in patients with advanced HCC has not yet been investigated. Thus, we carried out this trial to determine the recommended dose (RD).

Methods: Although 13 Child-Pugh class A or B patients with advanced HCC entered themselves for this P-I trial, one patient of them was excluded from this trial due to the breach of criteria. The patients received TAI with CDDP (infusion on day 1 of the courses) plus S-1 (daily oral administration on days 1–21 of the courses), every 5 weeks until disease progression.

Results: Three dose levels were used for the 12 patients. Dose-limiting toxicity was not observed in three patients at level 1 (CDDP; 65 mg/m² and S-1; 60 mg/m²), three patients at level 2 (CDDP; 65 mg/m² and S-1; 80 mg/m²), and seven patients at level 3 (CDDP; 65 mg/m² and S-1; 100 mg/m²); therefore, the RDs for CDDP and S-1 were considered to be 65 and 100 mg/m², respectively (level 3). Grade 3 adverse events were reported for 10 patients and were considered to be related to the study drugs for six patients: two patients, increased alanine aminotransferase level; two patients, increased aspartate aminotransferase level; one patient, anemia; and 1 patient, decreased platelet count. The total number of treatment courses was 25, with a mean of 1.5 courses per patient (range, 1–6 courses). The median progression-free survival time was 73 days. The disease control rate (DCR) was 92% (11 of 12). The median progression-free survival was 41.6% (5/12)/0% (0/12), respectively. Response rate (RR) was 50% (6 of 12) and disease control rate (DCR) was 92% (11 of 12). The median survival time was 6.0 months (95% CI: 3.3–10.0).

Conclusions: TAI with CDDP plus S-1 can be used safely with promising tumor control for treating advanced HCC. The RD to be used for a P-II study of this regimen was determined to be level 3.
Oral Session 25: Colorectal cancer anti-EGFR antibody

C2 - 059

PHASE II STUDY OF COMBINATION THERAPY WITH S-1 AND CETUXIMAB IN PATIENTS WITH KRAS WILD-TYPE UNRESECTABLE COLORECTAL CANCER, WHO HAD PREVIOUSLY RECEIVED IRINOTECAN, OXAPLATIN, AND FLURORPYRIMIDINES (KSCC0901)

M. Kitazono1, K. Kobayashi2, Y. Emi3, Y. Ikeuchi3, T. Takahashi4, Y. Akagi4, A. Taji1, K. Yoshida5, H. Baba6, H. Ogata4, M. Shimokawa4, S. Natsugoe4, Y. Maehara8
1Nippon Hospital, 2Department of Digestive Surgery, Breast and Throid Surgery, 3Kochi Health Science Center, 4Department to Surgery and Science, Graduate School of Medical Science, Kyusyu university, 5Gifu University Hospital, 6Departments of Surgery Kurume University School of Medicine, 7Kobe City Medical Center Hospital, 8Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, 9Kurume University Medical Center, 10Kyusyu University Hospital

Background: Anti-epidermal growth factor receptor (anti-EGFR) antibodies alone or in combination with irinotecan (IRI) can be considered standard third-line therapy for KRAS wild-type (wKRAS) unresectable colorectal cancer (UCRC). However, some UCNC patients cannot tolerate IRI-containing therapy. S-1, an oral fluorouracil (FU) derivative, enhances the anti-tumor effect by inhibiting dihydropyrimidine dehydrogenase and reducing digestive toxicity. Combination therapy with cetuximab (C-mab) may restore 5-FU resistance in 5-FU resistant CCs. Therefore, we examined the efficacy of S-1 + C-mab therapy in wKRAS UCNC patients who had previously received IRI, oxaplatin (OX), and FU.

Methods: The study design was multicenter, single-arm, open-label phase II study. The major inclusion criteria were written informed consent; histologically proven CC and clinically proven UCNC; presence of measurable lesions; previous therapy with IRI, OX, and 5-FU; documented progressive disease after 5-FU-based chemotherapy; wKRAS tumors; age over 20 years; performance status (PS) 0-1; and adequate organ function. The treatment protocol was as follows: weekly durable intravenous (DIV) C-mab administration at 400 mg/m^2 (day 1) and 250 mg/m^2/week (except day 1) and oral administration of 80 mg/m^2/day S-1 on days 1-28 of each 42-day cycle. The primary end point was progression-free survival (PFS). A sample size of 39 was planned for a threshold PFS of 3.5 months and expected value of 6.0 months, with one-sided alpha of 0.05 and beta of approximately 0.2.

Results: One patient was ineligible; 38 patients (PS 0/1, 32/6; 1/2/over 3 prior chemotherapy regimens, 4/23/11) were enrolled. The median PFS was 5.5 months; median overall survival (OS), 13.1 months; and the best OBR, 36.8%. The most common grade 3-4 adverse events were neutrophils, hypokalemia, rash, and dry skin.

Conclusion: S-1 + C-mab therapy may be a promising and well-tolerated treatment choice for wKRAS UCNC patients, who have previously received extensive treatment with IRI, OX, and FU.

Oral Session 26: Hepatobiliary and pancreatic cancer 2

C3 - 001

ABERRANT GLYCOGEN SYNTHASE KINASE 3β IS INVOLVED IN PANCREATIC CANCER CELL INVASION AND RESISTANCE TO THERAPY

T. Shimasaki1,2, A. Kitano3, H. Satoh4, T. Minamotot, Y. Motoo5
1Department Medical Oncology, Kanazawa Medical University; 2Division Translational Clinical Oncology, Cancer Research Institute, Kanazawa University; 3Medical Research Institute, Kanazawa Medical University, 4Division of Molecular Virology and Oncology, Cancer Research Institute, Kanazawa University

Purpose: The major obstacles to effective treatment of pancreatic cancer are the highly invasive nature of this tumor type and its resistance to chemo- and radiotherapy. Glycogen synthase kinase 3β (GSK3β) is a serine/threonine protein kinase that regulates multiple cellular pathways and has been implicated in various diseases including cancer. Here we investigate a putative pathological role for aberrant GSK3β in the highly invasive and treatment resistant phenotype of pancreatic cancer.

Methods: Pancreatic cancer cell lines were examined for GSK3β expression, phosphorylation and activity using western blotting and in vitro kinase assay. The effects of GSK3β inhibition on cancer cell survival, proliferation, invasive ability and susceptibility to gemcitabine and radiation were examined following treatment with a pharmacological inhibitor by RNA interference.

Results: Pancreatic cancer cells showed increased expression and deregulated activity of GSK3β that were associated with changes in their differential phosphorylation. Inhibition of GSK3β reduced the proliferation and survival of cancer cells, sensitized them to gemcitabine and ionizing radiation, and attenuated their chemotherapeutic migration and invasion. These effects were associated with decreases in cyclin D1 expression and RB phosphorylation. Inhibition of GSK3β also altered the subcellular localization of Rac-1 and F-actin and the cellular architecture, including lamellipodia. Coincident with these changes were the attenuation of cancer cell migration and invasion, reduced secretion of metalloproteinase-2 and decreased phosphorylated focal adhesion kinase.

Conclusion: The targeting of GSK3β may represent a novel and effective strategy to overcome the dual challenges of invasiveness and treatment resistance in pancreatic cancer.

C3 - 002

PATHOPHYSIOLOGICAL ROLE OF GHRELIN IN PATIENTS WITH ADVANCED PANCREATIC CANCER

Y. Fujikawa1, N. Chayahara2, N. Kyota1, K. Nakano1, T. Mukohara2, Y. Funakoshi1, Y. Imamura1, M. Toyota1, T. Shimada1, H. Tomioka2, K. Yakuishi1, A. Okamura2, H. Matsukawa2, H. Minami1
1Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, 2Medical Oncology/Hematology, Department of Medicine, Kobe University Hospital and Graduate School of Medicine

Background: Cancer-induced ghrelin is the most common paraneoplastic syndrome and is recognized as an indicator of poor prognosis. Cachexia often occurs in advanced pancreatic cancer, but its mechanism has not been fully elucidated. A number of hormones and cytokines are associated with cachexia. We previously investigated the role of fasting hormones and pro-inflammatory cytokines in cachexia patients with pancreatic cancer.

Methods: We enrolled patients with advanced pancreatic cancer in two groups, those with or without cachexia. Eligibility criteria for the cachexia group were >10% weight loss in 6 months, grade 1-4 anorexia, and PS 1-4. Eligibility criteria for the non-cachexia group were <5% weight loss in 6 months, serum albumin >3.5 mg/dl, grade 0-1 anorexia and PS 0-2. We compared patient characteristics and clinical data of the two groups, and measured the plasma level of IL-6, TNF-α and leptin.

Results: From December 2009 to July 2011, 21 patients (median age, 65 years; range, 36-77 years) were enrolled. In all, 16 (76.2%) patients were male, and 10 (47.6%) patients had stage IVA disease, and the rest had stage IVB disease. In the cachexia group (n = 9), median body weight loss was greater (15.5% versus 2.5%), PS 0, 1, 2, 3 was poorer (n = 0, 5, 3, 1 versus 4, 8, 0, 0) and anorexia (Grade 0, 1, 2, 3) was more severe (n = 8, 0, 1, 0 versus 5, 7, 0, 0) than in the non-cachexia group (n = 12). The median IL-6 level and TNF-α levels appeared higher and leptin concentration appeared lower in the cachexia group albeit without statistical significance (13.8 versus 6.8 pg/ml, P = 0.34; 7.1 versus 3.3 pg/ml, P = 0.27; 2.4 versus 4.0 ng/ml, P = 0.27).

Conclusions: In our study, the plasma level of IL-6, TNF-α and leptin appeared to be associated with cachexia in patients with advanced pancreatic cancer. Metabolomic analyses are underway.

C3 - 003

PLASMA LEVEL OF DES-ACYL GHRELIN PREDICTS DIGESTIVE SYMPTOMS IN PATIENTS UNDERGOING CHEMOTHERAPY FOR ADVANCED PanCREATIC CANCER

T. Mura1, S. Mitsunaga1, 2, N. Matsumoto1, M. Nakazato1, I. Ohno1, S. Shimizu1, H. Takahashi1, H. Okuyama1, A. Kuwahara1, M. Ikeda1
1National Cancer Center Hospital East, Division of Hematological and Pancreatic Oncology, 2National Cancer Center Hospital East, Division of Pathology, Research Center for Innovative Oncology, 3National Cancer Center Hospital East, Department of Palliative Care and Psycho-Oncology, 4University of Miyazaki, Faculty of Medicine, Department of Internal Medicine, Division of Neurology, Respirology, Endocrinology and Metabolism

Background: Ghrelin is a hormone produced mainly in the stomach and is responsible for stimulating appetite and attenuating mucosal damage caused by cytotoxic agents. Digestive symptoms such as appetite loss frequently occur in patients with pancreatic cancer (PC) who are undergoing chemotherapy and may be influenced by ghrelin. The aim of this study was to elucidate the role of plasma ghrelin levels in digestive symptoms among patients with advanced PC.

Methods: Patients with treatment-naïve advanced PC and no infectious conditions were eligible. All the patients were scheduled to undergo chemotherapy. Symptoms were rated numerically from 0 (not present) to 10 (as bad as you can imagine) using the Japanese version of the MD Anderson Symptom Inventory. Adverse events were evaluated according to the CTCAE, v3.0. The plasma des-acyl ghrelin (D-ghrelin) level was measured by N.M. and M.N. The measurements were carried out before chemotherapy and one month later. A two-tailed paired Student t-test was used to compare repeated measurements.

Results: Eighty-seven patients (female/male = 40/47, median age: 65 years, Karnofsky performance status [KPS] of 100–90/80–70/60–60/50–50/40–30/30–20/20–10/10–0) were enrolled. All the patients received chemotherapy (gemiitabine [GEM]/GEM-based/S-1: 47/24/16). The D-ghrelin level before chemotherapy (mean,
81 ± 5.4 fmol/ml) was lower than that observed 1 month later (mean, 68.0 ± 6.0 fmol/ml; P < 0.001). A high D-ghrelin level was defined as a value greater than the mean value observed before chemotherapy. Patients were divided into high (n = 43) or low (n = 44) D-ghrelin groups according to their high D-ghrelin level before chemotherapy. A poor KPS before chemotherapy, defined as a KPS score of ≤80, was frequently observed in the high D-ghrelin group (39.5%), compared with the low D-ghrelin group (18.2%; P = 0.034). When the repeated symptom scores for 1 month were compared, nausea and vomiting had worsened in the high D-ghrelin group (P = 0.002 and P = 0.001). A tendency toward a worsening of appetite loss after one month was observed in the high D-ghrelin group (P = 0.054).

Conclusion: A high plasma D-ghrelin level was related to a poor KPS and a worsening of nausea and vomiting in patients with advanced PC who received chemotherapy.

C03 – 004
EFFICACY OF GEMCITABINE AS SECOND-LINE THERAPY AFTER FAILURE OF S-1 THERAPY FOR METASTATIC PANCREATIC CARCINOMA

M. Fukahori1, S. Kondo1, H. Ueno1, S. Shimizu2, S. Mitsunaga2, M. Ikeda2, T. Yamaguchi1, Y. Sakamoto1, C. Morizane1, T. Okazaki1
1Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, 2Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Chiba, Japan

Background: S-1 is regarded one of the standard first-line regimens for advanced pancreatic cancer (APC) in Japan, because the GEST study, a randomized phase III clinical trial, revealed the non-inferiority of S-1 alone to GEM. However, no matter whether first-line therapy is S-1 or gemcitabine, no standard second-line chemotherapy has been established yet for cases of APC. In our study, we have evaluated the efficacy and outcomes of second-line GEM therapy after S-1 therapy failure for metastatic pancreatic carcinoma.

Method: We retrospectively examined the data for 27 patients with metastatic pancreatic carcinoma refractory to first-line S-1 therapy. All the patients had undergone second-line GEM therapy during October 2008—February 2009 at the National Cancer Center Hospital, Tokyo, Japan. Tumor responses were analyzed using the Response Evaluation Criteria in Solid Tumors (RECIST). The Kaplan–Meier method was used to evaluate tumor progression and survival.

Result: The Eastern Cooperative Oncology Group Performance Status was 0 or 1. The male:female ratio was 16:11 and median age was 62 years (range, 42–72 years). Four patients (14%) exhibited a partial response to second-line GEM therapy, 11 (40%) showed stable disease, and 12 (44%) showed progressive disease. Grade 3 adverse events for second-line GEM therapy were neutropenia in four patients and upper gastrointestinal hemorrhage in two. Grade 4 adverse events were not observed. The median progression-free survival was 70 days (95% confidence interval, 44–95 days) and the median OS after second-line GEM therapy was 229 days (95% confidence interval, 117–340 days).

Conclusion: Although this study had a small sample population and the design was retrospective, the results indicated that second-line GEM therapy exerted favorable antitumor activity with tolerable toxicity.

C03 – 005
PHASE 1 AND 2 TRIALS OF COMBINATION THERAPY WITH GEMCITABINE AND CANDESARTAN IN ADVANCED PANCREATIC CANCER

Y. Nakai1, H. Isayama1, H. Ichii1, T. Sasaki1, Y. Ito1, S. Matsuura1, H. Yagoku2, R. Nagano2, K. Kawakubo1, H. Kogure1, N. Yamamoto1, N. Sasahira1, K. Hirano1, M. Tada1, K. Koki1
1Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 2Department of Gastroenterology, Japanese Red Cross Medical Center, 3Department of Gastroenterology, Tokyo Metropolitan Police Hospital, 4Department of Gastroenterology, JRTokyo General Hospital, 5Department of Gastroenterology, Kanto Central Hospital

Background: Inhibition of renin-angiotensin (RA) system is one of the attractive targets in the treatment of pancreatic cancer (PaC). Our retrospective analysis showed the association of inhibition of RA system with better prognosis in advanced PaC (Br J Cancer. 2010;103: 1644–8). Here we reported the results of phase 1 and 2 trials of gemcitabine and candesartan (GECA) therapy in advanced PaC.

Patients: In phase 1 trial in normotensive patients, candesartan was administered orally at escalating dose (4, 8, 16 and 32 mg) qd daily and gemcitabine was administered 1000 mg/m2 30 min i.v. day 1, 8, 15, repeated every 4 weeks. DLT was defined as grade 4 hematological toxic effects, Grade 2 hypotension, abnormal creatinine or potassium and grade 3 or 4 other non-hematological toxic effects. In phase 2 trial, candesartan was administered 16 mg in normotensive patients and 8 mg in patients with hypertension, followed by increase up to 16 mg in cases without adverse events. Eligible criteria were unetectable locally advanced or metastatic PaC without any prior treatment, ECOG PS 0-2, normal renal function and without hypotension.

Results: In phase 1 trial, 14 patients (locally advanced/metastatic 7/7, candesartan 4 mg; 3 patients, 8 mg; 3 patients, 16 mg; 6 patients, 32 mg; 2 patients) were enrolled between July 2009 and October 2010. One of six patients at 16 mg demonstrated DLT of grade 4 neutropenia and grade 2 hypotension. The response rate (RR) and the disease control rate (DCR) were 0% and 79%. Progression-free survival and overall survival were 7.6 and 22.9 months. In phase 2 trial, 35 patients (locally advanced/metastatic 9/26) were enrolled between March 2011 and December 2011. Major adverse events were neutropenia 24% and thrombocytopenia 18%. Grade 2 hypotension was seen in three patients. RR and DCR were 11% and 63%. Median PFS and OS were 4.3 and 7.7 months.

Conclusion: GECA in advanced PaC appeared safe and promising, though a phase 2 study failed to meet our primary objective of 5-month median PFS.

C03 – 006
A PHASE II TRIAL OF GEMCITABINE FOR CHEMO-NAIVE METASTATIC PANCREATIC ENDOCRINE CARCINOMA TUMOR

C. Morizane1, H. Ueno1, S. Kondo1, S. Mitsunaga1, S. Shimizu1, I. Oihno1, H. Takahashi1, T. Yamaguchi1, Y. Sakamoto1, T. Okusaka1
1Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, 2Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, 4Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East

Background: Pancreatic endocrine carcinoma (PEC) is a fairly rare, heterogeneous disease entity. Gemcitabine is generally well tolerated and is active against pancreatic carcinoma and a wide range of malignancies including small-cell lung carcinoma, which shares many clinicopathological features with neuroendocrine carcinoma. Therefore, we conducted a phase II study of gemcitabine for chemo-naive metastatic pancreatic endocrine carcinoma.

Methods: Histologically proven chemo-naive PEC patients with an inoperable metastatic clinical stage were enrolled. Gemcitabine (1000 mg/m2) was administered as an intravenous 30-min infusion on days 1, 8, and 15 every 28 days. The primary end point of this study was an objective response.

Results: Fifteen patients were enrolled between January 2005 and December 2010. The median patient age was 59 years (range, 40–69 years). Ten patients (67%) had well-differentiated endocrine carcinoma (WDEC), and five patients (33%) had poorly differentiated endocrine carcinoma (PDEC; WHO 2004). The most common grade 3 or 4 adverse reactions were neutropenia (20%) and leukopenia (17%), although all the adverse reactions were tolerable and reversible. One confirmed radiologic response in a PDEC was observed (7% of all eligible patients and 20% of PDEC). Fourteen of the patients had stable diseases, and none of the patients had progressive disease. The median progression-free survival time and overall survival time of WDEC were 10.6 and 50.4 months. The median progression-free survival time and overall survival time of PDEC were 3.2 and 8.5 months, respectively.

Conclusion: Gemcitabine monotherapy revealed an insufficient response rate. However, gemcitabine seems to have some potentiality of activity in PDEC. In view of the favorable toxicity profile, its evaluation in combination with other agents might be of particular interest in improving the therapeutic results.

C03 – 007
MULTICENTER RETROSPECTIVE ANALYSIS OF SYSTEMIC CHEMOTHERAPY FOR ADVANCED POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMA OF DIGESTIVE SYSTEM

1Cancer Institute Hospital of the Japanese Foundation for Cancer Research, 2National Cancer Center Hospital, 3Shizuoka Cancer Center, 4National Cancer Center Hospital East, 5Chiba Cancer Center, 6National Hospital Organization, Shikoku Cancer Center, 7Hyogo Cancer Center, 8Department of Gastroenterology, Kitasato University East Hospital, 9Kobe University, 10Tskuba University, 11Aichi Cancer Center, 12Kanagawa Cancer Center, 13Department of Gastroenterology and Hematology, Faculty of Medicine, University of Toyama, 14Kyom University School of Medicine, 15Clinical Oncology, St. Marianna University

Background: No standard regimen is yet established for advanced poorly differentiated neuroendocrine carcinoma (PDNEC) although regimens for small-cell lung carcinoma are usually adopted such as irinotecan + cisplatin (IP) or etoposide + cisplatin (EP). Our aim was to respectively investigate the outcomes of advanced PDNEC of the digestive system according to patient characteristics and regimen.

Materials and methods: Data were collected from patients’ medical records at 23 hospitals. Selection criteria were as follows: (i) histologically proven PDNEC, small-cell carcinoma, mixed endocrine–neuroendocrine carcinoma with a PDNEC component, or histologically proven neuroendocrine tumor with rapidly progressive clinical course; (ii) primary tumor arising from the Gastrointestinal tract (GI) or the...
hepato-biliary-pancreatic system (HB/P); and (iii) inoperable or recurrent disease treated with systemic chemotherapy (Cs) between April 2000 and March 2011. Results: This study included 258 patients (males/females, 182/76) with a median age of 62.5 years. Primary sites were esophageal/rectal/stomach/small bowel colorectum/ hepatobiliary system/pelvis/cancer in 85/70/63/31/35/35 patients. According to the primary sites, the median overall survival period (mOS) was 13.4/13.3/29.7/7.6/7.9/ 8.5 months, and that of GI/HBP was 13.0/7.9 months, respectively. Most common regimen was IP (160 patients, 62%), followed by EP (46 patients, 18%). For IP/EP patients, response rates were 50%/27%, the median progression-free survival periods were 5.2/4.0 months. Second line Ct was carried out for 88 patients (55%) in 28 patients (61%), and mOs from first line Ct was 13.0/7.3 months in IP/EP groups. Multivariate analysis demonstrated that a primary site of HB/P (HR = 1.96, P = 0.003) and performance status of 2 and more (HR = 3.23, P = 0.01) were independent unfavorable prognostic factors of PDNEC.

Conclusions: PDNEC of HB/P had poorer prognosis than GI. IP was the most common treatment regimen and seemed to show better treatment outcome than EP.

Oral Session 27: Head and neck cancer 1: Chemoradiation

C03 – 008
IS ADJUVANT CHEMORADIOThERAPY NECESSARY FOR HIGH-RISK OROPHARYNGEAL CANCER AFTER SURGERY?

1Division of Gastroenterological Oncology, Shizuoka Cancer Center, 2Division of Head and Neck Surgery, Shizuoka Cancer Center, 3Pathology Division, Shizuoka Cancer Center, 4Division of Radiation Oncology, Shizuoka Cancer Center, 5Division of Medical Oncology, Shizuoka Cancer Center, 6Division of Plastic and Reconstructive Surgery, Shizuoka Cancer Center

Background: After surgical treatment of locoregionally advanced head and neck squamous cell carcinoma (HNSCC), (i) two or more regional lymph nodes involved (LN > 2), (ii) extracapular spread (ECS) of disease, or (iii) microscopically involved mucosal margins of resection (margin) upgrade the disease to high-risk status, which is often targeted with adjuvant chemoradiotherapy (CRT) to improve locoregional control and survival. However, the administration of CRT is associated with increase in the incidence of severe acute toxicity. Oropharyngeal squamous cell carcinoma (OPSCC) is recognized as distinct group of tumors with favorable clinical outcomes.

Objective: The objective was to evaluate the adjuvant therapy in patients with high-risk OPSCC characterized by LN > 2, positive ECS, and positive margins.

Methods: We retrospectively analyzed 45 patients with high-risk OPSCC who underwent resection of the primary tumor and/or neck dissection followed by an adjuvant therapy (n = 19), radiotherapy alone (RT) (n = 17), or CRT (n = 9), at the Shizuoka Cancer Center between 2003 and 2011.

Results: The median follow-up period was 37.2 months. Patients’ characteristics including gender, age, smoking status, and pathological findings (T/N-pathological stage, LN > 2, ECS, margin, keratinizing status) did not significantly differed among the three group. There were no significant differences in disease-free survival (DFS) for the RT group or the CRT group compared with the adjuvant group (RT: HR = 0.23, P = 0.067; CRT: HR = 0.71, P = 0.617). After adjustment for significant features by multivariate Cox regression analysis, positive margin, positive ECS, LN > 2, and no administration of adjuvant CRT were not significantly associated with worse DFS.

Conclusions: Adjuvant CRT may not be necessarily recommended for patients with OPSCC characterized by LN > 2, positive ECS, and positive margins. Specific category for high-risk OPSCC is warranted. The status of p16 expression is currently the most effective induction chemotherapy combination for locally advanced unresectable head and neck cancer. However, it remains unclear that induction chemotherapy added to concurrent chemoradiotherapy (sequential therapy) has a positive effect on survival when compared with concurrent chemoradiotherapy (CCRT) alone. The purpose of this study was to compare the sequential therapy with CCRT alone.

Methods: We analyzed newly diagnosed stage IV head and neck cancer patients who received CCRT (cisplatin 80 mg/m2 on day 1, 22, and 43 plus RT) with or without 3 cycles of TPF induction chemotherapy (docetaxel 75 mg/m2 day 1, cisplatin 75 mg/m2 day 1, and 5-fluorouracil 750 mg/m2/day by continuous infusion on days 1–4) at The Cancer Institute Hospital of JFCR between May 2006 and August 2010 retrospectively.

Results: There were 82 patients who received cisplatin-based CCRT, of which 15 patients (18.3%) received TPF induction before CCRT. Complete response (CR) after
Results: TPF induction chemotherapy was 1/15 (6.7%) and subsequently, 11/15 (73.3%) patients achieved CR after CCRT, while 50/67 (74.6%) patients achieved CR in CCRT alone with no significant difference (P = 0.58). With a median follow-up of 27 months, progression-free survival and overall survival had no significant benefit with TPF + CCRT compared with CCRT alone (hazard ratio 1.3: CI 0.56–3.53; 2-year PFS was 46.7 versus 71.6% and 2-year OS was 86.7 versus 79.6%, respectively. The poor prognostic factor were age over 65, nasopharyngeal cancer, and CR achievement after CCRT.

Conclusion: TPF induction chemotherapy is a feasible option before concurrent chemoradiotherapy. However, there is no significant benefit in this small retrospective study. Further prospective study is needed to assess the role of induction chemotherapy.

The Efficacy and Safety Analysis of Carboplatin and Paclitaxel Therapy for Patients with Inoperable, Recurrent or Refractory Adenocarcinoma of the Head and Neck

T. Uomori1,2, M. Yokoyama1, E. Nara1, N. Nishimura1, S. Sakaijir1, Y. Mishima1, Y. Teru1, S. Takahashi1
1Department of Medical Oncology, Cancer Institute Hospital of JFCR
2Department of Breast Surgery, Juntendo University School of Medicine

Background: Salivary gland cancers are rare neoplasms accounting for <5% of all cancers of the head and neck. To report the efficacy and safety of patients with inoperable, recurrent or refractory adenocarcinoma of the head and neck by carboplatin (CBDCA) and paclitaxel (PAC) therapy.

Patients and methods: From May 2004 to May 2011, 29 patients with adenocarcinoma of the head and neck were treated with CBDCA and PAC therapy on the first line in our institution. This method was delivered for every 3 weeks, CBDCA (AUC = 6 on d1) and PAC (200 mg/m2 on d1). We analyzed inoperable, recurrent or refractory adenocarcinoma of the head and neck by carboplatin (CBDCA) and paclitaxel (PAC) therapy.

Results: Median follow-up was 17.3 months, baseline patients characteristics included a median age of 60 years (range: 45–73 years), 23 men and 6 women. The pantoid gland was more frequently involved (n = 18) than minor (n = 1) or submandibular (n = 10) glands. Median progression-free survival, event-free survival, and overall survival were 9.1, 8.6 and 52.2 months, respectively. Progression disease was seen in 26 out of 29 patients (90%). Complete response was seen in 2 out of 29 patients (7%). These two patients have been alive and progression-free for 29 and 25 months. Grade 3/4 hematological adverse events were leukopenia (45%), neutropenia (55%), anemia (24%), and thrombocytopenia (35%), respectively. No treatment-related deaths were observed.

Conclusions: CBDCA and PAC therapy was effective and safety regimen for patients with inoperable, recurrent or refractory adenocarcinoma of the head and neck by carboplatin (CBDCA) and paclitaxel (PAC) therapy.

Docetaxel Plus Cisplatin as First-Line Chemotherapy in Patients with Recurrent or Metastatic Head and Neck Cancer

Y. Ohhara1, N. Nishimura1, E. Nara1, K. Nakano1, K. Ueda1, N. Nishimura1, S. Sakaijir1, Y. Mishima1, M. Yokoyama1, Y. Teru1, S. Takahashi1, H. Hatake1
1Department of Medical Oncology, Cancer Institute Hospital of JFCR

Background: The standard regimen for recurrent or metastatic head and neck cancer has not been established. We retrospectively analyzed the safety and efficacy of docetaxel plus cisplatin as first-line treatment in our institute.

Patients and methods: Between 2005 and 2010, 44 patients with metastatic or recurrent head and neck cancer received docetaxel (75 mg/m2 or 80 mg/m2, day 1) plus cisplatin (75 mg/m2, day 1) every 3 weeks were analyzed. This treatment was continued until disease progression or unacceptable toxicity. The overall response was evaluated using RECIST 1.0 during chemotherapy treatment, and adverse events were graded according to CTCAE ver. 3.0.

Results: Characteristics of patients were below: median age, 61 years old (range: 38–80); gender (male), 79.5%; extent of disease, distant metastatic/recurrent: 9/35; primary site, nasal or paranasal cavity/nasopharynx/oropharynx/hypopharynx/oral cavity/larynx: 1/413/178/1. The overall response rate (CR + PR) was 43.2%. Median progression-free survival was 6.6 months (95% CI: 5.2–8.0) and median overall survival was 14.2 months (95% CI: 11.2–17.2). Grade 3/4 neutropenia was observed in 90.9% of patients, and developed febrile neutropenia in 47.7%.

Conclusions: Docetaxel plus cisplatin is effective and feasible for Japanese patients with metastatic or recurrent head and neck cancer. However, the hematologic toxicity of this regimen should be carefully monitored and managed.

S-1 Monotherapy for Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck After Progression on Platinum-Based Chemotherapy

T. Yokota1, Y. Onozawa1, N. Boku1, S. Hamauchi1, T. Tsushima1, H. Taniguchi1, A. Totsuka1, N. Machida1, K. Yamazaki1, A. Fukutomi1, H. Yasui1
1Division of Gastrointestinal Oncology, Shizuoka Cancer Center
2Division of Medical Oncology, Shizuoka Cancer Center

Background: Platinum compound plays pivotal roles in the treatment of squamous cell carcinoma of the head and neck (SCCHN).

Objective: The objective was to evaluate the efficacy of S-1 monotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN) after failure of platinum-based chemotherapy.

Methods: We retrospectively analyzed 39 consecutive patients with R/M-SCCHN who received S-1 monotherapy after failure of platinum-based chemotherapy or chemoradiotherapy at the Shizuoka Cancer Center between August 2003 and October 2010. S-1 was given orally twice daily (80 mg/m2/day) for 28 days followed by a 14-day rest.

Results: The median follow-up period in survivors was 31.5 months. Among 38 patients with measurable lesions, 9 (24%) showed partial response and 15 (39%) showed stable disease. The median progression-free survival (PFS) was 4.9 months and the median overall survival was 13.2 months. The median PFS for oropharyngeal cancer (n = 7) was significantly longer than for other cancers (n = 32) (14.9 versus 4.7 months, P = 0.055). The response rate in patients with recurrence-free interval (RFI) was last platinum >60 months was significantly better than RFI ≤60 months (40% versus 13%, P = 0.0102). RFI >60 months also showed a significantly better PFS (6.0 versus 2.6 month, P = 0.045). The frequency of grade 3/4 toxic effects was <10%.

Conclusions: S-1 monotherapy shows promising signs of efficacy and tolerability in patients R/M SCCHN after failure of platinum-based chemotherapy in this retrospective cohort, and warrants further investigation in this population.

Correlative Study of Low Serum Creatinine and Hematologic Toxic Effects in Japanese Patients with Ovarian Cancer Treated by Dose Dense to Therapy

K. Matsumoto1, T. Onc1, A. Kita1, M. Tanioka1, S. Negoro1
1Medical Oncology Division, Hyogo Cancer Center

Background: Dose dense TC (ddTC) is a novel standard therapy for patients with advanced ovarian cancer, although hematologic toxic effects (hemTX), especially anemia, may increase as observed in NOVEL trial (IGOG3016). Low serum creatinine (LCr), especially <0.7 mg/dl, may lead to overestimation of GFR. GOG announced that patients with LCr ≥1 should use a minimum value of 0.7 mg/dl to estimate GFR. The correlation between LCr and hemTX treated by ddTC is unknown.

Methods: GFR was determined using the Cockcroft–Gault formula. Serum creatinine concentrations were measured using enzymatic assays. Minimum value of 0.7 mg/dl was not used during this period of time. The carboplatin clearance was then calculated by Calvert equation. HemTX were defined as, Grade 3 or 4 (by CTCAE ver.4) neutropenia, anemia, and thrombocytopenia. Using electrical chart, the frequency of hemTX and correlation between serum creatinine (<0.7 or not) was examined.

Results: From February 2010 to December 2011, 61 consecutive patients were treated with ddTC. LCr was observed in 73% of patients. No treatment-related death occurred. Among 61 patients, 50 (82%), 31 (51%), and 12 (19.6 %) patients experienced Grade 3/4 neutropenia, anemia and thrombocytopenia, respectively. HemTX in patients with LCr and the others were as in Table 1.

Patients with LCr

<table>
<thead>
<tr>
<th>LCr</th>
<th>Patients with LCr</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3/4 neutropenia</td>
<td>G3 (80%)</td>
</tr>
<tr>
<td>G3/4 anemia</td>
<td>24 (53.3%)</td>
</tr>
<tr>
<td>G3/4 thrombocytopenia</td>
<td>9 (20%)</td>
</tr>
</tbody>
</table>

Patients without LCr

<table>
<thead>
<tr>
<th>LCr</th>
<th>Patients without LCr</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3/4 neutropenia</td>
<td>G3 (18.5%)</td>
</tr>
<tr>
<td>G3/4 anemia</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>G3/4 thrombocytopenia</td>
<td>3 (18.8%)</td>
</tr>
</tbody>
</table>

Conclusions: LCr is frequent in Japanese female patients. ddTC in practice setting seems safe, and hemTX of ddTC are similar with those observed in NOVEL trial.
The rationale using a minimum value of 0.7 mg/dl should be further studied by larger population, such as patients in NOVEL trial.

C03 – 019 THE PROGNOSTIC SIGNIFICANCE OF MULTIPLE PELVIC NODE METASTASES IN CERVICAL CANCER PATIENTS TREATED WITH RADICAL HYSTERECTOMY PLUS ADJUVANT CHEMORADIOThERAPY

M. Okazawa1, S. Maebu1, E. Daimori2, T. Iwyma3, Y. Miyataka2, Y. Ohta2, K. Yoshino1, M. Fujita1, T. Enomoto1, S. Kamura1, T. Kimura1
1Department of Obstetrics and Gynecology, Osaka University; 2Osaka Medical Center for Cancer and Cardiovascular Diseases

Background: Lymph node metastasis is an important prognostic factor in cervical cancer. According to previous reports, the survival of early-stage cervical cancer patients with three or more positive nodes was significantly shorter than that of those with one or two positive nodes, indicating the prognostic significance of multiple pelvic node metastases. However, because these previous investigations were conducted before the introduction of concurrent chemoradiotherapy (CCRT), the prognostic significance of multiple pelvic node metastases in patients treated with CCRT is unknown. We investigated the prognostic significance of multiple pelvic node metastases in cervical cancer patients who were treated with radical hysterectomy plus adjuvant CCRT.

Methods: We retrospectively reviewed the medical records of 311 patients with FIGO stage IIB–IVB cervical cancer who had been treated with radical hysterectomy plus adjuvant RT between April 1996 and December 2008. Of these, 119 received adjuvant RT alone (RT group) and 192 received CCRT (CCRT group). Multivariate analysis for progression-free survival (PFS) was carried out using the Cox proportional hazards regression model. Survival was calculated using the Kaplan–Meier method and compared using the log-rank test.

Results: Multivariate analysis demonstrated pelvic node metastasis to be an independent prognostic factor for shorter PFS in both groups. When the node-positive patients were analyzed according to the number of positive pelvic nodes, we found that the patients with multiple pelvic node metastases (≥3) displayed significantly shorter PFS than those with 1 or 2 pelvic node metastases in the RT group. In contrast, in the CCRT group, the PFS of the patients with multiple pelvic node metastases (≥3) was similar to that observed of the patients with 1 or 2 pelvic node metastases.

Conclusions: The presence of multiple pelvic node metastases was not an independent predictor of shorter PFS in the CCRT group.

C03 – 020 A RANDOMIZED PHASE III TRIAL OF PACLITAXEL PLUS CARBOPLATIN (TC) VERSUS PACLITAXEL PLUS CISPLATIN (TP) IN STAGE IVA OR RECURRENT CERVICAL CANCER: JAPAN CLINICAL ONCOLOGY GROUP STUDY (JCOG0505)

1Department of Obstetrics and Gynecology, NTT Medical Center Tokyo, 2Department of Medical Oncology, Nippo Medical School Musashikosugi Hospital, 3JCOG Data Center, Multi-institutional Clinical Trial Support Center, National Cancer Center, 4Department of Gynecologic Oncology, Aichi Cancer Center, 5Department of Gynecologic Oncology, Osaka City General Hospital, 6Department of Obstetrics and Gynecology, Kurume University, 7Department of Obstetrics and Gynecology, National Defense Medical College Hospital, 8Department of Obstetrics and Gynecology, Tsukuba University, 9Department of Gynecologic Oncology, Satsuma Cancer Center, 10Department of Obstetrics and Gynecology, Jikei University, 11Department of Obstetrics and Gynecology, Tottori University, 12Department of Obstetrics and Gynecology, Kyushu University, 13JCOG Operations Office, Multi-institutional Clinical Trial Support Center, National Cancer Center

Background: TC is a less toxic regimen in terms of milder nephropathy, neuropathy and no need of hospitalization. This phase III trial was designed to evaluate the clinical benefits of TC compared with TP which is the current standard chemotherapy for stage IVB or recurrent cervical cancer.

Methods: Patients with stage IVC or recurrent cervical cancer—not amenable to curative therapy; ≥1 prior platinum; no prior taxanes—were randomized with the minimization method to receive TP (T 135 mg/m2 24h d1 + P 50 mg/m2 2h d2) or TC (T 175 mg/m2 3h d1 + C AUC5 1h d1), both for maximum six cycles every 21 days. Primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS), OS, disease-related effects, and the proportion of non-inferiority of TC to TP (threshold hazard ratio [HR] 1.29) in terms of OS. HR is estimated by a stratified Cox regression.

Results: From February 2006 to November 2009, 253 patients were enrolled. The median follow-up is 17.4 months. 27% of patients of the TP and TC arm each received six cycles. Results are as follows: as an interval for an interim analysis was <0.0001, the significance level for the final analysis is ~5% even after the multiplicity adjustment.

Conclusions: This first randomized, controlled trial comparing carboplatin doublet with cisplatin doublet showed significant non-inferiority of TC in terms of OS. More feasible and less toxic TC can be recommended as the new standard treatment of stage IVB or recurrent cervical cancer. TP TCOS (median) 18.3 months, 17.5 months, HR 0.99 (multiplicity adjusted 90% CI: 0.79–1.25), non-inferiority P = 0.032 (median) HR 1.04 (95% CI: 0.80–1.35) 6.90 months 6.21 months neutropenia G3–4 85.1% 76.4% thrombocytopenia G3–4 3.3% 16.0% 7.3% creatinine G2–4 9.8% 4.1% neuropathy (motor) G3–4 0.8% 2.4% neuropathy (sensory) G3–4 0.0% 4.9% NHP (P < 0.0001, Wilcoxon rank sum test) 46.4% 61.9%

C03 – 021 PROGNOSTIC FACTORS IN PATIENTS WITH LOCALLY ADVANCED UTERINE CERVICAL CANCER TREATED WITH RADIOTHERAPY AS A PRIMARY TREATMENT

R. Kagouchi1, N. Furukawa1, M. Kamuro2
1Department of Obstetrics and Gynecology, Nara Medical University; 2Oncology Center, Nara Medical University

Background: The aim of the present study was to assess prognostic factors for patients with locally advanced cervical cancer treated with radiation therapy as a primary treatment and to assess post-treatment squamous cell carcinoma (SCC) antigen cut-off levels to predict the 3-year survival.

Methods: One hundred sixteen patients with squamous cell carcinoma of the cervix (FIGO stage IB1–IVA) with radiation therapy or concurrent chemoradiotherapy (CCRT) were analyzed retrospectively. Kaplan–Meier life table analysis and the log-rank test were used to assess the survival rate and differences according to the prognostic factors. Multivariate analysis of the prognostic factors for overall survival (OS) was done using the Cox proportional hazards regression model.

Results: The median age was 68 years (range: 27–79 years). The complete response rate was 70.7% and the 3-year OS rate was 61.1%. The median level of pretreatment SCC was 11.5 ng/ml (range: 1.6–310 ng/ml), and post-treatment SCC decreased significantly to 0.9 ng/ml (range: 0.4–41.0 ng/ml) (P = 0.001). On univariate analysis, FIGO stage (P = 0.041), pretreatment hemoglobin levels <10.5 g/dl (P = 0.001), pelvic lymph node metastasis (P = 0.001), tumor size >40 mm (P = 0.001), CCRT (P = 0.016) and posttreatment SCC levels >1.5 ng/ml (P = 0.001) were independent prognostic factors for overall survival. Of these, pretreatment anemia (P = 0.041), pelvic lymph node metastasis (P = 0.016) and posttreatment SCC (P = 0.001) were independent prognostic factors of multivariate analysis. The SCC level cut-off point for the 3-year OS calculated using a receiver operating characteristic curve was 1.15 ng/ml (sensitivity 80.0%, specificity 74.0%).

Conclusion: In cases of locally advanced cervical cancer treated with radiotherapy, patients with pretreatment anemia, positive for pelvic lymph node metastasis and post-treatment SCC levels >1.5 ng/ml had a poor prognosis. Furthermore, post-treatment SCC level of 1.15 ng/ml or less predicted 3-year survival.

Oral Session 30: Breast cancer 1

C03 – 022 CONCENTRIC TUMOR SHRINKAGE BY CHEMOTHERAPY IS A GOOD PROGNOSTIC FACTOR IN NEOADJUVANT CHEMOTHERAPY FOR LUMINAL BREAST CANCER

Department of Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research

Background and objective: The important characteristics of breast cancer is its heterogeneity and attitude of response to neoadjuvant chemotherapy (NAC). We analyzed the patterns of tumor shrinkage as a prognostic indicator after NAC for luminal breast cancer.

Methods and results: Of the 503 patients who had received NAC in our hospital between January 2000 and December 2009, 142 luminal breast cancer were included in this study. Luminal breast cancer was defined as ER and/or PR-positive in more than 10% of cancer cells and HER2 negative (IHC 0, 1+ or FISH < 2.0). Before and after NAC, the primary lesion was evaluated by enhanced MRI. The median follow-up period was 45.8 months. Thirty-two patients (22.5%) experienced recurrence after a median DFI of 43.1 months. The 5-year survival rate was 90.6%.
The median age was 49 years, all patients received anthracycline anticancer drugs and 127 patients received taxane. The primary lesion was evaluable by imaging in 138 patients, 64 patients who experienced simple concentric tumor shrinkage, achieved a significantly more favorable histologic response to chemotherapy. Multivariate analysis identified strong ER positivity and the number of lymph node metastases as significantly favorable and unfavorable prognostic factors ($P=0.021$, $P=0.049$, respectively). Patients who did not experience simple concentric tumor shrinkage tended to have a poor prognosis ($P=0.0033$).

**Discussion:** The results suggest that concentric tumor shrinkage tends to be associated with a favorable prognosis, whereas scattered residual cancer cells are resistant to chemotherapy.

---

**C3 – 024**

**A PILOT NEoadjuvant STUDY of sequential nanoparticule albumin-bound Paclitaxel followed by Fec in advanced breast Cancer**

S. Ohnita$^1$, M. Kochi$^2$, K. Abe$^3$, Y. Sakata$^4$, K. Hiraki$^5$, Y. Fujikawa$^6$, Y. Iwamoto$^7$

$^1$Department of Breast Surgery, $^2$Department of Surgery, $^3$Department of Medical Oncology, Hiroshima City Hospital

**Background:** Neoadjuvant chemotherapy has become a standard treatment of advanced breast cancer. Various regimens have explored the addition of new agents to determine safety and efficacy. Our aim of this pilot study was to incorporate albumin-bound paclitaxel (ABP) with sequential anthracycline-based therapy as a neoadjuvant chemotherapy.

**Patients and methods:** Twenty-four women with advanced breast cancer but without prior treatment and regardless of hormone receptor or HER2 status were enrolled. All patients were to receive albumin-bound paclitaxel (260 mg/m$^2$) every 3 weeks for four cycles followed by 5-fluorouracil/etoposide/cyclophosphamide (FEC100) every 3 weeks for 4 cycles. Trastuzumab was allowed in HER2-positive patients. Efficacy and safety was analyzed.

**Results:** Twenty-three patients completed four cycles of ABP. 24 patients received at least two dose of FEC. Eight HER2$^+$ women received trastuzumab only concomitant with ABP. The PCr in breast and axilla was 20.8% (5 of 24). For the HER2$²$ subset, the PCr was 62.5% (5 of 8). Both ABP and FEC were well tolerated. The most significant toxic effects were grade 2/3 neuropathy (52%) with ABP and grade 3/4 neutropenia (54%) with FEC.

**Conclusion:** ABP given four cycles is well tolerated as neoadjuvant chemotherapy. ABP should be further evaluated in a randomized setting in a neoadjuvant trails.

---

**C3 – 026**

**WHICH IS YOUR CHOICE? NEoadjuvant adriAMYcin AND doxetAXel (AD) versus adriAMYcin, CYCLOPHOSPHAMIDE and PaclitAXel (AC-T) IN locally advanced breast CANCer**


$^1$Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, Korea, $^2$Department of Surgery, Ajou University School of Medicine, Suwon, Korea

**Background:** It is well known that neoadjuvant chemotherapy is acceptable for women with locally advanced breast cancer. However, it is not achieving consensus that what kind of regimen is most effective and tolerable, although lots of regimens and dosages were clinically used.

**Methods:** We compared the patients who were received adriamycin and doxetaxel (AD) and adriamycin, cyclophosphamide followed by paclitaxel (AC-T) as neoadjuvant chemotherapy and then received operation from 1 January 2006 to 30 September 2011. The group of AD regimen was scheduled for three cycles of AD (50 and 75 mg/m$^2$, respectively) with 3-week interval and then completes resection. The group of AC-T was scheduled for four cycles of AC regimen (50 and 500 mg/m$^2$, respectively) and then four cycles of paclitaxel (175 mg/m$^2$) with 3-week interval and then completes resection.

**Results:** The patients who were enrolled in this study were totally 78 (AD and AC-T were equally 39). The significant differences of patients’ characteristics between the two groups were not observed. However, the significant differences were identified in hematologic toxicity including neutropenia more than grade 3 ($P=0.001$), neutropenic fever ($P=0.001$), dose reduction rate due to hematologic toxicity ($P=0.012$) and chemotherapy-induced anemia ($P=0.012$), although chemotherapy-induced thrombocytopenia ($P=1.0$) was not different between the two groups. No differences were identified in non-hematologic toxicity including hepatic toxicity, gastrointestinal toxicity and peripheral neuropathy. The response of chemotherapy was no difference between the two groups, which was estimated by the conversion rate of breast conserving surgery, clinical response of chemotherapy ($P=0.046$) and pathologic complete response rate ($P=1.0$). There is no factor to predicting pathologic complete response or conversion to breast conservation in this study.

**Conclusions:** The neoadjuvant AC-T regimen is more tolerable with a similar clinical outcome compared with the AD regimen.

---

**C3 – 027**

**SAFETY AND EFFICACY OF HYPOFRACTIONATED RADIOTHERAPY IN ADJUVANT TREATMENT OF BREAST CANCER**

K. Nagura$^1$, T. Koyama$^2$, D. Gorni$^3$, T. Mikawa$^4$, M. Matsuoka$^5$, Y. Oyama$^6$, E. Fukunai$^7$, K. Shoji$^8$

$^1$Department of Medical Oncology, Kameda Medical Center, $^2$Breast Center, Kameda Medical Center, $^3$Department of Radiology, Kameda Medical Center

**Background:** Adjuvant whole breast irradiation reduces the risk of local recurrence; however, it is time consuming to patients. The shorter hypofractionation schedules have been tried mainly in Canada with reasonable outcomes.

**Methods:** We conducted a retrospective study of the efficacy and safety in patients with N0-1 invasive breast cancer who underwent radiotherapy at our hospital between January 2004 and January 2012. Radiotherapy was either conventional (50 Gy/25 Fractions) or accelerated hyperfractionation (44 Gy/26 Fractions).

**Results:** There were 257 patients who received conventional and 329 patients who received hypofractionation. The median observation period was 36 weeks. One patient in conventional (0.4%) and three patients in hypofractionation (0.9%) suffered local recurrence. No statistically significant differences were seen between the two groups. There was no increased toxicity in the skin or lung in the hypofractionation group.

**Conclusions:** These findings suggest that hypofractionated radiotherapy is effective and safe in at least short follow-up. We need longer prospective investigation to confirm these results.

---

**C3 – 028**

**PROGNOSTIC FACTOR KI67 FOR BREAST CANCER PATIENTS IN EACH SUBGROUP**


$^1$Department of Breast and Endocrine Surgery, Tokai University School of Medicine, $^2$Department of Pathology Tokai University School of Medicine, $^3$Department of Pathology, Nihon University School of Medicine

**Background:** Immunohistochemical (IHC) Ki67 has described it as a prognostic and predictive marker for breast cancer. The St. Gallen Consensus Meeting determined that Ki67-labeling index is chiefly important for distinguishing between Luminal A and Luminal B (HER2 negative) subtypes and is a predictive marker for chemotherapy efficacy. However, the high and low cutoff points remain controversial. Our objective is to compare survival in patients with low, intermediate and high Ki67 levels.

**Methods:** We retrospectively identified all the patients in the Tokai University breast cancer database for whom IHC Ki67 data were available between 1 January 2000, and 31 December 2010. Ki67 was defined as low if <10%, Ki67 was detected, as intermediate if 10-20%, Ki67 was detected, and as high if >20% Ki67 was detected. To assess Ki67 levels and survival outcomes, survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test.

**Results:** We identified 1331 primary breast cancer patients without metastasis; of whom, 686 received neoadjuvant or adjuvant chemotherapy. Patients with high Ki67 had poorer relapse-free survival (RFS) than patients with intermediate (P = 0.009) and low Ki67 (P < 0.001). Patients with intermediate Ki67 had poorer RFS than patients with low Ki67 (P = 0.001) and P = 0.002, respectively). In HER2-positive and ER-negative cases (n = 103), patients with high Ki67 had poorer RFS than patients with low Ki67 (P = 0.002). In triple-negative cases (n = 164), patients with high Ki67 tended to have poorer RFS than patients with low Ki67 (P = 0.064).

**Conclusion:** Our data demonstrated that low, intermediate and high Ki67 levels may be used to differentiate prognosis in ER-positive cancer patients as well as HER2-positive and triple-negative cancer patients.

---

**C3 – 029**

**TIME TO BRAIN METASTASIS (TTBM) FROM INITIAL DIAGNOSIS OF DISTANT METASTASIS IN BREAST CANCER: PREDICTION OF TTBM ACCORDING TO BREAST CANcer SUBTYPES AND TREATMENT EFFECT**


Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

**Background:** Brain metastasis (BM) from breast cancer (BC) is a growing problem. About 10–15% patients with metastatic breast cancer (MBC) developed BM, with a
1-year survival of 20%. Currently, one-third of MBC patients with either HER2+ve tumors or triple negative BC (TNBC) tumors develop brain metastases. We hypothesized that MBC patients may predispose to BM differently during the disease course according to BC subtype and type of treatment. We prospectively followed TBBM from initial diagnosis of distant metastasis to confirm how BC subtypes and treatment affect on TBBM.

Methods: We retrospectively investigated 189 consecutive patients who were diagnosed with BM from BC between 2000 and 2009 at Samsung Medical Center. We analyzed TBBM according to BC subtypes and treatment effect.

Results: The median age of 189 BM patients from BC was 48 (range 26–87) years. The numbers of patients with hormone receptor (HR) +ve and HER2-ve, HER2+ve irrespective of HR status, and TNBC were 43 (22.8%), 88 (46.6%), and 56 (30.7%), respectively. Median TTBMs of all 189 patients was 10.4 (95% CI, 7.7–13.1) months. We analyzed TTBMs into four groups considering BC subtypes and treatment; HR +ve/HER2-ve (n = 43), HER2+ve with trastuzumab (T) (n = 59), HER2+ve without T (n = 29), and TNBC patients (n = 58). The median TTBMs for each group were 17.7, 13.8, 4.3, and 2.9 months, respectively (P = 0.002). BM as an initial site of distant metastasis was much more common in HER2+ve without T and TNBC patients than in the other patient groups (40.2% versus 20.6%, P = 0.003).

Conclusions: TTBMs were much shorter in patients with HER2+ve without T and TNBCs than in other BC patients. Different approaches for evaluation and therapeutic strategy for BM at the time of distant metastasis may be considered for these populations.

Oral Session 31: Breast cancer 2

C3-030 MYELOID-DERIVED SUPPRESSOR CELLS ARE INCREASED AND CORRELATED WITH TYPE 2 IMMUNE RESPONSES IN BREAST CANCER PATIENTS

K. Gonda1,5, M. Shibata2, T. Ohtake1, T. Shimura2, K. Sakurai3, T. Machida4, H. Outo5, S. Takenoshita1
1Department of Organ Regulatory Surgery, Fukushima Medical University, 2Department of Tumor and Host Bioscience, Fukushima Medical University, 3Department of Surgery, Nihon University, School of Medicine, 4Department of Hematology and Hematopoietic Transplantation, National Medical Center, and 5Department of Immunology Fukushima Medical University, 2Department of Blood Transfusion and Transplantation Immunology, Fukushima Medical University

Background: Myeloid-derived suppressor cells (MDSC) have been identified in most patients and experimental mice with tumors by their Th2-related suppression of T-cell activation. In contrast to the situation in mice, MDSC involvement in human cancer pathophysiology has not been clarified.

Materials and methods: Here we report a study of 53 patients with breast cancer, including 31 preoperative, 22 postoperative and 8 having recurrent disease, and 11 metastatic lesions. Sixteen patients received adjuvant chemotherapy including 31 preoperative, 22 postoperative and 8 having recurrent disease, and 11 metastatic lesions. Sixteen patients received adjuvant chemotherapy.

Results: A highly significant increase was seen in MDSCs (CD11b+CD14-CD33+) levels in patients with breast cancer and it showed decrease after the removal of the tumor mass to range in healthy individuals, and these cells also decreased in response to gemcitabine administration. We retrospectively examined the efficacy of these antiemetic drugs without dexamethasone.

C3-031 ANTI-EMETIC THERAPY FOR HBV CARRIER OR DIABETIC BREAST CANCER: NON-DEXAMETHASONE CONTAINING COMBINATION TREATMENT OF PREVENTING EMEIS OF ANTHRACYCLINE REGIMENS IN BREAST CANCER PATIENTS

Y. Nakayama, Y. Ito, I. Fukata, T. Kobayashi, C. Tsutsumi, S. Takahashi, K. Hatake
Department of Medical Oncology, Cancer Institute Hospital

Background: Anthracycline-containing regimens for breast cancer are classified as highly emetogenic chemotherapy. Appreant (A), palonosetron (P), granisetron (G) and dexamethasone (D) are recommended as antiemetic drugs. However, patients with hepatitis B or diabetes mellitus had better avoid dexamethasone. We...
unmet need for additional treatment options that are effective, well-tolerated and easily administered. Erubinib is a water-soluble, non-taxane microtubule dynamics inhibitor. With a mechanism of action distinct from currently available tubulin-targeting agents, erubinib inhibits microtubule polymerisation but not depolymerisation and induces tumor cell apoptosis. In the single-arm, multicenter phase II trial in Japan, 80 patients pretreated with an anthracycline and a taxane were enrolled. Patients had received one to five prior chemotherapy regimens (median of 3) including 0 to 2 regimens (median of 2) in the metastatic setting. Erubinib 1.4 mg/m² was iv. administered over 2-5 min on days 1 and 8 of each 21-day cycle. The independent review indicated the overall response rate (ORR) of 21.3% for the primary efficacy end point. Stable disease (SD) occurred in 37% of patients (no grade 4). The study suggested that erubinib exhibited efficacy and tolerability in patients with heavily pretreated MBC. Recently, erubinib gained the approval for MBC in Japan, as in other countries. Since then, a number of patients with MBC were treated with erubinib in our hospital. The patients included who belonged to aged population, who received several regimens of prior chemotherapy and/or who showed worsened performance status. For eribulin treatment, we managed the hematological and non-hematological toxic effects by the appropriate modification of starting dose, dosing schedule or dose reduction dependent upon the patient conditions. Our clinical observations suggest that erubinib can be the potential drug to contribute to the long-term disease control in pretreated MBC patients. The considerable event and management will be reviewed and discussed in this session.

**Oral Session 32: Colorectal cancer chemotherapy**

**O3 – 005**

**PHASE II STUDY OF S-1 PLUS LEUCOVORIN (NEW 1 WEEK TREATMENT REGIMEN FOLLOWED BY 1 WEEK REST PERIOD) IN PATIENTS WITH UNTREATED METASTATIC COLORECTAL CANCER IN JAPAN AND CHINA**

H. Baba1, J. Li2, R. Xu1, J. Xu1, T. Denda3, K. Ikejiri6, L. Shen7, Y. Toh8, K. Shimada2, T. Kato10, K. Sakai11, A. Matsuyama12, H. Mishima13, J. Wang14

1Gastroenterological Surgery, Eishin University Hospital, 2Division of Oncology, Fudan University Shanghai Cancer Center, 3Division of Oncology, Sun Yat-sen University Cancer Center, 4No. 4 Division of Oncology, 5170 Hospital of PLA, 6Division of Gastroenterology, Chiba Cancer Center, 7Department of Surgery, Gastroenterology Center, National Hospital Organization Kyushu Medical Center, 8Division of Oncology, Cancer Institute Hospital of JFCR, 9Division of Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 10Department of Surgery, Kansai Medical University, 11Department of Surgery, Minoh City Hospital, 12Department of Surgery, Kumamoto University Hospital, 13Division of Hematology and Medical Oncology, Cancer Institute Hospital of JFCR, 14Division of Oncology, Chinese Institute and Hospital Chinese Academy of Medical Sciences

**Background:** The previous phase II study of the oral S-1 plus oral Leucovorin (LV) (2 weeks on/2 weeks off) for patients with untreated metastatic colorectal cancer (mCRC) have shown to be effective, but the grade 3 toxic effects (diarrhea, stomatitis, and anorexia) were observed with relatively high frequency. In this phase II study, we modified the administration schedule of S-1 plus LV regimens for well-tolerated toxic effects and evaluated the efficacy.

**Methods:** Patients were eligible as follows: histologically confirmed adenocarcinoma, age ≥20, ECOG PS 0-1, no prior chemotherapy, at least one measurable lesion by RECIST v1.0 criteria, adequate organ function, and written informed consent. S-1 (40-60 mg b.i.d.) and LV (25 mg b.i.d.) were orally administered for 1 week, followed by 1 week rest period. Treatment was repeated until the onset of disease progression or unacceptable adverse events occurred. The primary endpoint was the response rate (RR), and the secondary endpoints were efficacy and safety. This trial was supported by Taiho Pharmaceutical Co., Ltd. ClinicalTrials.gov Identifier: NCT00891332

**Results:** From October 2008 to June 2009, 73 patients were enrolled in Japan and China. Of the eligible 71 patients, the median age was 60 (range 27-84), male/female was 38/33, PS 0/1 was 39/32, and Japan/China was 32/39. RR as primary end point was 53.9% (95% CI, 41.3-65.5), and disease control rate was 83.1%. With a median follow-up period of 26.4 months, the median progression-free survival was 6.5 months. Median overall survival was 24.3 months with the survival rate of 77.5% at 1 year and 53.2% at 2 years. The incidences of grade 3 adverse drug reactions were diarrhea 8.3%, stomatitis 8.3%, anorexia 2.8%, neutropenia 9.7%, and there was no treatment-related death.

**Conclusions:** The modified treatment schedule of S-1 plus LV (1w on/1w off) showed similar good efficacy and better tolerability compared with the previous treatment schedule (2w on/2w off). This therapy showed promising activity in patients with untreated mCRC without the concurrent use of irinotecan, oxaliplatin, or molecular-targeted drugs.

**O3 – 040**

**COMPLIANCE WITH CAPECITABINE ON XELOX TREATMENT**

K. Kawakami1, E. Nakamoto2, T. Yokokawa3, Y. Ma3, K. Sugita4, M. Suenga5, N. Mizumura6, T. Yamaguchi2, T. Haras1

1Department of Pharmacy, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 2Gastroenterology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research

**Background:** Capecitabine plus oxaliplatin (XELOX) has been established as a first-line treatment of metastatic colorectal cancer. In order to achieve the curative effect, compliance with capecitabine is important. In this study, we clarified the compliance with capecitabine on XELOX treatment, and explored the factors which may deteriorate the compliance at our institution.

**Methods:** We had a research from 60 consecutive patients who received XELOX treatment between October 2009 and May 2010 in this study. Compliance with capecitabine was checked by pharmacists with a self-reported treatment diary at a pharmaceutical outpatient clinic. We set the compliance rate as the number of times capecitabine a patient took/28 in a cycle. We retrospectively surveyed the factors deteriorating the compliance in seven cycles from electronic patient record.

**Results:** The cases of 38 male and 22 female patients were included in the study. Compliance rates were 92.6% in the first cycle of XELOX treatment, 96.8% in the second cycle and 99.9% in the seventh cycle. The factors deteriorating the compliance with capecitabine were diarrhea (41.4%, 89 cases), nausea/vomiting (19.1%, 41 cases) and fever (16.3%, 35 cases).

**Conclusions:** The major factor deteriorating the compliance with capecitabine was mainly gastrointestinal toxicity associated with XELOX treatment. We have concluded that the assessment for compliance is contributed to the management of adverse effects in XELOX treatment.

**Oral Session 33: Bone and soft-tissue tumor**

**O3 – 044**

**NUMBER OF INVOLVED ORGANS IS PREDICTIVE FACTOR OF RESPONSE TO CYVADIC CHEMOTHERAPY FOR ADVANCED SOFT TISSUE SARCOMA PATIENTS**

K. Nakano1, S. Takeda1, N. Nishimura2, Y. Ishimura3, S. Sakaji1, M. Yokoyama1, Y. Terui1, N. Motoi2, K. Hatake1

1Division of Hematology and Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 2Division of Pathology, Cancer Institute Hospital of Japanese Foundation for Cancer Research

**Introduction:** Some advanced soft tissue sarcoma (STS) patients are highly responsive to combination chemotherapy, though combination chemotherapy for advanced STS has not proved to be superior to single-agent chemotherapy except for particular subtypes such as Ewing sarcoma. We tried to identify predictive factors for response to combination chemotherapy.

**Patients and methods:** We retrospectively reviewed advanced STS patients treated with CYVADIC chemotherapy between October 2005 and June 2011 in the Cancer Institute Hospital of JFCR. CYVADIC consists of cyclophosphamide (d2, 500 mg/ m²), vincristine (d1, 1.5 mg/m²/day, max 2.0 mg/body), doxorubicin (d1, 50 mg/m²), and dacarbazine (d1-5, 250 mg/m²). Objective response and prognosis were evaluated and statistical analysis was used for exploring predictive factors related to response and survival.

**Results:** Twenty-nine patients were included in the current study and median follow-up time was 17.1 months. Morphologic features of pathological specimens were as follows: 18 spindle cell sarcomas, 6 pleomorphic sarcomas, 2 myxoid sarcomas, 1 neuroblastoma and 1 sarcoma with rhabdoid features. Median age was 51 year old. Response rate was 31 %, median PFS was 7.4 months and median OS from CYVADIC induction was 16.9 months. There were no therapy-related deaths.
but three patients needed a dose reduction due to adverse events. Median treatment cycles were 6. Eleven patients failed to continue six cycles because of progression and number of involved organs (≥3) was the significant predictive factor by multivariate analysis. On the other hand, 12 patients had objective response or PFS longer than 1 year and number of involved organs (≥2) and ALP within normal limits were the significant predictive factor.

Conclusion: Response of CVYDAC for advanced STS is moderate and number of involved organs is the predictive factor to response to CVYDAC.

O3-045 RETROSPECTIVE ANALYSIS OF IFOSFAMIDE ENCEPHALOPATHY IN PATIENTS WITH BONE AND SOFT TISSUE SARCOMAS

1Department of Orthopedics, Sendai College of Medical and Pharmaceutical Sciences, 2Department of Orthopedics, Sapporo Medical University, 3Department of Anesthesiology, Sapporo Medical University

Background: Ifosfamide, an alkylating agent, is one of the pivotal drugs used to treat bone and soft tissue sarcomas. Ifosfamide encephalopathy is a central nervous system toxicity that develops in patients treated with ifosfamide. This study was conducted to examine incidence, severity and treatments for ifosfamide encephalopathy.

Methods: The files of 22 patients treated with ifosfamide-containing regimens were studied retrospectively at our department.

Results: Ifosfamide encephalopathy developed in 3 of 22 patients (13.6%). Three cases were considered as grade 3 nervous system disorders (NCI-CTCA v4.0). Akathisia, agitation and confusion were observed. The infusion of ifosfamide was not stopped in any of these patients. Two patients were treated with biperdin, which is approved as an anti-parkinsonism drug, and recovered completely within 24 h.

Conclusions: These results suggested that biperdin would be effective for ifosfamide encephalopathy.

Oral Session 34: Regional connection

O3-052 CURRENT ISSUES ON CHEMOTHERAPY SERVICE OF HOSPITALS IN TOHOKU DISTRICT: RESULTS OF A QUESTIONNAIRE SURVEY

S. Kato1, T. Ishida3, S. Ito2, M. Gamoh7, Y. Saji7, J. Sato8, H. Shibata9, T. Yoshikawa2, C. Ishikawa1
1Department of Clinical Oncology, IDAC, Tohoku University, 2Clinical Oncology Center, Fukushima Medical University Hospital, 3Hematology & Oncology, Department of Internal Medicine, Iwate Medical University School of Medicine, 4Iwate Citizens Hospital, 5Nagata University Graduate School of Medical and Dental Sciences, Department of Medical Oncology, 6Department of Pharmacy, Iwate Medical University Hospital, 7Department of Clinical Oncology, Graduate School of Medicine, Akita University, 8Department of Clinical Oncology, Faculty of Medicine, Yamagata University

For the elimination of cancer-care disparities, it is essential to improve the standard of cancer medical care in the general hospitals, as well as regional core cancer hospitals. Supported by Health Labour Sciences Research Grant, we carried out questionnaire survey for current situation on chemotherapy service of hospitals and extracted the underlying issues. One hundred fifty-three general hospitals, including the regional core cancer hospitals in Tohoku district, were subjected for the study. The answers were recovered from 61 hospitals, including 23 regional core cancer hospitals (total recovery rate 39.8%). Registration system of chemotherapy regimen and manuals for adverse events had been developed in almost all regional core cancer hospitals and about half of general hospitals. Providing common chemotherapy regimens and manuals of specialized facilities were general demands from general hospitals. Case conferences are held regularly at more than 90% of regional core cancer hospitals and about 40% of general hospitals. Although 75% of regional core cancer hospitals participated in clinical trials, there is a lack of information of clinical trials and of clinical research coordinators who support medical staffs. To improve these issues, the Tohoku Clinical Oncology Research and Education Group (T-CORE), supported by Health Labour Sciences Research Grant, is addressing the following tasks: publication and disclosure of common chemotherapy regimens, development of the regimen review system, and case conference by a tumor board on the Web.

O3 – 066 PHASE II STUDY ALTERNATING MFOLFOX 6 AND FOLFIRI (FIREFOX) PLUS BEVACIZUMAB (BEV) REGIMEN IN FIRST-LINE TREATMENT OF ADVANCED COLORECTAL CANCER IN JAPANESE PATIENTS (KSSC 0801)

Y. Endo1, Y. Ogasawara2, A. Akai3, Y. Kakei4, E. Okii5, H. Saito6, M. Shimokawa7, T. Tomiyama8, H. Samuragochi9, K. Shirouzu10, T. Tokunaga11, Y. Maehara11
1Department of Surgery, Saiseikai Fukoka General Hospital, 2Department of Surgery, Kurume Medical Center, 3Department of Surgery and Science, Kyushu University, 4Department of Surgery, Kurume University, 5Department of Surgery, Nakagami Hospital, 6Department of Surgery, Fukuoka University, 7Department of Gastrointestinal Surgery, Kumamoto University, 8Department of Gastrointestinal Surgery, Kogashima University, 9Medical Information Center, Kyushu University Hospital

Background: The Kyushu Study group of Clinical Cancer conducted a phase II study that evaluated the FIREFOX regimen. (KSSC0701, Akagi et al., J Clin Oncol 28:15s, 2010). This study demonstrated the efficacy and mild neurotoxicity of this regimen. The present study evaluated the efficacy and safety of the FIREFOX plus bevacizumab (bev).

Methods: Eligibility criteria included histologically confirmed advanced colorectal cancer, ECOG PS 0–2 and adequate bone marrow, renal and hepatic function. Patients received an alternating regimen of four cycles of mFOLFOX 6 followed by cycles of FOLFIRI plus bev (oxaliplatin 85 mg/m2, leucovorin 200 mg/m2, 5-FU 450 mg/m2/d for 5 days and a 46-h 200 mg/m2 5-FU infusion every 2 weeks) followed by four cycles of FOLFIRI plus bev (oxaliplatin replaced with irinotecan 150 mg/m2 d1). This schedule was repeated until unacceptable toxicity or disease progression occurred. The primary end point is progression-free survival. (UMIN000003132)

Results: Of the 52 patients enrolled from May 2008 to July 2009. Two of the patients did not fulfill the eligibility criteria. M/F, 30/20; median age, 59.5 years (range 37–79); ECOG PS 0/1/2, 46/4/0. The median number of administration cycles was 14 (range, 2–44). Response rate (RECIST criteria) for CR, PR, SD, PD and NE were 2 (4%), 8 (16%), 14 (28%), 4 (8%) and 2 (4%), respectively. An overall median progression-free survival was 14.2 months (95% CI: 10.6 M–16.3 M) and median overall survival was 27.5 M (95% CI: 22.4 M–not determined). The 2-year survival rate was 56.8%. Of the 52 patients evaluated for toxicity. The most common grade 3–4 adverse events were leukopenia (7.7%), neutropenia (32.7%), anemia (1.9%), fatigue (9.6%), anorexia (13.5%), stomatitis (3.8%), neurotoxicity (3.8%), hypotension (1.9%), diastolic hypertension (7.7%), febrile neutropenia (3.8%), nausea (9.6%), vomiting (5.8%), hypersensitivity (3.8%), and thrombocytopenia (1.9%).

Conclusions: The results of this phase II study show that the FIREFOX plus bev regimen is effective and well tolerated in the first-line treatment of advanced colorectal cancer. The low rate of neurotoxicity is also promising.

O3-067 A PHASE III STUDY OF BI-WEEKLY XELIRI PLUS BEVACIZUMAB FOR PATIENT WITH METASTATIC COLORECTAL CANCER AS SECOND- LINE CHEMOTHERAPY (BIXER STUDY): REPORTS OF INTERIM ANALYSIS OF PHASE II PART

M. Suenaga1, S. Matsuoka1, E. Shinohara1, M. Ozaka2, M. Ogura3, K. Chin4, K. Hatake5, N. Misumiwa6, T. Yamaguchi7
1Department of Gastroenterology, Gastroenterology Center, Cancer Institute Hospital, 2Division of Gastroenterological Surgery, Gastroenterology Center, Cancer Institute Hospital, 3Department of Medical Oncology, Cancer Institute Hospital

Background: Capcitabine is an oral fluoropyrimidine prodrug, which is converted to fluorouracil (5-FU) predominantly in the tumor cells. We conducted a phase I/II study to assess the safety and efficacy of capcitabine plus Irinotecan (CPT) (XELIRI) plus BV in Japanese patients with metastatic colorectal cancer (mCRC). The results of phase I part were reported at the previous meeting, and then planned interim analysis of phase II part was carried out.

Methods: Patients with prior chemotherapy including oxaliplatin and BV for mCRC, wild or hetero type of UGT1A1*28 were eligible for this study. This was a phase I study designed of two steps, and dose-limiting toxicity (DLT) was assessed during the first treatment cycle. Treatment comprised capcitabine 1000 mg/m2 twice daily from the evening of day 1 to the morning of day 8, intravenous CPT 180 mg/m2 on day 1, and BV 5mg/kg on day 1 every 2 weeks. To evaluate the initial safety, 3–6 patients received XELIRI + BV (CPT 150 mg/m2) in step 1, and 6 patients received XELIRI + BV (CPT 180 mg/m2) in step 2. If DLT occurred in one patient in step 1, three patients would be newly added to step 1, and if in none of 3 or 1–2 of six patients, the step 2 would be started. If DLT occurred in less than or equal to two of
Background: The results from a randomized phase II trial in the first-line treatment of mCRC indicated that SOL regimen (S-1, oral leucovorin; LV, and oxaliplatin) had promising activity with well-tolerated toxic effects compared with mFOLFOX6 (Ojima et al., ESMO 2011). The median progression-free survival (PFS) for SOL and mFOLFOX6 was 9.6 and 6.9 months, respectively (HR = 0.83). We evaluated the efficacy and safety of adding BV to SOL regimen in this study.

Methods: The inclusion criteria were: (i) histologically proven adenocarcinoma of colon or rectum, (ii) age ≥ 20 years, (iii) no prior treatment for metastatic disease, (iv) at least one target lesion by RECIST ver1.0 criteria, (v) ECOG Performance Status 0-1. Patients received S-1 (40–60 mg bid) and LV (25 mg bid) orally for 1 week and L-OHP (85 mg/m²), and BV (5 mg/kg) on day 1, every 2 weeks. The primary end point was the response rate (RR). This trial was supported by Taiho Pharmaceutical Co., Ltd. (JAPIC Clinical Trials information identifier: JapicCTI-090881).

Results: From October 2009 to April 2010, 31 patients were enrolled, and 29 patients were regarded as the population of full analysis set. Present data included the results of efficacy and safety up to 24 cycles or for at least a year. RR assessed by the independent review committee (IRC) was 86.2% (CR: 0 patients, PR: 25 patients), and disease control rate (DCR) was 100%. The median PFS assessed by IRC was 15.3 months, while further follow up is ongoing. One-year survival rate was 100%. The incidence of grade 3/4 adverse drug reactions were: neutropenia 16.7%, diarrhea 10.0%, hypertension 16.7%, and sensory neuropathy 53.3%. The median cumulative oxaliplatin dose was 915.0 mg/m² (range 330–1735 mg/m²). The high prevalence of grade 3 neuropathy seemed due to the prolonged treatment duration. Reasons for discontinuation of therapy were: tumor progression in 10 patients, and metastasectomy by tumor regression in 6 patients. The resection rate was 17.2%.

Conclusions: SOL + BV showed promising activity with high RR, DCR, PFS and resection rate with well-tolerated toxic effects in patients with unresectable mCRC.

Background: Bevacizumab (BV) is an active drug of anti-angiogenesis for colorectal cancer (CRC). NCCN and Japanese Guideline both recommend to use BV at 1st-line chemotherapy for CRC. Some reports suggested survival benefit of using BV beyond progression (BBP). We analyzed CRC patients with BBP retrospectively.

Results: From April 2007, 256 patients were received chemotherapy at our institute, 136 patients were treated with BV at 1st line, and BBP were 29 patients. RR assessed by IRC was 86.2% (CR: 0 patients, PR: 25 patients), and disease control rate (DCR) was 100%. The median PFS assessed by IRC was 15.3 months, while further follow up is ongoing. One-year survival rate was 100%. The incidence of grade 3/4 adverse drug reactions were: neutropenia 16.7%, diarrhea 10.0%, hypertension 16.7%, and sensory neuropathy 53.3%. The median cumulative oxaliplatin dose was 915.0 mg/m² (range 330–1735 mg/m²). The high prevalence of grade 3 neuropathy seemed due to the prolonged treatment duration. Reasons for discontinuation of therapy were: tumor progression in 10 patients, and metastasectomy by tumor regression in 6 patients. The resection rate was 17.2%.

Conclusions: SOL + BV showed promising activity with high RR, DCR, PFS and resection rate with well-tolerated toxic effects in patients with unresectable mCRC.