Session G: Melanoma – Sarcoma – Central Nervous System Tumors

G1
LOW DOSE INTERFERON-ALPHA + TAMOXIFEN IN THE TREATMENT OF RECURRENT MELANOMA PATIENTS.


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Background: In spite of contrasting opinion in international literature, interferon (IFN) represents the most effective agent in adjuvant therapy of cutaneous melanoma (CM) patients. However, little is known about treatment of patients who recur during adjuvant treatment. Our previous study about utilizing IFN increased dose after recurrences during or after adjuvant therapy with low dose IFN (LD-IFN) showed negative results (ECOC 10. Eur J Cancer 1999; 35: 3373-7) since 71% of treated pts died during therapy. The aim of the present study was to verify if low doses tamoxifen (TAM) are able to restore melanoma sensitivity to IFN.

Patients and Methods: From January 1999 to March 2000 21 consecutive CM patients (12 males and 9 females; median age 59 yrs, range 31-75 yrs) with local, transient or lymph node recurrences during adjuvant therapy with LD-IFN (IFN-α2b-10 MU s.c. TW SC), or LD-IFN (IFN-α2b-10 MU s.c. TW SC), or vaccine therapy (BCG+VAX or VAX+placebo, Morton et al Oncology 1993; 15: 1561-76), who had no evidence of disease (NED) after surgical treatment of metastases, were enrolled for a second line therapy with IFN-α2b 3 MU TW SC + TAM 20 mg p o daily; treatment was planned for 1 year.

Results: At present, 2 pts have completed 1 year of therapy (median 9 months, range 2-12 mos); however, only 1 pt has relapse after 2 months of therapy. Treatment is well-tolerated, and has never been suspended or reduced for toxicity. Main toxicity was flu-like syndrome related to IFN administration, and flushing and dizziness related to TAM.

Discussion: On the basis of our previous experience where, in previously treated with LD-IFN, IFN increased dose showed poor efficacy, these preliminary results show that, in spite of the short follow up and the small sample size, TAM potentiate IFN activity. In fact, in our previous study, relapse occurred mainly within early months of treatment.

G2
Merkel’s cell carcinoma: two case reports.

N.Bercoo*, L.Cuffi, G.Pavello, M.Lurato, C Nigro, A. Novarino, and G Berenzo
Divisione Oncologia Medica - Ospedale S. Giovanni Battista- Messina-Torino

Since 1998, year of the beginning of our survey in Messina Hospital, we have followed two cases of Merkel’s cell carcinomas of the thug. It is a very uncommon cancer, located in the basal layer of the epidermis and in the hair follicles, occurring mainly in elderly persons with an equal incidence in men and women. It usually grows rapidly and gives distant metastasis and regional lymph-nodes involvement, and often local recurrences occur. Because of these characteristics, the prognosis is often poor even after treatment.

Patient’s characteristics:

- a 65 years old woman, who in May 1994 underwent a surgical excision of a cutaneous lesion of the right thigh followed by adjuvant radiotherapy and five cycles of chemotherapy with a schedule containing Cyclophosphamide, Doxorubicin and Etoposide, reporting no toxicity Follow-up visits, biochemical and instrumental investigations (Chromogranin A, Neuron-Specific Enolase, Chromogranins) have never evidenced recurrences;
- a 65 years old man, who in June 1999 underwent an oncologic surgical excision of a cutaneous lesion of the right thigh, and he underwent another operation to obtain a radical resection of the neoplasm. After 2 months a local recurrence occurred, requiring a further resection including regional lymph-nodes (pT1N1G3). We began to follow the patient after the last surgical act, and he presented with a progressive disease in the chest, documented by computed tomography. Considering the age of the patient, we decided to begin with an Octreolide analogues therapy, after 2 months, because of the ineffectiveness of this kind of treatment, and of the rapid growth of the cutaneous lesions, he underwent radiotherapy obtaining a partial response. The good performance status induced us to start with a chemotherapy treatment with Etoposide 50 mg/die per os. We obtained a local control of the disease with Grade 2 neutropenia (WHO scale) for one week.

As reported in literature, chemotherapy is considered effective to avoid recurrence after complete surgical excision, and to control the evolution in advanced stages.

G3
ASKIN’S TUMOR: A RARE NEOECTODERMAL NEOPLASM OF THE CHEST WALL: RESULTS OF A COMBINED TREATMENT WITH CHEMOTHERAPY (CT), SURGERY ± RADIOTherapy (RT).


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2Servizio di Oncologia, Ospedale di Croc (Torino), Italy.

Askin’s tumor is a rare malignant soft-cell tumor of the thoracic region. The histogenesis of this neoplasm is unknown: however a neuroectodermal origin has been proposed as well for all the other Ewing’s sarcoma family tumors. Immunohistogenetic and genetic analysis are often necessary for differential diagnosis between Askin’s tumor and other Ewings sarcoma family tumors. Immunophenotypic and genetic analysis are often necessary for differential diagnosis between Askin’s tumor and other Ewings sarcoma family tumors. Immunophenotypic and genetic analysis are often necessary for differential diagnosis between Askin’s tumor and other Ewings sarcoma family tumors. Immunophenotypic and genetic analysis are often necessary for differential diagnosis between Askin’s tumor and other Ewings sarcoma family tumors.

13/23 (56%), 8/23 (34%), with a significant correlation in 11/23 pts treated with CT. Surgery ± RT and surgery ± CT have shown different results (18/23 (78%) vs. 12/23 (52%) 5 year survival, respectively) at a median follow up of 5.5 years. In our previous study, relapse occurred mainly within early months of treatment.

Discussion: On the basis of our previous experience where, in previously treated with LD-IFN, IFN increased dose showed poor efficacy, these preliminary results show that, in spite of the short follow up and the small sample size, TAM potentiate IFN activity. In fact, in our previous study, relapse occurred mainly within early months of treatment.

G4
GP170, bcl2, MIB1 AND Topo II expression in abdominal leiomysarcoma (AMS), leiomyosarcoma (LMS) and in ROUND CELLS SARCOMA (RCS). CORRELATION WITH BIOLOGICAL CHARACTERISTICS, GRADING AND RESPONSE TO CHEMOTHERAPY (CT).


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•Division of Pathology, Ospedale San Giovanni Antica Sede, Torino, Italy.
•Division of Surgery, Ospedale San Giovanni Antica Sede, Torino, Italy.

Patients and Methods: From January 1999 to March 2000 21 consecutive CM patients (12 men, 9 women, median age 42 years (range 22-73) with a PS 0-2 entered the study. Patients were selected on the basis of molecular biology examination: high expression of biological determinants (GP170, bcl2, MIB1 and Topo II) was considered a specific genetic marker.

We compared the expression of biological determinants in these two extremely different STS (23 AMS, 11 LMS) in order to determine the different biological behavior of these two neoplasms. Immunohistogenetic and genetic analysis are often necessary for differential diagnosis between Askin’s tumor and other Ewings sarcoma family tumors. Immunophenotypic and genetic analysis are often necessary for differential diagnosis between Askin’s tumor and other Ewings sarcoma family tumors. Immunophenotypic and genetic analysis are often necessary for differential diagnosis between Askin’s tumor and other Ewings sarcoma family tumors. Immunophenotypic and genetic analysis are often necessary for differential diagnosis between Askin’s tumor and other Ewings sarcoma family tumors.

Results: At present, 2 pts have completed 1 year of therapy (median 9 months, range 2-12 mos); however, only 1 pt has relapse after 2 months of therapy. Treatment is well-tolerated, and has never been suspended or reduced for toxicity. Main toxicity was flu-like syndrome related to IFN administration, and flushing and dizziness related to TAM.

Discussion: On the basis of our previous experience where, in previously treated with LD-IFN, IFN increased dose showed poor efficacy, these preliminary results show that, in spite of the short follow up and the small sample size, TAM potentiate IFN activity. In fact, in our previous study, relapse occurred mainly within early months of treatment.

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G5 SECOND LINE TREATMENT OF METASTATIC OR LOCALLY ADVANCED SOFT TISSUE SARCOMAS (STS) WITH CARBOPLATIN (CBDCA) AND DACARBAZINE (DTIC).  O. Dal Canton, A. Bogione, P. Bergnolo, M.P. Britzi, S. Chiadò Cuitin, C. Oliva, P. Pochettino, A. Corinna  Dept. Medical Oncology, Gradengo Hospital, Milano, Italy  A new combination of Carbo-platin (CBDCA) and dacarbazine (DTIC) was administered in 21 pts with 20 evaluable for response. This regimen was chosen because of the compromised clinical condition of the patients. The treatment was generally well tolerated.  We report the experience of a Phase II trial with 21 evaluable pts (8 male, 13 female, median age 45, range 12-79).  Pts were pretreated with cephalosporins, amphotericin B, and mitomycin C.  The initial cycle consisted of: carboplatin 120mg/m², PTX 100mg/m², and DTIC 375mg/m². Patients received a total of 3 cycles with maximum 4 monthly cycles with carboplatin 120mg/m², PTX 100mg/m², and DTIC 250mg/m².  The overall response rate was 28% (6 PR + 15 SD).  In the evaluable pts 15% had a PR and 85% SD. Three pts died for disease progression.  No severe side effects were observed. With a median follow-up of 20 months (range 6-64), the only grade 1 WHO leukopenia was registered and the dose reduced for a few days. Serial MR images obtained every 3 months, revealed stable disease, with a delay of 3 months of the progression-free survival compared to the untreated patients.  Considering the poor results of second line CT in relapsing or metastatic STS, these results must be considered as worthing, further investigation.

G6 HYDROXYUREA FOR TREATMENT OF UNRESECTABLE AND RECURRENT MENINGIOMA: CASE REPORT.  G. Farina, C. Mantica, B. Galassi, R. Rovere and A. Scanni  Department of Medical Oncology – Fatebenefratelli & Ospedale Rionale, Milan – Italy  Limited data are available concerning the outcome of patients with asymptatic and malignant meningiomas. Although the primary treatment is surgical, complete resection is often impossible because of the extent of tumor invasion. Recently Schell has presented first evidence that meningiomas respond to treatment with hydroxyurea, a long-term chemotherapeutic treatment taking into account that meningiomas are slowly growing tumors. Hydroxyurea was used because experimental data demonstrated that it inhibits growth of cultured human meningiomas cells and meningioma transplants in nude mice by inducing apoptosis. We report a case of bilateral optic nerve meningioma responding to hydroxyurea. The patient, a young man 23 year old, in July 1998 had significant rapidly evolving vision loss in the left eye. A biopsy of the left optic nerve was performed with diagnosis of meningioma. Post-operatively the patient has developed a complete irreversible loss of vision in the operated eye. In December 1998 the patient began a treatment with hydroxyurea at a dosage level of 1000 mg/day (approximately 15 mg/Kg/day). The treatment was well tolerated, only grade 1 WHO leukenopsia was registered and the dose reduced for a few days. Serial MR images obtained every 3 months, revealed stable disease, with a complete remission of the right eye visual disorder. Our data confirm that hydroxyurea provides true medical treatment in patients with unresectable meningiomas, replacing palliative surgery and radiotherapy in the management of this disease.

G7 POST-LIVER-TRANSPLANT CHEMOTHERAPY IN ORBIT RHADOMYOSARCOMA: CASE REPORT.  B. Galassi, C. Mantica, G. Foresta, S. Cobelli and A. Scanni  Department of Medical Oncology – Fatebenefratelli & Ospedale Rionale, Milano – Italy  Embryonal rhabdomyosarcoma is a small cell tumor that usually arises in the orbit or genitourinary tract in children. Embryonal rhabdomyosarcoma occasionally arises in adults, age is an important prognostic factor for survival, with worse outcome in older patients. The mainstay of treatment for all soft tissue sarcomas is surgical excision. Radiation therapy is generally used as a surgical adjuvant, for unresectable tumors or medically inoperable patients, radiation may be used alone. A variety of combination chemotherapy regimens have been studied in phase II trials. Most combinations include doxorubicin (or its analogue, epirubicin) and an alkylating agent. We report a case of a young woman who developed orbit rhabdomyosarcoma after liver transplantation Patient characteristics: 23 years old, female. 2-1-1997: Pulmonary viral hepatitis type B with a first liver transplantation (different ABO group). 3-2-1997: Fulminating viral hepatitis type B with a second liver transplantation (same ABO group). 6-1-1997: Second liver transplantation (same ABO group). 6-1-1997: Second liver transplantation (same ABO group). 2-1-1997: Second liver transplantation (same ABO group). 3-2-1997: Third liver transplantation (different ABO group). 6-1-1999: Development of orbit rhabdomyosarcoma after liver transplantation. Inoperable patients, radiation may be used alone. A variety of combination chemotherapy regimens are generally used as a surgical adjuvant, for unresectable tumors or medically inoperable patients. Radiation therapy is generally used as a surgical adjuvant, for unresectable tumors or medically inoperable patients. Radiation may be used alone. A variety of combination chemotherapy regimens are generally used as a surgical adjuvant, for unresectable tumors or medically inoperable patients. 17-1-1999: A biopsy of the left optic nerve was performed with diagnosis of meningioma. Post-operatively the patient has developed a complete irreversible loss of vision in the operated eye. In December 1998 the patient began a treatment with hydroxyurea at a dosage level of 1000 mg/day (approximately 15 mg/Kg/day). The treatment was well tolerated, only grade 1 WHO leukenopsia was registered and the dose reduced for a few days. Serial MR images obtained every 3 months, revealed stable disease, with a complete remission of the right eye visual disorder. Our data confirm that hydroxyurea provides true medical treatment in patients with unresectable meningiomas, replacing palliative surgery and radiotherapy in the management of this disease.

G8 CARCINOID TUMORS: REVIEW OF A SINGLE INSTITUTION EXPERIENCE  Gemmiini Maria Luisa, Panetta Achilles  Servizio di Oncologia Medica, Ospedale di Benevento, Azienda USL, Bologna Nord  BACKGROUND: Carcinoids, first described in 1888 by Lubarsch, are indolent tumors of neuroendocrine cell origin with the capacity for amine precursor uptake and decarboxylation. More than 80% of carcinoids occur in the gastrointestinal tract with 10% found in the lung and the remainder in various organs such as the larynx, kidney, ovary, skin, prostate and thymus. Carcinoid tumors are extremely heterogeneous, both with respect to histologic and endocrinologic features and to clinical presentation and behavior, including metastatic potential. METHODS: During a 5-year-period, we observed 10 cases of carcinoid tumor at our Institution: 7 females and 3 males. Median age was 60 years (range 14-73). Primary sites were: jejunum 5, appendix 3, pancreas 1, lung 1. At diagnosis, 4 pts had metastatic disease (liver 1, liver + skin 1, liver + bone 1, liver + peritoneum + ovary 1). Radical surgery was performed in 6 pts, palliative surgery in 2 pts. One pt received medical treatment alone (octreotide 0.1 mg x 3 and interferon-ω-chemotherapy). Three pts with metastatic carcinoid tumor (one pt not pretreated with surgery) were treated by intramuscular application of octreotide LAR once monthly. The dose of octreotide LAR was 20 mg. RESULTS: No locoregional recurrences and distant metastases occurred in pts with radical surgery. Stable disease was observed with respect to biochemical parameters, neuroendocrine markers and size of metastases in pts treated with octreotide LAR, no neuroendocrine symptoms were present and octreotide LAR was tolerated without any severe side effects. With a median follow-up of 20 months (range 6-64), 1 pt died for disease progression. CONCLUSIONS: Our data confirm that carcinoid tumors are frequently diagnosed in advanced phase. Surgical resection is the best curative modality. Preliminary data suggest that intramuscular application of octreotide LAR once monthly is a useful therapeutic option and improves quality of life in pts with metastatic carcinoid tumors.
G9  TREATMENT OF HIGH-GRADe ADULT BRAIN TUMORS WITH COMBINED HIGH DOSE SEQUENTIAL CHEMOTHERAPY, BLOOD CELL TRANSPANTATION AND RADIOTHERAPY: REPORT OF 14 CASES.


Divisioni di Oncologia Medica*, Neurologia** e Radioterapia*** Ospedale Niguarda Ca' Granda, Milano; Divisioni di Oncologia Medica e Servizio di Radioterapia**, IRCCS Fond. S Magheri, Pavia; Divisione di Neuroradiologia*** IRCCS Poliambulatorio S. Matteo, Pavia.

The prognosis of high grade brain tumors remains dismal despite combined treatment with surgery and radiation therapy (RT). The additional standard dose chemotherapy (CT) prolongs survival of anaplastic oligodendrogliaoma (AG) but not of other histologies. Based on the favorable experience in pediatric patients, we have designed a pilot study for evaluating feasibility and efficacy of sequential administration of the highest tolerable dose (HDS) of agents effective against high grade brain tumors in adults. Fourteen patients (median age 38 yrs, r: 29-60; 7 glioblastoma -GB-, 2 anaplastic astrocoma -AA-, 1 AO, 1 pineoblastoma -P-) were treated with cyclophosphamide 14 g/mq with LV rescue on week 1; vincristine 1.4 mg/mq and methotrexate 6 g/mq with LV rescue on week 4; and Thalidomide 900 mg/mq with GF support and cyclophosphamide-GF-modulated autologous blood cell transplantation (median CMV+ cells 14 x 10^6/kg on day 6). Before, HDs, 12/14 patients received primary surgery with minimal (n=7) or gross (n=6) residual disease; 2 patients had inoperable relapse of AO, and were treated after FST. After HDs, patients not previously treated with RT, received 60-70 Gy, received 60-70 Gy of RT starting from week 10. HDS was completed in all patients. No toxic death occurred. Laminogenic toxicity was transitory and consisted of grade III-IV polyneuropathy requiring prophylactic RBC and PLT transfusions, grade I-II (n=6) and grade III-IV (n=2) cerebrospinal, and 1 Gram negative sepsis. As of May 2000, 11/14 patients are alive at a median follow-up of 12 months (range 4-24) after surgery, with non-evidence of disease (NED) in 4 (2 GB, 2 AA), stable disease (SD) in 2 (AO), 1 progression after minimal response (P) and 2 progressive diseases (15, 1AA). Three patients died at 4, 11 and 14 months after surgery due to progression of their diseases. In conclusion, the HDS approach is feasible without relevant risks in patients with high grade brain tumors. These clinical results warrant further attention with a larger follow-up and analysis of quality of life in comparison with continuous conventional dose CT.

G10  MEDULLOUS CARCINOMA OF THE THYROID (MTC): three case reports.

P. Lupi, L. Cossutta, N. Brocco, G. Ristori, E. Bernoldi, M. Schena, D. Dongiovanni, O. Bentoro.

Divisione Oncologia Medica – Ospedale S. Giovanni Battista - Molinette - Torino University of Biomedical Sciences - Ospedale S. Giovanni Battista - Torino.

Since September 1998, year of the beginning of our activity, we have followed three patients affected by MTC in advanced stage Characteristics: - a 37 years old man carrier of Multiple Endocrine Neoplasia type IIb, who previously underwent a subtotal thyroidectomy because of a of a phaeochromocytoma, and a total thyroidectomy. When we began to follow him, he had metastases (nm) both in the spinal chod and in the regional lymph-nodes and elevated Calcitonin (C) value. He referred a diarrhoeal syndrome even if in therapy with Omeprazole analogues with a C value of 4330 ng/ml and important and diffused bone pain. Considering the spread of the disease he began a concomitant radio-chemotherapy treatment with 5-Fluoro Uracile (5-FU) 200 mg/mq in continuos infusion (c.i.) after 9 months of chemotherapy alone, we registered a progression (PD) of the bone axis with a C value reducing (31640 ng/ml), so that we decided to stop the infusion of 5-FU and to introduce Pazclitaxel (PT) in the chemotherapy from 5-FU 100 mg/mq c.i. stopped after two months because of the metastatic syndrome that required a radioterapeutic treatment and a second line CT with Pazclitaxel 70mg/mq weekly, for four months; he died because of pancreatic G2 (WHO Stage), abdominal, persistent diarrhoea G3 and stroming G1 with no response. He is nowadays under a close follow-up registering clinical state and Calcitonin level.

- a 67 years old man with metastatic, transcomeral lymph nodes, bone and lung metastasis with a C of 8957 ng/ml. He referred diarrhoea G2 and impetiginosis G1 with no response. He is nowadays under a close follow-up.

- a 55 years old man that supposed to have a non- small cell lung cancer with neuroendocrine differentiation (NSCLC-NE), with metastatic and laterocervical lymph- nodes metastasis; he underwent a chemotherapeutic treatment with Carboplatin AUC 5 according to Calvert day 1 and Etoposide 100mg/mq day 1-3 every 31 days. After six cycles a metastatic syndrome appeared, treated with radiotherapy. A review of the histology revealed the new diagnosis of MTC with a C level of 46 ng/ml and with no systemic symptoms, so he has been stated to the surgeon that excluded radical excision of the multiple nodes involved by the neoplasm and even a debulking. So he began a second line CT with 5-FU 250 mg/mq c.i. that has now obtained a minimal response with no toxicity.

Our experience, even if the number of cases is low, confirmed that chemotherapy (5-FU and Pazclitaxel) and radiotherapy can modify the natural history of the disease if MTC is discovered when already metastatic and with no possibility of a surgical cure.

G12  FERTILITY IN FEMALE PATIENTS TREATED WITH NEOADJUVANT AND ADJUVANT CHEMOTHERAPY FOR OSTEOSARCOMA AND Ewing's SARCOMA.

A. Longhi, B. Porca, S. Peracchi, A. Antenucci, G. Bacci.

Sezione di Chimioterapia dell'Istituto Ortopedico Rizzoli e Unità di Chirurgia Ginecologica deil'Umversita di Bologna.

We assessed the fertility and the ovarian function in 115 alive female patients treated at Istttuto Rizzoli from 1974 to 1999 with neo- and adjuvant chemotherapy for osteosarcoma and Ewing's sarcoma. After obtaining a written consent (previously mailed) a phone interview, with the consult of a gynecologist, was performed with question about patient's ovarian function before, during, and after chemotherapy, and eventual pregnancies. These patients had been treated with vincristine, doxorubicin, dactinomycin, cyclophosphamide, ifosfamide, methotrexate, and cisplatin, in different combinations according to different protocols successively activated. At the time of the interview (Dec. 1999) the mean follow-up of these patients was 6.5 years (range 2-42). The mean age at diagnosis was 16.6 years (range 1-43), the mean age at the moment of the interview was 25 years (range 13-50), 29 patients were pre-puberty at the time of chemotherapy. All of them had menstruated at the mean age of 11 years, we did differently from the mean age of the post-puberty patients, taken as a control-group. Fifty-one of the 86 patients who received chemotherapy post-puberty experienced transient amenorrhea during treatment, with no significant statistical difference between the ones who received alkylant drugs and those who did not (61% vs. 56%). Only 3 patients (18, 39, 43 years respectively) had permanent amenorrhea. At the time of interview, 62/115 patients did not want a pregnancy, 13/115 were looking for a pregnancy with no success, 33/115 avoided contraception, and 18/115 were pregnant: 12/115 after chemotherapy, and 6/115 during treatment, with no significant statistical difference between the ones who received alkylant drugs and those who did not (61% vs. 56%). Only 3 patients (18, 39, 43 years respectively) had permanent amenorrhea.

G13  TREATMENT OF NEUROENDOCRINE TUMORS (NETS) MIDGUT CARCINOID WITH INTERFERON-ALPHA (IFN) AND SOMATOSTATIN ANTAGONIST (SST): A REPORT OF TWO CASES.

Giuseppe Marinuzza, Giampiero Romano, Vincenzo Bellia, Mauro Minelli and Mauro Antoniti.


NETs constitute about 2% of all malignant gastrointestinal neoplasm. In the last ten years these diseases have gained increased attention, through the development of new diagnostic and therapeutic methods. From September 1996 to April 2000, 30 patients with NET have been observed in our department. In this paper we report the clinical and pathological features of two patients with NETs-midgut carcinoida and liver inoperable metastases. Both presented intestinal symptoms (diarrea) and osteoclast scintigraphy (Ocout). When the disease was discovered with a C value of 64 mg/ml he was sent to the surgeon that excluded radical excision of the multiple nodes involved by the neoplasm and even a debulking. So he began a second line CT with 5-FU 250 mg/mq c.i. that has now obtained a minimal response with no toxicity.

Our experience, even if the number of cases is low, confirmed that chemotherapy (5-FU and Pazclitaxel) and radiotherapy can modify the natural history of the disease if NETs is discovered when already metastatic and with no possibility of a surgical cure.

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G14  Antismural activity of Thalidomide in patients affected by refractory breast cancer and recurrent high grade gliomas.

Gianpiero Casparini, Sara Gilberti, Stefano Vitali, Marie Grazia Arena, Massimo Faccini, Girolamo Ranieri, Domenico Guttuso, Eduardo Biondi and Alessandro Morabito.

Division of Medical Oncology, Azienda Ospedaliera “Bianchi-Melacini-Morelli”, Reggio Calabria, Italy.

Thalidomide (Th) inhibits angiogenesis and induces apoptosis of established neovascularature in experimental models. The drug has excellent bioavailability and moderate side effects, resulting in a promising antiangiogenic agent. We administered Th for compassionate use to patients with advanced breast cancer or recurrent high-grade gliomas. For eligibility the patients with breast cancer had received at least two lines of chemotherapy for advanced disease and they had progressive disease. All the patients with high-grade gliomas were pretreated with surgery, radiotherapy and, in some cases, also with chemotherapy. Th was supplied in 100 mg capsules by Grunenthal A.G. and it was administered orally at the daily dose of 400 mg for two months followed by evaluation; patients who achieved an objective response or stable disease continued treatment until progression or toxicity. To date 22 patients have been accrued, 10 with high grade gliomas (8 males and 2 females) and 12 with refractory breast cancer, and all patients are valuable for toxicity and response. Median age was 53.5 years (range 38-77), PS ECOG was 2 in 12 patients, 1 in 8 patient and 0 in 2 patients. Th was well tolerated, with grade I and II sedation in 9 and 2 patients, respectively, grade II and III constipation in 9 and 1 patients, respectively. Two patients developed grade I peripheral neuropathy. No significant laboratory abnormalities were observed. No response or stable disease was achieved in patients with metastatic breast cancer. One minimal response and 3 stable disease (lasting 7 months in one case) were observed in the patients with high-grade gliomas. The results of this preliminary study suggest that, using this schedule, Th is well tolerated. Th appears to have some antismural activity in patients with recurrent high grade gliomas in progression after conventional treatments.

G15  GENETIC ALTERATIONS AT CHROMOSOME 9P21 IN PRIMARY TUMORS AND METASTASES OF MALIGNANT MELANOMA: DEFINITION OF THEIR CLINICAL SIGNIFICANCE.


The melanocytic skin lesions present in the skin represent the primary tumor and metastatic sites of melanocytic skin cancers in the majority of cases.

We administered Th for compassionate use to patients with advanced breast cancer or recurrent high-grade gliomas. Th was supplied in 100 mg capsules by Grunenthal A.G. and it was administered orally at the daily dose of 400 mg for two months followed by evaluation; patients who achieved an objective response or stable disease continued treatment until progression or toxicity. To date 22 patients have been accrued, 10 with high grade gliomas (8 males and 2 females) and 12 with refractory breast cancer, and all patients are valuable for toxicity and response. Median age was 53.5 years (range 38-77), PS ECOG was 2 in 12 patients, 1 in 8 patient and 0 in 2 patients. Th was well tolerated, with grade I and II sedation in 9 and 2 patients, respectively, grade II and III constipation in 9 and 1 patients, respectively. Two patients developed grade I peripheral neuropathy. No significant laboratory abnormalities were observed. No response or stable disease was achieved in patients with metastatic breast cancer. One minimal response and 3 stable disease (lasting 7 months in one case) were observed in the patients with high-grade gliomas. The results of this preliminary study suggest that, using this schedule, Th is well tolerated. Th appears to have some antismural activity in patients with recurrent high grade gliomas in progression after conventional treatments.

G16  EPIRUBICIN ALONE OR EPIRUBICIN + IFOSFAMIDE AS ADJUVANT CHEMOTHERAPY IN SOFT TISSUE SARCOMAS.


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From January 1985 and September 1995, 88 consecutive patients with primary stage 2-3 soft tissue sarcomas (STS) were entered in this study. Before surgery, each case was photographed with a Dermaphot (HEINE, Hirsching, Germany). Dermoscopic images were examined separately by two observers (M.P. and H.P.) according to an ABCD pattern analysis and standard dermoscopic criteria, and to achieve the dermoscopic diagnosis by pattern analysis and by the ABCD rule based on TDS, with excellent agreement, and the lowest was seen in the detection of pseudopods (K=0.49, fair to good agreement). The inter-observer agreement was determined by the K index: K index:<0.40, poor agreement; K index 0.40-0.69, fair to good agreement; K index 0.70-0.90, good agreement; K index >0.90, excellent agreement. The lowest was seen in the detection of pseudopods (K=0.49, fair to good agreement).

When a cut-off score of 5.45 vs > 5.45 was used, sensitivity of dermoscopic diagnosis by TDS ranged from 80% to 100% and specificity from 49% to 59%. Using a TDS of < 4.75 vs > 4.75 as a cut-off score, sensitivity ranged from 80% to 100% and specificity from 50% to 56%. The sensitivity and specificity of dermoscopic diagnosis by pattern analysis were 40 and 99%, respectively, for the two observers together. These results indicate dermoscopic diagnosis by TDS has high sensitivity and low specificity, while dermoscopic diagnosis by pattern analysis has low sensitivity and high specificity.

The area under the Receiver Operating Characteristic (ROC) curve of observer 1 (A.M.P.) was 0.81, demonstrating that in 81% of cases the melanoma was correctly identified. The area under the ROC curve of observer 1 (A.M.P.) demonstrated sensitivity and specificity of 60% and 75%, respectively. An interesting result of this study was that TDS was independent of the size of the lesion, we found lesions 2 mm in diameter to show a negative TDS.

The question remains whether small lesions that are histologically negative, with a TDS 2.45, are true negatives or constitute a limit of Stolz Index.

G17  DERMOSCOPIC DIAGNOSIS OF SMALL MELANOCYTIC SKIN LESIONS: AN INTER-OBSERVER AGREEMENT STUDY BY CLASSICAL PATTERN AND ABCD-RULE ANALYSES.


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A total of 129 small (≤5 mm) melanocytic skin lesions detected in 123 patients seen at the Centro di Riferimento Oncologico, Aviano, were evaluated in this study. Before surgery, each lesion was photographed with a Dermaphot (HEINE, Hirsching, Germany). Dermoscopic images were examined separately by two observers (M.P. and H.P.) according to a classical pattern analysis and standard dermoscopic criteria, and to achieve the dermoscopic diagnosis by pattern analysis and by the ABCD rule based on TDS, with excellent agreement, and the lowest was seen in the detection of pseudopods (K=0.49, fair to good agreement). The inter-observer agreement was determined by the K index: K index:<0.40, poor agreement; K index 0.40-0.69, fair to good agreement; K index 0.70-0.90, good agreement; K index >0.90, excellent agreement. The lowest was seen in the detection of pseudopods (K=0.49, fair to good agreement).

When a cut-off score of 5.45 vs > 5.45 was used, sensitivity of dermoscopic diagnosis by TDS ranged from 80% to 100% and specificity from 49% to 59%. Using a TDS of < 4.75 vs > 4.75 as a cut-off score, sensitivity ranged from 80% to 100% and specificity from 50% to 56%. The sensitivity and specificity of dermoscopic diagnosis by pattern analysis were 40 and 99%, respectively, for the two observers together. These results indicate dermoscopic diagnosis by TDS has high sensitivity and low specificity, while dermoscopic diagnosis by pattern analysis has low sensitivity and high specificity.

The area under the Receiver Operating Characteristic (ROC) curve of observer 1 (A.M.P.) was 0.81, demonstrating that in 81% of cases the melanoma was correctly identified. The area under the ROC curve of observer 1 (A.M.P.) demonstrated sensitivity and specificity of 60% and 75%, respectively. An interesting result of this study was that TDS was independent of the size of the lesion, we found lesions 2 mm in diameter to show a negative TDS.

In conclusion, sensitivity of TDS, and inter-observer agreement for this test were on the same level; it was useful to discriminate small melanocytic lesions.

The question remains whether small lesions that are histologically negative, with a TDS 2.45, are true negatives or constitute a limit of Stolz Index.
G18 THE TREATMENT OF METASTATIC NEUROENDOCRINE TUMORS: ACTIVITY OF A COMBINATION CHEMOTHERAPY

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Background and aims: Neuroendocrine tumors (NET) are so heterogeneous that there is no standard therapy, and the response to different treatments vary widely. Between 1994 and 1999, we created 78 consecutive patients (pts) with metastatic NETs. All of the pts were evaluated by histological type. The primary end-points were: objective, symptomatic and biochemical responses; the secondary end-points were: duration of response, safety, time to progression and overall survival. Patients and methods: The treatment consisted of fluorouracil (500 mg/m²), dacarbazine (300 mg/m²) and etoposide (30 mg/m²) (FDE regimen) given on days 1,2,3 every three weeks for at least three cycles (maximum nine). All of the pts were chemotherapy naive and had histologically confirmed, measurable or evaluable metastatic disease. Pts, adequate bone marrow, renal and hepatic functions. Ten pts had previous resected primary or hepatic metastases. Eighteen pts presented carcinoid syndrome, 3 of whom also had carcinoid-related cardiac disease. The histotype were: 37 neuroendocrine carcinomas, 33 carcinoids, 4 medullary thyroid carcinomas, 3 Merkel's carcinomas and 1 paraganglioma. The primary site of disease was: pancreas 26, unknown 18, bowel 12, lung 7, thyroid 4, stomach 2, rectum 2, breast 1, other 6. The metastatic sites were: liver (51), lymphnodes (37), bone (28), lung (20), skin (13), lung (9), other (6). Seventy one pts are evaluable for response and toxicity (4 did not receive 3 cycles, 4 refused treatment). Results: Objective responses were documented in 26% of the pts (6 complete response) carcinoids (20%), neuroendocrine tumors (28%), 2/3 Merkel's carcinoma and 1/4 medullary thyroid carcinoma.

The symptomatic responses were (55%), and biochemical responses were 13/28 (46%) CTC-NCI Bethesda toxicity was: neutropaenia grade 4 (11%) and grade 3 (12%), thrombocytopenia grade 3 (2%), anaeemia grade 3 (4%), vomiting grade 3 (4%). There were no cases of toxicity or death due to toxicity. Conclusions: The FDE regimen is efficacious and well tolerated in pts with advanced NETs. The results suggest that there may be a relationship between objective, symptomatic and biochemical responses.

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G19 EFFICACY OF 1-MONTH LANREOTIDE IN PATIENTS WITH NEUROENDOCRINE TUMOURS: PRELIMINARY RESULTS OF AN ITALIAN MULTICENTER STUDY

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A new slow-release formulation of the somatostatin analog lanreotide (LAN 60mg) is now available for monthly administration, with a significant improvement of compliance. An Italian multicenter study has been undertaken to evaluate the efficacy and tolerability of LAN 60mg in patients with gastrointestinal neuroendocrine tumors. All patients had been previously treated with LAN 30mg every 14-10 days for at least 3 months. LAN 60mg was to be administered every 28 days for a period of 6 months, with assessment of symptoms and tumor markers before every drug injection. Twenty four patients have been enrolled up to date. We report here the preliminary results obtained in 14 patients, 11 with carcinoid tumors, 2 with non-functioning pancreatic tumors, 1 with gastrinoma. None of these patients completed the study and the first 3 months' treatment. In all patients with carcinoid tumors, symptom normalization obtained with LAN 30mg was maintained with the 1-month formulation; in 1 patient presenting flushing episodes at inclusion, a decrease from 7 to 4 episodes per day was observed. At inclusion, urinary 5-hydroxyindoleacetic acid was elevated in 4 patients and normal or slightly above normal in 7. 5-HIAA levels were unmodified during the study in 5 patients, while a further decrease of -35% and -56%, respectively, was observed in 2 cases, and a 60% increase in 1 case. Serotonin chromogranin A was elevated in 8/14 patients: a biochemical response (>50% decrease) was observed in 1 patients, while CgA levels doubled during the first 4 months of the study, decreasing thereafter. Phaeochromocytomas: 3/6 +/-6% and 4% were seen as the remaining 5 patients. In 2 cases (1 gastrinoma and 1 carcinoid), serum gastrin significantly decreased returning to normal (from 139 and 127 pg/ml to 25 and 19 pg/ml). Tumor size remained unchanged in 19 patients completing the study, while a PR was seen in the patient also showing a biochemical response. These preliminary results indicate that the clinical and biochemical control obtained with the 1-month formulation is at least comparable to that of LAN 30mg, with a more favourable timing of administration.

G20 MANAGEMENT OF PATIENTS WITH CARCINOMA OF UNKNOWN PRIMARY SITE: A PRELIMINARY ANALYSIS

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Carcinomas of unknown primary site represent a heterogeneous group of patients (pts) who have historically been very difficult to characterize or treat effectively. Since May 1996, 29 pts with diagnosis of metastatic disease of unknown primary site were observed in our Institute. Pts characteristics were: M/F 21/8; median age 64 (range, 44-79 yrs), median PS 2 (range, 0-3); number of disease sites was 1 (10 pts), 2 (10 pts), 3 (7 pts), 4 (2 pts). Lymph node was the most common site (17/29) followed by lung (11/29), bone (9/29), liver (9/29), others (13/29). All pts underwent clinical history, full physical examination and radiological investigations in an attempt to locate the primary tumour. Immunostaining for epithelial, neuroendocrine and melanoma markers was routinely performed. For men with adenocarcinoma, staining for prostate-specific antigen was performed, as well. Serum tumor markers (as, PP, CA 125, CA 15-3, CA 19-9, CEA, TAG) were assessed in all cases. Twenty-one pts had histologically documented undifferentiated carcinomas while 8 pts had poorly differentiated adenocarcinomas. Only one pt had primary tumour detected into the breast. Nevertheless, based on both immunohistochemical testing and tumor markers, various subsets of tumor were identified: 1 neuroendocrine, 1 breast, 3 lung, 1 thyroid, 2 ovary, 3 gastrointestinal, 1 prostate. Two pts with undifferentiated carcinoma that involved only cervical lymph nodes, received radiation therapy and one pt with a solitary metastatic lesion to the left femur, after receiving palliative radiotherapy, lost to follow-up. Four pts were ineligible for treatment because of short life expectancy. Most of the pts received a cisplatin-based combination. Four partial responses have been observed among 22 treated pts (RR 18%). Final data on response to treatments, toxicity, and survival will be presented. Conclusions, an optimal strategy for diagnosis and treatment of pts with carcinoma of unknown primary site has not yet been delineated. A classification based on both clinicopathological parameters and serum tumor markers should be defined.

G21 TEMOZOLOMIDE AS SECOND LINE CHEMOTHERAPY IN THE TREATMENT OF RECURRENT MALIGNANT GLIOMAS

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Temozolomide (TM), a novel imidazotetrazine alkylating agent, has demonstrated a broad range of activity in phase I and II trials against several solid tumors including malignant gliomas. Recently, activity has been reported in recurrent gliomas previously treated with chemo-radiation. On the basis of these observations we decided to perform an open label, multicentric, phase II trial to evaluate response and toxicity after TM in recurrent, pretreated malignant gliomas. Methods: from January 1998 to September 1999, 62 patients were given 150 mg/m²/day for 5 consecutive days over 2 weeks; the dose could be increased to 200 mg/m²/day in the absence of grade 3-4 toxicity. 31 patients were confirmed to have glioblastoma multiforme, 20 anaplastic astrocytoma and 11 anaplastic oligodendroglioma. 48/62 patients (77%) had Krasofsky PS of 80-100%. All of them had previously received radiotherapy and chemotherapy (mostly Procarbazine, CCNU and Vincristine) Response was evaluated every 2 courses by MRI. Results intention-to-treat analysis of the patient population showed an objective response rate of 21% (3 complete and 10 partial responses) and stable disease in 37% of patients. At this moment 34 patients are alive and median survival has not been reached yet. Toxicity was mild (WHO grade 3 thrombocytopenia and neutropenia in 3 and 2 patients respectively). Conclusions: In our experience single agent TM confirmed a good activity/toxicity profile in recurrent pretreated gliomas.
Histocompatibility Antigens and Human Cutaneous Malignant Melanoma

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In the continuous and complex struggle between Immunity and Melanoma, even the histocompatibility of antigen expression has a determining role.

This study has the following aims:
- standardize Class I and Class II HLA antigens,
- highlight differences of incidence of some Ag HLA, between healthy subjects and patients with Cutaneous Malignant Melanoma (CMM);
- correlate the types of maps obtained with survival.

The study was carried out on a 15 cc blood sample with heparin, from fasting subjects. A battery of antisera defining Antigen HLA A-B-C, DR and DQ, was used. One group consisted of 62 malignant melanoma patients and the other group consisted of 65 healthy blood donors.

The comparison between percentage of Ag HLA in the CMM group and control group (healthy donors), highlighted that:
- in the group of 62 pts vs controls the HLA A11 (9 vs 15%), A28 (2 vs 7%), Aw32 (1 vs 11%), and Bw16 (2 vs 13%) antigen frequency was significantly decreased;
- high incidence frequency of Ag DR52 (37 vs 11%) was present in the CMM group.
- 2 years from standardization only 10% of patients that had Ag DR52 as well as down-expression of Class I Ag HLA, were alive.

Goals of the study were:
1. use standardization, in order to select in case of family history of CMM, the subjects that are more at risk,
2. modulate the choice of treatment, also taking into consideration the A HLA expression as prognostic factor,
3. addition of a new wedge to the complex and incomplete puzzle that is the immunogenetics of CMM;
4. has represented another cross point between research and clinic, for a more aimed therapeutic strategy.

Integrated Theraphy of Advanced Melanoma

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The systemic therapy of melanoma is one of the most frustrating tasks for the medical oncologist, in fact the treatment of advanced melanoma yields few durable remission and minimal impact on survival (<6 months).

The response rate rises to 50-60% with integrated treatment, but with more toxicity than chemotherapy regimens alone.

In our structure we have adopted an integrated regimen therapeutic (hormone-biologic-chemotherapy).

The scheme of treatment adopted includes:
- Tamoxifen 20 mg/die os sine die;
- Cisplatin 40 mg/m2 (i.v.) days 1,2;
- Dacarbazine 300 mg/m2 (i.v.) days 1,2;
- Interleukin-2 9,000,000 x 2 (i.c.) days 4,5,6,17,18;
- IFN alfa 3,000,000 (i.m.) days 4, 6, 16, 18;
- IFN alfa 9,000,000 (i.m.) days 8, 10, 12, 14

Repeated every 28 days.

We treated 18 patients, 3 are not evaluable at the moment because only one cycle had been completed. The patients are, in fact, 15 (6 men / 9 women, median age 58, range 31-63).

The results are encouraging: 10 R.O. (3R C., 7 R.P.), equal to 75% of total the patients treated.

The duration of response has been >6 months (range 4-11+). The found toxicity has been altogether moderate.

The results stimulate us to continue our study.

Session G: Melanoma – Sarcoma – Central Nervous System Tumors