A randomized controlled trial has been started in Japan to compare the utility of palliative chemotherapy containing paclitaxel and carboplatin (TC) with paclitaxel and cisplatin (TP) as a standard treatment for patients with the newly diagnosed Stage IVB, persistent or recurrent cervical cancer who are not amenable to curative treatment with local therapy. This trial was designed to evaluate the non-inferiority of TC as measured by the number of hospitalized days as an indicator of quality of life (QOL) when compared with TP combination therapy. The primary endpoint is overall survival. Secondary endpoints are progression-free survival, response rates, adverse events, severe adverse events and the proportion of non-hospitalization periods compared with planned treatment periods.

Key words: cervical cancer — palliative chemotherapy — recurrent — persistent — Stage IVB — cisplatin — carboplatin — paclitaxel
Europe and the USA is TP combination therapy. However, we have also reported a promising and feasible combination chemotherapy consisting of paclitaxel and carboplatin (TC) in a Phase II study (4). Although as single agents, carboplatin has a lower response rate than cisplatin, the reduced nephrotoxicity of carboplatin does not require hydration, enabling a 3 h administration of paclitaxel in this combination therapy. Thus, TC combination has been available in the outpatient setting. Recently, non-squamous cell cervical cancer has been increasing and treating this disease is a significant priority. Our Phase II study targeted not only patients with squamous cell cervical cancer but also those with non-squamous cervical cancer. We have started a Phase III trial to evaluate the benefit and reduced toxicity of TC for incurable patients with either squamous or non-squamous cell cervical cancer.

The study protocol was designed by the Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG), approved by the Protocol Review Committee of the JCOG on 12 January 2006 and activated on 21 February 2006. This trial was registered at the UMIN Clinical Trials Registry as C00000335 (http://www.umin.ac.jp/ctr/index.htm).

PURPOSE
This prospective study aims to evaluate the clinical benefits of TC compared with TP for patients with Stage IVB, persistent or recurrent cervical cancer.

STUDY SETTING
This study is a multi-institutional (30 specialized institutions), randomized controlled trial.

RESOURCES

ENDPOINTS
The primary endpoint of the study is overall survival. Secondary endpoints are progression-free survival, response rates, adverse events, severe adverse events and the proportion of non-hospitalization periods compared with planned treatment periods. The last endpoint is intended to evaluate the reduced inconveniency of hospitalization with TC therapy as a surrogate for quality of life (QOL).

ELIGIBILITY CRITERIA
INCLUSION CRITERIA
The inclusion criteria are as follows: (i) histologically proven uterine cervical cancer; (ii) squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the uterine cervix; (iii) one of the following: (a) newly diagnosed Stage IVB cervical cancer, (b) first relapse or persistent cervical cancer after curative or palliative first-line treatments, and (c) second relapse or persistent cervical cancer after curative or palliative second-line treatments including radiation therapy, chemotherapy, hormonal therapy or vaccination therapy; (iv) one of the following: (a) at least one metastatic lesion outside the pelvic cavity except in the paraaortic lymph node (LN) and/or inguinal LN, (b) no metastatic lesions outside the pelvic cavity except in the paraaortic LN and/or inguinal LN, and at least one of these lesions has been irradiated, and (c) all lesions are localized inside the pelvic cavity, and at least one of them has been irradiated; (v) recovery from effects of any prior therapy (at least 2 weeks from the last surgery or the last administration of chemotheraphy alone, 3 weeks from radiotherapy alone and 4 weeks from the last administration of concurrent chemoradiotherapy); (vi) no previous treatment with ≥51 Gy of palliative radiation therapy; (vii) no prior surgical resection of pulmonary metastases or radical resection of recurrent lesions inside the pelvic cavity including pelvic exenteration; (viii) no bilateral hydropneophrosis; (ix) no prior chemotherapy, or only one platinum-containing regimen; (x) no prior chemotherapy including taxanes; (xi) age ≥20 and ≤75 years; (xii) an Eastern Cooperative Oncology Group performance status (PS) of 0–2; (xiii) sufficient marrow, liver, kidney function and normal ECG; and (xiv) written informed consent.

EXCLUSION CRITERIA
The exclusion criteria are as follows: (i) neurological disturbance with functional disorder; (ii) symptomatic central nervous system metastasis; (iii) hypersensitivity to alcohol; (iv) active bacterial infection; (v) hepatitis B surface antigen-positive; (vi) poorly controlled hypertension; (vii) history of myocardiac infarction within 6 months; (viii) unstable angina; (ix) poorly controlled diabetes; (x) synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ; (xi) pregnant or lactating; (xii) mental disease or mental symptoms that would affect the participant’s decision to participate; and (xiii) continuous systemic steroid therapy.

TREATMENT METHODS
Chemotherapy is administered as follows. The TP regimen (standard arm) is paclitaxel 135 mg/m² intravenously (IV) for 24 h on day 1, followed by cisplatin 50 mg/m² IV for 2 h on day 2, which is repeated every 21 days. The TC regimen

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platelet counts.

The corresponding null hypothesis is that the hazard ratio of TC to TP is 1.29, the non-inferiority of TC to TP in terms of overall survival is confirmed. This study started in February 2006 with a planned accrual period of 2.5 years. The accrual of it, however, had been slow and the accrual period was revised to 3.5 years.

**INTERIM ANALYSIS AND MONITORING**

Interim analysis is scheduled once when half of the planned sample size has been accumulated and just after the nearest periodical monitoring data are available. Multiplicity is adjusted by the Lan and DeMets method with O’Brien and Fleming type boundaries. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis report and determine whether the study should be stopped early. In-house interim monitoring will be performed by the JCOG Data Center to ensure data submission and study progress. The monitoring reports will be submitted to and reviewed by the GCSG every 6 months.

**FOLLOW-UP**

All patients are followed up for 1 year after the study is closed for entry. Neurological adverse events are checked every 4 weeks, and the efficacy assessments are evaluated every 2 or 3 months.

**STUDY DESIGN AND STATISTICAL METHODS**

This study was designed as a randomized Phase III trial to demonstrate the non-inferiority of TC compared with standard TP using overall survival as the primary endpoint. Patients are randomized to each treatment arm by a minimization method with institution, PS (0, 1 or 2), histology (squamous cell carcinoma or adenocarcinoma) and tumor sites (all of them had prior radiotherapy or chemoradiotherapy or no therapy) as balancing factors at the JCOG Data Center (5,6).

If TC is not inferior to TP in terms of overall survival and is comprehensively superior in terms of other secondary endpoints of safety or QOL, TC will be the preferred treatment. The corresponding null hypothesis is that the hazard ratio of TC to TP is >1.29, the non-inferiority margin. It corresponds that the mean survival time (MST) of TC is inferior to TP (9 months) by >2 months under the proportional hazard assumption. Assuming exponential distributions and that the MST of TC is 10 months, 234 patients are needed to have >80% power to confirm the non-inferiority with one-sided α 5% after a 1-year follow-up period with 2.5 years of accrual. Even if MST of TC is 9.5 months, at least 70% of power is attained by 242 patients. On the basis of these considerations, the planned sample size is 250.

The primary endpoint is to be analyzed based on the Cox proportional hazard model with PS and histology as stratified factors. If the upper limit of the 90% confidence interval of the hazard ratio is <1.29, the non-inferiority of TC to TP in terms of overall survival is confirmed. This study started in February 2006 with a planned accrual period of 2.5 years. The accrual of it, however, had been slow and the accrual period was revised to 3.5 years.

**PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)**

Hokkaido University Hospital, Sapporo Medical University, Tohoku University Hospital, Institute of Clinical Medicine, Tsukuba University Hospital, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center (Saitama Medical School), Jikei Kashiwa Hospital, National Cancer Center Hospital, Jikei University Hospital, Cancer Institute Hospital, The University of Tokyo Hospital, Juntendo University School of Medicine, Kitasato University School of Medicine, Niigata Cancer Center Hospital, Sinski University, Aichi Cancer Center Hospital, Osaka City University Medical School, Kinki University School of Medicine, Kyoto University Hospital, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City General Hospital, Sakai Hospital, Kinki University School of Medicine, Hyogo Cancer Center Hospital, Faculty of Medicine, Tottori University, National Hospital Organization Kure Medical Center Chugoku Cancer Center, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center, Kurume University School of Medicine, Kyushu University Hospital, Faculty of Medicine, Saga University and Kagoshima City Hospital.

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**Conflict of interest statement**

None declared.
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