Phase II Study of Amrubicin Combined with Carboplatin for Thymic Carcinoma and Invasive Thymoma

North Japan Lung Cancer Group Study 0803

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Background: There has been no standard chemotherapy for advanced or recurrent thymic malignancies including thymic carcinoma (TC) and invasive thymoma (IT), though platinum and anthracycline have been reported as effective agents for the treatment of these diseases. The objective of this study was to evaluate the efficacy and safety of the combination of amrubicin (AMR), a new anthracycline agent, and carboplatin (CBDCA) in patients with advanced thymic malignancies.

Methods: Patients with histologically confirmed thymic malignancies received AMR (35 mg/m^2, days 1–3) and CBDCA (area under the curve 4.0, day 1) every 3 weeks. Patients who had received previous chemotherapy were treated with a reduced dose of AMR (30 mg/m^2). The primary end point was objective response rate (ORR), and secondary endpoints were progression-free survival, overall survival, and toxicity profile.

Results: From December 2008 to October 2012, 51 patients (33 TC and 18 IT) were enrolled. The median number of treatment cycles was four in each group. The ORR and progression-free survival were 30% (95% confidence interval, 14–46) and 7.6 months in the TC group, and 17% (95% confidence interval, 0–34) and 7.6 months in the IT group, respectively. The ORR of TC patients without previous chemotherapy (n = 19) was 42%. Although grade 3 or 4 hematological toxicities were common including neutropenia (82%) and febrile neutropenia (22%), these were transient and manageable. Nonhematological toxicities were moderate and no treatment-related death was observed.

Conclusions: The combination of AMR with CBDCA was active for TC with acceptable toxicity, although it was not effective for IT. Further investigation of this regimen for advanced TC is warranted.

Key Words: Thymic carcinoma, Invasive thymoma, Chemotherapy, Amrubicin, Phase II.

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Thymic carcinoma (TC) is a rare thymic epithelial tumor, which tends to metastasize and invade the surrounding tissues rapidly. Thus, the prognosis of TC is quite poor in the metastatic stage (2-year survival rate is approximately 50%).[1] Although invasive thymoma (IT) has a relatively good prognosis compared with TC, it is also a fatal disease when accompanied by distant metastasis. Patients with these advanced thymic malignancies are usually treated with systemic chemotherapy; however, due to the small number of patients with thymic malignancies compared with those with lung cancer, there has been no evidence available from large comparative studies and no standard treatment for these conditions. According to the guidelines of the National Comprehensive Cancer Network, patients with advanced TC should be treated with a regimen similar to that used for patients with IT.[2] Combined regimens consisting of platinum agent and anthracycline agents such as cisplatin, doxorubicin, and cyclophosphamide have been recommended for thymic malignancies,[3] although these do not show adequate efficacy and the severe toxicities (e.g., emesis or renal toxicity with cisplatin, and cardiac toxicity with anthracycline) sometimes produce a decline in the patient's quality of life.

Amrubicin (AMR) is a new anthracycline, which has achieved some promising results for advanced small-cell lung cancer in Japanese studies, as a single agent at a dose of 45mg/m^2 for three consecutive days, and also as a combined regimen with carboplatin (CBDCA, at a dose of area under

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the curve 4), at a dose of 35mg/m^2 on day 1 to 3.[4–6] Although care should be taken with regard to myelosuppression during the treatment with AMR, there have been few reports of cardiac toxicity induced by AMR to date. We postulated that the combination of AMR and CBDCA might show efficacy in treatment of advanced thymic malignancies with acceptable toxicities, and therefore conducted this phase II study.

PATIENTS AND METHODS

Patient Selection

This multicenter phase II trial was conducted in accordance with the Helsinki Declaration of the World Medical Association and the protocol was approved by the institutional review board of each participating institution. Patients older than 20 years with histologically confirmed TC or IT were enrolled in this study. Other eligibility criteria included Eastern Cooperative Oncology Group performance status 0 to 1, measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, estimated life expectancy greater than or equal to 3 months, and appropriate organ functions as follows: white blood cell count greater than or equal to 4000/mm^3, absolute neutrophil count greater than or equal to 2000/mm^3, platelets greater than or equal to 100,000/mm^3, hemoglobin greater than or equal to 9.0 g/dl, serum bilirubin less than or equal to 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase less than or equal to 100 IU/L, creatinine level less than or equal to 1.5 mg/dl, arterial oxygen pressure greater than or equal to 60 mmHg). Written informed consent was obtained from all the enrolled patients. Patients with symptomatic brain metastasis, interstitial lung disease, massive effusion requiring drainage, or severe comorbidities such as uncontrolled diabetes or cardiac disease were excluded. Patients who had received previous chemotherapy with doxorubicin within 400 mg/m^2 in total were included.

Treatment Schedule

AMR was diluted in 50ml of normal saline and administered by 10-minute intravenous infusion at a dose of 35 mg/m^2 on days 1 to 3 of each treatment cycle. Patients who had received previous chemotherapy were treated with a reduced dose of AMR (30 mg/m^2) to reduce the risk of myelotoxicity. CBDCA was diluted in 250 ml of 5% glucose solution or normal saline and administered by ≥30-minute intravenous infusion at a dose of area under the curve 4.0 on day 1 after AMR. Doses of both the agents were determined according to our previous phase II study of this combination for untreated small-cell lung cancer patients.[6] The treatment was repeated on a 21-day cycle. Premedication with corticosteroid and antiemetic serotonin antagonist was recommended. The dose of AMR was reduced by 5 mg/m^2 in each subsequent cycle in case of severe toxic effects such as grade 3 or more nonhematological toxicities, thrombocytopenia less than or equal to 20,000/mm^3, grade 4 neutropenia lasting greater than or equal to 4 days, or febrile neutropenia occurring in the previous cycle. Granulocyte colony-stimulating factor (G-CSF) was permitted for neutropenia but not for use as a prophylactic. No prophylactic antibiotic support was scheduled. All the patients were scheduled to receive at least three cycles of treatment unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue the treatment. Subsequent chemotherapy after disease progression was permitted.

Patient Assessment

Patient assessment, including physical examination, complete blood count, and biochemistry, were repeated once a week in the first cycle and at least once per each cycle later. Measurement of tumors was carried out with respect to baseline assessment by computed tomography scans. Computed tomography examination was performed at least once per two cycles until disease progression. Tumor response was assessed according to RECIST version 1.1. Confirmation of complete and partial responses required at least 4 weeks duration of such responses, and stable disease required at least 4 weeks duration from the initiation of the protocol treatment. All response evaluations were performed by independent extramural review. Toxic effects were assessed according to the National Cancer Institute-Common Toxicity Criteria version 4.0.

Statistical Analysis

The primary end point of this study was objective response rate (ORR), and secondary endpoints included progression-free survival (PFS), overall survival, and toxicity profile. Overall survival was evaluated for a period from the introduction of protocol treatment to the date of death. Assuming that ORR of 45% and 75% would indicate potential usefulness whereas ORR of 20% and 50% would be at the lower limit of interest, with alpha = 0.10 and beta = 0.20, for TC and IT, respectively, the estimated accrual was 18 for each group. Survival estimation was performed using the Kaplan-Meier method. Differences between Kaplan-Meier curves were evaluated by log rank test.

RESULTS

Patient Characteristics

From December 2008 to October 2012, 51 patients (33 TC and 18 IT) were enrolled from 18 institutions in Japan. Because the patient accrual was relatively slow in the IT group, accrual of the TC group was also expanded accompanied with the IT group. Patient characteristics are shown in Table 1. Twelve patients had previously received platinum-based regimen such as CBDCA plus paclitaxel (nine patients) or cisplatin plus etoposide (four patients), and seven patients had been treated with doxorubicin mostly as doxorubicin, cisplatin, vincristine, and cyclophosphamide regimen before entering this study. Twenty-six (51%) patients received subsequent chemotherapy including CBDCA plus paclitaxel (12 patients) or S-1 (nine patients) after the protocol treatment.

Efficacy

The median number of treatment cycles was four in each group (range, 1–6 in TC, 2–15 in IT). Responses in all the 51 patients were evaluated. The ORR and disease control rates were 30% (95% confidence interval, 14–46) and 85% in