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Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide followed by surgery for thymic carcinoma

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Abstract

Objective: We present our experience treating the patients with thymic carcinoma using induction chemotherapy according to weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide (CODE) followed by surgery.
Patients and methods: From January 2001 to December 2010, 17 patients were diagnosed as having thymic carcinoma at our hospital. We performed CODE chemotherapy for induction treatment followed by surgical resection in 7 of these patients.
Results: Seven patients consisted of 6 men and 1 woman, with an average age of 47.3 years (range 25–67 years). Five patients were clinically staged as Masaoka Stage III, and 2 were Stage IVa. A partial response was identified in 5 patients, and stable disease was observed in 2 patients. No cases of progressive disease were seen. Surgical resection was performed in all the patients: 6 underwent an R0 resection and 1 underwent an R1 resection. The estimated overall survival rates at 5 and 10 years were both 80%, and the relapse-free survival rates at 5 and 10 years were 68.6% and 53.6% respectively.
Conclusions: Induction chemotherapy using the CODE regimen, followed by a complete surgical resection can be performed with a promising survival outcome for patients with thymic carcinoma with borderline resectable lesions.

Keywords: Thymic carcinoma; Weekly chemotherapy; Induction chemotherapy

Introduction

Thymic carcinoma is a relatively rare malignant tumor derived from thymic epithelium, with a reported incidence of 5–36% of all thymic epithelial tumors.[1–4] The clinical course of thymic carcinoma is characterized by early and frequent metastasis and a poor prognosis. The tumors have an aggressive histopathological appearance and have often invaded neighboring organs or disseminated throughout the thoracic cavity at the time of diagnosis.[1,5,6] Although some reports have suggested that tumor resectability, tumor stage, or tumor histology grading influence the outcome, a standard treatment for thymic carcinoma has not yet been established.[7,8] Several reports have stated that thymic carcinomas respond to cisplatin-based combined chemotherapy[6,9–11]; however, the optimal chemotherapy regimen for thymic carcinoma remains uncertain. Yoh et al.[12] reported that the CODE regimen, which includes the combination of cisplatin, vincristine, doxorubicin and etoposide, demonstrated a good response and was well tolerated in patients with advanced thymoma and thymic carcinoma. Here we present our experience treating 7 patients with thymic carcinoma, who underwent induction chemotherapy according to the CODE regimen, followed by surgery.

Patients and methods

Patients and pretreatment evaluation

We retrospectively reviewed patients with thymic carcinoma who had been treated at the National Hospital Organization Okinawa Hospital, Okinawa, between January 2001 and December 2010. The histological diagnosis of thymic carcinoma was diagnosed based on the WHO criteria.[13]

Abbreviations: CODE, cisplatin, vincristine, doxorubicin, and etoposide; CT, computed tomography; MRI, magnetic resonance imaging.

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The clinical stage of thymic carcinoma was assessed according to the criteria proposed by Masaoka et al.[14] A clinical evaluation, including a medical history and physical examination, blood examination, chest roentgenogram and CT, and an examination for extrathoracic metastasis, involving an abdominal CT, brain MRI, and bone scintigram, was performed for each patient. Borderline resectable patients with a good performance status were selected as candidates for induction CODE chemotherapy if an incomplete resection had been deemed likely if they were to undergo initial surgery alone. Candidates were also required to have good organ function. Patient selection was decided at a case conference, and each patient provided informed consent.

Induction chemotherapy regimens

The selected patients underwent CODE chemotherapy on a preoperative basis. Briefly, the CODE regimen consisted of a weekly dose of cisplatin (25 mg/m^2, intravenously [i.v.]), vincristine (1 mg/m^2, i.v.) during weeks 1, 2, 4, 6, and 8, doxorubicin (40 mg/m^2, i.v.) during weeks 1, 3, 5, 7, and 9, and etoposide (80 mg/m^2, i.v.) for 3 days during weeks 1, 3, 5, 7, and 9. Prophylactic recombinant human granulocyte colony-stimulating factor (G-CSF; 50 μg/m^2) was administered subcutaneously on the days when the cytotoxic drugs were not given. Each treatment cycle was repeated at 1-week intervals. If the toxicities were acceptable and the tumor responded to the treatment, the patient was expected to complete a maximum of nine cycles of chemotherapy.[12]

Toxicities and response

Toxicities associated with chemotherapy were evaluated using with National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2. Objective response was evaluated using a computed tomography scan according to the guidelines set forth by the Response Evaluation Criteria in Solid Tumors[15] and were classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). The pathologic effect of the induction therapy was determined using resected specimens according to the General Rule for Clinical and Pathological Record of Lung Cancer, 6th edition, as described below.[16] A complete response (Ef.3) was defined as pathologically complete cancer cell death. A major response (Ef.2) was defined as viability in lesser than one-third of the cancer cells. A moderate response (Ef.1b) was defined as viability in more than one-third but less than two-thirds of the cancer cells. A minor response (Ef.1a) was defined as viability in more than two-thirds of the cancer cells.

Adjuvant treatment and follow-up

Postoperative irradiation therapy was added in patients with an incomplete resection, and was performed in an adjuvant setting for patients with a complete resection. Postoperative chemotherapy was planned for patients with incomplete resections and was performed as adjuvant in patients who were deemed capable of tolerating the treatment.

Statistical analysis

Categorical data were analyzed using the Chi-square analysis, while continuous variables were examined using the Student *t*-test. The survival duration was defined as the time from the day of first treatment (or the visiting day for those who did not receive any treatment) until the day of death or the last follow-up contact. The survival curves were estimated using the Kaplan–Meier method, and comparisons among the survival curves were made using the log-rank test. Differences were considered statistically significant when the *P* value was less than 0.05.

Results

Patients' characteristics

From January 2001 to December 2010, 68 thymic epithelial tumor patients were admitted and underwent treatment at the National Hospital Organization Okinawa Hospital. During the same period, 17 patients were diagnosed as having thymic carcinoma. The patients consisted of 15 men and 2 women with an average age of 54.6 years (renege, 25–67 years). We performed CODE therapy for induction treatment in 7 of these patients (Table 1). The candidate for induction CODE chemotherapy were mainly selected because of good performance status and tended to be younger, although a significant relation was not seen. Tables 1 and 2 show the characteristics of the patient who underwent induction CODE chemotherapy. Six men and 1 woman, with an average age of 47.3 years (range 25–67 years) underwent treatment. Among these 7 patients, 5 had a history of smoking. Four patients had some complaints, such as coughing, dyspnea, and chest pain. Three patients were asymptomatic, and their tumor was detected incidentally on a chest roentgenogram performed as part of an annual health examination. Six patients had squamous cell carcinoma, and one patient had adenosquamous cell carcinoma. According to the clinical staging system described by Masaoka et al., five patients had Stage III disease and two patients had Stage IVa disease.

Treatment outcomes and prognoses

Table 3 shows the treatment outcomes and prognoses of 7 patients who received induction CODE chemotherapy. Three patients received 6 weeks of CODE chemotherapy, 2 patients received 4 weeks, and 1 received 3 weeks, and 1 received 7 weeks. The average number of chemotherapy weeks was 5.1. Among the 7 patients, 5 patients

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