Salvage Chemotherapy with Carboplatin and Paclitaxel for Cisplatin-resistant Thymic Carcinoma – Three Cases

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Abstract. The optimal chemotherapeutic regimen for thymic carcinoma remains uncertain and the utility of salvage therapy has also not been reported. Three cases of unresectable and locally advanced thymic carcinoma, resistant to prior chemotherapy with cisplatin are reported. These patients were treated with carboplatin and paclitaxel chemotherapy, as salvage chemotherapy. Although concomitant thoracic radiotherapy was performed in one patient, two showed a partial response and the other showed a minor response after carboplatin and paclitaxel chemotherapy. Thymic carcinoma is sensitive to platinum-based chemotherapy and paclitaxel appears to have significant activity against thymic carcinoma.

Thymic carcinoma differs from thymomas not only morphologically, but also biologically (1,2). Thymic carcinoma is a thymic epithelial neoplasm with cytological malignant features and a clinical course that tends to be much more aggressive than that of thymoma (2-6). Thymic carcinoma also tends to metastasize widely, which leads to a highly lethal course (2-6). Thus, the role of systemic chemotherapy may be important in the treatment of thymic carcinoma. Cisplatin-based chemotherapy has repeatedly been shown to benefit certain patients (4-8), but an optimal regimen and the role of second-line and/or salvage chemotherapy remain unclear. In this paper, three cases of unresectable and locally advanced thymic carcinoma treated with carboplatin (CBDCA) and paclitaxel, that were resistant to prior cisplatin-based chemotherapy, are described.

Patients and Treatment Profiles

From 2003 to 2006, three patients were diagnosed with unresectable thymic carcinoma. In each case, percutaneous computed tomography (CT) guide biopsy was performed and the lesions were confirmed histologically to be epidermoid-type thymic carcinoma. Clinical staging included medical history and physical examination, complete biochemical profile, chest radiographs, chest CT scans and bronchoscopy. In addition, to examine extrathoracic distant metastasis, abdominal and brain CT and bone scans were performed. According to the classification of Masaoka et al. (9), the patients had unresectable, locally advanced disease (IVa).

All patients were initially treated with a combination of cisplatin (50 mg/m²) and doxorubicin (40 mg/m²) on day 1, vincristine (0.6 mg/m²) on day 3, and cyclophosphamide (700 mg/m²) on day 4 (ADOC chemotherapy). All drugs were administered intravenously. Partial response (PR) was defined as a decrease of more than 50% in the size of the main measurable lesions. Stable disease (SD) was defined as regression of less than 50% of measurable lesions. If measurable lesions increased or new lesions appeared after chemotherapy, the case was defined as showing progressive disease. Evaluation was performed after at least two courses of each chemotherapy regimen. The chemotherapy profiles of the three patients are summarized in Table I and the clinical courses, in each case, were as follows.

Case 1. A 52-year-old man was admitted to our hospital because of facial edema, in October 2003. A chest CT revealed a large anterior mass (Figure 1A). After the histological diagnosis, the patient was treated with 2 cycles of ADOC chemotherapy, but showed no response to treatment. His symptoms due to superior vena cava syndrome progressed (Figure 1B) and palliative intrathoracic radiotherapy was started, in mid-December 2003. Chemotherapy consisting of CBDCA (450 mg/body, day 1) and paclitaxel (100 mg/body, days 1, 8, and 15) was started one week after the beginning of radiotherapy. The efficacy of chemoradiation treatment seemed good and thus
a total of 60 Gy (2 Gy x 30 days) radiotherapy and 4 cycles of CBDCA and paclitaxel chemotherapy were performed. The therapy was well tolerated and there were no specific toxicities. The patient showed PR (Figure 1C), and had a disease-free survival period of 12 months, after chemoradiotherapy, but showed a local relapse in the anterior mediastinum and the chest wall. The patient died 23 months after the beginning of chemotherapy.

Case 2. A 38-year-old man was admitted to our hospital because of dyspnea, in July 2003. A chest CT indicated a large anterior mediastinal mass (Figure 2A). The patient was initially treated with 4 cycles of ADOC chemotherapy followed by 2 cycles of cisplatin (80 mg/m², day 1) and irinotecan (60 mg/m², days 1, 8 and 15) (IP) chemotherapy. However, no response was observed to either chemotherapeutic regimen (Figure 2B). Subsequently, he was treated with thoracic radiotherapy (total 54 Gy), which resulted in SD (Figure 2C). Nine months later, the disease relapsed on the right side of the anterior upper mediastinal space (Figure 3B) and the patient was treated with combination chemotherapy of CBDCA (AUC2) plus paclitaxel (120 mg/m²) biweekly in December 2005. After 8 courses of chemotherapy, the mass showed a reduction in size and PR was achieved (Figure 2D and Figure 3C).

Case 3. A 48-year-old woman was admitted to our hospital because of acute onset of dyspnea, in August 2004. A chest CT revealed a large anterior mediastinal mass (Figure 4A) and massive pericardial effusion. After histological diagnosis, the patient was initially treated with 4 cycles of ADOC chemotherapy. Although the pericardial effusion disappeared, the size of the anterior mass did not change (SD). As second-line chemotherapy, two cycles of IP chemotherapy were performed, but the patient did not show a favorable response (Figure 4B). CBDCA (AUC2) plus paclitaxel (120 mg/m²) biweekly chemotherapy was started in March 2006. The size of the anterior mass was reduced slightly, but the patient did not achieve PR after 6 courses of chemotherapy (Figure 4C). To date, the patient has been treated with the same chemotherapy.

Patients 2 and 3 are still alive at 36 and 24 months, respectively, after the start of ADOC chemotherapy.

Discussion

We reported our experience with salvage chemotherapy with CBDCA and paclitaxel for thymic carcinoma, in cases resistant to prior cisplatin-containing chemotherapy. Two out of the three cases showed good responses to CBDCA and paclitaxel. Based on our findings, we emphasize that thymic carcinoma is chemosensitive and that CBDCA and paclitaxel may be useful as an alternative chemotherapy regimen for thymic carcinoma.

Chemotherapy is commonly employed for patients with unresectable and/or metastatic thymic carcinoma (4-8). It was recently suggested that thymic carcinoma is relatively sensitive to combination chemotherapy. Yoh et al. (5) evaluated the efficacy of CODE (cisplatin, vincristine, doxorubicin and etoposide) therapy for thymic carcinoma and reported a response rate of 42%. We also reported a response rate of 75% to ADOC chemotherapy in thymic carcinoma (6). In addition, Kitami et al. (10) described 4 cases with successful outcomes, among 7 cases of advanced thymic carcinoma, treated with modified ADOC chemotherapy. These findings and several case reports indicated that combination chemotherapy, particularly a regimen containing cisplatin, was effective against thymic carcinoma (4-8, 10). However, to our knowledge, there have been no previous reports of the utility or trials of second-line chemotherapy. Our observations suggest that treatment with CBDCA and paclitaxel is a useful alternative regimen for patients resistant to or relapsed after cisplatin-containing chemotherapy.

In the present cases, ADOC chemotherapy was performed as first-line chemotherapy, in all cases. However, the therapy failed to evoke favorable responses and cases 2 and 3 were also resistant to subsequent IP chemotherapy. However, encouraging results were obtained in cases 1 and 2. The CBDCA regimen plus paclitaxel represented the first effective chemotherapy in their clinical courses.

CBDCA and paclitaxel is one of many standard regimens for several types of malignancy (11). However, little information is available about the response of thymic tumors to the combination of CBDCA and paclitaxel. Morio et al. reported a case of thymic carcinoma with complete

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<th>Case</th>
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<td>3</td>
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Figure 1. Chest computed tomography in case 1. A) On admission. B) After two cycles of ADOC chemotherapy. C) After CBDCA/paclitaxel chemotherapy with concomitant thoracic radiotherapy.

Figure 3. Chest computed tomography in case 2, upper mediastinal level. A) After thoracic radiotherapy. B) Before CBDCA/paclitaxel chemotherapy. C) After CBDCA/paclitaxel chemotherapy.

pathological response to cisplatin/paclitaxel and concomitant thoracic radiotherapy (12). Greene et al. described a case of thymic carcinoma with extensive invasion, treated with en bloc surgical resection, followed by 6 cycles of carboplatin and paclitaxel (13). In addition, successful treatment with paclitaxel was reported in patients with recurrent metastatic thymoma (14). Thus, our experience with this type of chemotherapy provides new insight into the treatment of advanced thymic tumors.

Radiotherapy has been considered as a therapeutic tool for locally advanced thymic carcinoma, especially squamous cell carcinoma (1, 4). Indeed, several cases treated successfully with systemic chemotherapy, combined with concurrent or sequential radiotherapy, were reported (4, 7, 8). Since concomitant radiotherapy was performed in case 1, the benefit of the combined-modality therapy over CBDCa and paclitaxel was also suggested. With regard to the risk factors of combined agents contributing to the development of radiation pneumonitis, CBDCa and paclitaxel were feasible and well tolerated in lung cancer patients (15). Thus, with combined radiotherapy, this regimen may also be useful in the treatment of thymic carcinoma.

In summary, we emphasize that thymic carcinoma is a chemotherapy-sensitive type of tumor. The carboplatin-plus-paclitaxel regimen shows good activity as salvage therapy for patients with advanced thymic carcinoma. This novel regimen merits further clinical investigation for treatment of patients with this malignancy.

References


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