Successful Salvage Chemotherapy with Amrubicin for Invasive Thymoma Associated with Myasthenia Gravis

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Anthracycline-based regimens with cisplatin have been commonly used for inoperable and relapsed thymoma. However, little information is available regarding the usefulness of salvage chemotherapy. Here, we describe a case of invasive thymoma associated with myasthenia gravis that showed a marked response to third-line chemotherapy, with single-agent amrubicin, a synthetic anthracycline analog and potent deoxyribonucleic acid topoisomerase II inhibitor. Amrubicin appears to have significant activity against invasive thymoma.

Key words: relapsed thymoma – chemotherapy – anthracycline – topoisomerase II inhibitor

INTRODUCTION

Thymoma is one of the most common neoplasms in the anterior mediastinum and ~70% of the disease are well encapsulated and therefore considered benign (1). However, the malignant potential of thymoma is its invasiveness to adjacent organs within the thorax or distant metastasis. Systemic chemotherapy is commonly employed for patients with metastatic disease or patients who relapsed after local therapies such as surgery or radiation. Anthracycline-based combination regimens such as cisplatin, doxorubicin, vincristine and cyclophosphamide are recommended as an initial chemotherapy for inoperable and relapsed thymoma. However, the efficacy has not been studied extensively because of the relatively small number of patients. In particular, little information is available regarding the role of second-line and/or salvage chemotherapy (1–3). Here, we described a case of invasive thymoma associated with myasthenia gravis that showed a marked response to third-line chemotherapy, with single-agent amrubicin, a synthetic anthracycline analog and potent deoxyribonucleic acid topoisomerase II inhibitor.

CASE PRESENTATION

A 35-year-old woman was admitted to our hospital in December 1998 because of further examination for chest radiographic abnormality detected by routine health survey. Chest computed tomography (CT) showed a large anterior mediastinal mass and the histological analysis by percutaneous CT-guided biopsy revealed thymoma. According to the classification of Masaoka et al., the patient had unresectable, locally advanced disease (IVA). The patient was initially treated with four cycles of cisplatin, doxorubicin, vincristine and cyclophosphamide, resulting in the significant reduction in the tumor size. She underwent a thoracotomy in March 1999. The left brachiocephalic vein and the left upper lung were simultaneously excised in order to resect all visible tumors. The World Health Organization histological classification was type B2. The patient had mediastinal radiotherapy (50 Gy) thereafter. However, a relapse in the left pleural dissemination was observed in May 2003. Since three cycles of carboplatin and paclitaxel chemotherapy failed to reduce the relapsed lesions, partial resection of the intrathoracic mass was performed as the second surgery.

During follow-up, regrowth of the mass in the left upper pleural and anterior chest wall was observed. In addition, she developed dysphagia, ptosis and weakness in the neck, and was diagnosed with anti-acetylcholine receptor antibody (AChR-AB) positive myasthenia gravis in November 2010. She has been treated with prednisolone (10–15 mg/day) and tacrolimus (0.3 mg/day). The symptoms of myasthenia gravis were relieved.
and remained stable by the treatment. However, left intrathoracic tumors grew further and she developed left chest pain with deep inspiration in October 2013 (Fig. 1A). For the third-line setting, amrubicin administration was begun at the dose of 40 mg/m² on Days 1–3, every 4 weeks. A chest CT after six cycles of amrubicin treatment demonstrated a significant reduction (45% reduction) in the size of the masses, confirming partial response (Fig. 1B). The response continued to be present for 3 months after the last chemotherapy. In addition, the response was associated with a reduction in AChR-AB from 148.0 to 102.0 nmol/l and no obvious changes were observed in clinical symptoms of myasthenia gravis during chemotherapy. The adverse events related to amrubicin were no higher than Grade 1 in severity, according to the Common Toxicity Criteria for Adverse Events, ver. 4. Only Grade 1 neutropenia and leukopenia were observed. There were no significant findings on electrocardiography or echocardiography even before or after chemotherapy.

DISCUSSION

Regarding the usefulness of amrubicin in thymic tumors including invasive thymoma or thymic carcinoma, several case studies were reported (4–8). Igawa et al. (4) reported a marked response to amrubicin monotherapy in a patient with thymic small cell carcinoma. In addition, in combination with platinum compounds, feasibility and efficacy of amrubicin for thymic carcinoma were reported as a second-line and beyond chemotherapy for recurrent thymic carcinoma (5,6). In addition, two abstracts demonstrated that 1 among 11 cases and 2 among 18 cases with invasive thymoma showed a partial response to amrubicin single and combination with carboplatin, respectively (7,8). Thus, amrubicin showed a modest activity for thymic malignancies. In the present case, amrubicin was used as third-line chemotherapy, and to our knowledge, this is the first report to demonstrate the efficacy of single-agent amrubicin as salvage chemotherapy for advanced relapsed thymoma. In general, hematological toxicity is considered to be a major toxicity of amrubicin (4–9). Since the present case was under chronic immunosuppression status with prednisolone and tacrolimus, hematological toxicity and infectious complication were cautious. However, only Grade 1 neutropenia and leukopenia were observed during fifth and sixth cycles of amrubicin in the present case. The present case showed a good response to previous chemotherapy, combined with cisplatin, doxorubicin, vincristine and cyclophosphamide, not carboplatin plus paclitaxel. The previous response to doxorubicin might suggest subsequent use or efficacy of amrubicin in the case of relapsed thymoma. However, the accumulative or synergic cardiac toxicities of amrubicin following doxorubicin should be paid attention.
In summary, our case could provide a new insight for treatment in patients with relapsed thymoma. Amrubicin could be a novel agent for the salvage therapy for invasive thymoma. This agent merits further clinical investigation for treatment in patients with thymic tumors.

**Conflict of interest statement**

None declared.

**References**