Editorial

Chemotherapy for advanced and metastatic thymic carcinoma

Takurou Noguchi, Tomonobu Koizumi

Department of Comprehensive Cancer Therapy, Shinshu University School of Medicine, Asahi, Matsumoto, Japan

Correspondence to: Tomonobu Koizumi, MD. Department of Comprehensive Cancer Therapy, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. Email: tomonobu@shinshu-u.ac.jp.

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Thymic carcinoma is a rare epithelial neoplasm with malignant cytological features, which accounts for approximately 10% of all thymic epithelial tumors. The clinical course of thymic carcinoma tends to be much more aggressive than that of thymoma, and thymic carcinoma also tends to metastasize widely, thus resulting in poor outcome. Therefore, although systemic chemotherapy plays an important role in the treatment of thymic carcinoma, the optimal regimen has not been established because of the rarity of this malignancy. There have been only a few reports describing possible chemotherapy strategies for advanced thymic carcinoma, and these were based on small series and/or retrospective studies.

Ko *et al.* (1) analyzed the survival time by retrospectively collecting a large number of patients in the North-East Japan Study Group, who were initially treated with chemotherapy for unresectable thymic carcinoma. In fact, the data from 286 patients were sufficiently promising to support our anecdotal decision making in practice for unresectable advanced and/or metastatic thymic carcinoma. First-line chemotherapy included platinum-based doublets in 62.2% of patients, monotherapy in 3.5%, and other multidrug chemotherapy [e.g., cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC)] in 34.3%. The response rate was 38.2% in platinum-based doublets and 41.0% in ADOC chemotherapy. In platinum-based doublets, carboplatin plus paclitaxel was the best common regimen with a response rate of 40.0%. The median overall survival time (MST) from the start of first-line chemotherapy was 30.7 months [95% confidence interval (CI), 25.9–35.9 months]. Although these results were similar to those of previous small studies (2), the efficacy of chemotherapy in patients with advanced and metastatic thymic carcinoma was confirmed in the largest study by Ko *et al.* (1). Intriguingly, this result was considered at least comparable or potentially better than the efficacy observed in patients with other thoracic malignancies. For example, stage IV advanced non-small cell lung carcinoma showed a response rate of 29–35% and MST of 10–12 months. Moreover, the MST of stage IV mesothelioma is ~12 months. Thus, based on the present study, it should be emphasized that thymic carcinoma is more sensitive to chemotherapy compared to other common types of cancer in the thoracic cavity.

These observations raise questions regarding the specific type(s) of stage IV patients that would benefit from chemotherapy. The results of the present study indicated significantly better prognosis of patients with intrathoracic metastases and negative for N factors (Masaoka-Koga stage IVa) compared to those with either extrathoracic metastases or positive for N factors (stage IVb) (42.8 *vs.* 21.3 months, respectively). Twenty-three patients underwent volume reduction surgery and showed favorable prognosis (survival period, 52.0 months) compared to those without volume reduction surgery (survival period, 28.9 months). In addition, among stage IVb patients, survival was relatively short either when they were not eligible for volume reduction surgery or when the extrathoracic metastases were extended beyond the lymph nodes. These observations from this single study do not have sufficient statistical strength to allow definitive conclusions to be made. However, several other studies also yielded similar results (3). Based on the analysis of surgically treated patients with thymic carcinoma, only complete resection was an essential prognostic factor for overall survival in patients with thymic carcinoma (3). However, the data suggested the potential

survival benefit of incomplete and subtotal resection. The survival curves for patients with microscopically incomplete and macroscopically incomplete but subtotal tumor resection were similar, but survival was significantly superior to that in the macroscopic non-resection group. Therefore, maximal debulking surgery by near-total or subtotal resection may be useful to improve survival. It seems important for tumor dissemination to neither extend beyond the thoracic cavity nor to be lymphogenous in terms of favorable prognosis. Overall, the results of Ko *et al.* suggested that patients with disease limited to within the thoracic cavity and without lymph node metastases will likely respond to chemotherapy resulting in prolonged survival.

The role of antitumor immunity in patients with thymic carcinoma is intriguing. Thymic carcinoma indeed was reported to show expression of high levels of PD-L1 in the tumor microenvironment. As the expression of PD-L1 is positively regulated by the inflammatory cytokine, interferon-γ (IFN-γ), which also activates tumor cell killing pathways by T cells, this observation indicates that anti-tumor immune inflammation (i.e., IFN-γ) usually exists in the tumors, but that it is suppressed by the immune inhibitory PD-1/PD-L1 pathway. To test this hypothesis, a single-arm phase 2 study has recently been conducted and showed that pembrolizumab, an anti-PD-1 immune checkpoint inhibitor, is active in patients with advanced thymic carcinoma (4). In a population of 40 patients, the response rate was 22.5% (95% CI, 10.8–38.5%); 1 (3%) patient achieved a complete response, while the remaining 8 (20%) patients achieved partial responses. These response rates were similar to other malignancies. Thus, PD-1 inhibitor maybe a promising treatment option in patients with thymic carcinoma, and a therapeutic strategy using immune checkpoint inhibitors are expected to show efficacy in patients with advanced and metastatic thymic carcinoma.

In summary, the data from a large number of patients reported by Ko *et al.* (1) provided insight into the rare disease, thymic carcinoma. Due to their rarity, an international prospective study should be designed to evaluate chemotherapy regimens for thymic epithelial neoplasms.

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