



Treatment options for stage IVA thymic malignancies

Nicolas Girard

Department of Thoracic Oncology, Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France

Correspondence to: Nicolas Girard. Department of Thoracic Oncology, Institut du Thorax Curie-Montsouris, Institut Curie, 26 rue d'Ulm, 75248 Paris, Cedex 05, France. Email: nicolas.girard2@curie.fr.

Abstract: The management of thymic malignancies is based on multidisciplinary collaboration. Stage IVA tumors are defined as tumors associated with intrapleural or intrapericardial dissemination of tumor cells without any distant metastasis. These tumors represent a specific entity with the opportunity of surgical treatment as well as the use of systemic agents if local treatment is not achievable or in combination with surgery, possibly through intrathoracic delivery. Here we describe the available opportunities in such situations, discussing recently available data. Taken together, multidisciplinary tumor board is key for the assessment of patients with stage IVA thymic epithelial tumors (TETs).

Keywords: Thymoma; thymic carcinoma; chemotherapy; immunotherapy; targeted agents

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Introduction

Thymic malignancies are rare mediastinal tumors, which are classified according to the World Health Organization (WHO) histopathologic classification, that distinguishes thymomas from thymic carcinomas (1). Staging of thymic tumors is currently based on the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging classification (2). Stage IVA tumors are defined as tumors associated with intrapleural or intrapericardial dissemination of tumor cells without any distant metastasis.

The management of stage IVA thymic epithelial tumors (TETs) is actually a paradigm of cooperation between clinicians, surgeons, and pathologists from establishing the diagnosis to organizing the multimodal therapeutic strategy (3).

Systemic treatment may be delivered in a curative-intent approach, for patients presenting with locally-advanced tumor at time of diagnosis, with invasion of intra-thoracic neighboring structures, and/or dissemination to the pleura and the pericardium, precluding upfront complete resection to be achieved. In such cases, chemotherapy has been used both to reduce the tumor burden—possibly allowing

subsequent surgery and/or radiotherapy—and to achieve prolonged disease control (3). While the TNM staging may help to better define the resectability of the mediastinal lesion, clinicians should remain aware that stage IVA in thymic tumors may still be eligible for curative-intent multimodal treatment (4).

Chemotherapy is also a palliative-intent treatment of unresectable, metastatic, and recurrent tumors, which are more frequently carcinomas than thymomas (5). Several consecutive lines of chemotherapy may be administered when the patient presents with tumor progression. Recent real-life evidence provides landmark efficacy data for such strategies (6).

Stage IVA adds a third opportunity for chemotherapy that may be delivered through intrathoracic approach after surgical pleurectomy (7). As studies regarding such intrathoracic chemohyperthermia (ITCH) were conducted on limited cohorts of patients given the rarity of thymic tumors, multidisciplinary discussion is always key in those patients.

Surgery for stage IVA thymic tumors

Surgery for disseminated pleural involvement is not well defined from debulking to extra pleural pneumonectomy

(EPP) and hyperthermic intrathoracic chemotherapy. Surgery may offer better recurrence free and overall survival (OS) when feasible especially in thymomas. Higher rates of recurrences and mortality are encountered in thymic carcinomas.

Debulking has been defined as removing 90% or more of tumor burden (8,9). The indication of debulking still remains controversial but may be proposed in non-resectable TETs with clearly inferior results as compared to standard, carcinologic surgery (10,11), actually providing better results in thymomas than in thymic carcinomas (12). Some authors advocate the place of debulking to improve efficacy of high doses radiotherapy by minimizing fields and showed significantly better survival in stages III and IVA.

A multicentric analysis of the European society of thoracic surgery (ESTS) thymic working group (13) of 152 patients with pleural involvement highlighted the benefit of surgery (26% EPP, resection of pleural implants 58% and total pleurectomy 15%) on OS. Three- and 5-year OS were 91% and 87% respectively and 3 and 5 years progression-free survival (PFS) were 58% and 43%. Once again, OS and PFS were worst in thymic carcinomas. A significant prognosis factor was the number of pleural implants (14,15). Finally, a study comparing 5 and 10 years OS between patient surgically managed [110] *vs.* non-surgically [172] was in favor of pleural surgery: 5 years OS 79% *vs.* 52% and 10 years OS 54% *vs.* 36% (16). EPP also provides good results on OS in selected patients; 5 and 10 years OS from 60% to 75% and 30% to 66% with unfortunately major adverse effects (20% to 41%) as broncho-pleural fistulas, significantly higher in univariate analysis in patients with myasthenia gravis, probably secondary to corticoids impregnation (17-19). In those series, 30 days mortality rate was 18% and 90 days mortality rate was 29%.

ITCH

Recently was introduced ITCH based on Cisplatin (from 50 to 100 mg/m²) possibly associated with other agents, and subtotal pleural decortication (4,7) with interesting results on PFS, OS and post-operative morbidity. One year and 5-year OS were 90–100% and 70–100% respectively (4,20-22). PFS was available in two studies from 42.0 to 47.2 months. In a series of 77 patients who underwent ITCH, only one post-operative death was numbered (1.3%) and morbid events were encountered in 26 (33%) from post-operative prolonged air leak to re-intervention

for wound sepsis or bleeding.

Systemic chemotherapy

As for other thoracic malignancies, chemotherapy regimens are selected in accordance with the intended use in patients with advanced thymic tumors. This depends on the tumor size, signs of infiltration on imaging, stage and histology. Thymic tumors are generally chemosensitive, although thymomas are more sensitive to chemotherapy than thymic carcinomas. Chemotherapy strategies include chemotherapy used both as initial treatment and as treatment in case of recurrence. Chemotherapy as initial treatment can be further divided into chemotherapy with curative intent (primary or preoperative chemotherapy or post-operative chemotherapy) and chemotherapy with palliative intent (5). Exclusive (palliative) chemotherapy is administrated in patients medically or technically not qualified for surgical procedures, or for patients with metastatic disease.

Primary (induction, preoperative) chemotherapy

The major goal of induction chemotherapy is to downstage the tumor prior to surgery. Therefore, chemotherapy regimens have to be evaluated based on their ability to induce response (3,5,6). In 2013, a Cochrane meta-analysis was performed to evaluate the role of induction therapy. Forty-nine relevant, randomized studies were identified, but none of them met the criteria necessary for a Cochrane analysis (23). Therefore, all published guidelines related to multimodal treatment of thymic neoplasm continue to be based on expert opinions. The majority of reported primary chemotherapy regimens are part of multimodality treatments. This may include presurgical or additional postoperative radiotherapy with and without chemotherapy. Therefore, the rate of complete resections (R0) and the response rates after induction chemotherapy are often difficult to evaluate, because different regimens are used. On average, for patients with stage III–IV thymic neoplasm, induction therapy achieved a response rate of 71% (29% to 100%) and surgery resulted in a complete resection in 68% (22% to 86%) (6). All regimens consisted of a combination of multiple drugs. The backbones of the induction therapies were cisplatin, anthracyclines, etoposide, and cyclophosphamide. Patients treated with induction treatment with multiple-drug chemotherapy have to be medically fit enough to have a performance status after induction that allows major surgery. However,

patients with thymic malignancies tend to be younger with less comorbidities compared with patients who have lung cancer. This means that even intense chemotherapy regimens with multiple drugs can be administered in this patient population.

Exclusive (palliative) chemotherapy

In cases when metastatic spread, or other reasons, prohibits local treatment with surgery or radiotherapy, exclusive chemotherapy with palliative intent is offered. Patients with relapse after curative-intent therapy are also treated with palliative chemotherapy. Monotherapies with cisplatin, ifosfamide, and paclitaxel were used in these patients (5). The current standard is combination chemotherapy, based on cisplatin regimens (5). No randomised studies have been conducted and which regimen should be considered standard remains unknown. Multiagent combination regimens and anthracycline-based regimens appear to have improved response rates compared with etoposide-based regimens (5,6). Combination of cisplatin, doxorubicin and cyclophosphamide is preferred (5).

Other treatments

Innovative treatments for advanced, refractory TETs are described in another article of this issue.

Conclusions

The management of stage IVA thymic malignancies is based on multidisciplinary collaboration. These tumors represent a specific entity with the opportunity of surgical treatment as well as the use of systemic agents if local treatment is not achievable or in combination with surgery, possibly through intrathoracic delivery. Taken together, multidisciplinary tumor board is key for the assessment of patients with stage IVA TETs.

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