Role of chemotherapy in malignant thymoma

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Thymomas and thymic carcinomas, wich are rare epithelial tumors arising from the thymus gland, are the most common tumors of the anterior mediastinum. Surgery is the principal treatment and is curative in early stage disease. Radiation therapy, either alone or in combination with chemotherapy, may be an option both in not completely and completely resected disease. Chemotherapy is offered to patients with locally advanced or metastatic thymoma and induces excellent responses race and prolonged survival.

KEY WORDS: Chemotherapy, Induction therapy, Paraneoplastic syndrome, Target therapy, Thymic malignancies.

Introduction

Thymoma is an epithelial malignancy arising from the thymus gland, accounting for nearly all primary tumours of the anterior superior mediastinum. Although most thymomas appear histologically benign, some cases behave as invasive epithelial malignancies, invading local structures or metastasizing to distant organs [1]. The term thymoma is generally used to describe neoplasms that show no overt atypia of the epithelial component. Although classically considered indolent, thymoma has malignant potential, as evidenced by its invasive potential. A thymic epithelial tumor that exhibits clear-cut cytologic atypia and histologic features no longer specific to the thymus is known as thymic carcinoma (also known as type C thymoma) [2,3]. Confusion exists because of previous "benign" or "malignant" designations. Currently, the terms *non invasive* and *invasive* are preferred. Non invasive thymomas have an intact capsule, are movable, and are easily resected, although they may be adherent to adjacent organs. In contrast, invasive thymomas involve surrounding structures and may be difficult to remove without *en bloc* resection of adjacent structures, despite their cytologic benign appearance. Thymic carcinoma is a rare aggressive thymic neoplasm that has a poor prognosis. Like thymoma, it is an epithelial tumor, but cytologically it exhibits malignant features. Extensive local invasion and distant metastases are common. Thymomas, including both *invasive* and *not invasive,* are relatively rare tumors, accounting 0.2%-1.5% of all malignancies [4]. Thymic carcinomas represent less than 0.1% of all thymic neoplasms [5].

Thymomas are generally indolent tumours, with patients' survival often measured in decades. Relapses following complete resection are uncommon. The peak incidence of thymoma occurs in the fourth to sixth decade of life with no predilection for gender. Children are rarely affected. Nearly half of the patients are asymptomatic, and the diagnosis is made incidentally by means of chest X-ray. Common symptoms include chest pain, cough, dyspnea, dysphagia, horseness, respiratory tract infections and superior vena cava obstruction. Most thymomas are confined to the mediastinum at the time of diagnosis. Distant metastases are rare, but when they occur often involve the pleural surfaces and lung parenchyma. Many paraneoplastic syndromes have been associated with thymoma. About 30-40% of thymoma patients have myasthenia gravis (and myasthenic symptoms); conversely, 10-15% of patients with myasthenia gravis have an underlying thymoma [6]. Paraneoplastic autoimmune syndromes associated with thymoma include also polymyositis, lupus erythematosus, rheumatoid arthritis, thyroiditis, Sjogren's syndrome, pure red cell aplasia and hypogammaglobulinemia [7].

The stage is the most important prognostic factor in thymomas. The Masaoka Staging System is the most commonly used system [8].

Unlike the TMN system commonly in cancer staging,

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the Masaoka staging system is based on the degree of invasion. Stage I tumors are completely encapsulated with no evidence of microscopic or macroscopic invasion. Stage II tumors have evidence of microscopic capsular invasion or macroscopic invasion into surrounding fat or pleura. Stage III tumors invade locally into surrounding structures, such as lungs, great vessels, and mediastinal structures, while stage IV tumors present with more distant lymphatic or hematogenous metastases.

General therapeutic strategies

Non invasive and locally invasive disease

For patients with curable thymic tumors (Masaoka stage I) the complete resection is a critical prognostic factor. Locally advanced tumors (Masaoka stage II) have a relatively high risk of recurrence and decreased rates of long-term survival. Surgery is the mainstay treatment of thymic malignancies, and complete resection represents the best prognostic factors in this disease. Radiation therapy is not indicated following complete resection of a well-encapsulated thymoma. However, it should be considered in the rare cases when a noninvasive thymoma is incompletely resected and when the patient has a poor surgical risk [9]. Locally advanced tumors (Masaoka stage III e IVA) are often treated with combined modality treatment including surgery, radiation, and chemotherapy.

Advanced disease

Chemotherapy has an important role in the treatment of advanced thymic tumors. Combination chemotherapy has been shown to produce a 40-80% objective response rate [10]. Anecdotal reports documenting single agent chemotherapeutic responses were published in the 1970s [11]. Because of the rarity of advanced thymomas, no large-scale chemotherapy clinical trial has been conducted. However, several small prospective trials have clearly shown the activity of of chemotherapy in the management of advanced thymoma (Table 1). The Eastern Cooperative Oncology Group (ECOG) reported that single agent cisplatin had modest activity in patients with advanced or recurrent thymoma. In the trial, two partial responses (PR) were observed in 21 patients, with a 10% overall response rate [12]. In 13 patients treated with single-agent ifosfamide, there were five complete responders (CR) and one partial responder, with an overall response rate about of 46% [13]. The estimated 5-years survival rate after ifosfamide treatment was estimated to be 57%.

Combination chemotherapy, particularly platinum-containing regimens, has been shown to have higher activity compared to single agent. A retrospective study of 37 patients with advanced (stage III or IV) disease treated with the ADOC regimen (adriamycin, cisplatin, vincristine, and cyclophosphamide) resulted in an overall response of 91.8% with 43% complete responders [14]. However, median duration of response and median survival were only 12 and 15 months, respectively. In a prospective phase II trial conducted by several U.S. cooperative groups [15], the combination of cisplatin, doxorubicin, and cyclophosphamide (PAC) was found to reach an overall response rate of 50% (three CRs plus 12 PRs) with a median duration of response of 12 months. The median survival was 38 months. The addition of etoposide to this regime (PACE) with granulocyte colony-stimulating factor (GCSF) support was evaluated in 14 patients with advanced thymoma or thymic cancer [16]. There were six PRs (three of whom had thymoma) for an overall response rate of 43%, with a median survival of 14.7 months. However, in this study a substantial hematologic toxicity was observed despite the prophylactic use of G-CSF. Furthermore, the inclusion of thymic carcinoma confounds the assessment of the result concerning thymoma. The European Organization for Research and Treatment of Cancer (EORTC) reported the results of a trial using cisplatin plus etoposide for locally advanced or metastatic thymoma [17]. In 16 assessable patients, five CRs and four PRs were observed for an overall response rate of 56%. Median response duration and median survival were 3.4 years and 4.3 years, respectively. A phase II

Table I

Author	Regimen	N.	Overall response rate (%)	Complete response rate (%)	Median survival (months)
Bonomi, et al	Cisplatin	21	10	NA	12
Highley, et al	Ifosfamide	13	46	38.5	NA
Fornasiero, et al	ADOC	37	92	43	12
Loehrer, et al	PAC	30	50	10	37.7
Oshita, et al	PACE	14	43	0	14.7
Giaccone, et al	EP	16	56	31	51.6
Loehrer, et al	VIP	28	32	0	31.6

Abbreviations: ADOC, doxorubicin, cisplatin, vincristine, and cyclophosphamide; PAC, cisplatin, doxorubicin, and cyclophophamide; PACE, cicplatin, doxorubicin, cyclophosphamide, and etoposide; EP, cisplatine and etoposide; VIP, etoposide, ifosfamide, and cisplatin; NA, not available.

Intergroup trial using etoposide, ifosfamide, and cisplatin (VIP) with G-CSF support in advanced thymoma and thymic cancer showed 9 PR out of 28 evaluable patients; no CR was observed. Seventeen patients had stable disease, whereas two patients developed progressive disease. The overall objective response rate was 32%, the median duration of response was 11.9 months and the median overall survival was 31.6 months [18]. However, due to the short follow-up (2 years), the results of this trial appear lower than other chemotherapy regimens.

Induction chemotherapy

A few studies have reported on neoadjuvant chemotherapy followed by surgery with or without radiation therapy in patients with locally advanced disease [19,20]. In one series patients with stage III or IVa invasive thymomas were treated with primary ADOC chemotherapy and all achieved a clinical response. Eleven patients had microscopic residual tumor and received postoperative radiation therapy. The median survival of the entire group was 66 months [19]. Another similar study in 12 patients reported 100% survival and 73% disease-free survival al 7 years [21]. Additional clinical studies are needed to confirm the value of preoperative chemotherapy before it might be routinely recommended in this disease.

Salvage therapy

Octreotide, in combination with prednisone, has been evaluated based on the observation that thymoma cells highly express the somatostatin receptor on their surface and radiolabeled octreotide exhibits high specificity for thymoma in comparison to thymic hyperplasia and other benign thymic disorders [22]. Complete clinical response in a patient with malignant thymoma and pure red-cell aplasia has been reported with octreotide and prednisone [23]. Some anecdotal cases explored the role of stem-cells transplantation in invasive thymoma [24,25]. A clinical trial on the role of the transplant of stem cells derived from umbilical cord is currently recruiting patients (http:/www.clinicaltrials.gov). Some activity of targeted therapies, specifically gefitinib, has been reported as well [26]. Twenty-six patients with metastatic or recurrent thymic malignancies (19 thymoma, 7 thymic carcinoma) received 250 mg gefitinb daily for six cycles if there was no evidence of progression after 2 months. One partial response lasting of 14.8 months was obtained. Although monotherapy with TK inhibitors seems disappointing, the strategy of combining new drugs with chemotherapy may be promising.

Personal experience

Between 1984 and 2006 20 patients with thymic tumors underwent a multimodality treatment in our department of Medical Oncology. Both surgery and radiotherapy were performed in our institution. Men/women ratio was 1:1; mean age was 49 years (range, 22 to 70 years). All patients underwent an extended thymectomy. According to the Masaoka staging, 3 patients had stage I, 7 patients had stage II, 8 patients had stage III and 2 patients had stage IV thymoma. The postoperative pathologic diagnosis, reviewed according to the World Health Organization histologic classification, showed 1 type A thymoma, 4 type AB, 1 type B1, 8 type B2, 4 type B3, and 2 type C. Four patients underwent neoadjuvant chemotherapy and surgery, followed by radiotherapy (2 patients) or chemoradiotherapy (2 patients). 14 patients underwent primary surgery and adjuvant therapy consisting of radiotherapy (n = 5) or chemoradiotherapy (n = 6); the other 3 patients in this group had stage I and were treated only by surgery. Finally, 2 patients had stage IV and received chemotherapy alone. One of these underwent surgery both for primary tumor and for liver metastases due to the good clinical response and young age. Fifteen patients are still alive. Of the 10 patients who experienced recurrence of disease, 3 were resubmitted to surgery for mediastinal relapse, 2 patients had lung metastases, 1 patient had liver and bone metastases and 4 patients had a not resecable mediastinal relapse. Considering all patients, median overall survival (OS) was 117 months, while time to progression (TTP) was 77 months. In stage I and II median OS was not yet reached, while in stage III the OS and TTP were 76 and 56 months, respectively. Considering only stage III disease, patients who underwent adjuvant chemotherapy had a better outcome, but ou cohort is not so large for detecting a significant difference.

Conclusions

Thymoma is a rare neoplasm with a mostly indolent growth pattern. Due to its potential for invasion and local recurrence, however, a multidisciplinary approach is recommended since the diagnostic phase. Although they are responsive both to chemotherapy and radiation, the mainstay of treatment is surgical resection. For inoperable patients an induction chemotherapy followed by surgery and adjuvant radiation therapy is suggested.
Durable responses can be obtained both in the metastatic and recurrent disease, and new drugs are currently being explored. Because of the low incidence of thymomas, innovative combinations have to be evaluated in multi-center cooperative trials. In this scenario a major role of medical oncologist in the initial clinical balance and therapeutic planning is emerging. Several new drugs might be evaluated: cytotoxic agent (such as the taxanes and topoisomerase I inhibitors), somatostatin analogs, high dose chemotherapy with stem cell rescue, investigational agents (such as flavonoids, signal trasduction inhibitors, and anti-angiogenic agents) as well as chemoradiation therapy. Furthermore, laboratory correlative studies in invasive thymoma are mandatory to investigate the tumor molecular characteristics, with the aim of developing more rational antitumor approaches.

Riassunto

I timomi sono le neoplasie più comuni del mediastino anteriore; originano dall'epitelio del timo e sono per lo più capsulate e quindi facilmente asportabili chirurgicamente. Tuttavia, una percentuale non trascurabile tende ad invadere altre strutture mediastiniche adiacenti, quali la pleura, il pericardio, il diaframma e i grossi vasi. Le metastasi a distanza non sono la regola, ma, quando si manifestano, interessano il polmone, il fegato e le ossa. La chirurgia è il trattamento di elezione nelle forme non invasive o nei casi con limitata invasività locale. La radioterapia è raccomandata come trattamento post-operatorio nelle forme invasive sia dopo chirurgia radicale che dopo resezioni incomplete. La chemioterapia viene comunemente riservata alle forme avanzate e/o metastatiche oppure alla ripresa della malattia dopo chirurgia non più trattabile con la radioterapia. Per problemi di numerosità statistica, la maggior parte degli studi clinici sulla chemioterapia è rappresentata da studi di fase II. I regimi chemioterapici di combinazione contenenti platino si sono dimostrati di maggiore efficacia se confrontati con i singoli farmaci. Gli schemi più usati sono ADOC (doxorubicina, cisplatino, vincristina, ciclofosfamide), PAC (cisplatino, doxorubicina, ciclofosfamide) ed EP (etoposide e cisplatino). La chemioterapia di induzione può essere efficace nel *downstaging* di timomi non candidabili inizialmente alla chirurgia. I pazienti con recidiva di malattia possono essere trattati nuovamente con regimi contenenti platino se è intercorso un intervallo libero di malattia di almeno 12 mesi mentre in pazienti chemiorefrattari si è dimostrata efficace una terapia di salvataggio con analoghi della somatostatina e cortisonici.

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