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The multimodality treatment of thymic carcinoma ☆

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Abstract

Objectives: Thymic carcinoma is a rare neoplasm more invasive and with a poorer prognosis than ordinary thymoma. Complete curative resection is sometimes not possible, but good response rates to chemotherapy are reported in literature. We report our experience with seven cases of thymic carcinoma, who took part to a multimodality treatment including neoadjuvant chemotherapy, surgery and post-operative radiotherapy in our center. **Methods**: Since June 1989, seven previously untreated patients were enrolled. The primary chemotherapy consisted of three courses of cisplatin (P; 75 mg/m^2 i.v., day 1), epidoxorubicin (E; 100 mg/m^2 i.v., day 1) and etoposide (VP16; 120 mg/m^2 i.v., days 1, 3 and 5), every 3 weeks. Surgery was performed following complete hematological recovery. After surgery, all patients underwent radiation therapy to the tumor areas, operatively marked with clips, at doses of 45 (complete resection) or 60 Gy (incomplete resection). **Results**: The pre-operative diagnosis of thymic carcinoma was performed in four cases by a mediastinotomy, and in the remaining cases, by an ultrasound-guided ($n = 2$) or a computed tompography-guided ($n = 1$) fine needle aspiration. All patients responded (one completely) to the chemotherapy regimen. Surgical resection was complete in four cases (histological examination negative in one case). Three patients are still alive and well (62–136 months from the diagnosis), two are alive with relapse at 16 and 85 months, one patient died at 86 months from another cause, and one patient died at 18 months from local relapse and lung metastases. **Conclusions**: A pre-operative shrinkage of the thymic carcinoma by means of neoadjuvant multi-drug chemotherapy may improve the resectability, and therefore, the survival rate. Our experience, although preliminary, is encouraging and merits additional study in a multicenter trial with a sufficient number of patients to draw definitive conclusions.

Keywords: Thymic carcinoma; Mediastinum; Neoadjuvant chemotherapy; Cisplatin; Survival

1. Introduction

Thymic carcinoma has been recently named type C thymoma, and defined as a thymic tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs by Rosai and the WHO [1]. Reviewing the literature and excluding the well-differentiated thymic carcinomas or atypical thymomas, which appear in most of the series and mislead the clinical outcome, it is clear that thymic carcinoma is more invasive and with a poorer prognosis than ordinary thymoma [2–6]. At diagnosis, they are mostly invasive or metastatic (stage III and IV by Masaoka) and complete curative resection is sometimes not possible to achieve. Good response rates to chemotherapy are reported in the literature [7,8] and multimodal strategies have been advocated [5]. We report our experience with seven cases of invasive thymic carcinoma, who took part to a multimodality treatment including neoadjuvant chemotherapy, surgery and post-operative radiotherapy.

2. Patients and methods

From June 1989 to April 1999, seven cases of thymic carcinoma underwent multimodal treatment in our division. The diagnosis of thymic carcinoma was confirmed by a review of microscopic sections by one pathologist (F.B.) and re-confirmed by an independent pathologist (G.F.).

The criteria for diagnosis of thymic carcinoma were those recently stated by Rosai and the WHO [1]: a thymic tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus in the absence of a primary tumor at sites other than the anterior

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mediastinum, either at the time of presentation or at follow-up.

The collection of data and follow-up were performed by reviewing medical charts and phone contact or visiting of patients. The patient characteristics are shown in Table 1.

Patient eligibility criteria were: histologically confirmed thymic carcinoma, clinical or radiological signs of involvement of major vessels and surrounding organs, age of less than 75 years, no history of malignancy, performance status (ECOG) of 0–3, adequate bone marrow reserve and liver and renal function, good left ventricular ejection and no active cardiac disease. Pre-operative staging included a complete history and physical examination, chest radiography, bronchoscopy, whole body computed tomography, abdomen ultrasonography and bone scan.

Tumor specimens, fixed in 10% buffered formaldehyde and embedded in paraffin, were stained with hematoxylin and eosin, periodic acid–Schiff and Masson's trichrome.

Sections were also analyzed immunohistochemically by using monoclonal antibodies against cytokeratin, epithelial membrane antigens (EMA), leukocyte common antigen and CEA. All cases showed uniform reactivity for keratin proteins, EMA and CEA, but none expressed the leukocyte common antigen.

Histologically, thymic carcinomas have been subdivided according Rosai's classification [1]:

1. Epidermoid keratinizing carcinoma.
2. Epidermoid non-keratinizing carcinoma.
3. Lymphoepithelioma-like carcinoma.
4. Sarcomatoid carcinoma.
5. Clear cell carcinoma.
6. Basaloid carcinoma.
7. Mucoepidermoid carcinoma.
8. Papillary carcinoma.
9. Undifferentiated carcinoma.

The neoadjuvant chemotherapy included three courses of intravenous cisplatin (75 mg/m^2 on day 1), epirubicin (100 mg/m^2 on day 1), and etoposide (120 mg/m^2 on days 1, 3 and 5), repeated every 3 weeks, depending on the patient's hematological status and in the absence of heart or general disorders.

Restaging was repeated 3 weeks after the third course, and in cases of response, the patients underwent surgery.

All of the operations were performed through a median sternotomy (in two cases, it was necessary to enlarge the operative field with a left anterior thoracotomy). A complete exeresis of the tumor was always attempted and whenever it was not possible (R1, surgical margins microscopically positive; R2, gross residual tumor), the residual tumor was clipped in order to better define the radiation therapy portals. All patients underwent a total thymectomy.

Post-operative staging was performed according to the staging system of Masaoka [9]. After surgery, all patients underwent radiation therapy to the mediastinal or residual tumor areas, using opposite anterior and posterior parallel fields at doses of 45 Gy for complete resections or 60 Gy for incomplete resections delivered in 5 or 6 weeks, respectively. The last three patients whose primary tumors or surgical relapses showed a high uptake of 111In-DTPA-D-Phe1 octreotide were treated with long-acting somatostatin analogue-based therapy. Survival was calculated from the date of the diagnosis until the date of the last follow-up (1st June 2000).

3. Results

The clinical outcomes of the seven patients who underwent the multimodality treatment are shown in Table 1.

All of the patients maintained or improved their pre-operative performance status. The hematological and non-hematological toxicities were mild to moderate and well tolerated. No patient had to stop the chemotherapy. Three patients had a tumor shrinkage of greater than 75%, and four between 50 and 75%. The staging procedure, repeated after chemotherapy, confirmed, in all cases, the absence of distant metastases.

A complete resection was possible in four cases (no evidence of tumoral cells in patient 3); in the remaining three cases, the resection was partial, two with gross (in the wall of the superior cava vein) and one with microscopic residual disease. There was no operative mortality or major perioperative morbidity.

At the last follow-up, five patients were alive and three of these are disease-free. One patient (patient 5), who experienced a single liver metastasis 46 months after the operation, underwent a liver resection and intrahepatic chemotherapy. Eleven months after the liver resection, the patient developed a hepatic hilum with lymph node involvement and he was operated on again. A second line of chemotherapy with ifosfamide, gemcitabine, vinorelbine was begun. Somatostatin receptor scintigraphy showed the presence of somatostatine receptors in these metastases, and therapy with long-acting somatostatine was administered. At the time of writing, he is still alive with new liver metastases.

One patient (patient 2) died due to a car accident, without evidence of disease at the autopsy.

One patient died with mediastinal recurrence, pulmonary and liver metastases, and one is living with bone metastases which appeared 10 months after the operation.

4. Discussion

Thymic carcinomas account for between 5 and 36% of all thymic neoplasms in most of the series [2–5]. The difference in incidences reflects differences in the pathological classification of so rare a tumor; however, considering the thymic carcinoma as defined by the WHO and excluding well-differentiated thymic carcinomas and atypical thymomas, the realistic incidence is 5–15%.

Table 1
Demographic data of the patients[a]

Patient number	Sex, age	Paraneoplastic syndromes	Clinical signs	Biopsy procedure	Objective response (%)	Masaoka stage	Type of surgery	Histology	Adjuvant therapies	Status	Disease-free	Survival (months)
1	M, 26	–	–	US-FNA[b]	$50 < x < 75$	III	PR (R1)	Undifferentiated	Radiotherapy	Alive	Yes	136
2	M, 51	–	SVCS	CT-FNA	> 75	III	CR	Lymphoepithelioma-like	Radiotherapy	Dead	Yes	86
3	M, 34	–	SVCS	US-FNA[b]	> 75	III	PR (R2)	Squamous-cell	Radiotherapy	Alive	Yes	130
4	M, 34	–	SVCS	Mediastinotomy	$50 < x < 75$	III	CR	Lymphoepithelioma-like	Radiotherapy	Dead	No	18
5	M, 51	–	Cough	Mediastinotomy	$50 < x < 75$	III	CR	Lymphoepithelioma-like	Radiotherapy	Alive	No	85
6	F, 64	–	SVCS	Mediastinotomy	> 75	III	CR	Squamous-cell	Radiotherapy	Alive	Yes	62
7	M, 56	–	Pain	Mediastinotomy	$50 < x < 75$	III	PR (R2)	Lymphoepithelioma-like	Radiotherapy	Alive	No	16

[a] SVCS, superior vena cava syndrome; CR, complete resection; PR, partial resection.
[b] Pre-operative diagnosis of thymoma.

The dismal prognosis of thymic carcinoma has determined the necessity to find prognostic factors capable of predicting the outcome and to experiment with new treatment modalities [5]. Neoadjuvant chemotherapy has been advocated, but only a few case reports exist in the scientific literature [10,11].

Blumberg et al. [5] recently presented the Memorial Sloan Kettering Cancer Center experience on 43 cases treated between 1949 and 1993. However, the incidence of type II thymoma (proper thymic carcinoma) was 27%, and the reported 42% incidence of stage I and II thymic carcinomas is much more than described in most of the papers. In the same report, the authors questioned the validity of the Masaoka staging applied to the prognosis of thymic carcinoma. Masaoka stressed that advanced stages of disease were prevalent in their series, with 18 out of 19 thymic carcinomas in stages III and IV [12]. In agreement with Masaoka, in the period of 1984–1999, we found only one stage II tumor, and we feel, even if we are not able to prove it, that it may be more useful to analyze the survival according to the extent of the disease (metastatic vs. not metastatic) and the extent of the resection (complete vs. partial) than according to the Masaoka staging.

Suster and Rosai [2] correlated the morphological features of the tumors with the clinical outcomes of patients, identifying low-grade and high-grade histologies.

The high-grade group (essentially the lymphoepithelioma-like carcinoma) had a higher rate of recurrences and a worse prognosis than the low-grade (essentially squamous-cell carcinoma).

In our series, three out of the four patients with low-grade carcinomas developed recurrences; that seems to confirm Suster's hypothesis.

Surgery and radiation therapy are the mainstay of the treatment in thymic carcinoma, however, chemotherapy has proven to be efficient in the treatment of metastatic thymic carcinoma [7,8].

In 1988, we started a prospective study of neoadjuvant chemotherapy, surgery and post-operative radiation therapy for invasive thymoma and our preliminary experience was described in 1991 [13]. At that time, the thymic neoplasms were analyzed all together and, as a consequence, three out of the seven patients in that report had proper thymic carcinomas.

Now, with more experience and a longer follow-up, four more patients with thymic carcinomas have been treated by neoadjuvant chemotherapy. There was a 100% objective response with one complete response, confirming the chemosensitivity of the thymic carcinoma that was postulated by Weide et al. [8].

All seven patients underwent surgery, and four complete resections have been performed. We did not experience any major technical difficulty, but we did not resect and reconstruct the superior vena cava when it was widely involved because we believed in the ability of radiation therapy to sterilize the tumoral field compared with surgical proce-

dures that, in the past, were considered to carry a high morbidity. Two tangential resections of the SVC have been performed, and in one case, the surgical margin was not free of tumor. Two of the three incompletely resected patients are still disease-free.

As a consequence, we support the role of radiotherapy in the adjuvant setting as an effective alternative to extended resections of major vessels when the tumor appears to be largely invasive, even if the replacement of the superior vena cava with a PTFE graft may be the best choice in selected cases.

In the beginning, we treated all the eligible patients with invasive thymic neoplasms with a multimodality treatment, including neoadjuvant chemotherapy, surgery, and post-operative radiation therapy, sometimes guided by the pre-operative diagnosis obtained by needle biopsy. Now, we no longer trust the reliability of needle biopsy in distinguishing thymic carcinoma from invasive thymoma and an epithelial thymic neoplasm from a mediastinal lymphoma, and we always perform a surgical biopsy of the mediastinal tumor by means of a mediastinotomy or a thoracoscopy.

The pre-operative study of the last three patients with somatostatin receptor scintigraphy deserves special comment. All of the patients showed the uptake of indium-111-octreotide, meaning that somatostatin receptors are also expressed in thymic carcinoma cells [14]. This evidence may undergo future development as a diagnostic and staging procedure: in the follow-up of asymptomatic patients in order to detect recurrences earlier than with CT or NMR, and in the differential diagnosis between relapse and surgical scar. More importantly, thymic carcinoma, as well as metastatic and invasive thymoma, may respond to treatment with somatostatin analogues [15–17]. If somatostatin analogues prove to be effective in the treatment of metastatic or inoperable thymic carcinoma, it will be interesting to test such drugs in the neoadjuvant setting.

We are treating patients 5 and 7, who experienced liver and bone metastases, with a long-acting somatostatin analogue, but it is too early to draw any conclusions.

The uptake of indium-111-octreotide is further evidence of the neuroendocrine differentiation of the thymic carcinomas, which, in the pathological field, some investigators confirmed by light microscopy and immunohistochemistry [18,19].

Our cisplatin regimen induced a 100% objective response with acceptable toxicity, but new chemotherapeutic regimens with new drugs should be tested before stating what is optimal.

In conclusion, a multimodal approach including primary chemotherapy is feasible and effective in thymic carcinomas, as well as in invasive thymomas; it seems to improve the resectability of thymic carcinoma invading the mediastinum and may reduce the otherwise high recurrence rate.

Obviously, in so rare a disease with an ominous prognosis, further single-institution, or better multi-institution experiences, also with different chemotherapeutic regimens, are necessary to validate our experience.

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