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Multimodal treatment for stage IVA thymoma: A proposable strategy

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ABSTRACT

A retrospective review of a series of consecutive patients was carried out to evaluate the feasibility and the efficacy of a multimodal treatment in the management of stage IVA thymoma at first diagnosis. From 1998 to 2008, 18 patients affected by stage IVA thymoma underwent neoadjuvant chemotherapy, surgery and subsequent mediastinal radiation therapy. There were 10 males and 8 females, mean age 54.5 years (range 29–68). Not specific symptoms were present in 12 cases and thymus-related syndromes were reported in 4. Histological subtypes were 1 AB, 2 B1, 4 B2, 7 B3, 1 mixed B1–B2, 1 mixed B1–B3 and 2 mixed B2–B3 thymomas. Neoadjuvant chemotherapy (4 courses of cisplatin-based chemotherapy) was well tolerated in all cases. Those patients demonstrating clinical response at restaging (16/18) received surgical resection: "en-bloc" thymoma, residual thymic tissue and tumour involved organs resection was carried out together with the pleural implants removal. Complete macroscopic resection was achieved 10/16 patients (64%). Postoperative mortality and morbidity were null and 24%, respectively. Adjuvant radiation therapy consisted of 45–54 Gy administered by a 6 MV linear accelerator to the whole mediastinum and previous tumour bed. Mean follow-up was 82 ± 33 months (range 31–143); overall survival was 85% and 53% at 5- and 10-years. Disease-related survival of the entire cohort was 100% and 58% at 5- and 10-years, whereas freedom from relapse survival for patients submitted to complete resection was 58% and 42% at 5- and 10-years. Disease-related survival when complete and not complete resection were considered were 100% and 52% and 72% and 0% at 5- and 10-years respectively ($p = 0.048$). Multimodal management based on induction chemotherapy, subsequent surgery and postoperative mediastinal radiation allows a good complete resection rate and it is demonstrated to be a safe and effective treatment to warrant a good long-term survival in stage IVA thymoma patients.

1. Introduction

Today surgery is considered the corner-stone therapy of thymoma. Completeness of resection, WHO histological classification and the Masaoka stage of the tumour are the most important factors affecting long-term prognosis [1–5]. Masaoka stage IVA describes a locally advanced tumour with pleural or pericardial dissemination without distant metastases [1]. The treatment of stage IVA thymoma is still controversial. The literature on stage IVA thymoma is limited owing to the rarity of the disease, series span several decades, old histological classifications are not comparable to the currently accepted one and therapeutic schemes and surgical techniques differ during the time.

Even if locally advanced, the localization of the disease into the chest is the substrate for a potential surgical resection. Although surgery has an established role in the plan of a multimodal treatment, the surgical procedure to be done is still debated. Some authors in the past proposed a radical approach with extrapleural pneumonectomy (EPP), whereas other ones advocated the use of lung-sparing procedures with good long-term survival of patients with stage IVA thymoma, in excess of 45% at 10 years [6–8].

Several reports suggest that multimodality therapy in advanced thymoma may improve outcomes by potentially increasing the resection rate and reducing recurrences [6,8–10].

The purpose of this study was to determine the feasibility and outcome of a multimodal therapy in a contemporary series of consecutive patients with Masaoka stage IVA thymoma at first diagnosis.

2. Materials and methods

Between 1998 and 2008, 126 patients affected by thymic tumours were observed. Of these, 20 patients had stage IVA

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thymoma with pleural implants. Two out of 20 were excluded from surgery: one because of his refuse and one because of an impaired cardiac function. A series of 18 consecutive patients who underwent neoadjuvant chemotherapy, surgery, and radiotherapy is retrospectively reviewed. Surgical specimens have been re-evaluated and the diagnosis of thymoma has been confirmed on the basis of the WHO classification of thymic tumours [11]. Clinical, radiological, pathological and follow-up data have been collected from the medical charts and direct examination of the patients (the local Institutional Review Board approved the study). The institutional policy of treatment was as follows:

Inclusion criteria: confirmed diagnosis of thymoma, clinical and radiological stage IVA disease [1], patients younger than 70 years with no history of previous cancer and no previous chemo- or radiotherapy, ECOG performance status 0–2, adequate bone marrow reserve (leukocyte count > 4000/mm^3; platelet count > 150,000/mm^3) and adequate liver (bilirubin < 1.5 mg/dl) and renal (serum creatinine < 1.5 mg/dl with creatinine clearance > 65 ml/min) function.
Exclusion criteria: previous surgery for thymic tumours or thymic-related syndromes, previous chemo- or radiotherapy for thymoma or affected by systemic diffuse disease (Masaoka stage IVB) [1], pathological diagnosis of type C tumour (thymic carcinoma) or thymic carcinoid [11].

On the basis of the above criteria, all the 18 reviewed patients have been submitted to a cisplatin-based neoadjuvant polichemotherapy. Two different chemotherapy regimens have been utilised during the period of the study. Twelve patients received four courses of intravenous adriamicin (40 mg/m^2) and cisplatin (50 mg/m^2) on day 1, vincristine (0.6 mg/m^2) on day 2 and cyclophosphamide (700 mg/m^2) on day 4 repeated every 3 weeks (ADOC scheme). Six patients received four courses of intravenous cisplatin (100 mg/m^2) on day 1 and etoposide (100 mg/m^2) on day 1 and 3 every 3 weeks (VP16 scheme). Patients were restaged 3 weeks after the 4th course. Response to preoperative therapy was graded according to the RECIST criteria (Response Evaluation Criteria in Solid Tumours) [12]. Partial response was defined as a 30% decrease and progressive disease as a 20% increase in the longest diameter of target lesion. Stable disease after chemotherapy was considered as a response too (in terms of no disease progression during treatment). Patients with demonstrated response to the neoadjuvant chemotherapy (stable disease and different grades of response) underwent surgical excision of the tumour. Complete exeresis of the tumour "en-bloc" with the involved organs and residual thymic tissue was always attempted; in the case of proved not resectable disease, the residual disease left behind has been clipped to better define the radiotherapy target. Post-operative staging was confirmed according to the Masaoka staging system [1].

Adjuvant radiotherapy was administered with a 6 MV linear accelerator. The treatment volume was the whole mediastinal field including the primary tumour bed, with the upper margin at the thoracic inlet and the lower margin at the diaphragmatic crurae. Patients were treated with antero-posterior opposed fields with the spinal cord dose limited to 45 Gy in all patients. Two anterior, wedge portals or off-cord, oblique, opposed portals were used to boost the anterior mediastinum to higher doses in the case of residual disease.

Survival analysis was performed using the Kaplan–Meier method and was calculated from the date of surgery to the date of death or to the last update of the series data-base (December 31, 2010). Freedom from relapse survival was determined in only those patients who had undergone a complete macroscopic resection and was calculated from the date of surgery to the date of the first detection of recurrent disease (complete cases) or to the date of last follow-up or of death for causes not related to the disease (censored cases); in this case autoptic confirmation of absence of recurrence was obtained whenever possible.

3. Results

3.1. Clinical and pathological data

From January 1998 to December 2008, 18 patients with stage IVA thymoma underwent a multimodal treatment including surgery. There were 10 male and 8 female, mean age 54.5 years (range 29–68). No differences were recorded when mean age were compared between sexes. Twelve patients (66%) were symptomatic at the time of first diagnosis: 6 had thoracic pain, 4 dyspnoea, 2 cough, 2 superior vena cava syndrome whereas 6 patients were completely asymptomatic. Four patients suffered for a thymic-related syndrome: 3 myasthenia gravis and 1 pure red cell aplasia. No associated diseases were described except for 2 cases of mild hypertension.

Pathological confirmation before multimodal treatment has been obtained by tumour biopsy trough anterior mediastinotomy in 16 cases and by computed tomography (CT) guided core-biopsy in 2 cases. The histological classification of the tumours was as follows: 1 AB, 2 B1, 4 B2, 7 B3, 1 mixed B1–B3, 1 mixed B2–B3 and 2 mixed B2–B3 type thymomas.

3.2. Preoperative treatments and response rate

The total number of neoadjuvant chemotherapy courses delivered was 72 (mean interval between courses 24.5 days). Median granulocyte, platelet and haemoglobins nadirs were 702/mm^3, 129,000/mm^3 and 10.1 gr/dl, respectively. Neutropenic fever occurred in 19 courses (27%). The most common not-haematological toxicities were alopecia (51/72) and nausea/vomiting (53/72), usually mild to moderate (grade 1 or 2 of the WHO scale).

There were 2 cases of progressive disease, 4 cases of stable disease, 11 cases of partial response, and 1 case of complete response. The response rate (stable disease plus partial plus complete response) was 16/18 (86%). Two cases with progressive disease have been excluded from the present study.

3.3. Surgical treatment and completeness of exeresis

Sixteen out of 18 patients received surgical resection of their tumour through an hemi-clamshell (5 cases), sternotomy plus hemi-clamshell (6 cases), lateral thoracotomy (2 cases) and sternotomy plus lateral thoracotomy (2 cases) incision. On the basis of the operation charts and pathological review of the specimens, complete macroscopic resection was carried out in 10 cases, whereas 6 patients had not completely resected disease. In particular, not complete resection occurred in 2 out of 4 cases (50%) of stable disease and in 4 out of 11 cases (30%) of partial response after induction chemotherapy.

Ten patients submitted to complete macroscopic exeresis of their disease had residual thymic gland and thymoma resected "en-bloc" with other tumour involved organs or structures; in some cases prosthetic replacement was required. The extended procedure beside the thymic and mediastinal tumour component resection is listed in Table 1.

The six patients submitted to incomplete exeresis received "en-bloc" thymectomy and thymomectomy together with macroscopic pleural implants removal (6 cases) and pulmonary wedge resections (4 cases), but macroscopic disease was left behind (R2) because of the not resectable involvement of the great vessels (5 cases) and bilateral phrenic nerve involvement (2 cases).