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Thymomas and Thymic Cancers: About a Moroccan Population

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Abstract

Background: Thymic epithelial tumors are rare tumors with variable prognosis. They include thymomas and thymic carcinomas. The therapeutic strategy depends on the anatomo-clinical stage. However, significant differences are observed in therapeutic response and survival. The aim of this study is to describe the epidemiological, clinical, pathological characteristics, therapeutic results and the prognosis of thymomas and thymic carcinomas.

Materials and methods: This is a retrospective study of a series of thymomas and thymic carcinomas collected at the Medical Oncology Department of the Hassan II Hospital in Fez during a period of 7 years [October 2010 to May 2017]. Epidemiological, clinical, pathological and therapeutic results were analyzed by Excel. Disease-free survival, progression-free survival and overall survival were calculated using the Kaplan-Meier method.

Results: Thymomas represent a frequency of 0.1% of all cancers treated in the Oncology Department. The median age of the study population was 49.64 years [22-81 years] and the sex ratio was 2.4. Dyspnea and chest pain were the most common revealing symptoms. Myasthenia represents the essential paraneoplastic syndrome encountered in our series. Majority of cases were diagnosed at locally advanced and metastatic stages (82.3% of cases). 70.6% of cases were thymomas and 29.4% thymic carcinomas. Two cases in this study underwent surgery, it was complete and without microscopic residue in both cases. Two patients received radiotherapy adjuvant to surgery or after neoadjuvant chemotherapy. Chemotherapy was prescribed in 13 patients mostly in a palliative setting. Two patients were cured, 8 patients died from disease, 3 patients were lost of view, the remaining patients were in locoregional and distance control.

Conclusion: Thymic epithelial tumors, including thymomas and thymic carcinomas, are rare tumors and belong to the group of orphan tumors. They present specific problems, from pathological diagnosis to the treatment requiring multidisciplinary therapeutic strategy.

Keywords: Thymic cancer; Thoracic oncology; Chemotherapy; Pathological diagnosis; Therapeutic strategy; Carcinomas

Introduction

Thymic epithelial tumors represent the most common anterior mediastinal tumors and account for 50% of all these tumors. Thymic epithelial tumors are rare, representing 0.2% to 1.5% of neoplasias. The annual frequency of thymomas is 0.15 cases per 100,000 people [1-4], whereas thymic carcinomas, are even more rare, representing less than 1% of all thymic tumors. The objective of this study was to evaluate the epidemiological and therapeutic aspects of thymoma and thymic carcinoma in a Moroccan population.

Research Methodology

This is a retrospective study carried out on patients followed for thymoma or thymic carcinoma in the department of medical oncology of Hassan II University Hospital of Fez between 2010 and 2017. We have included any patient over 18 years old who has thymoma or thymic carcinoma and whose histological diagnosis was made through a CT scan guided biopsy or surgical excision. We determined the clinical, radiological and biological data as well as the treatments received. The type of treatment response was specified based on the RECIST V1.1 criteria. Statistical analysis included measuring frequencies, calculating medians and means. We also calculated median follow-up duration, median overall survival, and disease-free survival (in localised diseases) or progression-free survival (in advance diseases).

Results

A total of 17 cases of thymic tumors were recorded. The annual frequency of these tumors was 2.42 new cases per year representing less than 0.1% of all cancers. The mean age of our patients was 49.64 years old with extremes of 22 years and 81 years. Male predominance (70.58% of cases) was noted. The mean time between onset of symptomatology and consultation was 8.6 months with extremes of 2 and 18 months.

Fifteen patients in our series (88.23% of cases) presented suggestive symptoms of mediastinal involvement ; thoracic pain was noted in 11 patients (64.7% of cases), dyspnea was noted in 9 patients (52.9%), dysphonia was found in one patient (5.8%), vena cava syndrome was noted in 7 patients (41.1%) and cough with mucous expectorations were noted in 3 patients (17.6%).

The discovery of a basi-cervical mass was indicative of the thymic tumor in one patient (5.8% of cases) while the disease was discovered during the etiological workup of myasthenia in two patients (11.6% of cases).

Sixteen patients (94.1% of cases) maintained a good performance status (ECOG 0 or 1). Physical examination revealed signs of local extension (restrosternal wall mass in one patient ; 5.8% of cases), regional extension (cervical lymphadenopathy in 3 patients ; 17.6% of cases) or signs of compression (facial edema associated with superior vena cava syndrome in 7 patients ; 41.1% of cases). In our study, radiological explorations were mainly based on thoracic CT scan. Histological diagnosis was based on surgical excision specimen in two patients (11.7% of cases). For the remaining patients, a CT guided transthoracic needle biopsy was made in 14 patients (82.3% of the cases) and a surgical biopsy through thoracoscopy in one patient (5.8% of the cases). The two predominant histological types in our series were B2 thymoma (N=6, 35.2% of cases) and thymic carcinoma (N=5, 29.4% of cases). The histological type has been correlated with the stage of the disease. Thus,

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the thymomas were mainly staged III (41.6% of cases) and IV b (33.3% of cases) while thymic carcinomas were mainly metastatic (80% of cases). Neoadjuvant chemotherapy was performed in 6 patients (46.15% of cases). The regimen was based on Cisplatin (50 mg/m^2), Adriamycin (50 mg/m^2), Cyclophosphamide (500 mg/m^2). The mean number of cycles was 4.6 (extremes: 2-8 cycles). Two initially unresectable diseases were converted to resectable disease after neoadjuvant chemotherapy. Surgery was carcinologic without any microscopic residue in all the resected cases.

Two patients received adjuvant radiotherapy. In both cases, the total dose was 60Gy. Adjuvant chemotherapy was not performed under any circumstances. In the metastatic setting, first-line metastatic treatment consisted of a triple therapy based on the CAP protocol in 5 patients and two patients received dual therapy based on Carboplatin and Paclitaxel. Four patients (30.7% of cases) received second-and third-line chemotherapy. After a median follow-up of 19 months [3-27 months], we noted: a median disease free survival of 25 months [8-27] in patients who received curative treatment, a median progression-free survival of 6 months [3-13 months] in patients who received palliative treatment and a median overall survival of 9 months [3-27 months]. The data set of the 17 patients is summarized in Table 1.

Discussion

Epidemiological characteristics

In our series, thymic tumors represented less than 0.1% of the cancers treated in the oncology department of Hassan II University Hospital confirming to the rarity of this tumor. Indeed, the frequency of thymic tumors is 0.1 to 0.2% of all cancers [1-4]. According to a French multicentre study, conducted by Dahan in 1988 in 500 cases of thymoma, the mean age of patients was 47.7 years. The 40-50 age group was the most affected [5]. Thymic tumors is a disease of young adults, however exceptional cases in children have been observed [6]. These data were confirmed in our series since the mean age of our patients was 49.64 years old. Similarly, the male predominance found in our series has been documented in the literature [3].

Clinical features

Our series revealed an important delay in the cancer diagnosis in our population with a mean delay between onset of symptoms and consultation of 8.6 months. As a result, the majority of our patients, (52.94% of the cases) consulted at the stage of locoregional invasion made of superior cell syndrome, dyspnea or dysphonia.

N	Gender	Age	Clinical presentation	ECOG	Histo-logical subtype	Stade MASAOKA	Treatment	Evolution
1	M	22	Thoracic pain Dyspnea Vena cave sup	1	B1	III	Neo-adjuvant chemotherapy 3 CAP (No surgery)	- Progression: Yes - PFS: 3 months - Death: Yes - OS: 9 months
2	M	57	Thoracic pain Dyspnea Vena cave sup	1	B1	IVb	Palliative chemo-therapy: 4 CAP	- Progression: Oui - PFS: 6 months - Death: Oui - OS: 10 months
3	F	63	Thoracic pain	1	B2	IVb	Palliative chemo-therapy: 10 CAP	- Progression: ND - PFS: 13 months - Death: No - OS: 13 months
4	M	28	Myasthenia	0	Thymic Carcinoma	III	Neo-adjuvant chemotherapy 8 CAP , surgery and radiotherapy	- Reccurence: No - DFS: 27 months - Death: No - OS: 27 months
5	M	37	Dyspnea Vena cave sup	1	B2	IVb	Palliative chemo-therapy: 3 CAP	- Progression:Yes - PFS: 6 months - Death: Yes - OS: 3 months
6	M	81	Thoracic pain Dyspnea Dysphonia	1	B3	IIb (Non operable)..	Neo-adjuvant chemotherapy 2 Carbo-pacli then radiotherapy 60 Gy	- Recurrence: No - DFS: 8 months - Death: No - OS: 8 months
7	F	22	Thoracic pain Basi cervical mass Vena cave sup	0	Thymic Carcinoma	IVb	Palliative chemo-therapy L1: 3 CAP L2: 10 cycles 5FU L3: 3 Paclitaxel and zometa	- Progression: Yes - PFS: 6 months - Death: Yes - OS: 18 months
8	F	43	Thoracic pain Dyspnea	1	B2	III	Neo-adjuvant chemotherapy 8 CAP. Discussion of surgery	- Progression: No - DFS: ND - Death: No - OS: 9 months

9	M	40	Dyspnea Vena cave sup	1	B3	III	Neo-adjuvant chemotherapy CAP 3 cycles then radiotherapy	-Progression: Yes - PFS: 3 months - Death: No - OS: 6 months
10	M	70	Thoracic pain Cough	1	B2	IVb	No treatment (deceased before starting any treatment)	- Death: Yes - OS: 4 months
11	M	24	Thoracic pain Dyspnea Vena cave sup	1	Thymic Carcinoma	IVb	Palliative chemo-therapy L1: 6 Carbo-Pacli L2: 3 Gemcitabine L3: 3 Pacli hebdo+ zometa	-Progression: Yes - PFS: 6 months - Death: Yes - OS: 15 months
12	M	53	Thoracic pain Dyspnea Vena cave sup	1	Thymic Carcinoma	IVa	Palliative chemo-therapy L1: 6 Carbo-Pacli	-Progression: ND - PFS: 6 months - Death: No - OS: 6 months
13	F	53	Cough + expectorations	1	B2	IVa	Palliative chemo-therapy L1: 3 CAP L2: 10 Gemcitabine L3: 7 Paclihebdo+ zometa	-Progression: Yes - SSP: 3 months - Death: No - OS: 22 months
14	F	61	Dyspnea	0	B1	IIb	Surgery	Recurrence: No DFS: 25 months Death: No OS: 25 months
15	M	75	Thoracic pain	3	Thymic Carcinoma	IVb	Palliative care	Death: Yes OS: 3 months
16	M	56	Thoracic pain Myasthenia	1	B2	III	Neo-adjuvant chemotherapy 4 CAP then lost of follow up	-Progression: ND -PFS: 6 months -Death: ND -OS: 6 months
17	M	59	Cough+ expectorations	0	A	III	No treatment (Lost of follow up)	- Progression: ND - PFS: 3 months - Death: ND - OS: 3 months

F: Female, M: Male, PFS: Progression Free Survival,, DFS: Disease Free Survival, OS: Overall Survival, ND: Not Determined, CAP: Cyclophosphamide, Adriamycin And Cisplatin, Carbo-Pacli: Carboplatin and Paclitaxel

Table 1: Summary of the clinical, paraclinical, therapeutic aspects and evolution of thymic tumors in our series.

Many paraneoplastic syndromes can accompany or reveal a thymic tumor. Myasthenia is the most common paraneoplastic syndrome, whose frequency varies from 10 to 75% depending on the series. This association was found in 11.76% of our patients similarly with other international studies [7].

Histological characteristics

The confirmation of a thymic tumor is based on the histological examination of the excised specimen in encapsulated, noninvasive tumors. Thymomas are usually lobulated by fibrous septa. These partitions sometimes contain radiologically visible calcifications. Thymomas typing is based on the shape of the epithelial cells and the proportion of associated lymphocytes. Thymic carcinomas are mostly epidermoid carcinomas, well differentiated or not. Other types of carcinomas are very rare: basaloid, mucoepidermoid, lymphoepithelioma, sarcomatoid, clear cell type, or adenocarcinoma. The existence of border forms between histological subtypes (15% of cases), and heterogeneous tumors combining several subtypes (25% of cases), explains the difficulties of thymic tumors diagnostic.

Some immunohistochemical staining may be useful especially in biopsy specimens. Thymic carcinomas often express the CD5 (T lymphocyte marker) antigen and the CD117 antigen. Unlike digestive stromal tumors, this latter expression is not linked to a mutation in the cKit gene. In AB thymomas, epithelial cells often express the CD20 antigen (B lymphocyte marker). For all thymic epithelial tumors, the study of molecular therapeutic targets (in particular EGFR and IGFR, but not CerB2) is promising [8].

Staging and treatment

Staging is done according to the Masaoka-Koga-ITMIG system, on the basis of which therapeutic decisions are established. Surgical resection is the main treatment of thymic tumors. The recommended surgical approach is median sternotomy [9,10]. The importance of resection depends directly on the level of tumor invasion. Stage I-II thymomas require only total thymectomy. Stage III and IV tumors require, however, a bulky resection of the tumor and adjacent invaded structures (pleura, pericardium, large vessels) with lymph node dissection of the anterior mediastinal region and sampling of other regions (paratracheal region, aortopulmonary window, subcarinal area). For thymic carcinomas, lymph node dissection of the mediastinal anterior, supraclavicular and low cervical regions is recommended in all the stages. Post-operative mortality does not exceed 3% [11]. The rate of complete resection depends on the stage of the disease; it is about 100% for stages I and II, 85% for stages III and 42% for stages 4 [9-13], and represents, after tumor stage, the most significant prognostic factor for overall and recurrence free survivals [10].

Adjuvant radiotherapy should begin within 2 to 3 months after surgery. The target volume includes all of the thymic bed and any tumor extensions (pericardium, large vessels, pleura, lung parenchyma, etc.) [14]. The dose delivered is usually between 45 and 50 Gy after complete resection in standard fractionation (1.8 to 2 Gy per session). In the case of incomplete resection, an overprint of up to 54-60 Gy is required for R1 resection and up to 66 Gy for R2 resection. The indications for postoperative radiotherapy after complete surgical resection are based on retrospective series with contradictory results [15,16]. It may be indicated in thymic carcinomas or stage III thymomas.

In the case of locally advanced tumors (stage IIIB), radiotherapy at a dose of 60 to 70 Gy is the standard treatment. The combination of chemotherapy and radiotherapy has the advantage of improving the survival of non-extirpable tumors compared with exclusive radiotherapy. Indeed, Loehrer et al. investigated the feasibility and tolerance of the combined approach in unresectable tumors. The objective response rate was 69.6% and the median overall survival was 23 months [17].

Neoadjuvant chemotherapy should be suggested in locally advanced non-resectable tumors (Masaoka-Koga stages III to IVA). The optimal therapeutic sequence in these situations is multimodal and includes 3 to 4 courses of chemotherapy, surgical resection, and post-operative radiotherapy. Postoperative chemotherapy, after R0 or R1 resection, is not recommended. It may be exceptionally discussed in cases of stages II, III, and IV thymic carcinoma.

In metastatic diseases, exclusive chemotherapy is the standard treatment. Cisplatin (50 mg/m^2), Adriamycin (50 mg/m^2), Cyclophosphamide (500 mg/m^2) (CAP) administered every 21 days is the most commonly used protocol and probably gives the best response rates. Loehrer evaluated the CAP protocol in 1994 in 29 metastatic and recurrent patients. The objective response rate obtained was 50% with a median survival of 38 months [18].

Combinations of carboplatin (AUC 5 to 6) and paclitaxel (150 to 200 mg/m^2) is the most widely used alternative after CAP, especially in cases of thymic carcinoma. In a phase II study conducted by Lemma et al in 46 cases of thymoma and thymic carcinoma, the objective response rate under the combination Carboplatin and Paclitaxel ranged from 21.7% for thymomas to 42.9% for thymic carcinomas [19].

Angiogenic and mTOR inhibitors were also tested in the metastatic setting. A phase II trial demonstrated the efficacy of sunitinib, in terms of response rate and disease control in patients with thymic carcinoma or recurrent thymomas [20]. Everolimus also showed response rates of 69% and progression-free survival of 11.3 months [21].

The role of immune checkpoint inhibitors also emerges in thymic tumors. In a phase II study, 40 patients with refractory thymic carcinoma were treated with pembrolizumab [22]. The objective response rate was 22.5%. These responses were relatively durable, with a median duration of 22 months.

Prognosis of thymic tumors depends mainly on the histological subtype and the stage of the disease. Indeed, the 5 years survival rate varies from 74% (stage I) to 45% (stage IV) in thymomas and from 74% (stages I and II) to 24% (stage IV) in thymic carcinomas [23]. In our series, a reserved prognosis has been documented and this was due to several factors: the limited number of patients included in the study in comparison with that of other series reviewed in the literature, the delay of diagnosis related to a delay of consultation, the high rate of advanced and metastatic stages in our series. Therefore, the treatment was mainly palliative and the prognosis was pejorative.

Conclusion

Thymic tumors are rare mediastinal tumors. Throughout the literature it can be deduced that thymic tumors are generally of good prognosis. However, in our study a reserved prognosis has been documented. Therefore, the treatment was mainly palliative and the prognosis was pejorative. Finally, to improve the therapeutic and prognostic results of these patients, it is proposed to establish prospective studies of thymic tumors and more codified treatments through thymic tumors network.

Ethics Approval and Consent to Participate

This is an observational study that analyzed retrospectively and anonymously data from the patients' medical records. No ethics approval was demanded

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests

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Author's Contributions

ZB and HB: Designed the study, analyzed data, and interpreted data as well as provided critical revision of the content and provided approval of the final version; LA and FE: Have been involved in revising the manuscript and provided approval of the final version; SA and NM: Provided analysis of the data, provided critical revision of the content, and provided approval of the final version

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