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Original article

Refractory Thyroid Carcinomas: Experience of the Medical Oncology Department of Hassan II Hospital in Fez, Morocco

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Abstract

Background: Refractory thyroid carcinomas are rare. The prognosis of these carcinomas depends on several factors including the histological type and the evolutionary stage. ***Aim:*** Determine the epidemiological, pathological and prognostic characteristics of refractory thyroid carcinomas and to focus on the therapeutic modalities used for the treatment of these cancers. ***Methods:*** Our work is a retrospective descriptive study on 28 cases collected in the medical oncology department of Hassan II hospital in Fez over a period of 7 years, from January 2012 to January 2019. The statistical analysis of the results was done by SPSS version 23. Survival was calculated by the Kaplan-Meier method. ***Results:*** The average age was 57.3 years, with a sex ratio F/M of 1.3. Thyroid nodule and multi-hetero nodular goiter were present in 32.1% and 28.5% of cases, respectively. The most common carcinoma was the papillary (36%) followed by the vesicular (25%), the anaplastic (25%) and the medullary (14%). The first line treatment was based on SORAFENIB (administered to 40% of patients) and on conventional chemotherapy (60%). After an average number of 4 courses, the objective response rate was 47%. The median of progression-free survival was 15 months and that of overall survival was 25 months. ***Conclusion:*** Overall, refractory thyroid cancers are rare. Systemic treatments have evolved considerably in recent years with the development of targeted therapies, pending the advent of immunotherapy that could improve the prognosis of patients with these cancers, particularly those with anaplastic carcinoma.

Keywords: ***thyroid, refractory carcinoma, prognosis.***

Introduction

Thyroid cancer is a rare endocrine cancer, accounting for 2.5% of all cancers [1]. Its incidence has increased in recent years due to early detection. In contrast, refractory thyroid cancers (RTC) are uncommon, and their annual incidence has remained stable [2]. These cancers include undifferentiated or anaplastic carcinomas [3], locally advanced or metastatic medullary carcinomas not accessible to surgical treatment [4] and locally advanced or metastatic differentiated carcinomas refractory to iratherapy [5]. The prognosis of these tumors depends on several factors including the histological type and the stage of development, but generally the prognosis remains poor. Knowledge of molecular biology and oncogenic pathways involved in the genesis of thyroid cancer has enabled the development of targeted therapies with promising results [6,7]. The objective of our study is to determine the epidemiological, anatomopathological and prognostic features of these tumors and to provide an update on the therapeutic modalities used for the treatment of these cancers, based on a review of the literature.

Methods

Our work is a descriptive retrospective study of 28 cases of refractory thyroid carcinomas, collected at the medical oncology department of the Hassan II hospital in Fez, over a period of 7 years, from January 2012 to January 2019. The carcinomas included in our study are those confirmed histologically. The statistical analysis of the results was done by SPSS version 23 software, the qualitative variables are expressed in frequency and percentage and the quantitative variables are expressed as median and mean. Survival was calculated by the Kaplan-Meier method.

Results

In our series, the average age was 57.3 years with age extremes ranging from 31 to 80 years. The most affected age group was

between 51 and 60 years old. There was a slight female predominance with a sex ratio F/M of 1.3. 25% of the patients were followed for a goiter and only one patient for a benign hypertrophy of the thyroid. None of our patients was the victim of accidental or iatrogenic irradiation, and no cases of familial thyroid carcinoma have been reported.

Thyroid nodule and multihetero-nodular goiter were present in 32.1% and 28.5% of cases respectively (Fig1), signs of compression (dysphonia, dyspnea, dysphagia) and signs of metastatic involvement (bone pain, respiratory signs, neurological signs) were found in 28.5% and 17.8% of patients respectively. 72% of the patients had a PS (1-2) at the time of diagnosis and 28% had a PS of 3. All the patients underwent an extension assessment by a cervical-thoraco-abdomino-pelvic computed tomography (Fig2). The elective site of metastases was in descending order: lung (57%), lymph nodes (53%), bone (43%), liver (3%), brain (3%) and chest wall (3%).

In order to obtain a definite histological diagnosis, 82% of patients performed a total thyroidectomy, 7% a subtotal thyroidectomy and 11% a lymph node biopsy. Pathological examination revealed the presence of papillary carcinomas in 36% of cases, vesicular carcinomas in 25% of cases, anaplastic carcinomas in 25% of cases and medullary carcinomas in 14% of patients.

Hormone replacement therapy was prescribed in 82% of patients who underwent total thyroidectomy. Radioactive Iodine I-131 therapy was prescribed in 61% of cases at a dose of 100 mCi for patients with carcinomas of follicular strains. Palliative radiotherapy was indicated in 28% of patients. The indications were: External Beam radiation therapy for analgesia in 5 patients, decompressive radiotherapy in 3 patients and encephalic radiotherapy in one patient. The bone modulating agent has been prescribed in patients with bone metastases. Palliative care was indicated in 28% of patients who had deteriorated general condition (PS 3) at the time of diagnosis. First-line treatment was essentially based on systemic treatment, initiated in 72% of patients. SORAFENIB was administered in 40% of patients with an average duration of 25.3 months and conventional chemotherapy in 60% of patients. The CISPLATIN-DOXORUBICIN combination was administered in 6 patients, The CARBOPLATIN-PACLITAXEL combination in 3 patients and DOXORUBICIN as monotherapy in 3 patients (Table 1). After an average number of 4 cures, the objective response rate was 47%. All the patients who received first-line SORAFENIB are currently on treatment. The median progression-free survival (PFS) was 15 months and that of overall survival (OS) was 25 months. For patients who have progressed on 1st line chemotherapy, they may have received either SUNITINIB or DOXORUBICIN 2nd line. Adverse reactions induced by tyrosine kinase inhibitors (TKIs) were asthenia in 87.5%, diarrhea in 50% of cases, hematotoxicity in 50% of cases and hand-foot syndrome in 37.5% of cases. High blood pressure was observed in 12.5% of cases. Grade 3 and 4 toxicities were in the order of 37.5%. The most common side effects seen with chemotherapy were haematological complications (58%) and peripheral neuropathy (25%).

Table No 1: Patient characteristics

Characteristics		**Number (%)**
Gender	Male	12(43)
	Female	16(57)
Age	<=60 years	17(61)
	> 60 years	11(49)
Risk factors	Goiter	7(25)
	Benign thyroid enlargement	1(3.6)
	Previous irradiation	0(0)
	Family cases	0(0)
Clinical signs	Cervical swelling	9(32.1)
	Goiter	8(28.5)
	Signs of compression	8(28.5)
	Signs of metastatic involvement	5(17.8)
Performance Statut (PS)	1-2	20(72)
	3	8(28)
Metastatic sites	Lung	16(57)
	lymph nodes	15(53)
	Bone	12(43)
	Liver	1(3)
	Thoracic wall	1(3)
	Brain	1(3)
Diagnostic methods	Total thyroidectomy	23(82)
	Subtotal thyroidectomy	2(7)
	Lymph node biopsy	3(11)
Histological type	Papillary carcinoma	10(36)
	Vesicular carcinoma	7(25)
	Medullary carcinoma	7(25)
	Anaplastic carcinoma	4(14)
Palliative treatment	Hormone replacement therapy	23(82)
	Iratherapy	17(61)
	Palliative radiotherapy	8(28)
	Conventional chemotherapy	12(43)

First line treatment	Targeted therapy (Sorafenib)	8(29)
	Palliative care	8(28)
Conventional chemotherapy	CISPLATIN-DOXORUBICIN	6(50)
	CARBOPLATIN+PACLITAXEL	3(25)
	DOXORUBICIN	3(25)

Table 2: Main phase II studies of tyrosine kinase inhibitors in patients with differentiated thyroid cancer refractory to iodine-131.

Tyrosine kinase inhibitor	Number of patients	Partial response (%)	Stability> 6 months (%)
AXITINIB Cohen **(22)**	45	31	38
MOTESANIB Sherman **(23)**	93	14	33
PAZOPANIB Bible **(24)**	37	49	NR
SUNITINIB Carr **(25)**	29	28	46
VANDETANIB Leboulleux **(26)**	73	0	57
NR : Not reached			

Table 3: Main phase III studies of tyrosine kinase inhibitors in patients with refractory thyroid carcinoma.

Study	Treatment	Number of patients	Response rate %	Progression-free survival Median (months)	Value-P
DECISION (6)	Sorafenib vs placebo	207 vs 210	-	10.8 vs 5.8	<0.001
SELECT (7)	Lenvatinib vs placebo	261 vs 131	64% vs 1.5%	18.3 vs 3.6	<0.001
ZETA (27)	Vandetanib vs placebo	231 vs 100	45% vs 13%	30.5 vs 19.3	<0.001
EXAM (28)	Cabozantinib vs placebo	219 vs 111	28% vs 0%	11.2 vs 4	<0.001

Discussion

Thyroid cancer is a relatively rare pathology, its incidence has increased in recent years, it is estimated at 15/100,000 inhabitants in the United States [8], while in France, thyroid cancer affects around 8,000 cases per year [9]. It is a predominantly female disease; it affects 3 to 4 times more women than men demonstrated in several studies [10,1]. In our series, thyroid cancer was more common in women than in men.

Refractory thyroid cancers are uncommon, account for 5 to 15% of thyroid cancers, their incidence has remained stable, but they present a high risk of relapse and death [10,11].

Pathologically, there are 3 categories of thyroid cancer: the first type includes differentiated carcinomas derived from follicular stem cells, they represent more than 90% of thyroid cancers [10,12], they are tumors with a good prognosis but around 10 % of these tumors relapse after the initial treatment, relapses most often occur at the cervical lymph node level and almost in a 1/3 of cases at a distance in the lung and bone [13]. The second type is represented by medullary carcinomas, they represent 3 to 5% of all thyroid cancers [14], they start from C cells. Approximately 1/3 of these carcinomas are hereditary [15], linked to a germline mutation of the RET gene. The majority of patients relapse after surgical treatment, except 1/3 of patients who can be cured. The risk of relapse depends on several factors including the presence of a residual tumor mass and the speed of progression. Relapse can occur either at the lymph node level or in the lung, bone or liver [4,16]. The last type is that of anaplastic or undifferentiated carcinoma, it represents only 2% of thyroid cancers; it is the most aggressive histological type responsible for almost half of the mortality. Its prognosis is very poor with a median survival of 3 to 9 months [15,17]. In our series, follicular stem cell carcinomas were the most frequent with a percentage of 61% followed by anaplastic carcinomas (25%) then medullary carcinomas (14%).

Therapeutically, systemic treatment remains the only modality that could improve the prognosis of patients. Before the development of targeted therapies, chemotherapy was the only treatment available. Several chemotherapy drugs have been tested in phase II studies for the treatment of patients with thyroid carcinoma, either as monotherapy or in combination, such as bleomycin, doxorubicin, platinum salts and taxanes [18,19,20]. All of these regimens have shown limited efficacy with response rates varying between 0 and 20%. Among these drugs, doxorubicin was the most frequently used [21] but there was no consensus regarding the most effective cytotoxic molecule given the absence of randomized studies comparing the different regimens due to the rarity of these tumors. In our series, the majority of patients (60%) received conventional chemotherapy due to the unavailability of targeted therapies in our department.

Better knowledge of the molecular alterations responsible for the onset of the disease has led to the development of therapies targeting these abnormalities. These agents evaluated in phase II trials include: axitinib [22], motesanib [23], pazopanib [24], sunitinib [25] and vandetanib [26] (table 2). With these agents, partial responses have been observed. This has led to the performance of randomized phase III placebo-controlled studies to demonstrate the benefit in terms of progression-free survival in favor of these therapies. However, four phase III studies evaluating sorafenib, lenvatinib, vandetanib and cabozantinib that were positive (table 3).

I'm starting with sorafenib, it was approved by the FDA in November 2013 for the treatment of differentiated thyroid cancers refractory to iratherapy following the publication of the DECISION study [6]. The median progression-free survival (PFS) was 10.8 months versus 5.8 months [hazard ratio (HR) 0.49; 95% CI 0.39–0.61; p <0.0001] in favor of sorafenib versus placebo. Lenvatinib was studied in the SELECT trial [7]. The results of this study showed a significant increase in PFS with a median of 18.3 months versus 3.6 months (p <0.001) in favor of lenvatinib versus placebo

without benefit in overall survival (p <0.10). The FDA cleared it on February 13, 2015, despite its toxicity. It should be noted that sorafenib and lenvatinib have been evaluated in patients with differentiated thyroid carcinomas, these two molecules have demonstrated a benefit in terms of progression-free survival. It is difficult to conclude that one molecule is superior to another given the lack of a direct comparison of these two molecules.

In patients with medullary carcinoma, two drugs have been shown to be effective in this type of tumor. These molecules are vandetanib and cabozantinib. Vandetanib was approved by the FDA in 2012 for the treatment of medullary thyroid carcinoma. The ZETA study which was conducted by Wells and colleagues [27] showed satisfactory results in PFS (p <0.001). The median PFS in the vandetanib group was not reached, but it was estimated at 30.5 months versus 19.3 months in the placebo group. The second TKI which showed a benefit in medullary carcinoma is cabozantinib, it showed its superiority in the EXAM study [28] in terms of PFS of 11.2 months compared to 4 months in the placebo group (p < 0.001).

In our study, 40% received sorafenib; they are all undergoing treatment with an average duration of 25.3 months. The other TKIs are not available within our training.

Grade 3 and 4 side effects found with these TKIs were around 75% with lenvatinib, 69% with cabozantinib, 37% with sorafenib and 30% with vandetanib [6,7,27,28]. In our study, the grade 3 and 4 toxicities associated with sorafenib were 37.5%. Adverse events induced by TKIs not only reduce the quality of life of cancer patients, but also reduce the dose intensity and sometimes lead to discontinuation of treatment. It would therefore be interesting to reason well and select patients well before introducing these treatments.

Somatostatin analogues have been tested in medullary carcinomas [29,30]. But, they have not shown any benefit in this type of tumor. For the role of immunotherapy in the management of thyroid cancer, several trials are underway and promising.

Conclusion

Globally, refractory thyroid cancers are rare. Systemic treatments have evolved considerably in recent years with the development of targeted therapies, in particular for papillary and medullary thyroid carcinomas. Only anaplastic carcinomas do not currently benefit from these therapeutic advances; thus, chemotherapy remains the main option despite its very limited effectiveness, pending the advent of immunotherapy which could improve the prognosis of these patients.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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