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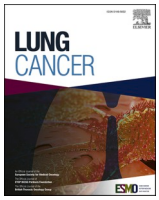

Therapeutic management of patients with advanced thymic malignancies: A review for clinicians

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ABSTRACT

Thymic epithelial tumors (TETs) are a heterogeneous group of rare tumors that arise from thymic epithelial cells in the anterior mediastinum. They can be divided into three different histological subtypes: thymomas, thymic carcinomas (TC), and neuroendocrine carcinomas (TNET). TCs and TNETs are rarer but more aggressive entities with frequent distant metastasis. Thymomas occur in 90 % of cases in a localized/locally advanced stage, on the other hand about 70 % of TCs are locally advanced at the time of diagnosis.

Surgery plays a primary role in the management of patients in whom complete resection is feasible. The benefit of post-operative radiotherapy (PORT) is still controversial, since it could be related to stage, histotype, and preoperative chemotherapy. If the tumor is unresectable at diagnosis, radiotherapy or concurrent chemo-radiotherapy is the most commonly used approach. Cisplatin and anthracycline-based regimens are standard of care in patients with unresectable or metastatic thymomas, but, at the same time, regimens with carboplatin and paclitaxel are the most widely used especially in patients with contraindications to cisplatin/anthracyclines, due to better tolerance. Recently, the anti-VEGFR antibody Ramucirumab has shown promising activity in combination with carboplatin plus paclitaxel in previously untreated advanced TCs. Several clinical trials with chemotherapy combination, target therapy and immunotherapy are still ongoing to define the best therapeutic strategy in this disease, also for the second line treatment, for which in daily practice there is currently no standard of care for patients who went into progression to the first line.

1. Introduction

Thymic epithelial tumors (TETs) are an heterogeneous group of rare tumors (incidence 0.15/100.000 person-years [1]) that arise from thymic epithelial cells in the anterior mediastinum. A minimal difference in incidence is described between males and females (1.4:1) [1], with a mean age at diagnosis of 50–60 years and a peak in the seventh decade of life [2]. Due to the rarity and specific clinical features of these tumors, treatment requires a close collaboration between specialists in high volume centers. In this review, we aim to discuss the clinical approach for locally advanced unresectable disease – defined as stage III/IV according to Masaoka-Koga staging system and multidisciplinary discussion in dubious cases; see "Staging" section below – and first and second line treatment of patients with metastatic TETs.

2. Pathological features and diagnostic work-up

The World Health Organization (WHO) classification of thoracic

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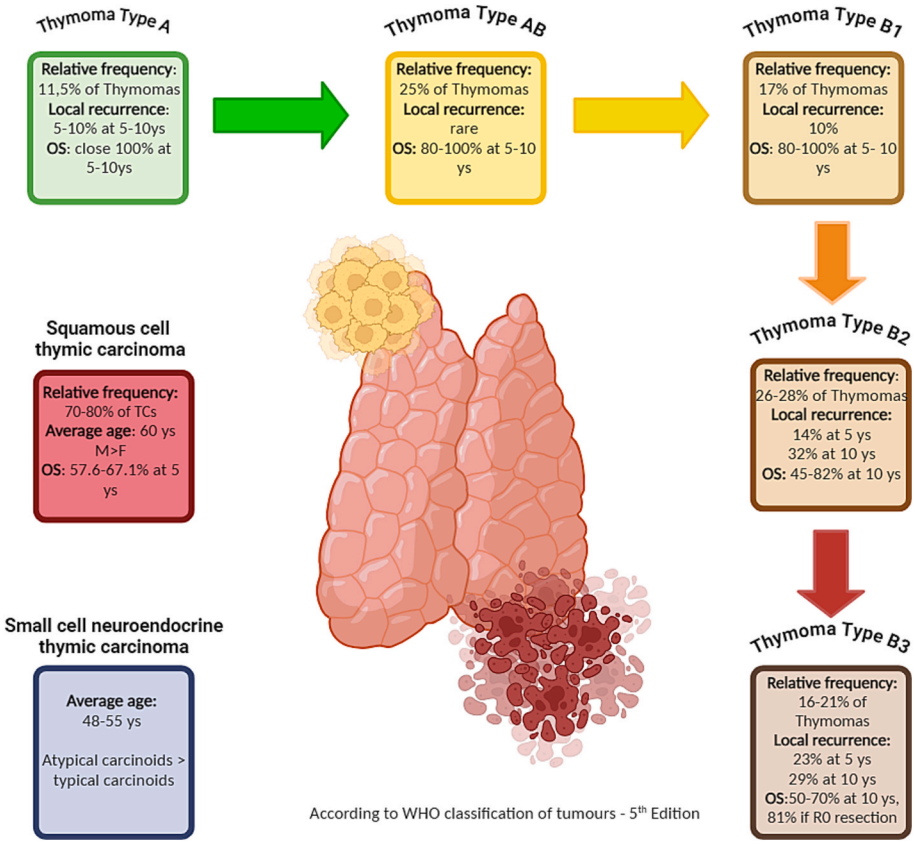

Fig. 1. TETs. OS, overall survival.

tumors distinguishes TETs into thymomas and thymic carcinomas (TCs) [1], the latter including the most frequent squamous cell carcinoma (SQCC) and several other rare histopathologic subtypes, that often mirror those diagnosed in other organs [3]. Thymomas are further subdivided into different types (A, AB, B1, B2, B3, micronodular thymoma with lymphoid stroma and metaplastic thymoma [4]) based upon the amount of neoplastic cells in the thymic epithelium and the non-neoplastic lymphocytic component [1]. Clinical aggressiveness and metastatic potential increase from type A to B3 to thymic carcinoma (type C), the latter characterized by frequent lymphatic and hematogenous distant spread [5]. TETs include also neuroendocrine tumors (TNET), an extremely rare (2–5 % of TETs and 0.4 % of all neuroendocrine tumors) [6,7] and aggressive entity, prone to invasion and metastasis, with poor prognosis even after a radical resection (Fig. 1). TNETs, like pulmonary neuroendocrine tumors, are classified into low-grade typical carcinoids (TCs), intermediate-grade atypical carcinoids (ACs), and two high-grade malignancies, large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (SCC) [6,7]. AC and LCNEC are the most frequent subtypes arising from the thymus [6]. Approximately 50 % of TNETs are associated with endocrine paraneoplastic syndromes, and about 30 % of patients with thymomas show autoimmune and/or paraneoplastic syndromes at diagnosis, especially myasthenia gravis (MG), pure red cell aplasia, systemic lupus erythematosus and hypogammaglobulinaemia [10,11]. Non-active TNETs are often associated with the multiple endocrine neoplasia type I syndrome (MEN-1) [9]. Most patients with TNET (about 69 %) have advanced disease at diagnosis, confirming the aggressive behavior of these tumors [8].

Computed tomography (CT) of the chest is the first imaging modality to characterize anterior mediastinal lesions [11]. Magnetic Resonance imaging (MRI), has higher specificity in distinguishing benign thymic hyperplasia or thymic cysts from malignant neoplasms [12], while 18Fluorodeoxyglucose (18FDG) positron emission tomography (PET)/CT scanning is reserved for detection of possible occult metastases [10], and to assess the treatment response [13].

3. Staging

For more than 40 years, TETs staging relied on the Masaoka-Koga surgical staging system. The Masaoka–Koga surgical staging classification includes [10]:

- stage I: intact thymic capsule;
- stage II: microscopic transcapsular invasion (A)/macroscopic invasion into adjacent mediastinal fat but not through mediastinal pleura or pericardium (B);
- stage III: macroscopic invasion into adjacent organs without invasion of great vessels (A)/with invasion of great vessels (B);
- stage IV: pleural or pericardial dissemination (A)/distant metastases (B).

Another staging system is the one proposed by the Union for International Cancer Control/American Joint Committee on Cancer TNM (Tumor-Nodal-metastasis) which is now in the VIII edition and can be used for all TETs [4,11]. It describes the invasion into mediastinal fat (T1a), mediastinal pleura (T1b), pericardium (T2), and other surrounding structures or organs (T3, T4). The N parameter distinguishes between involvement of N1 (anterior/perithymic) and N2 (deep intrathoracic/cervical) lymph nodes. The M parameter indicates presence of pleural and pericardial nodules (M1a) or distant organ metastases (M1b) [14]. Recently, the IX edition of the TNM classification has been proposed by the International Association for the Study of Lung Cancer (IASLC); the T parameter was reassessed considering the prognostic value of the tumor size, significant in early-stage tumors, and the difficulty to recognize and report the mediastinal pleura invasion [15]. According to the literature, approximately 70 % of thymic carcinomas are

locally advanced at the time of diagnosis. Data from the American National Cancer Institute's Surveillance, Epidemiology and End Results (SEER), showed that patients with localized/locally advanced TNETs at diagnosis are almost 70 %. Thymomas, on the other hand, occur in 90 % of cases in a localised/locally advanced stage (Masaoka Stage I-III) and only in 10 % of cases are unresectable/metastatic stage [16].

4. Unresectable/locally advanced disease

The involvement of a multidisciplinary tumor board (MTB) including medical oncologists, radiation oncologists, thoracic surgeons and radiologists is essential in the management of the patient with TETs [10]. Surgery is pivotal in the management of patients in whom complete resection is feasible [11], however if complete resection is not deemed achievable upfront, like in the case of Masaoka-Koga stage III/IVA tumours (classified as stage IIIA/T3, IIIB/T4, /IVA in the IASLC/ITMIG TNM system), a biopsy should be carried out, followed by induction chemotherapy.

The three most relevant prognostic factors for thymomas are histotype, disease stage at diagnosis, and complete resection. Therefore, the clinician's goal when treating stage III/IV non-resectable thymic malignancy with induction chemotherapy as first approach is to enable complete resection with clear margins [17]. The treatment usually consists of regimens based on cisplatin, doxorubicin, and cyclophosphamide (CAP), sometimes with the addiction of vincristine (ADOC), or cisplatin and etoposide, administered for two to four cycles, followed by radiological reassessment of the disease to evaluate the resectability of the tumor. The ideal treatment regimen is based on studies conducted for metastatic disease: regimens with higher response rates include cisplatin instead of carboplatin and incorporate anthracyclines for thymomas. However, for thymic carcinoma, there are no differences in outcomes between using or not using anthracyclines [19,20]. A recent single-centre study, explored the role of neoadjuvant chemoradiotherapy in 33 patients with potentially unresectable, Masaoka-Koga stage III-IV, high-grade thymic tumors showing an objective response rate of 48.5 % with 23 of patients undergoing surgery with radical intent (R0 resection rare: 82.6 %) [21].

The overall response rate (ORR) is around 70–80 %, and in patients for whom R0 resection is considered feasible, complete resection is achieved in approximately 50 % of cases. When resection is deemed feasible, radical thymectomy including the tumor, the residual thymus and *peri*-thymic fat is the preferred approach [11] along with pleural/pericardial implant removal usually followed by postoperative radiotherapy (PORT, 45–50 Gy) [10] in case of pathological N1 disease and/or positive resection margins [18].

5. Definitive radiotherapy and chemoradiotherapy

If the tumor is unresectable at diagnosis, radiotherapy (60–70 Gy) or concurrent chemoradiotherapy is the preferred approach [10]. In selected cases with stage IV thymoma, upfront surgery may be proposed, in patients for whom rapid tumor debulking should be obtained (e.g highly symptomatic patients with MG). Following debulking or R2 resection, postoperative chemoradiotherapy, which includes cisplatin and etoposide chemotherapy along with a total radiation dose of 60 Gy in 30 fractions, may be considered [18].

When dealing with TC, evidences supporting the role of surgery in stage IV disease are not available. Indeed, considering the high biological aggressiveness of these tumors, surgical approaches should be discussed on a case-by-case basis. The same applies to stage IVB thymoma. In both tumor types, borrowing data from other solid tumors, locoregional treatments (stereotactic body radiation therapy, radiofrequency ablation, etc. etc.) can be discussed when facing oligoprogression to maintain disease control while delaying further systemic treatments.

6. Post-operative radiotherapy

The use of post-operative radiotherapy (PORT) is still controversial. Its application has undergone a decreasing trend in recent years following data extracted from clinical trials and retrospective analysis that showed the absence of survival benefit after radiotherapy in stage I thymoma or after R0/1 resection of stage II–III thymoma and no recurrence-free survival (RFS) benefit for PORT after R0 resection of thymoma [22–24]. The limit of these retrospective analyses is due to the fact that PORT has often been used in the setting of higher-risk patients (higher stage, incomplete resection), potentially undermining the benefit on survival [23]. Additionally, thymic epithelial tumors (TETs) recur in over 60 % of cases outside the mediastinum. The French RYTHMIC network is currently conducting the RADIORYTHMIC trial, which will assess the impact of PORT on relapse-free survival (RFS) and overall survival in patients with thymoma, stratifying them by stage, histology, and preoperative chemotherapy.

In thymic carcinoma, post-operative radiotherapy has been used more widely, due to the more aggressive nature of the disease. Recently, a study showed that in TC with R0 resection, PORT was associated with increased OS only in advanced stages and not in early stages of the disease (I-II). In patients with advanced stage and a R1/2 resection, PORT was associated with a significant benefit in OS [25]. Literature data about PORT in cases with M1a resected disease are scant.

7. Adjuvant chemotherapy

Postoperative chemotherapy is not routinely recommended by guidelines after complete resection of thymoma due to the lack of demonstrated benefit in overall survival (OS) from prospective studies [26]. The 5-year expected survival rate in resected thymic carcinoma is approximately 80 %, and the rarity of the disease makes it difficult to enroll patients in clinical trials comparing adjuvant chemotherapy with follow-up alone. In the largest retrospective study available, Kim et al. demonstrated that adjuvant therapy showed no benefit in patients with pathological stage IIB disease who had R0 resection [27]. The use of adjuvant therapy should be strongly considered for pathological stage IIB cases with positive margins and all stage III patients, given the OS benefit in these categories (HR, 0.19; 95 % CI, 0.07 to 0.55; HR, 0.63; 95 % CI, 0.44–0.89, respectively). Indeed, while adjuvant chemotherapy should be considered for these categories, we strongly advocate for a careful evaluation of each case in a multidisciplinary tumor board (MTB).

8. First line treatment

Cisplatin and anthracycline-based regimens, including cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC [28]) or cisplatin, doxorubicin, and cyclophosphamide (PAC), are standard of care in patients with unresectable or metastatic thymomas [5]. A pooled analysis including 15 studies of patients with advanced thymoma showed that platinum-based chemotherapy in combination with anthracyclines is superior to platinum-based chemotherapy without anthracycline in terms of overall response rate (ORR 69.4 % vs. 37.8 %) [5,10,20]; the platinum-anthracycline combination are therefore ideal combination for patients affected by thymoma in good clinical conditions.

In contrast, TCs seem to be less responsive to anthracycline-based chemotherapy (ORR 30 % in TC as compared to 50–92 % in thymomas) [29], although a small study involving 12 patients with treatment-naive TC showed a ORR of 42 % with the CODE regimen (cisplatin, vincristine, doxorubicin and etoposide) [30]. Neutropenia and other hematological toxicities are the main side effects related to platinum/anthracyclines-based chemotherapy. Notably, caution should be exercised in the use of anthracyclines because of their well-known cardiotoxicity. Indeed, patients with cardiac comorbidities (especially

Table 1
Most active first-line regimens used in treating TETs. TETs, thymic epithelial tumors; TC, thymic carcinoma; T, thymoma; PFS, Progression Free Survival.

Regimen	Drugs	Author	Stage	Tumor	mPFS	ORR	mOS
ADOC	Doxorubicin + Cisplatin + Vincristine + Cyclophosphamide	Berruti et al. [1999]	III, IVa	T	33.2 months	81.2 %	47.5 months
CAP	Cisplatin + Doxorubicin + Cyclophosphamide	Kim et al. [2004]	III, IV a,b	T	PFS rate at 7 years 77 %	77 %	OS at 7 years 79 %
PE	Cisplatin + Etoposide	Giaccone et al [1996]	III, IV a,b	T	2.2 years	56 %	4.3 years
VIP	Etoposide + Ifosfamide + Cisplatin	Loehrer et al [2001]	III, IVa, b	T, TC	11.9 months	32 %	31.6 months
CODE	Cisplatin + Vincristine + Doxorubicin + Etoposide	Kunitoh et al. [2010]	III	T	4.5 years	62 %	OS rate at 8 years 69 %
Carbo-PTX	Carboplatin + Paclitaxel	Takeda et al. [2013]	III, IV a,b	TC	8.1 months	36 %	NR
		Lemma et al [2011]	III, IV	T, TC	16.7 for T, 4.5 for TC	42,9 % T, 21,7 % TC	NR for T, 20 m for TC
CDDP-PTX	Cisplatin + Paclitaxel	Park et al [2013]	III, IVa, b	T, TC	PFS rate at 4 years 40.6 %	63 %	OS rate at 4 years 79.4 %
CAP-GEM	Capecitabine + Gemcitabine	Buonerba et al [2014]	III, IV	T, TC	11 months for T, 6 months for TC	100 %	NR
Carbo-PTX-Ramucirumab	Carboplatin + Paclitaxel + Ramucirumab	Proto et al [2024]	III, IV	T, T + TC areas	18.1 %	80 % (57 % at blinded review)	43.8 %
		Tsao et al [2024]	III, IV	TC	8 months		NR

hypokinetic cardiomyopathies) or those who require thoracic radiotherapy, should be preferentially treated with anthracycline-free regimens [29]. In patients unfit for cisplatin, carboplatin is often used, although a formal comparison between the two compounds has never been performed. Of note, when dealing with TCs, some studies showed higher activity of cisplatin-based chemotherapy when compared to carboplatin-based chemotherapy (ORR 53.6 % vs. 32.8 %) [10]. However, carboplatin-paclitaxel chemotherapy is the most commonly used first-line regimen for TCs, since it showed a favorable toxicity profile and provided an ORR of 42.9 % in thymoma and 21.7 % in thymic carcinoma, with a median progression-free survival (mPFS) of 16.7 and 5.0 months, respectively [31]. Case reports have indicated that gemcitabine-cisplatin is active in TCs too [3,29]. Table 1 summarizes data about the most common first-line regimens used in treating TETs.

Angiogenesis significantly influences carcinogenesis in TETs, and vascular endothelial growth factor (VEGF)-A and its receptors (VEGFR-1 and-2) are overexpressed in these tumors [1,5]. Moreover, VEGF expression and micro vessel density are associated with invasiveness and tumor stage [5]. For this reason, antiangiogenic agents have been actively studied in TETs advanced treatment lines [1]. Recently, the open-label, single-arm, phase II trial RELEVENT (n = 37) demonstrated an overall response rate (ORR) of 57.6 % for Ramucirumab, a fully human monoclonal antibody (IgG1) that acts as a VEGFR2 antagonist, in combination with carboplatin plus paclitaxel in previously untreated advanced TCs [32]. At a medium follow up of 31.6 months, mPFS was 18.1 and median overall survival (mOs) was 43.8 months, respectively, showing remarkable activity in treatment naïve patients with advanced TC. The results were confirmed by Tsao et al., who evaluated the triplet regimen of Carboplatin, Paclitaxel, and Ramucirumab in a cohort of 21 patients with thymic carcinoma in the S1701 study. The response rate was 88 % for the treatment arm with the antiangiogenic agent vs 40 % in the chemotherapy only arm, with no differences observed in terms of progression-free survival (PFS). Overall survival (OS) data are immature [33].

Recently, data about the combination of chemotherapy and immune checkpoint inhibitors in TETs have been reported. In the phase II MARBLE study, 48 patients with chemotherapy-naïve, locally advanced or metastatic thymic carcinoma received 4 to 6 cycles of carboplatin + paclitaxel + atezolizumab followed by atezolizumab maintenance for up to 2 years [34]. After a median follow-up of 15.3 months, the ORR was 56.3 %, while the mPFS and mOS were 9.6 months and NR, respectively. Grade 3 or higher adverse events were observed in 75 % of patients, and the rate of high grade immune-related adverse events was 66.7 %. Smaller studies using other molecules directed against the programmed death protein 1 (PD-1) and its ligand 1 (PD-L1) axis led to similar results [35,36].

Regarding thymic NETs, the largest collection of patients (n = 205) showed as the only independent prognostic factor for survival the radicality of surgical resection [37]. In terms of systemic therapy, recent studies showed a mOS of 20 months for patients treated with Temozolomide vs 18 months for patients treated with platinum-based chemotherapy in the first-line setting [37,38]. Therefore, giving its favorable toxicity profile, temozolomide could be considered as a first-line treatment in well- and moderately differentiated thymic NETs, leaving platinum-based chemotherapy to poorly differentiated TNETs [12–37].

9. Second-line treatment

It is estimated that 50 % to 70 % of patients with recurrence receive a second line chemotherapy. However, metastatic TETs are usually less chemosensitive to second-, and also third-line chemotherapeutic regimens, and no standard of care for patients who went into progression to the first-line platinum and/or anthracycline based chemotherapy is currently available in daily practice [5].

In patients with platinum-refractory TETs, various chemotherapy regimens containing pemetrexed, etoposide and ifosfamide have been tested, showing response rates ranging from 10 % to 40 %. Notably, the combination of gemcitabine and capecitabine demonstrated objective response rates (ORR) of 40 % in patients with thymoma and 38 % in those with thymic carcinoma, with median progression-free survival (PFS) of 11 and 6 months, respectively [39].

In the setting of second line treatment of thymic carcinoma, the use of anti-angiogenic agents has shown promising results. Sunitinib and lenvatinib demonstrated response rates of 26 % and 40 %, respectively. In the Phase II REMORA trial, lenvatinib showed a median duration of response of 11.6 months in 42 patients with thymic carcinoma. However, these results were associated with a 17 % discontinuation rate due to toxicity (hypertension) and 100 % of patients experiencing dose reductions [40].

In the era of immunotherapy, anti-PD-1/PD-L1 agents have also been tested in Phase I/II trials as second-line treatment for thymoma or thymic carcinoma [41,42,43]. Response rates vary from 10 % to 50 %, but these results are accompanied by the risk of immune-related adverse events (irAEs) in patients already predisposed due to the thymoma.

Table 2
Ongoing clinical trials in thymic malignancies (updated as of February 16th, 2025 on actually enrolling clinical trial in thymic malignancies)TETs, thymic epithelial tumors; TC, thymic carcinoma; T, thymoma; CT, chemotherapy; ORR, overall Response Rate; TNET thymic neuroendocrine carcinoma; DCR, Disease control Rate; PFS, Progression Free Survival; MTD, Maximum Tolerated Dose; RD, Recommended Dose; DoR, Duration of Response; MTD, Maximum tolerated dose; DLT, Dose-limiting toxicity.

Trial	NCT	Tumor type	Drug	Drug Target	Target Accrual	Phase	Endpoint
Shanghai Pulmonary Hospital	NCT04667793	TET	Toripalimab + CT	Anti PD-1	15	II	–
National Cancer Institute (NCI)	NCT04417660	TC, T	Bintrafusp alfa (M7824)	Bi-functional Protein targeting TGF-β + PD-L1	38	II	ORR
National Cancer Institute (NCI)	NCT05104736	TC, T	PT-112	Pyrophosphate-platinum conjugate	53	II	ORR
Georgetown University	NCT06248515	TC, T	Sacituzumab Govitecan	Anti TROP-2	18	II	ORR
Ohio State University Comprehensive Cancer Center	NCT03463460	TC	Pembrolizumab, Sunitinib malate	Anti PD-1; multitarget TK receptor inhibitor	30	II	Safety, ORR, PFS, OS
National Cancer Institute (NCI)	NCT03076554	TC, T	Avelumab	Anti PD-L1	60	II	Safety, ORR
National Cancer Center, Japan	NCT05832827	TC	Pembrolizumab, Lenvatinib	Anti PD-1, multitarget TK receptor inhibitor	35	II	ORR, PFS, OS, DoR
Shanghai Jiao Tong University School of Medicine	NCT06141369	TC	mRNA-0523-L001	Neoantigen-specific CD4 + and CD8 + T lymphocyte responses	21	NA	MTD, DLT, ORR, PFS
M.D. Anderson Cancer Center	NCT03295227	TC, T	Pembrolizumab	Anti PD-1	37	I	ORR, PFS, OSS
Novartis Pharmaceuticals	NCT05544929	TC	KFA115 + Pembrolizumab	Immunomodulatory agent, Anti PD-1	180	1	MTD
VM Oncology, LCC	NCT03556228	TC	VMD-928	TrkA inhibitor	74	1	Safety, Activity

Thymic carcinomas exhibit a higher mutation rate compared to thymomas and some clinical trials showed encouraging results of immune checkpoint inhibitors (ICIs) in TCs [44], especially in patients with high tumor-infiltrating lymphocyte densities [45].

The combined experience of anti-angiogenic drugs and immunotherapy has led to testing their combinations in second-line treatment: the CAVEATT trial with the combination of Avelumab and Axitinib, and the PECATI trial with the combination of Pembrolizumab and Lenvatinib in patients with thymic carcinoma or B3 thymoma. The response rates were 34 % and 23 %, respectively, with median progression-free survival (PFS) of 7.5 and 14.9 months. PD-L1 expression not associated with RR, PFS or OS.

Participation to clinical trials in this setting is recommended.

10. Future perspectives

In the era of target therapy, a better comprehension of the hallmarks in TETs could be the way for the identification of targets for effective therapeutic drugs. In this context, a phase II, investigator-initiated, non-randomized, open-label, single-arm, multicenter study (ARTEMIS) is ongoing to evaluate the efficacy and safety of Carboplatin/Paclitaxel/Lenvatinib/Pembrolizumab combination for previously untreated advanced or recurrent thymic carcinomas [46]. Other similar trials are also investigating the role of ICIs in combination with chemotherapy. Table 2 reports ongoing clinical trials in TETs.

11. Conclusions

Thymic neoplasms are a heterogeneous group of tumors, whose main treatment in localized stages is surgery. The use of post-operative radiotherapy (PORT) is still controversial, as well as adjuvant chemotherapy in most patients. For this reason, the involvement of a multidisciplinary tumor board (MTB) is essential in the management of the patient with TETs. In locally advanced and metastatic disease, cisplatin and anthracycline-based regimens are the standard of care for patients affected by TETs, even if in clinical practice carboplatin-paclitaxel chemotherapy is the most commonly used first-line regimen for TCs, due to a favorable efficacy/toxicity ratio in this disease subgroup.

The recent advent of immunotherapy, despite all the challenges posed by the immunological substrate of the thymus, and anti-angiogenic therapies are expected to change the therapeutic landscape of patients with TETs (especially thymic carcinomas) even in combinations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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