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Tumour Review

Thymic malignancies: Moving forward with new systemic treatments

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ABSTRACT

Thymic neoplasms are rare malignant tumours, for which the mainstay of treatment is surgical resection. Platinum-based chemotherapy remains the principal treatment in metastatic tumours, with no standard second-line option. Many genes implicated in tumour onset, growth and metastases have been demonstrated to be therapeutic targets in thymic malignancies. Other current efforts to improve outcomes are based on a better understanding of the stromal compartment and tumour microenvironment, facilitating novel therapeutic approaches such as angiogenesis inhibition and immunotherapy. This review seeks to explore the present cutting edge for systemic treatment of advanced thymic neoplasms, examining novel agents under clinical investigation such as cytotoxic therapies, targeted therapies and immunotherapy. Based on the literature review we have selected potential treatment schemes, which could be used in daily clinical practice as second-line treatment.

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Introduction

Thymic Epithelial Tumours (TET) are rare cancers with an incidence, unaffected by gender, of 1.7 and 1.3 per million per year in Europe [1] and the US [2], respectively. The current histological classification of TET distinguishes thymomas (T) (types A, AB, B1, B2, B3) that are more indolent, but not thymic carcinoma (TC), which displays a more aggressive phenotype, frequently associated with distant metastases to the liver, lymph nodes and bones [3]. Five-year overall survival (OS) is 80% and 40% for T and TC, respectively [4,5]. Stage of disease, complete surgical resection and tumour histology are the most important prognostic factors [1,6].

Surgery remains the treatment of choice for operable TET, whereas platinum-based chemotherapy is the principal treatment for metastatic, inoperable or recurrent disease. Number of reviews have described the efficacy of combination chemotherapies as first-line treatment [7] and it would not be a topic in this review. Response rate (RR) of TET to current chemotherapy agents differs according to histological diagnosis. In a recent pooled-analysis, the RR to first-line platinum in combination with anthracycline-based chemotherapy in T was higher than for platinum with non-anthracyclines-based chemotherapy (69.4% *vs.* 37.8%, $P = <0.0001$), whereas in TC there was no difference (41.8% *vs.* 40.9%; $P = <0.82$). TC was however noted to respond better to cisplatin-rather than carboplatin-based chemotherapy (53.6% *vs.* 32.8%, $P = 0.0029$) [8]. The rarity of these tumours has precluded development of their treatments through large phase II and III trials, slowing the progress of new drug delivery.

This review seeks to explore the present cutting edge for systemic treatment of advanced TET, examining novel agents under clinical investigation such as cytotoxic therapies, targeted therapies and immunotherapy. Based on the literature review we have selected potential treatment schemes, which could be used in daily clinical practice as second-line treatment (Table 1).

Cytotoxic therapies

Palliative chemotherapy with cisplatin, doxorubicin and cyclophosphamide (CAP) represents the preferred and most suitable options as first-line treatment because of advantage outcome (RR 50% and mOS 37.7 months) with acceptable toxicity profile [9]. Owing to its rarity, multicentric randomized trials are not available in TET. One consequent deficit is that no standard treatments are available for advanced TET after failure of first-line platinum-based chemotherapy. In a recent pan-European survey on thymic malignancies, the preferred first choice combination for second-line chemotherapy in TET chosen by the physicians was carboplatin and paclitaxel (36% for T and 31% for TC), whereas cisplatin and etoposide was chosen as the second choice (13% for T and 18%

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Table 1
Selected schemes for daily clinical practice. w: weeks.

Treatment	Does	Expected toxicities
Pemetrexed [12,13]	500 mg/m^2 D1 every 3 weeks	Fatigue, nausea, constipation
Etoposide oral [14]	25 mg/8 h, 3 weeks on 1 week off vo	Anaemia, neutropenia, thrombocytopenia
Gemcitabine Xeloda [17]	G: 1000 mg/m^2 on days 1 and 8 every 3 w X: 650 mg/m^2/12 h on days 1–14	Neutropenia hand-foot syndrome
Everolimus [49]	10 mg/d oral	Asthenia, dyspnoea
Sunitinib [60]	50 mg/day, 4 weeks on 2 weeks off	Hypertension, lymphocytopenia, asthenia, mucositis

for TC). The expected outcome with second-line chemotherapy by the physicians in RR was 36% in T and 23% in TC, the expected progression free survival (PFS) was 8 months *vs.* 4 months and the expected OS of 15 months and 9 months for T and TC, respectively [10].

Single agents are also considered as treatment options in subsequent lines [11]. For example, pemetrexed has been associated with a 17% partial response (PR) in T and 10% PR in TC in a small retrospective analysis of 16 patients. In this study, the median PFS and OS was 13.8 months *vs.* 6.5 months and 20.1 months *vs.* 12.7 months for T and TC, respectively, without grade $\geqslant$3 hematologic adverse events (AEs) [12] (Table 2). A phase II study reported as an abstract, describes 27 patients (16 T and 11 TC) who received pemetrexed every 3 weeks for a maximum of six cycles. In 23 fully evaluable patients, 2 PR and 2 CR (ORR: 17%) were noted. Among the total population, median time to progression (TTP) was 45 weeks (45.4 weeks for T and 5.1 weeks for TC), and OS was 29 months [13]. Taken together, these results suggest that there is a clinical activity of pemetrexed in pre-treated TET patients.

The efficacy and tolerability of oral etoposide (25 mg/8 h, 3 weeks out of 4) has been tested in 13 pre-treated TET patients (8 TC and 5 T). Oral etoposide reported 15% PR (T: 20% and TC: 13%) and 70% of SD (T: 80% and TC: 63%). The median PFS was 9 months (53 months *vs.* 9 months, for T and TC, respectively), mOS 40 months (92 months *vs.* 22 months, for T and TC, respectively), with grade 3–4 toxicities which included anaemia (15%), neutropenia (23%) and thrombocytopenia (8%), without toxic related deaths [14]. These data support potential activity of this drug and further investigation is warranted.

Recently, two-phase II trials have reported promising second-line efficacy of amrubicin (a third generation anthracycline and topoisomerase II inhibitor) and capecitabine in combination with gemcitabine. In the former trial, which recruited 14 T and 19 TC patients with progressive disease or relapse after $\geqslant$1 prior chemotherapy regimen, amrubicin was administered at 35 mg/m^2 IV days 1–3 on a 21-day cycle with prophylactic GCSF support; this was modified from an initial dose at 40 mg/m^2 IV days 1–3 on a 21-day cycle due to febrile neutropenia in 7 patients with 1 treatment-related death. The ORR, all of which were partial responses, was 18%: 29% in T and 11% in TC. There were no differences in response rate according to race. Overall disease control rate (DCR) at first assessment was 88% (100% in T and 79% in TC), mPFS was 8.5 months (8.7 months for T and 8.5 for TC) and mOS 30.1 months (not reached for T *vs.* 18.1 months for TC) (Table 2). There was no unexpected toxicity (reported grade 3/4 AEs were: fatigue 21%, febrile neutropenia 21%, anaemia 12%, neutropenia 9% and thrombocytopenia 6%) or significant change in LVEF on serial echocardiograms [15]. In a Japanese phase II trial carboplatin and amrubicin conferred a 30% RR in TC and 17% in T, with an equal mPFS of 7.6 months. In treatment naïve TC patients, the ORR with the combination was 42%. The main toxicities was hematological, including a 22% rate of grade 3–4 febrile neutropenia [16]. Thus, although amrubicin has promising activity, and could be considered as another option in second-line treatment, its toxicity profile and practicality as an intravenous infusion for 3 days might limit its applicability in daily clinical practice.

The second phase II trial investigated the combination of capecitabine (650 mg/m^2/12 h on days 1–14) plus gemcitabine (1000 mg/m^2 on days 1 and 8 every 3 weeks) in 30 TET patients (22 T and 8 TC) who had received >1 systemic chemotherapy (63% of patients showed disease progression within 2 months from the last systemic therapy). Median number of treatment cycles administered was 8, with an ORR of 40% (3 complete responses and 8 partial responses), which included a 38% RR in the TC subpopulation. The mPFS was 11 months (11 months *vs.* 6 months for T and TC, respectively), and the 1-year and 2-year OS was 90% and 66%, respectively. Grade 3/4 neutropenia was reported in 30% of patients, and grade 3 hand-foot syndrome in 13% of patients [17]. Thus, chemotherapy is a treatment option in recurrent TET, and combination chemotherapies improve the RR without a clear impact in PFS or OS.

Molecular aberrations in TET

Given the poor survival in the metastatic setting, especially for TC, there is a clear need for new treatment options. Further understanding of the molecular pathogenesis of TET is required for characterising druggable mutations such as in non-small cell lung cancer (NSCLC). However, several factors hamper clear examination of relevant genetic alterations and subsequent development of effective targeted therapies in TET, despite significant efforts to dissect the molecular pathway of the disease: its histological heterogeneity, low incidence, poorly understood molecular pathogenesis, and lack of specific preclinical animal models [18–20].

An analysis of 28 resected TET using next-generation sequencing reported a missense mutation in GTF2i (located in chromosome 7) which was of higher incidence in indolent compared to aggressive TET (82% in type A and 74% in type AB, rarely in aggressive subtypes) correlating with improved survival [20]. These results were confirmed in an independent cohort of 94 patients where the GT2Fi mutation was reported in 29% of TETs, again predominantly in type A (85%) and AB (46%) thymomas [21], confirming that mutation in GTF2i represents an oncogenic event in TETs. Somatic genetic variations identified in 78 advanced-stage TET (47 TC and 31 T) [22] included non-synonymous sequence variations affecting 39 genes in 33 out of 78 (42%) TET. There was a significantly higher incidence of these mutations in TC compared to T (62% *vs.* 13%; $P < 0.0001$), suggesting that TC is molecularly distinct from T. *TP53* was the most frequently mutated gene (17% overall, 26% in TC, $P = 0.0097$) and was associated with poorer OS ($P = 0.0003$). Histone modification (e.g., *BAP1* 13%, *SETD2* 11%), chromatin remodelling (such as *SMARCA4* 4%), and DNA methylation genes and c-*KIT* were also frequently mutated in advanced-stage TCs (Table 3). Of note, TET patients with somatic mutations exhibited a worse OS than patients without mutations (59 months *vs.* 142 months; $P < 0.05$) [22]. A nine-gene signature has also been developed and validated to predict the metastatic behaviour of thymoma [23], while the Cancer Genome Atlas (TCGA) includes thymoma as part of its ongoing project. All of this knowledge might help to identify druggable targets, laying the foundations for improving OS with personalised medicine for TET patients in the future.

Randomised clinical trials based on molecular alterations in rare diseases such as TET are very difficult. An alternative approach

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