Everolimus in thymic epithelial tumors: practical considerations

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Thymoma and thymic carcinoma are known as thymic epithelial tumors (TETs) given their shared origin as epithelial neoplasms arising from the thymus. The understanding of the relationship between thymoma and thymic carcinoma has evolved over time. Thymic carcinoma was initially classified as type C thymoma in the 1999 World Health Organization (WHO) classification (1), but was separated as its own entity in later WHO classifications (2). Although thymoma is the most common tumor of the anterior mediastinum, it is rare with a reported incidence of 0.15 per 100,000 person-years (3). Thymic carcinoma is rarer still, accounting for perhaps 10% of all TETs. Surgery is the only curative intervention for both thymoma and thymic carcinoma, with chemoradiation offered to patients with metastatic disease, however there are no standard treatment options for patients who progress on chemotherapy (7,8). The rarity of thymic carcinoma in particular has posed a major barrier to clinical trial development and accrual, resulting in a lack of robust clinical evidence to guide treatment decisions. One of the largest series in thymic carcinoma patients at a high volume center included 135 patients over 30 years, and confirmed the aggressive nature of thymic carcinoma, which is more often diagnosed at a later stage and has a poorer prognosis than the more indolent thymoma (9). Recently, several phase II studies have been reported in TET with some agents demonstrating promising efficacy (Table 1).

In nearly all of these studies, TET are combined for the purpose of efficacy analysis. Only two recent studies were limited to patients with thymic carcinoma, the largest of which accrued 41 patients. Given the unique challenges of studying this clinical entity, Zucali and collaborators are to be congratulated on accruing a total of 51 patients with TET over 2 years to their phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy (18).

This single arm, multicenter study revealed a high disease control rate (DCR) for patients with TET treated with everolimus, but unique toxicities occurred including fatal pneumonitis.

Everolimus is an oral MTOR-inhibitor that is approved for use in renal cell carcinoma, neuroendocrine tumors, and breast cancer, among others (19,20). Despite response rates typically under 5%, treatment with everolimus has resulted in prolonged periods of stable disease for patients with these cancers. Preclinical data suggesting a role of PI3K in TET, as well as promising reports of clinical activity in this patient population, led Zucali and collaborators to evaluate the role of everolimus in the treatment of patients with refractory TET. This phase II study included 51 patients with TET, 50 of whom received study drug (32 patients with thymoma, 18 patients with thymic carcinoma). This was a single-arm, open-label, multi-center phase II study of everolimus dosed at 10 mg daily continuously in patients with TET who had progressed on prior platinum-based chemotherapy. The primary objective was to evaluate the efficacy of everolimus in this patient population, with a primary endpoint of DCR including complete and...
partial responses and stable disease. Secondary endpoints included progression free survival (PFS), overall survival (OS), duration of response, and safety, as well as time to treatment failure (TTF), although TTF was not a pre-planned secondary endpoint. Overall, 50 patients were included in the intention-to-treat analysis, however only 46 patients were evaluable for response to treatment after 4 patients discontinued therapy prior to imaging due to either drug-related adverse events (n=3) or non-drug-related events (n=1). Disease control was observed in 44 of 50 patients for a DCR of 88% [95% confidence interval (CI), 78.7–95.5%]. Five partial responses were observed (10%) and one complete response was seen (2%) in a patient with thymic carcinoma. The median duration of response was 7.1 months (range, 1.2–25.9 months). Disease control rate varied by histology, observed in 30 patients with thymoma (93.8%; 95% CI, 79.2–99.2%) compared with 14 patients with thymic carcinoma (77.8%; 95% CI, 52.4–93.6%). For the 6 patients who experienced either a PR or CR, the durability of response differed for patients with thymoma (3.3, 25.5, 29.9 months) compared to those patients with thymic carcinoma (1.2, 5.9, 8.3 months). The time to treatment failure overall was 8.4 months (0.66–44.3 months) and also varied for patients with thymoma (median 11.3 months) compared to thymic carcinoma (median 5.6 months, P=0.001). The median OS overall was 25.7 months for the whole population (95% CI, 16–NR); median OS was not reached for thymoma patients and was 14.7 months (95% CI, 3.5–24 months) for patients with thymic carcinoma. In correlative studies, tumor positivity for p4E-BP1 and IGF1-R were associated with poorer survival, and expression of p4E-BP1 was higher in thymic carcinoma patients than in thymoma patients (57%; 25%: 10%, P=0.003). However, the study did not identify any
predictive biomarkers for response to everolimus.

The most common toxicities reported were stomatitis (n=33, 66%), fatigue (n=24, 48%), mucositis (n=18, 36%) and pneumonitis (n=18, 36%), and the rate of serious toxicities (grade 3 or 4) was 28% (n=14). Overall, 70% of patients required dose interruption, 18% required permanent discontinuation of treatment due to toxicity, and 28% required dose reduction. The high rate of pneumonitis in the study is certainly concerning. Most worrying was the occurrence of fatal pneumonitis in 3 patients (6%). There were no clear risk factors to identify patients at risk for pneumonitis, although it occurred more commonly in thymoma than thymic carcinoma (P=0.064).

The results of this study must be put into the context of the changing landscape of treatment options for patients with refractory TET. As can be seen in Table 1, there are several promising new agents available for this patient population, including both targeted agents and immunotherapies. Given the high expression of PD-L1 in TET (23-25), checkpoint inhibitor immunotherapy has emerged as a possible treatment approach in patients with TET (8), but the risk of immune-related adverse events including pneumonitis and myocarditis must be weighed against any potential benefit of these therapies. With multiple new agents being evaluated, the optimal sequencing of these therapies has yet to be determined. The high rate of pneumonitis in patients treated with everolimus should be considered in the sequencing of treatment options, since the risk of pneumonitis or other immune-related toxicities with subsequent immunotherapy is unknown. In the current study, no patients were reported to have received treatment with prior immunotherapy. Additionally, unique immune toxicities have occurred in patients with TET, including a higher risk of myocarditis than in other patient populations (8), which may be affected by prior or subsequent therapies.

In a separate study, Thomas and collaborators conducted a phase II study of sunitinib in TET and reported an objective response rate (ORR) of 26% in 25 patients with thymic carcinoma. DCR was 91% (95% CI, 72.0–98.9%) in patients with thymic carcinoma and 81% (95% CI, 54.4–96.0%) in patients with thymoma. Median PFS was 7.2 months for patients with thymic carcinoma treated with sunitinib (Table 1), and after a median follow-up of 17 months, median OS was not reached for patients with thymic carcinoma and 15.5 months for patients with thymoma (95% CI, 12.6–NR). Grade 3 or 4 adverse events occurred in 70% of patients treated with sunitinib (n=28), including fatigue and mucositis in 8 each (20%), and 3 patients (8%) died during treatment with sunitinib due to progressive disease, sepsis, and treatment-related ventricular fibrillation. Importantly, the median duration of response for patients with thymic carcinoma was 16.4 months (range, 1.4–16.4 months), which is considerably longer than that experienced by patients treated with everolimus, acknowledging the limitations of cross-trial comparisons. Both everolimus and sunitinib were associated with high rates of serious toxicities, with pneumonitis being more common in patients treated with everolimus and cardiac and skin toxicities being frequent in patients treated with sunitinib.

The vastly different outcomes in terms of response and survival between thymoma and thymic carcinoma in this study and others, as well as possible differences in toxicity to both targeted agents and immunotherapy, point to the importance of evaluating these entities separately. For instance, the recently reported phase II study of pembrolizumab accrued only patients with thymic carcinoma out of concern for exacerbating or precipitating paraneoplastic events in thymoma patients (8). Several ongoing phase II studies focus only on thymic carcinoma patients (Table 2). The rarity of these diseases should not preclude the ability to study them independently, which can be accomplished by leveraging multi-institutional collaborations in order to accrue patients, such as with the French RHYTMIC network or the International Thymic Malignancy Interest Group. In this context, Zucali et al. have demonstrated that accrual for a rare disease can still be accomplished in an acceptable time frame when done in collaboration.

In summary, Zucali and collaborators have demonstrated a high rate of disease control with everolimus in TET, including one complete response in a patient with thymic carcinoma. However, this came at the cost of a higher than expected rate of pneumonitis, including fatal pneumonitis in 3 (6%) of patients. The disparate outcomes by histology argue for the importance of including pre-planned efficacy analyses by histology, or better yet, designing studies for each histology independently. With several new treatment options being investigated for patients with thymoma and thymic carcinoma, the optimal sequencing of therapies is unknown and will be important to investigate in future studies.
Table 2 Ongoing select phase II studies in TET

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Sponsor</th>
<th>Setting</th>
<th>Intervention</th>
<th>Phase</th>
<th>Date open*</th>
<th>Enrollment (planned)</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01011439</td>
<td>Tiziana Life Sciences</td>
<td>Thymic carcinoma (2nd line)</td>
<td>Milciclib maleate</td>
<td>2</td>
<td>March 2009</td>
<td>60</td>
<td>PFS rate at 3 months</td>
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<tr>
<td>NCT01301391</td>
<td>Tiziana Life Sciences</td>
<td>Thymoma (&gt;2nd line)</td>
<td>Milciclib maleate</td>
<td>2</td>
<td>January 2011</td>
<td>30</td>
<td>PFS rate at 3 months</td>
</tr>
<tr>
<td>NCT02636556</td>
<td>Fudan University, China</td>
<td>Inoperable locally advanced (stage III/IVA) thymoma or thymic carcinoma</td>
<td>Cisplatin, etoposide, and radiotherapy</td>
<td>2</td>
<td>January 2013</td>
<td>56</td>
<td>PFS</td>
</tr>
<tr>
<td>NCT02220855</td>
<td>Indiana University Simon Cancer Center, USA</td>
<td>Thymoma (&gt;2nd line)</td>
<td>Buparlisib</td>
<td>2</td>
<td>October 2014</td>
<td>14</td>
<td>ORR</td>
</tr>
<tr>
<td>NCT02364076</td>
<td>Georgetown University, USA</td>
<td>Thymic carcinoma (&gt;2nd line)</td>
<td>Pembrolizumab and epacadostat</td>
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<td>March 2015</td>
<td>67</td>
<td>ORR</td>
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<tr>
<td>NCT03449173</td>
<td>Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy</td>
<td>Type B3 thymoma or thymic carcinoma (&gt;2nd line)</td>
<td>Sunitinib</td>
<td>2</td>
<td>March 2017</td>
<td>56</td>
<td>ORR</td>
</tr>
<tr>
<td>NCT03076554</td>
<td>National Cancer Institute (NCI), USA</td>
<td>Thymoma and thymic carcinoma (&gt;2nd line)</td>
<td>Avelumab</td>
<td>2</td>
<td>April 2017</td>
<td>24</td>
<td>Co-primary endpoints: safety and ORR</td>
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<td>NCT03466827</td>
<td>Rigshospitalet (Copenhagen University Hospital, Denmark)</td>
<td>Thymoma and thymic carcinoma (&gt;2nd line)</td>
<td>Selinexor</td>
<td>2</td>
<td>October 2017</td>
<td>25</td>
<td>ORR</td>
</tr>
<tr>
<td>NCT03295227</td>
<td>M.D. Anderson Cancer Center, USA</td>
<td>Thymoma and thymic carcinoma (any line)</td>
<td>Pembrolizumab</td>
<td>1/2</td>
<td>December 2017</td>
<td>30</td>
<td>Feasibility and toxicity (phase I); ORR (phase II)</td>
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<td>NCT03134118</td>
<td>European Organization for Research and Treatment of Cancer-EORTC</td>
<td>Type B3 thymoma and thymic carcinoma (&gt;2nd line)</td>
<td>Nivolumab</td>
<td>2</td>
<td>April 2018</td>
<td>55</td>
<td>PFS rate at 6 months</td>
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<td>NCT03463460</td>
<td>Ohio State University Comprehensive Cancer Center, USA</td>
<td>Thymic carcinoma (&gt;2nd line)</td>
<td>Pembrolizumab and sunitinib</td>
<td>2</td>
<td>June 2018</td>
<td>40</td>
<td>ORR</td>
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</tbody>
</table>

*, trials are active or ongoing as per clinicaltrials.gov. PFS, progression free survival; ORR, overall response rate; TET, thymic epithelial tumors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


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