Perspective towards the clinical application of eribulin in soft tissue sarcomas

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Introduction
Eribulin mesilate (trade name Halaven®) is a synthetic macrocyclic analogue of the marine halichondrin B. This anticancer drug was approved both by the U.S. Food and Drug Administration and the European Medicines Agency in 2010, for treatment of patients with metastatic breast cancer who have received at least two prior chemotherapy regimens for late-stage disease, including both anthracycline- and taxane-based chemotherapies (1), and recently, for the treatment of unresectable or metastatic liposarcoma in patients who received prior at least one line of systemic therapy including chemotherapy based on anthracyclines (2).

Eribulin—mechanism of action
Eribulin has with unique mechanism of action leading to the inhibition of microtubule dynamics, which is distinct from that of other tubulin-targeted drugs. Eribulin binds predominantly to a small number of high affinity sites at the plus ends of existing microtubules, which exerts its anticancer effects by triggering apoptosis of cancer cells following prolonged and irreversible mitotic blockade (1,3). In soft tissue sarcomas (STS) eribulin has lead also to tumor vasculature remodeling, what could induce differentiation of tumor cells (4).

STS
Sarcomas are rare mesenchymal tumors comprising more than 60 subtypes, which are clinically and biologically different. The standard first-line therapy for advanced STS is doxorubicin, either as monotherapy or in combination with ifosfamide. A limited number of drugs have shown activity in treatment-refractory disease, including dacarbazine, gemcitabine +/- docetaxel, trabectedin, or pazopanib (5,6). Due to the rarity of these tumors, routinely clinical trials in sarcoma included all subtypes and they are mainly initiated by academic research groups. So far, there have been only few phase III studies investigating the efficacy of target therapies in patients with advanced L-sarcomas (leiomyosarcomas or liposarcomas). None of these studies reported a significant difference in overall survival between the treatment groups.

Pivotal phase III trial with eribulin in previously treated advanced liposarcoma or leiomyosarcoma
Data supporting approval of eribulin in liposarcoma comes from a phase 3 randomized, open-label clinical trial reported by Schöffski et al. (6). Based on data from phase 2 study, where only the strata for leiomyosarcoma and liposarcoma met the primary endpoint of progression-free-survival at 12 weeks (2), in the phase 3 study patients with advanced STS limited to these subtypes were included, after failure of at least two previous systemic regimens for advanced disease (including anthracycline). The primary endpoint was overall survival and 446 patients were randomly (1:1) assigned to arm receiving eribulin mesilate (1.4 mg/m²) intravenously on days 1, 8 (n=228), or dacarbazine (850 mg/m², 1,000 mg/m², or 1,200 mg/m²) intravenously on day 1, every 21 days (n=224) until disease progression or unacceptable toxicity. The
The findings from this study showed a median overall survival improvement of 2.6 months (13.5 vs. 11.5 months) in all patients treated with eribulin versus dacarbazine [hazard ratio (HR), 0.768; 95% confidence interval (CI), 0.618–0.954; P=0.017]. The subgroup analysis suggested that the survival benefit with eribulin was mainly observed in patients with liposarcoma (HR, 0.51; 95% CI, 0.35–0.75; median survival 15.6 vs. 8.4 months), but the study was not powered for drawing final conclusions from subgroup analysis. Despite overall survival benefit there was no significant difference in progression free survival between treatment groups, what is difficult to explain.

There are some limitations of the study, dacarbazine were investigator's choice. Fifty percent of patients in eribulin arm received more than two previous lines of systemic therapy, 32% of patients had liposarcoma.

Toxicity profile of eribulin was consistent with investigator's brochure, and no unexpected or new safety findings were observed. In this study, the most common adverse events in eribulin arm were: neutropenia, asthenia/fatigue, nausea, alopecia and constipation. Grade 3 or higher adverse events were more common in eribulin arm than dacarbazine arm. The most common grade 3 or higher adverse events in eribulin arm were: neutropenia, asthenia/fatigue, nausea, alopecia and constipation. Grade 3 or higher adverse events in dacarbazine arm were: cytopenias, nausea, vomiting and fatigue. Grade 3 or higher adverse events in placebo arm were: fatigue and nausea.

All patients finished eribulin due to toxicity. There were often studied together in several trials, but not for liposarcomas, trabectedin is approved for both of L-sarcomas. Although control group outperformed the overall survival expectations, still the eribulin cohort showed significantly better outcomes. Based on these phase 3 results, eribulin was approved in refractory liposarcoma, and cannot be prescribed in clinical practice to other sarcoma subtypes.

The summary of clinical trials in advanced STS including L-sarcomas beyond first line of treatment is presented in Table 1. To summarize, pazopanib is approved for leiomyosarcomas but not for liposarcomas, trabectedin is approved for both of L-sarcomas, and eribulin is approved for liposarcoma subtype. It has demonstrated significant progression-free survival in pazopanib arm vs.

Table 1 The summary of clinical trials in advanced STS including L-sarcomas beyond first line of treatment

<table>
<thead>
<tr>
<th>Tumor type, phase (reference)</th>
<th>Line of therapy</th>
<th>Arms (experimental vs. control)</th>
<th>Response rate (%)</th>
<th>Clinical benefit rate (%)</th>
<th>Median PFS (months, P value)</th>
<th>Median OS (months, P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS, phase 2, n=122 (7)</td>
<td>Maximal fourth</td>
<td>Gemcitabine 900 mg/m² + docetaxel 100 mg/m² vs. gemcitabine 1,200 mg/m²</td>
<td>16 vs. 8</td>
<td>69 vs. 61</td>
<td>6.2 vs. 3.0 (P&lt;0.0001)</td>
<td>17.9 vs. 11.5 (P&lt;0.0001)</td>
</tr>
<tr>
<td>Leiomyosarcoma, phase 2, n=90 (8)</td>
<td>Second (after anthracycline)</td>
<td>Gemcitabine 900 mg/m² + docetaxel 100 mg/m² vs. gemcitabine 1,200 mg/m²</td>
<td>Median PFS 15.6 vs. 19.1, non-uterine 72 vs. non-uterine 68 vs. 73</td>
<td>Uterine 4.7 vs. 5.5; non-uterine 3.8 vs. 6.3</td>
<td>Uterine 20 vs. 23; non-uterine 15 vs. 13</td>
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<tr>
<td>Non-adipocytic soft tissue sarcoma, phase 3, n=369 (9)</td>
<td>Second or later (after anthracycline)</td>
<td>Pazopanib 800 mg/m² vs. placebo</td>
<td>6 vs. 0</td>
<td>73 vs. 38</td>
<td>4.6 vs. 1.6 (P&lt;0.0001)</td>
<td>12.5 vs. 10.7 (P&lt;0.025)</td>
</tr>
<tr>
<td>Liposarcoma and leiomyosarcoma, phase 3, n=518 (10)</td>
<td>Second or later (after anthracycline)</td>
<td>Trabectedin 1.5 mg/m² vs. dacarbazine 1,000 mg/m²</td>
<td>10 vs. 7</td>
<td>61 vs. 42</td>
<td>4.2 vs. 1.5 (P&lt;0.001)</td>
<td>12.4 vs. 12.9 (P&lt;0.037)</td>
</tr>
<tr>
<td>Liposarcoma and leiomyosarcoma, phase 3, n=452 (6)</td>
<td>Third or later (after anthracycline)</td>
<td>Eribulin mesylate 1.4 mg/m² vs. dacarbazine 850–1,200 mg/m²</td>
<td>5 vs. 4</td>
<td>57 vs. 52</td>
<td>2.6 vs. 2.6 (P=0.23)</td>
<td>13.5 vs. 11.5 (P&lt;0.01)</td>
</tr>
</tbody>
</table>

STS, soft tissue sarcomas; PFS, progression-free survival; OS, overall survival.

and no other effective treatment options such as trabectedin or pazopanib (excluding liposarcomas) were allowed. Although control group outperformed the overall survival expectations, still the eribulin cohort showed significantly better outcomes. Based on these phase 3 results, eribulin was approved in refractory liposarcoma, and cannot be prescribed in clinical practice to other sarcoma subtypes.
placebo (4.6 vs. 1.6 months; HR, 0.31; P<0.001; with similar range of benefit in leiomyosarcoma subgroup), but without significant difference in median overall survival. Based on the results of this trial pazopanib is approved for treatment of non-adipocytic STS (9).

Gemcitabine +/- docetaxel has been studied in several trials, but only the study with a Bayesian adaptive randomization design demonstrated overall survival improvement with median survival of 12.9 months in combination arm as compared to 11.5 months in the gemcitabine only arm (7). In French Sarcoma Group phase II trial in treatment refractory leiomyosarcoma population there was no benefit of combination arm relative to single-drug gemcitabine, and the drug activity was clearly better in uterine leiomyosarcoma group (8).

For refractory L-sarcomas in similar to eribulin trial population, Demetri et al. (10) conducted a randomised phase 3 trial on 518 patients, which compared trabectedin with dacarbazine. This study, in contrast to the Schoffski’s trial, showed a significant improvement in progression-free survival in trabectedin cohort (4.2 vs. 1.5 months in control arm, P<0.001), but no significant difference in overall survival. Benefit was seen in both uterine and non-uterine leiomyosarcomas and in all liposarcoma subtypes, although the benefit compared with dacarbazine was most pronounced (median PFS 5.6 vs. 1.5 months) in the myxoid/round cell liposarcoma subtype (which seems to be particularly sensitive to trabectedin). In both studies, the number of objective responses was low, so patients should be counselled that such treatment can rather control disease than shrink tumors. The toxicity profiles of both eribulin and trabectedin are manageable. Some patients might prefer eribulin, in view of its survival benefits.

Conclusions

The findings from the trial suggest that eribulin might be another important treatment option in armamentarium for patients with previously treated liposarcoma. There are currently limited treatment options available, but now, we are a step closer to being able to offer them a treatment with a proven overall survival benefit after decades of no progress. Interesting (after encouraging phase 2 trial results) (11) phase 3 trial comparing doxorubicin without and with olaratumab is underway. Eribulin is the first-ever single agent therapy to show such a survival benefit in sarcomas, which makes this trial even more important for patients and clinicians worldwide.

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Footnote

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