Commentary

Perspective towards the clinical application of eribulin in soft tissue sarcomas

Piotr Rutkowski, Iwona Lugowska

Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, Warsaw, Poland

Correspondence to: Piotr Rutkowski, MD, PhD. Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, Roentgena 5, 02-781 Warsaw, Poland. Email: piotr.rutkowski@coi.pl.

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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

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

Tumor type, phase (reference)	Line of therapy	Arms (experimental *vs.* control)	Response rate (%)	Clinical benefit rate (%)	Median PFS (months, P value)	Median OS (months, P value)
STS, phase 2, n=122 (7)	Maximal fourth	Gemcitabine 900 mg/m^2 + docetaxel 100 mg/m^2 *vs.* gemcitabine 1,200 mg/m^2	16 *vs.* 8	69 *vs.* 61	6.2 *vs.* 3.0 (P<0.0001)	17.9 *vs.* 11.5 (P<0.0001)
Leiomyosarcoma, phase 2, n=90 (8)	Second (after anthracycline)	Gemcitabine 900 mg/m^2 + docetaxel 100 mg/m^2 *vs.* gemcitabine 1,200 mg/m^2	Uterine 24 *vs.* 19, non-uterine 5 *vs.* 14	Uterine 62 *vs.* 72, non-uterine 68 *vs.* 73	Uterine 4.7 *vs.* 5.5; non-uterine 3.8 *vs.* 6.3	Uterine 20 *vs.* 23; non-uterine 15 *vs.* 13
Non-adipocytic soft tissue sarcoma, phase 3, n=369 (9)	Second or later (after anthracycline)	Pazopanib 800 mg/m^2 *vs.* placebo	6 *vs.* 0	73 *vs.* 38	4.6 *vs.* 1.6 (P<0.0001)	12.5 *vs.* 10.7 (P=0.25)
Liposarcoma and leiomyosarcoma, phase 3, n=518 (10)	Second or later (after anthracycline)	Trabectedin 1.5 mg/m^2 *vs.* dacarbazine 1,000 mg/m^2	10 *vs.* 7	61 *vs.* 42	4.2 *vs.* 1.5 (P<0.001)	12.4 *vs.* 12.9 (P=0.37)
Liposarcoma and leiomyosarcoma, phase 3, n=452 (6)	Third or later (after anthracycline)	Eribulin mesylate 1.4 mg/m^2 *vs.* dacarbazine 850–1,200 mg/m^2	5 *vs.* 4	57 *vs.* 52	2.6 *vs.* 2.6 (P=0.23)	13.5 *vs.* 11.5 (P=0.01)

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

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/m^2) intravenously on days 1, 8 (n=228), or dacarbazine (850 mg/m^2, 1,000 mg/m^2, or 1,200 mg/m^2) intravenously on day 1, every 21 days (n=224) until disease progression or unaccepted toxicity. The doses of 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 [152 (67%)]. There was one death related to eribulin, 6% of patients finished eribulin due to toxicity.

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 was chosen as the active control despite its modest efficacy in sarcomas at this stage, its dose was different (850–1,200 per m^2) 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.

The landscape of systemic therapy of advanced L-sarcomas

L-sarcomas comprise the interesting heterogenous group of STS—liposarcomas (several subtypes) and leiomyosarcomas. There were often studied together in several trials, but still limited options of systemic therapy exist beyond the first line of treatment. The comparison of the recent trials in STS including L-sarcomas is presented in *Table 1*. To

summarize, pazopanib is approved for leiomyosarcomas but not for liposarcomas, trabectedin is approved for both of the L-sarcomas, and eribulin is approved for liposarcomas but not leiomyosarcomas.

The phase 3 PALETTE study compared an activity of a multitargeted tyrosine-kinase inhibitor—pazopanib with placebo in patients with metastatic treatment refractory STS excluding liposarcoma subtype. It has demonstrated significant progression-free survival in pazopanib arm *vs.* placebo (4.6 *vs.* 1.6 months; HR, 0,31; P<0.0001; 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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