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Eribulin in soft-tissue sarcoma

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Sarcomas are unusual tumours that can occur at any anatomical site. Although they account for less than 1% of malignant tumours, they can be divided into more than 50 clinically and biologically distinct subtypes. Until recently, all soft-tissue sarcomas were treated the same way, but in the past decade, progress has been made in identifying clinical, histological, and molecular features to guide management.[1] In a randomised open-label phase 3 trial in *The Lancet*, Patrick Schöffski and colleagues[2] report that eribulin improves overall survival in patients with advanced leiomyosarcoma and liposarcoma. Their report raises several interesting questions.

Schöffski and colleagues randomly assigned treatment-refractory patients with leiomyosarcoma and liposarcoma to eribulin (228 patients) or dacarbazine (active control; 224 patients). The study population was younger (median age 56 years) and fitter (96% had performance status 0 or 1) than many patients seen in routine clinical practice. The investigators report a significant improvement in overall survival for assignment to eribulin versus dacarbazine (hazard ratio [HR] 0·77, 95% CI 0·62–0·95; p=0·0169) with a difference in median overall survival of 2 months (13·5 *vs* 11·5 months), despite similar numbers of patients who responded to the drugs and no significant difference between treatment groups for progression-free survival. Subgroup analysis suggests that the survival benefit with eribulin was mostly observed in patients with liposarcoma (HR 0·51, 95% CI 0·35–0·75; median survival 15·6 *vs* 8·4 months). Although promising, the study was not designed or powered for drawing conclusions from this analysis.

In the protocol, the study design assumed a median survival of 6 months in the active control group, and was powered to detect a clinically significant 2·5 month improvement in overall survival. The survival in both treatment groups was better than expected, but the reported HR of 0·77 failed to meet the pre-specified HR of 0·71. Interestingly, a similar pattern of significant improvement in overall survival with little change in progression-free survival was also noted in the licensing study of eribulin in advanced breast cancer.[3] The findings in both tumour types suggest that eribulin enhances the response to subsequent chemotherapy.

What is special about leiomyosarcoma and liposarcoma – often grouped together as L-sarcomas? These terms encompass several biologically and clinically disparate tumour subtypes. The present investigators stratified patients by liposarcoma and leiomyosarcoma histologies, but did not distinguish further between biologically distinct subtypes. The decision to restrict the study to these sarcomas was based on the results of a stratified phase 2 study that assessed eribulin in the treatment of leiomyosarcoma, liposarcoma, synovial sarcoma, and a mixed group of other subtypes.[4] Only the strata for leiomyosarcoma and liposarcoma met the primary endpoint of at least 30% of patients being progression-free at 12 weeks and so were included in the phase 3 study. Therefore, the phase 3 results should not be used to extend eribulin prescribing in clinical practise to other sarcoma subtypes.

And what is special about eribulin? The standard firstline therapy for advanced soft-tissue sarcoma is doxorubicin, either as monotherapy or in combination with ifosfamide. A number of drugs have shown activity in treatment-refractory disease, including dacarbazine, ifosfamide, gemcitabine-docetaxel, and trabectedin. In this study, dacarbazine was chosen as the active control despite its modest efficacy.[5] 34% of patients assigned to eribulin received dacarbazine post-study, which might have reduced the observed overall survival difference. Eribulin is a synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*. It is a

microtubule-targeting drug with a mechanism of action distinct from taxanes and vinca alkaloids. In addition to its cytotoxic effects, it has other properties that might contribute to its therapeutic effect.[6] Eribulin induces vascular remodelling in tumour xenografts, including those for breast cancer.[7] These changes in the vasculature enhance tumour response to subsequent chemotherapy, and might partly explain the survival gain reported in the present study. The PALETTE study[8] provided good evidence that some sarcomas are sensitive to antiangiogenic treatment. This randomised controlled trial of pazopanib versus placebo in patients with treatment-refractory soft-tissue sarcoma reported a significant improvement in progression-free survival but not in overall survival; however only 45% of patients treated with pazopanib went on to receive post-study chemotherapy. Notably, patients with liposarcoma were specifically excluded from the PALETTE study on the basis of phase 2 data that suggested liposarcomas are less sensitive than leiomyosarcoma to antiangiogenic therapy.[9] It would be of interest to compare the effects of eribulin and pazopanib on the tumour vasculature.

How should eribulin be used in soft-tissue sarcoma? It is interesting to contrast these results with those of another randomised phase 3trial in patients with treatment-refractory liposarcoma and leiomyosarcoma, which compared trabectedin with dacarbazine.[10] This 518 patient trial recruited a similar patient population, but in contrast to the Schöffski study, showed a significant improvement in progression-free survival with assignment to trabectedin, but no significant difference in overall survival. In both studies, the number of objective responses was low (4·4% *vs* 8·9%), so patients should be counselled that treatment is offered to control disease, rather than shrink tumours. The toxicity profiles of both eribulin and trabectedin are manageable. Many patients might prefer eribulin, in view of its survival benefits.

Should eribulin be used earlier in the patient pathway? In the present study, eligible patients had received at least two lines of standard chemotherapy for advanced disease. Given the low number of

objective responses, eribulin is not attractive as a firstline option for advanced soft-tissue sarcoma. If eribulin enhances the response to subsequent chemotherapy, should eribulin be used in combination or sequenced with other systemic treatments, and with which other drugs? Further study of mode of action of eribulin and identification of biomarkers to guide patient selection would help to place it in the algorithm of treatments for relapse.

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We declare no competing interests.

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