Commentary

Eribulin in the soft tissue sarcoma therapeutic landscape: little is good, then more is better

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Soft tissue sarcomas (STS) are a rare and heterogeneous group of mesenchymal tumors accounting for approximately 1% of adult solid malignancies (1). Chemotherapy remains the mainstay of treatment for patient with metastatic STS. Molecular-targeted therapies are active in selected and very rare histological subtypes such as crizotinib in ALK-rearranged inflammatory myofibroblastic tumor (2). To our knowledge, PD(L)1 inhibitors seem not to have significant activity in STS, but it is too early to conclude (3). Up to now second line treatment options (dacarbazine, ifosfamide, gemcitabine-docetaxel, trabectedin and pazopanib) were based on the results of phase II/III studies in which overall survival (OS) is not the primary endpoint or without significant improvement in OS (4-7). Recently, Patrick Schöffski and colleagues reported in a randomised multicentre phase III trial that treating advanced liposarcoma (LPS) and leiomyosarcoma (LMS) with eribulin an improvement in OS compared with dacarbazine (8).

Eribulin was first approved for metastatic breast cancer based on the results of the EMBRACE study (9). Activity of eribulin in pretreated STS patients was first shown by Schöffski *et al.* in a non randomised phase 2 study. Eribulin did not met the primary objective [12 weeks progression-free survival (PFS) >40% in synovial sarcoma and other sarcoma patients] but interestingly 12 weeks PFS was 46.9% and 31.6% of patients with LPS and LMS (10). Based on these data, Schöffsky *et al.* have conducted a phase III study assessing the efficacity of eribulin compared to dacarbazine in pretreated patients with metastatic LPS or LMS after at least 2 previous line of chemotherapy (with anthracyclines) (8). The primary endpoint was intent-to-treat OS. A total of 452 patients were randomly assigned to receive eribulin mesilate (n=228) or dacarbazine (n=224). Treatment assignment was not masked. The study met its primary endpoint and eribulin significantly improved OS compared with dacarbazine [median, 13.5 months (95% CI, 10.9–15.6) *vs.* 11.5 months (9.6–13.0); HR 0.77 (95% CI, 0.62–0.95)]. Subgroup analysis suggested that OS was improved in only LPS [median OS, 15.6 months (95% CI, 10.2–18.6) *vs.* 8.4 months (95% CI, 5.2–10.6)]. Results were surprising in terms of PFS, which was found similarly in both treatment groups (2.6 months). There were no complete responses to either drug. Treatment-related grade 3 or higher adverse events were more common with eribulin (67% *vs.* 56%). The authors concluded that eribulin could be a treatment option for advanced LMS or LPS (8). Based on these results FDA approved eribulin on January 2016 for the treatment of metastatic LPS only for patients who received prior chemotherapy that contained an anthracycline drug.

One prior phase II randomized trial of dacarbazine plus gemcitabine combination versus dacarbazine has suggested an improvement in OS with experimental arm, but this finding was not confirmed in a phase III trial (5). Consequently, the eribulin trial is the first randomised controlled trial of single agent systemic therapy to show an improvement in OS in pretreated patients with metastatic LPS and LMS.

These provocative results of eribulin open the door to a new strategic option in STS patients. Nevertheless, it will be of interest to explore why this inconsistency between OS and PFS improvement in this study. Important percentage of patients who received eribulin were treated afterwards with dacarbazine (34%), but according to the authors this reason

may be insufficient to enlighten the observed difference in OS while PFS is similar in both groups (8). Eribulin mesilate is a marine synthetic analog of halichondrin B and act as a unique microtubule targeting agent that can be distinguished from the other microtubule-targeting agents partially due to the known effect on angiogenesis, vascular remodeling, and epithelial-to-mesenchymal transition (11). This might explain partially the inconsistency between OS and PFS improvement in this study. Also looking closely at the objective response in this trial and similarly to the PFS no difference was seen between the two groups with low response rates (4% with eribulin *vs*. 5% with dacarbazine) (8). Of note, the same observation has been seen in the EMBRACE study in advanced breast cancer (9) suggesting indeed that eribulin did not act as classical chemotherapy agent and other tumor effects may interfere with the tumour microenvironment and cancer cell growth. Preclinical data in STS and breast cancer suggest that eribulin triggers cellular differentiation and improves vascular perfusion leading to a more functional microenvironment. This may reduce metastatic potential or enhance the response to subsequent chemotherapy (12-14).

Eribulin is now in its way into the STS therapeutic landscape and particularly LPS. Other treatment options have been studied after anthracyclines and/or ifosfamide failure but only few phase III trials are available. Gemcitabine has been largely studied in STS either as monotherapy or in combination with docetaxel or dacarbazine in phase II trials suggesting some interesting activity with a need for confirmation from phase III trials (5,6). More recently, trabectedin and pazopanib were approved for clinical use in STS (respectively LPS/LMS and non adipocytic STS). Trabectedin registration was based on the results of a randomised phase III, in which trabectedin was superior to dacarbazine by improving PFS of advanced LMS and LPS after failure of prior cytotoxic chemotherapy. No evidence of improved OS was shown so far (7). No difference was observed across the two sarcoma subtypes. In the PALETTE study, pazopanib was shown to be an active single-agent regimen in patients with advanced non-adipocytic STS (4) with a statistically significant improvement in PFS but also did not demonstrate an improvement in OS (4). Following the disappointing results of pazopanib in LPS in a previous phase II study (15), the PALETTE study excluded LPS subtypes (4). In both registration phase III studies, either OS was not the primary endpoint or no significant improvement was found. As the present study is the first randomised controlled trial to show an improvement in OS, eribulin may be favored over trabectedin at least in LPS patients. For patients with advanced or metastatic non adipocytic STS who progress after an anthracycline-containing regimen or ifosfamide, pazopanib is the alternative option. These aforementioned studies suggest a different efficacy profile depending on the histological subtypes (4,7,8). Despite their heterogeneity (more than 50 individual histological subtypes), STS were till recently treated with no selection based on histological subtypes. Tailoring therapy to histological and molecular subtype for STS is currently a viable treatment strategy (16). Finally, despite the promising results of eribulin, we agree with Young *et al*., who suggested not to go earlier in the STS clinical developement strategy (14). In fact, it is unlikely that eribulin as a single agent would overcome efficacy of anthracycline in the first-line given the observed low response rate with eribulin in this study (4%).

Treatment options in STS remains limited with an unmet need for developing new therapeutic strategies. Eribulin showed potential in the treatment of STS. The development of histological subtypes dedicated trials as well as identification of biomarkers for response will help to personalize use of eribulin in STS. In addition, eribulin's mechanism of action and preclinical data suggest enhanced response to further administration of chemotherapy. These findings also support the significant role of vascular remodeling in STS as shown previously with pazopanib and regorafenib (multi-targeted tyrosine kinase inhibitors) in pretreated non adipocytic sarcomas (4,17). Combinations with anti-angiogenic agents, or with immune checkpoint inhibitors may also be a clinical research option (12). Indeed, despite there is a good rationale for immunotherapy use in STS (presence of chromosomal translocations, high expression of cancer testis antigens, and some genetic mutations) (3), no satisfactory positive signal has been seen yet. New combination strategies may be an interesting lead for improved efficacy (18). Further studies intelligently designed are warranted to define the full potential of eribulin for the treatment of STS.

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