Redefining the standard of care in metastatic leiomyosarcoma

Sarcomas are rare heterogeneous tumours of mesenchymal origin composed of over 70 histological subtypes, each with a unique biology and response to treatment. Inevitably, drug development is challenging in such a molecularly diverse group of diseases. Despite these obstacles, progress has been made in some subtypes; neoadjuvant and adjuvant chemotherapy in Ewing’s sarcoma, osteosarcoma, and embryonal rhabdomyosarcoma has resulted in substantial improvements in survival, and imatinib in gastrointestinal stromal tumours has typified targeted treatment of solid tumours. In most clinical trials, biologically distinct histological subtypes have not been assessed as separate diseases, and the disappointing results of chemotherapy in soft-tissue sarcoma might to some extent be due to this grouping of soft-tissue sarcoma.

Leiomyosarcoma is one of the most common sarcoma subtypes. Doxorubicin, either alone or with ifosfamide, is generally accepted as first-line treatment for metastatic soft-tissue sarcoma. Over the past decade, gemcitabine plus docetaxel, gemcitabine plus dacarbazine, trabectedin, and pazopanib (second line and higher) have emerged as useful treatments. Trabectedin has been approved by the European Medicines Agency for patients with advanced soft-tissue sarcoma who are unfit for or have progressed after anthracyclines and ifosfamide, on the basis of findings from several phase 2 trials, with efficacy data mainly in patients with leiomyosarcoma and liposarcoma.

Combining trabectedin and doxorubicin showed promising activity in phase 1 trials in soft-tissue sarcoma, but at the price of greater toxicity. Since these two drugs are both active in metastatic leiomyosarcoma, Patricia Pautier and colleagues did a phase 2 trial of the combination as first-line treatment in metastatic or locally advanced uterine and soft-tissue leiomyosarcoma. In the uterine leiomyosarcoma group, 28 of 47 patients (59-6%, 95% CI 44-3-73-6) achieved a partial response and 13 (27-7%, 15-6-42-6) had stable disease. In the soft-tissue leiomyosarcoma group, two of 61 patients (3-3%, 0-4-11-7) had a complete response, 22 (36-1%, 25-0-50-8) had a partial response, and 32 (52-5%, 40-8-67-3) had stable disease.

Tumour regression is desirable in localised borderline resectable cases and this regimen seems promising in this regard. However, whether a higher proportion of patients with a response or disease control directly translates to better overall survival in metastatic soft-tissue sarcoma remains uncertain. In an EORTC phase 3 trial, in which patients with metastatic soft-tissue sarcoma were randomly assigned to doxorubicin alone or with ifosfamide, significantly more patients in the combination group had an overall response, but overall survival was not significantly better in the combination group.

In the Article by Pautier and colleagues, compared with those with uterine leiomyosarcoma, patients with soft-tissue leiomyosarcoma had longer median progression-free survival (12-9 months, 95% CI 9-0-14-4 vs 8-2 months, 7-0-9-0, respectively) and overall survival (34-5 months, 95% CI not reached vs 20-2 months, 15-1 to not reached). These data compare favourably with results from the previous French Sarcoma Group trial, in which patients with uterine and non-uterine leiomyosarcoma were randomly assigned to gemcitabine or gemcitabine and docetaxel. Median progression-free survival for patients with uterine leiomyosarcoma were 5-5 months in the gemcitabine group and 4-7 months in the gemcitabine plus docetaxel group, and for those in the non-uterine group these data were 6-3 months and 3-4 months, respectively. Although outcomes in both the uterine and non-uterine leiomyosarcoma groups seemed better with the doxorubicin and trabectedin combination than with the gemcitabine and docetaxel combination in the previous trial, there are caveats. In the study by Pautier and colleagues, documented progression before study entry was not a requirement. In the uterine leiomyosarcoma group, 21% of patients had locally advanced disease and 36% received pelvic radiation treatment before enrolment, which can favourably bias the group towards a better outcome. The soft-tissue leiomyosarcoma group was a composite of many different anatomic variants, some with indolent behaviour such as leiomyosarcoma of the inferior vena cava. Furthermore, central radiology response review was not done, and responses were not confirmed after a prespecified time. These features might have biased the results, but in general progression-free and overall survival should not be affected. Finally, surgery of
residual disease was permitted after completion of chemotherapy, even though resection of metastatic disease remains a controversial area; outcome is generally believed to be improved after surgery, whether due to the intervention itself or patient selection. These caveats show the substantial challenges in the development of systemic treatments and trials in sarcoma, and the issue of subtype heterogeneity in the interpretation of data.

Compared with doxorubicin, trabectedin was well tolerated, having fewer adverse effects and the added benefit of no cumulative toxicity. The combination of both drugs was toxic; nausea and vomiting (19% grade 3) and thrombocytopenia (37% grade 3–4) were common. Neutropenia (78% grade 3–4) occurred, despite regular use of prophylactic granulocyte colony stimulating factor, and dose reductions were necessary in over half of patients. These findings raise the question of whether this increased toxicity is acceptable in the setting of incurable metastatic disease. A phase 3 trial could potentially compare combination with sequential treatment, with quality-of-life analyses. In this study, trabectedin was stopped after six cycles. In a randomised phase 2 study in advanced soft-tissue sarcoma, 10 median progression-free survival was shorter when trabectedin was interrupted after six cycles and restarted upon progression compared with continual administration. This issue has been raised by the investigators and should be investigated further.

Pautier and colleagues are to be congratulated for their successful collaboration and for showing that undertaking subtype-specific trials is feasible. Several promising drugs are being investigated in metastatic soft-tissue sarcoma, including aldorubicin, TH-302, Morab-004, and olaratumab. A recent press release has reported that eribulin had an overall survival advantage compared with dacarbazine in a randomised phase 3 trial in patients with leiomyosarcoma and liposarcoma. Additionally, a first-line trial of maintenance pazopanib (NCT02367651) is underway, and another comparing doxorubicin with gemcitabine plus docetaxel (Eudra CT 2009-014907-29) has closed to enrolment. The results of the phase 3 trial in which patients with leiomyosarcoma and liposarcoma are randomly assigned to trabectedin or dacarbazine (NCT01343277) are eagerly awaited, and will have implications for the further development of trabectedin. The French Sarcoma Group plan to undertake a phase 3 trial of the doxorubicin and trabectedin combination compared with standard therapy. Although limiting the study of this regimen to leiomyosarcoma is encouraged, the difficulty will lie in defining the standard treatment in the control group, particularly in the context of ongoing trials. Beyond histology-specific trials, identification of predictive molecular and imaging biomarkers might prove helpful for the selection of patients for clinical trial participation and treatment. By undertaking well designed trials such as that by Pautier and colleagues, the therapeutic options available to treat soft-tissue sarcoma according to subtype will hopefully increase.

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