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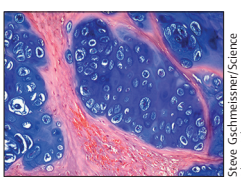
Fusion gene-oriented precision medicine in soft tissue sarcoma

Collection of clinical data and development of drugs for rare cancers is difficult because of the small numbers of patients who have the disease. Soft tissue sarcoma is one such rare cancer, which comprises more than 50 histological subtypes.[1] Doxorubicin has been the gold standard drug over the past 30 years because it is the most effective and first choice drug for soft tissue sarcomas in general. The combination of ifosfamide and doxorubicin is the next standard treatment owing to its high toxicity. Gronchi and colleagues[2] introduced a histotype-tailored chemotherapy regimen in the ISG-STS 1001 study to account for probable differences in the efficacy of the standard chemotherapy according to the different histological subtype. Patients were randomly assigned to standard chemotherapy (with epirubicin) versus trabectedin for the treatment of high-grade myxoid liposarcoma, gemcitabine plus dacarbazine for leiomyosarcoma, high-dose ifosfamide for synovial sarcoma, etoposide plus ifosfamide for malignant peripheral nerve sheath tumour, and gemcitabine plus docetaxel for undifferentiated pleomorphic sarcoma. However, none of the histotype-tailored regimens were more efficacious than the standard chemotherapy regimen. Through the development of the first molecular targeted drug in this niche field, pazopanib became the first approved molecular targeted drug for non-adipocytic soft tissue sarcoma, after publication of the results of a randomised, double-blind, placebo-controlled phase 3 trial (PALLETTE).[3] Although oral pazopanib resulted in significant efficacy in progression-free survival compared with placebo, it is more commonly used as a second-line treatment following previous chemotherapy (such as doxorubicin).

Extraskeletal myxoid chondrosarcoma is an extremely rare subtype of soft tissue sarcoma, characterised by middle-age onset, and very slow but steady growth. The typical scenario is that the gradually spreading disease deteriorates patient's prime of life over a long period of time. At the molecular level, this disease is characterised by the fusion of the genes EWSR1–NR4A3 or TAF15–NR4A3. Stacchiotti and colleagues[4] reported the effectiveness of doxorubicin for extraskeletal myxoid chondrosarcoma in a retrospective study in 2013. The results showed partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) in four patients, stable disease in three patients, and progressive disease in three patients, with a median progression free-survival of 8 months (range 2–10). These results differed from those of previous reports, which showed poor responses of extraskeletal myxoid chondrosarcoma to chemotherapy.[5] The authors explained that this discrepancy might be due to the distinct diagnostic criteria of extraskeletal myxoid chondrosarcoma restricted to positive NR3A4 translocation. Following this analysis, they used sunitinib for the treatment of patients with progressive metastatic extraskeletal myxoid chondrosarcoma. The results were partial response in six cases, stable disease in two cases, and progressive disease in two cases.[6] The median progression-free survival was not reached at the median follow-up of 8·5 months (range 2–28). Notably, patients with a EWSR1–NR4A3 fusion gene were significantly more responsive than those with the TAF15–NR4A3 fusion gene. On the basis of these results, a prospective, multicentre, single-arm, phase 2 trial of pazopanib was done.

In *The Lancet Oncology*, Silvia Stacchiotti and colleagues7 report the results of this phase 2 trial. A total of 23 eligible patients were recruited during approximately 2·5 years, despite the extreme rarity of this disease, and received oral pazopanib (800 mg/day). Four patients had a partial response, 16 patients had stable disease, and two cases patients had progressive disease; radiographically detectable tumour shrinkage was measured in 12 patients. The median progression-free survival was 19 months (95% CI 11–27) with a median follow-up of 27 months (IQR 18–30). A significant difference in progression-free survival



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according to the fusion gene type was reported from a post-hoc analysis, with a progression-free survival of 19·4 months for patients with EWSR1–NR4A3 fusion and 4·1 months (0·7–7·5) for patients with TAF15–NR4A3 fusion. These results raised some questions, including whether sunitinib should be approved due to its better response compared with pazopanib, and whether tumour shrinkage and duration of response are more practical than RECIST to assess response to treatment for these tumours. Nevertheless, the clear descriptions of the promising effectiveness by tumour shrinkage and intensive analysis of the comparison of effectiveness between fusion gene types are noteworthy as important references in treatment trials for rare fusion gene-related sarcomas. In addition, the VEGF and Notch pathway activation of the sensitive group in the transcriptional analysis provides desired information for patients who want to use pazopanib. The elucidation between *EWSR1* and the VEGF or Notch pathways is awaited for other *EWSR1*-related sarcomas.

In soft tissue sarcomas, several rare histological subtypes have specific fusion genes, including clear cell sarcoma (*EWSR1–ATF1*), synovial sarcoma (*SS18–SSX*), alveolar rhabdomyosarcoma (*PAX3*, *PAX7–FOXO1*), myxoid liposarcoma (*FUS–DDIT3*), Ewing family tumours (*EWSR1–FLI1*, *ERG*, *ETV*, and *FEV*), alveolar soft part sarcoma (*ASPL–TFE3*), inflammatory myofibroblastic tumour (*TMP3*, *TMP4–ALK*), infantile fibrosarcoma (*ETV6–NTRK3*), Ewing sarcoma-like small blue round cell tumour (*CIC–DUX4*), and solitary fibrous tumour (*NAB2–STAT6*).[8] Although these fusion genes were identified decades ago, the molecular mechanism is still not used as a drug development target. It might be appropriate to develop a driver gene-oriented or signalling pathway-oriented drug development for each rare sarcoma rather than a stale trial for soft tissue sarcomas in general. Similar to the approval of pembrolizumab for microsatellite instability-high tumours,[9] it might be necessary to investigate the oncogenetic signalling pathway of each rare entity and develop a new statistical strategy for clinical trials in these rare populations. Therefore, for specific entities, the first-line drug might change from doxorubicin to molecular targeted drugs.

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I declare no competing interests.

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The necessity for rigour in rare disease study design

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In *The Lancet Oncology*, Maud Toulmonde and colleagues[1] report the results from the phase 2 DESMOPAZ trial. The study findings suggest that pazopanib at a daily dose of 800 mg could be considered a valid treatment option for patients who have progressive growth of a desmoid tumour.[1] The study was described as a non-comparative randomised trial. The treatment population was randomly assigned to receive pazopanib or a chemotherapy combination of methotrexate and vinblastine at a ratio of 2:1. Desmoid tumour, also called aggressive fibromatosis, is a rare disease that does not have metastatic potential, but can be invasive and lead to substantial morbidity. Unfortunately, desmoid tumour can recur even after a complete resection. Common reasons for systemic therapy include multiple recurrences, unresectable tumours, and treatment of a