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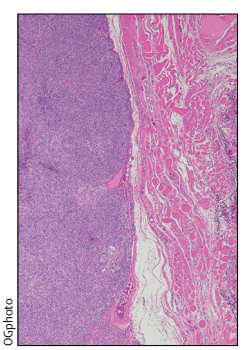
Anti-angiogenic therapy for malignant solitary fibrous tumour: validation through collaboration



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See Articles page 134

Solitary fibrous tumour is a rare mesenchymal neoplasm with varied clinical behaviour and presenting symptoms. The pleura is a common site of initial presentation, but solitary fibrous tumours can occur in a variety of non-pleural soft tissue locations throughout the body. Although most typical solitary fibrous tumours present as localised disease and behave in an indolent fashion, malignant and dedifferentiated forms can act more aggressively, resulting in substantial morbidity and mortality.

Cytotoxic chemotherapy has traditionally been thought to be of limited value for patients with advanced disease, with small case series and retrospective studies suggesting marginal benefit. A retrospective study[1] of 21 patients who received conventional chemotherapy at the University of Texas MD Anderson Cancer Center (Houston, TX, USA) revealed a best response of stable disease in the majority of patients, with 5 (28%) having an average duration of stability of at least 6 months. The Centre Léon Bérard retrospectively evaluated 23 patients with advanced solitary fibrous tumours who received cytotoxic chemotherapy and reported a partial response in 2 (9%), with a median progression-free survival of 5·1 months (95% CI 0·7–9·6).[2] A retrospective study[3] from the Italian Sarcoma Group evaluated the use of anthracycline-based chemotherapy and single-agent ifosfamide therapy for patients with solitary fibrous tumours and revealed an overall response of 20% among 30 patients who received anthracycline-based chemotherapy and 10% among 19 patients who received single-agent ifosfamide therapy. In a separate retrospective study,[4] single-agent dacarbazine therapy in eight patients revealed a partial response in 3 (38%) patients.

A growing number of studies have highlighted the promising activity of antiangiogenic drugs in the treatment of advanced solitary fibrous tumours, and the clinical use of Choi criteria as more appropriate indicators of response in patients with sarcoma than traditional RECIST criteria.[5] In a study of bevacizumab in combination with temozolomide in 14 patients with advanced hemangiopericytoma or solitary fibrous tumours, 11 (79%) patients achieved a partial response according to Choi criteria, with a median progression-free survival of 9·7 months.[6] Among 31 evaluable patients with solitary fibrous tumours treated with sunitinib, two (6%) had a partial response according to RECIST, but 14 (48%) had a partial response according to Choi criteria.[7] In a subgroup analysis of five patients with solitary fibrous tumours from a study by the French Sarcoma Group,[8] two (40%) of five patients with solitary fibrous tumours treated with sorafenib showed stable disease. In another study of 13 patients with solitary fibrous tumours treated with pazopanib,[9] 1 (9%) had a partial response according to RECIST, but 5 (46%) had a partial response according to Choi criteria. The limitation all of these studies have in common is the retrospective manner in which they were done.

In *The Lancet Oncology*, Javier Martin-Broto and colleagues[10] report a multi-centre, single-arm, phase 2 trial of pazopanib for the treatment of advanced malignant and dedifferentiated solitary fibrous tumours.[10] This trial is the result of a robust collaboration between the Spanish, Italian, and French

sarcoma groups. The authors and respective sarcoma groups should be congratulated for doing the first prospective study in this rare disease. Working together, 36 patients (34 with malignant solitary fibrous tumours and two with dedifferentiated solitary fibrous tumours) were enrolled in less than 36 months; an impressive accomplishment given the rare nature of the disease. The study was amended to halt enrollment of patients with dedifferentiated solitary fibrous tumours, given the marked progression observed in two enrolled patients. The primary endpoint of the study was overall response measured by Choi criteria. Strengths of the study include the use of both central pathology review (including analyses for *NAB2-STAT6* fusions) and central radiology review. Based on central radiology review 18 (51%) of 35 patients had partial responses, which is particularly noteworthy given that one third of patients had received previous systemic therapy, including two patients who had received previous antiangiogenic treatment with sunitinib (and ended up being sensitive to pazopanib). The results also appear favourable and consistent with the retrospective studies mentioned above. Median overall survival was not reached, and overall survival at 24 months was 73% (95% CI 58–88). Particularly interesting is the fact that the median overall survival for patients with partial response by Choi but progressive disease by RECIST was approximately 24 months. These results add to the data suggesting that RECIST criteria might not be the most appropriate measure for response assessments in soft tissue sarcoma, solitary fibrous tumours included. The safety profile for pazopanib was consistent with what has been seen in previous clinical trials and ongoing clinical experiences.

An accompanying translational component of the study explored potential prognostic biomarkers for pazopanib, based on differential survival outcomes for patients enrolled, with high expression of *BCL2* correlating with improved outcomes based on univariate analyses and high expression of *ISG15* correlating with worse survival outcomes based on both univariate and multivariate analyses. Although the results are interesting, ongoing work will be needed to establish both *ISG15* and *BCL2* as validated prognostic biomarkers.

The treatment of soft tissue sarcoma has become increasingly complex and nuanced. Clinical trials are becoming appropriately more subtype-specific and it is clear that collaboration is needed to make clinically meaningful advances in a field with more than 50 different individual disease states. Our colleagues at the Spanish, Italian, and French sarcoma groups have shown us the power of teamwork and collaboration in providing validation for the use of antiangiogenic therapies in a rare subtype of soft tissue sarcoma. The sarcoma community has a rich history of collaboration and will need to continue ongoing efforts to advance the field and improve outcomes for patients. As a result of the study by Martin-Broto and colleagues,[10] antiangiogenic therapies—specifically pazopanib—for the treatment of malignant solitary fibrous tumours should be considered a viable and reasonable approach.

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