Objective response to sorafenib in advanced clear-cell sarcoma

Clear-cell sarcoma (CCS), previously known as malignant melanoma of the soft parts, is a rare mesenchymal malignancy
molecularly characterised by a specific translocation, 
t(12;22)(q13;q12), involving the EWS gene (usually EWSR1-
ATF1 or more rarely EWSR1-CREB1) [1, 2].

An 18-year-old man was diagnosed with a CCS of the knee, harbouring the EWSR1-ATF1 translocation. He underwent surgery (R1 resection) followed by adjuvant radiation therapy. Six months later, a local relapse with ipsilateral inguinal node metastasis was diagnosed. He received six cycles of doxorubicin, ifosfamide and cisplatin, with a stable disease for 5.2 months. A multifocal, local (Figure 1, panels A and B) and distant disease progression was then diagnosed, including a cardiac metastasis [with a left ventricular ejection fraction of 45% as assessed by cardiac magnetic resonance imaging (MRI)] and bone metastases requiring opioid analgesics. He was subsequently referred to our tertiary cancer centre.

Given the lack of validated therapeutic option in this setting [3], the patient was started on sorafenib at the dose of 400 mg b.i.d. on a compassionate basis. The treatment was well tolerated, with grade 1 diarrhoea and grade 2 hypophosphatemia being the worse toxic effects, as previously described [4]. Sorafenib plasma concentrations determined by high-performance liquid chromatography, as routinely monitored in our institution [5], were within the range of those described in previous studies [6]. Functional polymorphisms of UGT1A9 and CYP3A5 that could have altered sorafenib clearance were absent.

After 4 months under treatment, a clinical benefit was seen with a marked regression of pain allowing the withdrawal of opioid analgesics. The cardiac function remained stable (left ventricular ejection fraction of 50%), and an objective regression of the knee tumour was seen on MRI scans (Figure 1, panels C and D). Remarkably, a hemorrhagic effusion to the skin above this lesion was observed, as previously reported in a CCS patient treated with sunitinib [7]. After response duration of 8.2 months, lung metastases were diagnosed and the treatment was switched to trabectedin (ET-743). At the time of this report, the patient is still alive, 14 months after the diagnosis of metastatic disease.

CCS is a rare soft tissue sarcoma subtype particularly resistant to conventional chemotherapy agents [8]. Sorafenib, a multikinase inhibitor targeting the vascular endothelial growth factor receptor (VEGFR) 2–3, platelet-derived growth factor receptor beta (PDGFRβ), c-Kit and BRAF kinases, has shown significant activity against various bone and soft tissue sarcomas in phase II studies [9, 10] and could play a role in the management of advanced CCS.

Recent data indicate that PDGFRβ is expressed and activated in a large proportion of CCS. As well, BRAF activating mutations and c-Met activation have also been described in CCS and therefore represent potential therapeutic targets [11, 12] for investigational agents such as vemurafenib and crizotinib.

In our patient, sorafenib induced an objective tumour regression and a clear clinical benefit on non-measurable lesions. Of note, the response duration of this second-line therapy was longer than that observed with the first-line conventional doxorubicin-based chemotherapy.

In line with our findings, Stacchiotti et al. [7] have reported an objective tumour response in a patient with advanced CCS treated with sunitinib, another multikinase inhibitor. Taken together, these observations suggest that the role of oral multikinase inhibitors targeting the VEGF and PDGF signalling pathways should be further investigated in the treatment of advanced CCS.

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Figure 1. Magnetic resonance imaging scans of the knee before (panels A and B) and after 4 months of treatment (panel C and D) with sorafenib. Panels A and C are coronal STIR-weighted images. Panels B and D are axial, fat saturated, contrast-enhanced T1-weighted images.
disclosure

FG has acted as paid consultant for Bayer and Pfizer. OM has acted as paid consultant for Roche. Other authors have no conflict of interest to declare.

references


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