

Tumor response to sunitinib malate observed in clear-cell sarcoma

We report on a tumor response to sunitinib malate (SM) in a 46-year-old female patient with metastatic clear-cell sarcoma (CCS).

The tumor appeared in December 2008, with two close lesions located to the soft tissues of the left knee. It was initially treated elsewhere with a marginal excision plus local-regional lymph node dissection, followed by radiation therapy on the primary tumor site. The presence of the tumor-specific *EWSR1* chromosomal rearrangement was assessed by FISH analysis and confirmed the diagnosis. In June 2009, the disease relapsed at multiple sites. The patient was treated with chemotherapy with anthracycline plus ifosfamide for two cycles, with progression. Meanwhile, the analysis of a series of naive CCS preliminarily showed evidence of platelet-derived growth factor receptor beta (PDGFRB) immunohistochemical expression and biochemical expression/activation in seven of nine cases. On this basis, lacking any conventional alternative for this patient, we biopsied one of her recurrent lesions, which proved positive for PDGFRB on immunohistochemistry. Therefore, in September 2009, she was treated with SM 37.5 mg/day on a continuous dosing regimen. Treatment was provided within a compassionate use program, with the approval of the Institutional Ethics Committee. SM is a multitargeted tyrosine kinase inhibitor and antiangiogenic drug with activity against VEGFR, PDGFRA/B, KIT, FLT3, RET, and M-CSFR approved for the treatment of gastrointestinal stromal tumor and renal cancer. Evidence of activity in selected soft tissue sarcomas has been provided [1, 2]. The disease was extended to the left laterocervical nodes, soft tissues (multiple lesions to the trunk

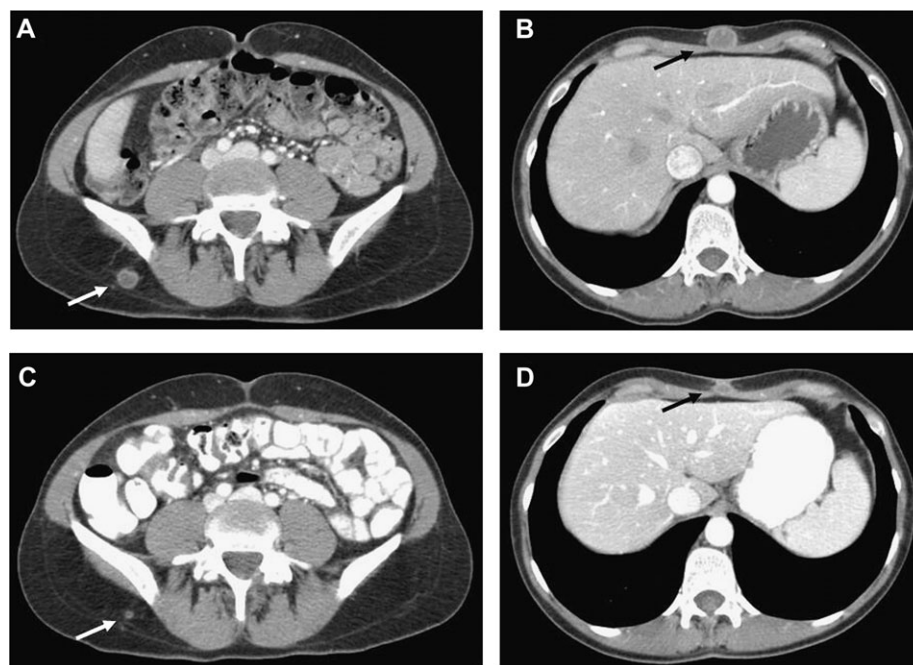


Figure 1. Computed tomography scan before (A and B) and after (C and D) treatment with sunitinib. The drug was provided by Pfizer.

and buttocks), breast, and left thigh. Concomitant palliative radiotherapy to the left thigh was done. Decrease in size of most lesions was evident on clinical examination after few days of treatment. Interestingly, a hemorrhagic effusion to the skin above each lesion was observed as well. Computed tomography scan after 2 months from SM onset confirmed a dimensional response to all lesions (Figure 1), with the exception of the breast one. Indeed, the latter increased in size, but with a clear-cut concomitant decrease in tumor density. Patient is still on treatment and responsive after 3 months.

CCS, also known as malignant melanoma of the soft part, is a very rare sarcoma. It often expresses the melanocyte-specific form of the microphthalmia transcription factor (MITF), thus supporting its melanocytic differentiation [3]. Yet, it is marked by a specific translocation, t(12;22)(q13;q12), involving the *EWS* gene (more often *EWSR1-ATF1*) [4] or, alternatively, by gain of chromosome 22 and chromosome 8. This makes CCS a genetically unique entity, clearly distinct from melanoma. Clinically, CCS is characterized by an aggressive behavior: a high incidence of metastases (>60%) is reported with a subsequent very poor prognosis. CCS is poorly sensitive to chemotherapy. Anecdotal responses to regimens containing dacarbazine, vincristine, anthracyclines, and cyclophosphamide and to interferon-alpha-2b have been reported. Recently, the activity of Met-inhibitor has been reported too [5].

We already described the activity of SM in alveolar soft part sarcoma [2]. There are similarities between this sarcoma and CCS (both are translocation related, belong to the MITF-family tumors, and show activation of PDGFRB). The tumor response observed in this case suggests that this may be clinically relevant.

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