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LETTER TO THE EDITOR
Alveolar Soft Part Sarcoma in Childhood: Is Sunitinib-Sutent® Treatment an Effective Approach?

To the Editor: Alveolar soft part sarcoma (ASPS) is a rare, highly malignant, chemo- and radio-resistant mesenchymal tumor. ASPS is characterized by an unbalanced recurrent translocation t(X;17)(p11;q25), which leads to a chimeric transcription factor ASPL-TFE3 [1,2].

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are involved in tumor growth, tumor angiogenesis, and metastatic progression of cancer. The rationale is based on the fact that autophosphorylation of mesenchymal epithelial transition factor (MET), by fusion protein ASPSCR1-TFE3, activates cell signaling pathways governing angiogenesis, cell division and growth, and cell survival [3,4]. Sunitinib has also demonstrated an effect in Xp11 renal cell carcinoma, known to sometimes share the same transcript, with objective responses, and prolonged progression-free survival [5,6].

We report two cases of patients heavily pretreated for metastatic ASPS with the presence of ASPSCR1-TFE3, with metastatic progressive disease and who responded to sunitinib-Sutent®.

The first female developed at 13 year an ASPS of the right thigh with initial bilateral pulmonary metastases. After several treatments, included chemotherapy (3 courses of IVADo (ifosfamide-vincristine-D-actinomycin and doxorubicin) and bevacizumab-Avastin®, then 9 courses of trabectedine-Yondelis®, local (R0 resection) and bilateral lung surgery followed by local radiotherapy to the thigh (50.4 Grays), progressive bilateral pulmonary disease was observed.

The second patient, an 8-year-old female, developed a left pectoralis minor ASPS with bilateral pulmonary metastases, resistant to many treatments including two cycles of ifosfamide–doxorubicin with stable disease, then local surgery (R1 resection) and focal radiotherapy (50.4 Grays) followed by bilateral pulmonary progression despite right pulmonary metastasectomy.

This poor response associated with metastatic disease led to initiate treatment with sunitinib at the initial dose of 12.5 mg/day, for 4 weeks every 6 weeks [3], then increased to 50 mg/day for the first case and 25 mg/day, for the second case, for 4 weeks every 6 weeks. A slow decrease of all pulmonary metastases was observed after 3 months of therapy. A very good partial response of pulmonary metastases persisted after 10 and 18 months of treatment justifying continuation of treatment (Figs. 1 and 2).

The main side effects were NCI grade II hypothyroidism treated by hormone replacement (both patients pts), hair discoloration, grade II asthenia (1 pt) requiring modification of treatment (37.5 mg/day instead of 50 mg/day for 4 weeks every 6 weeks from the fifth cycle) and transient grade I palmo-plantar syndrome (1 pt).

These two cases with control of ASPS metastases in children by a tyrosine kinase inhibitor argue in favor of a histological-driven strategy that should be tested in children. Long-term safety of prolonged administration of sunitinib in children is unknown [7]. A phase-I study has demonstrated cardiotoxicity in pediatric patients pre-treated with anthracycline. The maximum tolerated dose of sunitinib for patients without cardiac risk factors was 15 mg/m^2/day for 28 days followed by a 14-day break [8]. Other tyrosine kinase inhibitors have shown activity and a phase II trial of cediranib for ASPS is ongoing (www.clinicaltrials.gov—NCT01337401).

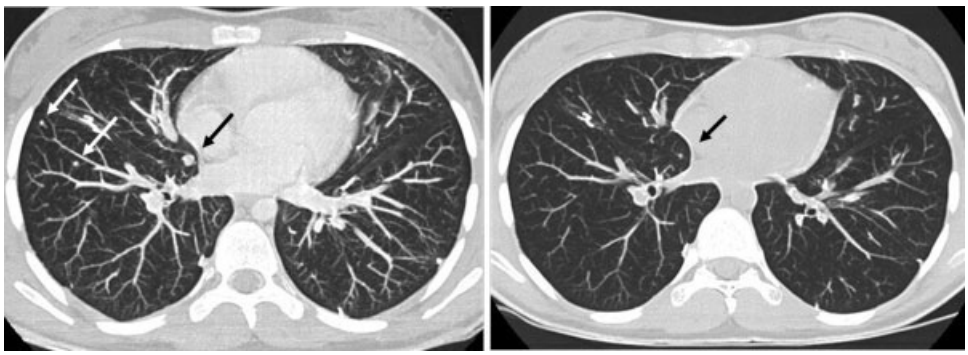

Fig. 1. Chest CT scan (unenhanced 1.25 mm slice thickness with 8 mm maximum intensity projection reconstruction) of patient no. 1 before and after 18 months of sunitinib therapy, demonstrating complete regression of two right lower lobe metastases and very good partial response (1.5 mm vs. 6.5 mm) of one right middle lobe metastasis.

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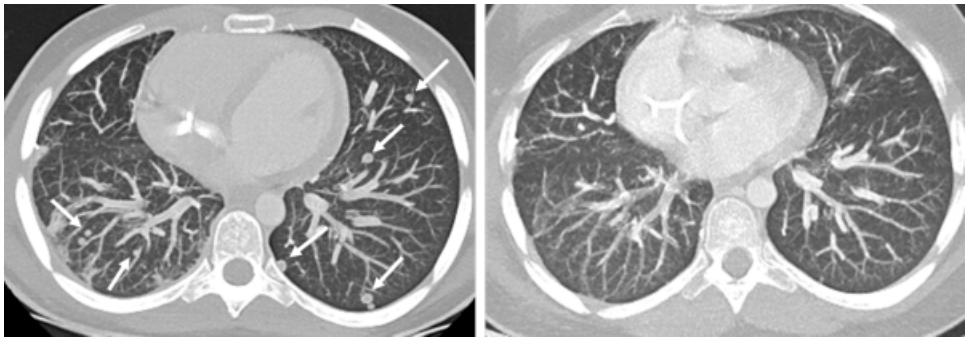

Fig. 2. Chest CT scan (unenhanced 1.25 mm slice thickness with 8 mm maximum intensity projection reconstruction) of patient no. 2 before and after 10 months of sunitinib therapy, demonstrating complete regression of lower lobe metastases.

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