Long-lasting Clinical Benefit of Sunitinib Malate in the Treatment of a Case of Heavily Pre-treated Metastatic Liposarcoma

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Abstract. *Background: Soft tissue sarcomas are a heterogeneous group of malignant neoplasms including several distinct entities with different cell differentiation and clinical prognosis, but which are often treated as a single disease. Case Report: We report the case of a male patient, heavily treated for a metastatic well-differentiated liposarcoma occurring in the left lateral neck. He received radiotherapy and different lines of standard chemotherapy with local progression and lung metastasis. In November 2009, on the basis of a phase II study demonstrating the efficacy of sunitinib in patients with liposarcoma, the patient was treated with sunitinib at 37.5 mg daily in 4-week cycles on a compassionate use basis. Until November 2012 he received a total of 23 cycles of sunitinib treatment achieving a stable disease in all sites. Therapy with sunitinib is still ongoing without side effects. Conclusion: Our findings confirm that sunitinib may be a useful therapeutic tool in the treatment of some cases of pre-treated liposarcoma.*

Soft tissue sarcomas (STS) represent an heterogeneous group of malignant mesenchymal neoplasms constituting about 1% of all cancers in adults (1). STS range from slow-growing lesions to local and regionally destructive lesions up to systemic disease. Prognosis remains poor because there are no effective systemic therapies for these tumours, which are often treated as a single disease.

At the molecular level, some types of sarcomas exhibit peculiar genetic alterations involving druggable genes and may be effectively inhibited by molecular-targeted therapies, as well-demonstrated in gastrointestinal stromal tumours (2).

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STS arise anywhere in the body but do not commonly manifest in the head and neck region, where they represent fewer than 10% of all STS. Survival of patients with head and neck STS depends on prognostic factors such as tumour grade, marginal status and tumour size (3). Liposarcoma is one of the most common STS occurring in adults and also rarely develops in the head and neck region (4). Liposarcoma is classified into different types from well-differentiated to pleomorphic and de-differentiated neoplasms. Histological subtype and tumour grade may have a prognostic value, superficial well-differentiated liposarcoma possibly showing local recurrence when surgical resection is incomplete but rarely metastasizing.

We report the case of a heavily pre-treated metastatic liposarcoma of head and neck treated with sunitinib malate, a multi-targeted inhibitor of tyrosine kinases (TKI) that has indication in patients with imatinib-resistant gastrointestinal stromal tumour (GIST) and in those with metastatic renal cell carcinoma.

We report the case of a 66-year-old male patient, submitted in 1993 to surgical removal of two lipomas localized to the left cheek, which recurred in the same cheek and which were removed again in 1997. The following year, a new nodule appeared near the site of the previous surgical resection. Because a benign lipoma was suspected on a clinical basis, the patient was submitted only to clinical follow-up. However, since the size grew progressively to produce a lesion of 6×2 cm, in December 1999, the tumour was removed. Histological examination showed a well-differentiated liposarcoma (Figure 1). At immunohistochemistry, tumour cells did not show any staining for cluster of differentiation-117 (CD117) or platelet-derived growth factor receptor (PDGFR)-α and -β. A molecular analysis of v-kit Hardy-Zuckerman-4 feline sarcoma viral oncogene homolog (c-KIT) exons 9, 11, 13, 14 and 17, PDGFR-α exon 12, 14 and 18 and PDGFR- β exons 12, 14, 18, 19 and 20 from microdissected tumour cells, was performed as described previously (5). Since the neoplasm infiltrated the muscular plane involving the resection margins, the patient underwent three cycles of adjuvant chemotherapy

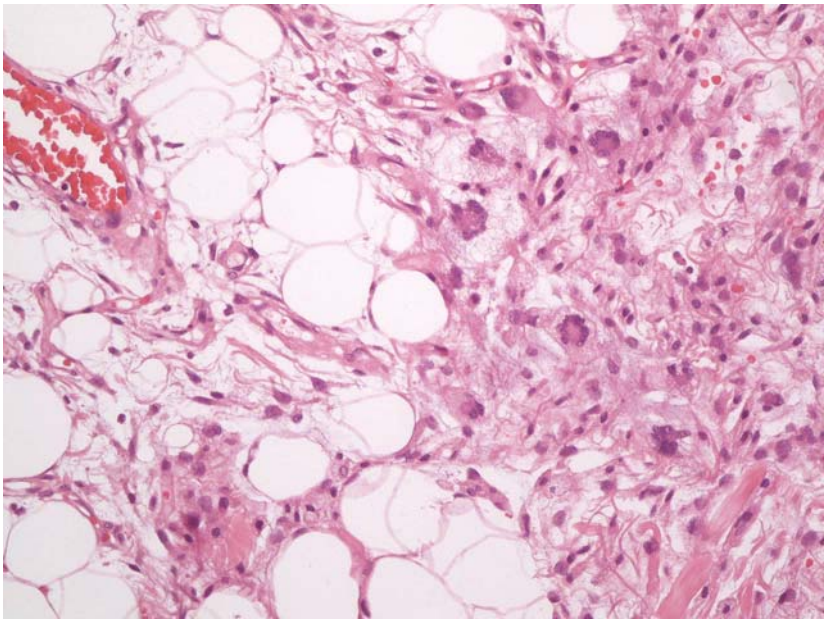

Figure 1. *Pathological examination of well-differentiated liposarcoma of the neck removed in 1999.*

with epirubicin and iphosphamide (from 28 February to 17 April 2000) and was therefore submitted to radical surgery (15 May 2000), followed by two cycles of the same schedule of adjuvant therapy.

From August 2000, the patient was followed-up until March 2004, when the tumour relapsed again in the supraclavicular site. A surgical resection was performed with histhological confirmation of recurrence of a well-differentiated liposarcoma. After six months, a new local recurrence was judged unresectable because of the extension to paratracheal tissues and the occurrence of lung metastasis. The patient underwent three cycles of epirubicin and iphosphamide with progressive disease at both local and distant sites. From 2005 to 2009, radiotherapy and different lines of chemotherapy were administered, including dacarbazine, vinorelbine, gemcitabine, docetaxel, trabectedin, and paclitaxel, with continuous slow progression of the neck tumour size and of lung metastasis. Over these years, the increasing size of the tumour caused compression of the trachea and oesophagus, with consequent onset of symptoms such as dyspnea and dysphagia, for which the patient was submitted to precautionary tracheotomy and percutaneous gastrostomy for artificial nutrition. In November 2009, the neck tumour reached the size of 87×50 mm and requested treatment (Figure 2).

On the basis of a phase II study published on 2008 at the american society of clinical oncology (ASCO) Annual Meeting that demonstrated activity of sunitinib in patients with certain subtypes of STS (6), such as liposarcoma, we obtained sunitinib for use on a compassionate basis. Detailed informed consent was previously obtained. Blood count, hepatic and renal profiles were performed at each cycle while computed tomography (CT), thyroid-stimulating hormone (TSH), and heart ultrasound was carried out every 3 cycles. The basal ejection fraction was 58%.

On November 11th, 2009, sunitinib treatment was initiated at a dose of 50 mg once daily for four weeks, followed by a two-week rest. The drug was diluted in apple juice by percutaneous gastrostomy because of solid dysphagia. The therapy was well-tolerated, except for the occurrence of persistent grade 2/3 diarrhoea that determined interruptions of treatment and dose reduction of sunitinib to 37.5 mg daily from the second cycle. After dose reduction, no grade 3-4 toxicities were present and only grade 1-2 diarrhoea occasionally occurred, which caused some short interruptions of therapy. A CT performed in August 2010 showed a partial response of the lung metastatsis and stabilisation of the size of the neck mass (84×57 mm).

By November 2012, the patient had continued with the same therapy and received a total of 23 cycles of treatment with sunitinib. At the last CT on (October 2012), overall, the disease was judged as stable.

Therapy with daily sunitinib at 37.5 mg, for four weeks in every six is still ongoing, without serious side-effects, at 37 months from the initiation of therapy.

Discussion

Sunitinib is a multi-targeted inhibitor of tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3, PDGFR-α and -β, c-KIT and FMS-like tyrosine

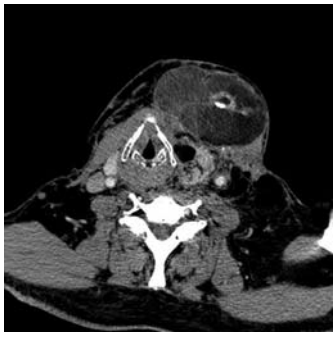

Figure 2. *Computed tomography in October 2009 showing the size of the neck mass. The tumour had reached a size of 87×50 mm.*

kinase-3 (FLT3), administered orally at a dose of 50 mg once daily in six-week cycles consisting of four weeks of treatment followed by two weeks without treatment, with an acceptable toxicity profile. Currently, sunitinib malate is registered for the treatment of patients with metastatic renal cell carcinoma (7) and in those with imatinib-resistant GIST (8). The activity of sunitinib has been explored in several other malignancies, such as the one of breast (9) and lung (10), in which sunitinib has shown promising activity both as a single agent and in combination with a variety of cytotoxic agents in pre-atreated patients, with a good toxicity profile and flexible administration schedule. Recently, sunitinib malate, sorafenib and pazopanib were tested against advanced STS in phase II clinical trials. Mahmood *et al*. studied activity of sunitinib in some of the most frequent STS histologies, such as liposarcoma, assuming that many subtypes of STS express various tyrosine kinase receptors and pro-angiogenic growth factors that have a role in tumour pathogenesis and angiogenesis. They consider a 3-month progression-free survival >40% suggestive for activity of sunitinib malate in STS, at least in liposarcomas and leiomyosarcomas (11).

In our case, the lack of PDGFR and c-KIT alterations in immunohistochemical expression and the absence of somatic mutations at the genetic level strongly suggest that the efficacy of sunitinib in liposarcoma was not related to an inhibitory activity against these type III tyrosine kinase receptors. The lack of mutational events involving c-KIT and PDGFRs were also confirmed in a series of five other well-differentiated liposarcomas (data not shown). It is thus reasonable to speculate that sunitinib may have a generic angiogenetic, effect even in liposarcoma.

Given the lack of effective therapy for unresectable or metastatic chemoresistant liposarcoma, sunitinib malate seems to be an interesting molecule for targeted therapy of STS. Phase II and III studies are necessary to evaluate its efficacy in the treatment of STS, to identify molecular targets of sunitinib in the different STS histologies.

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