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TYROSINE KINASE INHIBITORS IN TREATMENT OF FIBROUS HISTIOCYTOMA

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Aim: **To describe potential beneficial effects of tyrosine kinase inhibitor in the treatment of unresectable/metastatic fibrous histiocytoma.** ***Methods:*** **We report a case of advanced stage fibrous histiocytoma with locally recurrent disease plus lung and bone metastatic deposits. Patient was treated with the tyrosine kinase inhibitor sunitinib.** ***Results:*** **Treatment with Sunitinib resulted in disease stabilization in the regional lesion and in good partial response for metastatic foci (reduction in number and size). After 13 months of treatment the patient is doing well with no tumor progression.** ***Conclusions:*** **This case appears to be one of the first documentations of beneficial effect and potential long-term benefit of TKIs in the treatment of fibrous histiocytoma.**
Key Words: **tyrosine kinase inhibitors, sunitinib, fibrous histiocytoma, sarcoma.**

Malignant fibrous histiocytoma is a common form of soft-tissue sarcoma in adulthood [1]. Surgical management remains the cornerstone of therapy for soft tissue sarcomas. Unfortunately, approximately 40% of patients with soft tissue sarcoma will develop local or distant disease recurrences [2], and systemic chemotherapy with palliative intent is conventionally used to treat the metastatic disease [3].

Targeted biological treatment with the use of tyrosine kinase inhibitors (TKIs) entered medical oncology practice the last decade. The advances in understanding the molecular biology of many sarcomas have led to the development of new targeted treatment options. Imatinib is a small molecule inhibitor that blocks the aberrant tyrosine kinase activity of the BCR-ABL fusion oncoprotein, and it is the actual standard of care in the management of unresectable and metastatic gastrointestinal stromal tumors (GIST) [4, 5].

Sunitinib is an oral multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-Kit, and FLT-3 kinase, that has potent antiangiogenic and antitumour activities [6, 7]. Treatment with sunitinib is actually recommended in the management of renal cancer [8, 9] and second line treatment of gastrointestinal stromal tumors [10].

Herein, we describe a case of metastatic fibrous histiocytoma successfully treated with sunitinib. In July 2008, a 62 year-old man came at the ambulatory department for a second opinion for management of side effects of TKIs treatment. The patient reported he was treated with Sunitinib (50 mg once daily for four weeks followed by two weeks rest) and referred weight loss with a reduced appetite, dermatologic lesions, symptoms of neuropathy and severe mucositis. Clinical evaluation revealed hand and foot syndrome-grade 3, gingivitis-grade 2–3 and anemia. Full blood count showed macrocytic anemia, while the rest of the biochemical blood exams were normal.

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Abbreviations used: PDGFR – platelet-derived growth factor receptor; TKIs – tyrosine kinase inhibitors.

Patient referred having renal cancer since February 2005 for which he had undergone a left kidney nephrectomy in April 2005. He reported that the neoplastic mass was invading the small intestine, with no renal vessels invasion or regional lymph node involvement. After the operation, oncologists recommended adjuvant treatment with adriamycin and iphosphamide, which he refused. In June 2007, chest and upper abdominal CT scans revealed local relapse, metastases in both lungs and bone involvement. Treatment with Sunitinib and bisphosphonates was initiated. Long lasting objective responses were observed in both bone and lung metastases and disease stabilization was observed in the regional relapse. In August 2008, the patient was still responding to treatment (Figure).

In general, renal cancer does not infiltrate the small intestine. Moreover, the absence of local lymphadenopathy and blood vessel invasion, as well as the indication of adjuvant intravenous chemotherapy for renal cancer, indicated a diagnostic-therapeutic bias. Indeed, the referred diagnosis of renal cancer did not cope with patient's disease report. Therefore, patient was asked to submit the nephrectomy pathology report on the following visit. A malignant fibrous histiocytoma, invading the lower pole of the left kidney, the perinephric adipose tissue and the small intestine was reported. No evidence of renal adenocarcinoma was found from patient's medical-chart audit. Despite the diagnostic-therapeutic bias and the fact that, tyrosine kinase inhibitors are not recommended for the treatment of malignant fibrous histiocytoma, the patient is doing well, with a 13 months progression free interval. Due to the patient's clinical response, continuation of the treatment was decided. Sunitinib side effects were managed with dose reduction to 37.5 mg per day and administration of oral pyridoxine and benzydamine hydrochloride mouthwash.

At our knowledge, this case represents the third report presenting clinical beneficial effects of TKIs in the treatment of fibrous histiocytoma and the second one documenting the potential long term benefit of the treatment. Indeed, two previous studies including 13 and 11 fibrous histiocytoma patients, respectively, evidenced

high percent of stable disease but no complete or partial responders [11, 16]. These reports represent an important cornerstone, to trigger and extend the research on the role of TKIs in the treatment of different types of sarcoma.

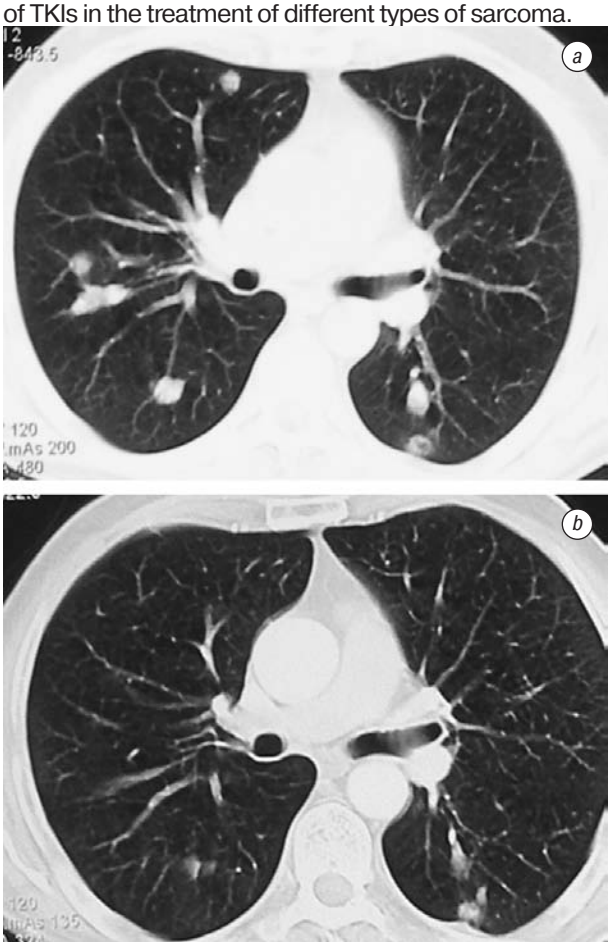

Figure. Pulmonary metastases before treatment (*a*) and after treatment with tyrosine kinase inhibitors for 13 months (*b*). Notable reduction in number and size of pulmonary metastases during the course of Sunitinib treatment was observed

As a matter of fact, the TKIs' beneficial effects reported in our patient should not surprise. TKIs are the treatment of choice for gastrointestinal stromal tumor in both 1st and 2nd line setting [10, 12]. Furthermore, there are few recent reports outlining the potential value of sunitinib and other multitargeted tyrosine kinase inhibitors, such as sorafenib and pazopanib, for treating subtypes of sarcomas other than fibrous histiocytoma [13–17]. Moreover, preclinical data evidenced that imatinib mesylate reduced tumor growth of fibrous histiocytoma cell lines expressing PDGFR and c-Kit [18]. Thereafter, the possibility that TKI may effectively work on patients affected by malignant fibrous histiocytoma is consistent.

Anyhow, despite the positive effects observed, we discourage deliberate administration of TKIs for treatment of fibrous histiocytoma, until TKIs will be clearly indicated for the treatment of the disease. Thereafter, their use should be considered still investigatory and not tried out of strict research protocols.

Nevertheless, pour considering the limits of our report, it is only a retrospective case (identified by medical chart audit), characterized by TKIs administration out of a strict research protocol, we believe that, the observed good response and long lasting beneficious effects should be taken into consideration. This case may be an important step for the treatment of these sarcomas. Extensive controlled research has to be conducted to confirm these findings.

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