Imatinib mesylate in a patient with metastatic disease originating from a dermatofibrosarcoma protuberans of the scalp

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Dermatofibrosarcoma protuberans is a soft-tissue tumor that may recur locally and rarely causes metastases to vital organs. Dermatofibrosarcoma protuberans has specific chromosomal abnormalities involving the platelet-derived growth factor β-chain locus that may render these tumors responsive to targeted therapy with the tyrosine kinase inhibitor imatinib mesylate. A patient with locally recurrent and metastatic dermatofibrosarcoma protuberans who had already undergone surgery 22 times was initially treated with imatinib mesylate 400 mg/day. The treatment dose was increased after 7 days to 400 mg twice daily. The patient was followed up for response and toxicity by physical examination and imaging studies, comprising computed tomography and fluorodeoxyglucose positron emission tomography. Clinical response could be demonstrated after the first month of treatment, and subsequent computed tomography and positron emission tomography documented a response to imatinib mesylate therapy. Our patient is now in sustained remission with minimal toxicity. We conclude that antitumor activity of metastatic dermatofibrosarcoma protuberans can be obtained with imatinib mesylate treatment with minimal side-effects. *Anti-Cancer Drugs* 17:1223–1225 © 2006 Lippincott Williams & Wilkins.

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Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare malignant tumor of the subcutaneous tissues characterized by slow but infiltrative growth. The standard treatment of localized disease is local surgical resection with wide margins [1]. Local recurrence rates, however, are high (13–60%) [2,3]. In addition, 1–4% of DFSP may develop distant metastases [4]. Effective systemic therapy for locally advanced, inoperable or metastatic disease would clearly be useful in the management of these tumors.

More than 90% of DFSP features a translocation involving distinct regions of chromosomes 17 and 22 [5]. This t(17;22) breakpoint region is usually repeated within a ring chromosome [6]. The translocation breakpoint generally involves the second exon of the platelet-derived growth factor-B gene on chromosome 22, which is fused with the collagen-1 α-1 gene on chromosome 17. This distinctive translocation is likely to alter transcriptional up-regulation of the platelet-derived growth factor-B gene resulting in activation of the platelet-derived growth factor receptor-β [7]. This observation led to the hypothesis that inhibitors of the platelet-derived growth factor receptor-β, such as the tyrosine kinase inhibitor imatinib mesylate, might have cytostatic activity in DFSP. After encouraging preclinical studies [8], there have been several reports indicating a clinical antitumoral activity of imatinib mesylate in DFSP [9–12], even in young children [13]. One larger series includes 10 patients with locally advanced or metastatic DFSP being treated with imatinib mesylate, including four complete responses, five partial responses and one stable disease [14].

Case report

We report about a 50-year-old patient with a DFSP of the scalp diagnosed in 1980. He underwent multiple surgical resections in 1986, 1989, 1993 and 2000, including several large skin transplantations. By the time he was transferred to our Medical Oncology Clinic in 2001, he presented a tumor located parietal left. The tumor was completely resected and found to be a DFSP. The patient underwent further surgical resections in 2002 and 2004; altogether he was operated on 22 times for local recurrences of the DFSP of the scalp.

In October 2005, duodenal and retroperitoneal metastases were found. Biopsies showed the same histological pattern as the primary tumor. CD34 was found to be positive and CD117 was negative. Owing to these metastases, the patient developed gastrointestinal bleeding of the duodenum, making a surgical intervention

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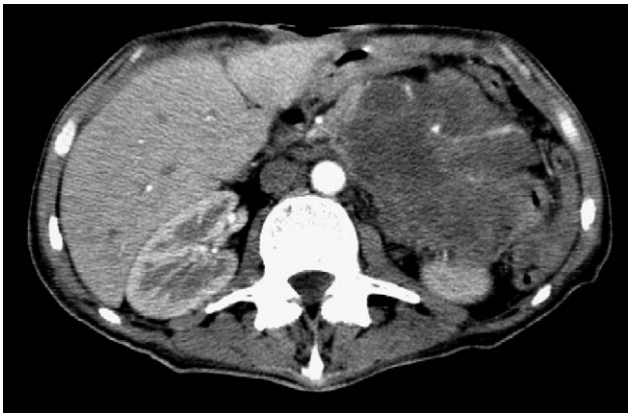
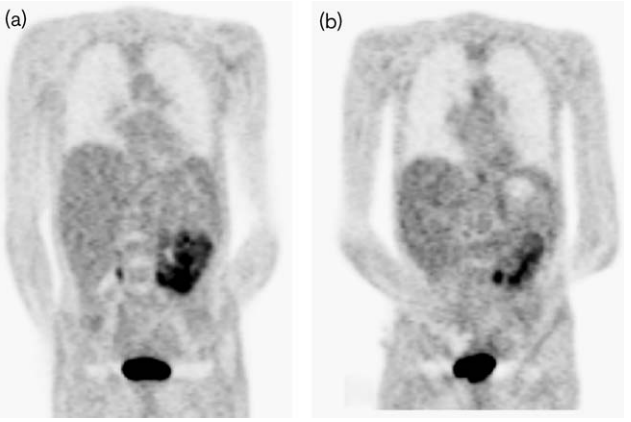
Fig. 1



The computed tomography before start of treatment with imatinib mesylate demonstrates an enormous mesenterial mass of $10 \times 8 \times 11$ cm with retroperitoneal lymph nodes.

Fig. 2



The positron emission tomography scan showed the mesenterial metastatic mass seen in the computed tomography: (a) before start of treatment with imatinib mesylate with a high metabolic uptake and (b) after 1 month of treatment with imatinib mesylate showing a SUV decrease from 11.8 to 6.5.

necessary. Before starting therapy with imatinib mesylate in February 2006, a baseline computed tomography (CT) and positron emission tomography (PET) using 2-deoxy-2-[^{18}F]fluoro-D-glucose were performed. The CT showed a mesenterial mass of $10 \times 8 \times 11$ cm with retroperitoneal lymph nodes (Fig. 1). The PET scan showed intense captivation of the 2-deoxy-2-[^{18}F]fluoro-D-glucose at the mesenterial mass (SUV_{max}: 11.8). Treatment with imatinib mesylate was started at a daily dose of 400 mg. As there were no side-effects observed after 7 days of treatment, the therapeutic dose was increased to 400 mg twice daily, a dose also being used in other cases reported in the literature. No clearly known dose effect of imatinib mesylate in DFSP, however, is observed; the dose data come from studies of gastrointestinal stromal tumors. Even 1 month after the beginning of therapy with imatinib mesylate, the PET examination showed a decrease of the SUV from 11.8 to 6.5, indicating a metabolic partial response (Fig. 2); no metabolic activity was found at the primary site of the DFSP. According to RECIST criteria, stable disease could be confirmed by CT with a slight reduction of the tumor mass to $9 \times 6.6 \times 9.2$ cm. After a further 12 weeks of treatment, the PET shows sustained metabolic partial remission (SUV_{max}: 4.7); CT demonstrates stable disease (8.3×5.9 cm).

Discussion

DFSP is a soft-tissue tumor that may recur locally and rarely causes metastases to vital organs. Most localized DFSPs can be managed by local surgery. Excellent outcomes of DFSP treated with surgery alone have been reported [15]. Recurrence rates, however, are up to 60% high. Moreover, there is a lack of alternative treatment options such as chemotherapy or radiotherapy having only minimal therapeutic effect on DFSP [16]. It has been reported that imatinib mesylate may assist in disease control in patients with locally advanced or metastatic disease. We observed the same phenomenon in our patient. After multiple local recurrences of the DFSP of the scalp and a total of 22 surgical interventions, imatinib mesylate was added to the treatment armamentarium in the metastatic situation causing life-threatening complications with gastrointestinal bleeding. It was able to achieve a metabolic partial response using PET scan even after 1 month of treatment. According to RECIST criteria, stable disease has been documented by CT. Nevertheless, as we have learned from gastrointestinal stromal tumors, evaluation of clinical remissions according to RECIST criteria might not be the adequate form of response evaluation. Often tumors that do not change by RECIST criteria demonstrate significant necrosis.

As for all soft-tissue sarcomas, however, complete surgery remains the treatment option of choice for DFSP. Nevertheless, imatinib mesylate could be indicated in the following situations: (1) in a neoadjuvant setting for locally advanced inoperable disease with the option of achieving operability or in cases in which disfiguring surgery is needed (e.g. for large face lesions), (2) in the metastatic situation not treatable by surgery, or (3) even in the adjuvant setting to prevent relapse. As there is no effective systemic therapy for locally advanced, inoperable or metastatic DFSP, imatinib mesylate seems to be an interesting candidate for further evaluation in clinical trials. Meanwhile, three clinical trials have been initiated; two of them evaluating the effect of imatinib mesylate in the neoadjuvant clinical setting.

Other compounds acting as platelet-derived growth factor receptor inhibitors are currently in clinical development such as SU11248 or SU9518. For sunitinib (SU11248), extensive experimental data highlight the potential therapeutic advantage of targeting the platelet-derived growth factor receptor. At a dose of 50 mg/day, sunitinib displays manageable toxicity and antitumor activity supports further studies [17]. For SU9518, preclinical data demonstrated potential inhibition of radiation-induced fibroblast and endothelial cell activation and proliferation in a co-culture model [18]. Although here is no further preclinical data available so far, these agents may also be effective in treating patients with DFSP.

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