Cancer Chemother Pharmacol (2009) 64:635–640
DOI 10.1007/s00280-009-1010-0

SHORT COMMUNICATION

Response of imatinib-resistant extra-abdominal aggressive fibromatosis to sunitinib: case report and review of the literature on response to tyrosine kinase inhibitors

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Received: 29 December 2008 / Accepted: 12 April 2009 / Published online: 29 April 2009

Abstract
Purpose Aggressive fibromatosis (AF) is usually a slowly growing locally invasive tumor, but may exhibit a much more aggressive phenotype. The role of chemotherapy in AF is not well defined, but can be useful in some cases. We examined the response of a case to both imatinib and sunitinib.
Methods We report a case of an aggressive multicentric extra-abdominal AF that was responsive to sunitinib, but resistant to imatinib.
Results A 23-year-old woman developed painful multifocal AF of both legs and gluteal muscles that progressed after surgery and treatment with methotrexate/vinblastine and pegylated-liposomal doxorubicin. She received six cycles of ifosfamide/etoposide (IMV), and obtained a good response with elimination of pain. After 5 months, she developed progression and again received six cycles of IMV, with cessation of symptoms. After 13 months, tumors recurred. Although the AF was symptomatic and progressing, she was hesitant to receive chemotherapy and began treatment with sunitinib 50 mg/day for 28 days of a 42-day cycle. At 4 months, she could walk on her heels without pain. After 13 months of sunitinib, therapy was changed to imatinib 400 mg/day; after 7 days she noticed increasing pain in the AF lesions and decreased knee flexibility. Imatinib was continued, but after 2 months of imatinib, she could only walk a few steps due to pain. Sunitinib was reinstituted at 37.5 mg/day and symptoms improved within 1.5 weeks, with a marked reduction of symptoms at 1 month. She was doing well with a normal activity level, 32 months after initially beginning sunitinib.
Conclusions We conclude that sunitinib may be useful in some cases of AF.

Keywords Fibromatosis · Desmoid · Sarcoma · Tyrosine kinase · Sunitinib · Imatinib · Chemotherapy · Cancer · Angiogenesis · VEGF

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Introduction

Aggressive fibromatosis (AF), or desmoid tumor, is a locally invasive tumor composed of a monoclonal proliferation of myofibroblastic cells with variable collagen deposition [3, 17, 21, 22, 25, 32]. Although AF does not metastasize, it frequently recurs after surgery (as high as ~40% in some series) and may occasionally be multifocal (~5%). These tumors have some histologic similarities to the proliferative phase of wound healing and have been associated with trauma, pregnancy and the use of oral contraceptives [4]. Although of unknown etiology, desmoid tumors may occur sporadically or in association with familial

polyposis (FAP) and Gardner syndrome, where it is 1,000-fold more common [10, 14, 32]. Some cases of "cranial fasciitis" appear to share features of AF [29]. Alterations in the regulation of the WNT/beta-catenin signaling pathway, generally by inactivation of APC or activation of CTNNB1, have been strongly implicated in the pathogenesis of AF [2, 4, 7, 8, 30, 32, 38]. Beta-catenin has a nuclear function, in which it binds transcription factors and acts as a transcriptional activator, and a cell membrane function, in which it is a component of epithelial cell adherens junctions. An analysis of gene expression, searching for genes over-expressed in AF compared with normal tissues, reported that ADAM12 (a disintegrin and metalloproteinase domain12), WISP-1 (WNT-1-inducible signaling pathway protein-1), SOX-11 and fibroblast activation protein-alpha were selectively over-expressed in AF compared with 16 different normal tissues [33, 34].

AF is known to be a disease with a variable clinical course in different patients. In a series of 12 cases of AF not associated with Gardner syndrome, gene expression studies suggested the existence of at least two distinct subsets of AF [34, 36]. A recent report also suggests that certain mutations in the CTNNB1 gene, which codes for beta-catenin, may correlate with a higher risk of recurrence after surgery [18].

The optimal treatment for AF is not universally agreed upon [[6, 17, 19, 20, 31, 32, 37], and options include surgery, radiation therapy, chemotherapy or even observation in selected cases. While the role of chemotherapy in AF is not well defined, it can be useful in selected cases [5, 13, 26–28, 40].

Case reports have described meaningful responses to imatinib [11, 23, 39], and in a series of 19 patients with AF, imatinib was shown to have some activity with a partial response rate of ~16%, with four additional patients with stable disease [15]. Imatinib inhibits the kinase activity of the products of KIT, ABL, ARG (Abl-related gene product), PDGFR-A, PDGFR-B and FMS (CSF-1R), and, at higher concentrations, possibly other kinases. Sunitinib has a more broad spectrum of kinase inhibition and is known to inhibit the kinase activity of the VEGF receptor as well as the products of KIT, ABL, ARG, PDGFR-A, PDGFR-B, RET and FLT3 (CD135). We report a case of an aggressive extra-abdominal AF that was responsive to sunitinib, but resistant to imatinib.

Case report

A 22-year-old woman developed painful aggressive fibromatosis tumor in her left thigh one month after a horse fell on her left leg. In retrospect, she had noted decreased flexibility of both legs beginning at about age 13. The leg tumor

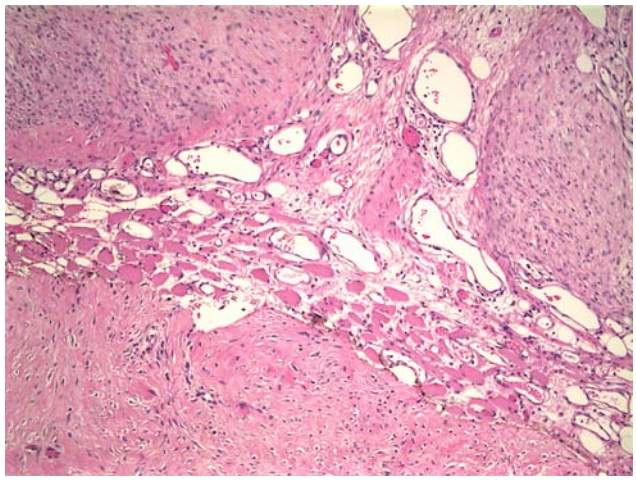

Fig. 1 Musculoaponeurotic fibromatosis from left hip. Residual entrapped skeletal muscle fibers and dilated capillaries (*center*) are surrounded by fibrous proliferation; the latter is more cellular ("active") on the *top right* and *left*, and more collagenous and less cellular ("quiescent") on the *lower left* (hematoxylin and eosin stain; original magnification ×100)

was removed and pathologic examination revealed aggressive fibromatosis (Fig. 1). One year later she developed painful multifocal aggressive fibromatosis of both legs and gluteal muscles. Her history was also notable for depression, controlled with lexapro, gastro-esophageal reflux disease, controlled with prevacid, and a history of nephrolithiasis. She had been on oral contraceptives since age 12 for irregular periods. Family history was notable for ovarian carcinoma in a paternal grandmother and an uncle with mental retardation with an undiagnosed thigh mass.

The AF lesions progressed on treatment with methotrexate/vinblastine, and she was begun on pegylated-liposomal doxorubicin, but the disease progressed. She then received six cycles of monthly infusional ifosfamide with oral etoposide (IMV) using a previously described regimen [35] and obtained a good response with elimination of pain and an increase in leg flexibility. Oral contraceptives were stopped and she became pregnant shortly after completing IMV. She fell 5 months later, traumatizing the left leg and developed pain at the sites of AF and loss of leg flexibility that increased over several days and then stabilized. She delivered a baby 5 months after the fall, and an IUD was placed. Three months after giving birth (13 months after the last IMV), she noted an increase in pain and swelling of the left knee, both legs and right buttock; imaging revealed significant disease recurrence and she again began treatment with IMV. She had a good symptomatic response and treatment was stopped after six cycles. One year later, she developed increasing pain in the legs and right buttock, with loss of knee flexibility, itching in the left knee and discomfort sitting due to an enlarging buttock lesion. Physical examination was remarkable for obesity and tender warm masses

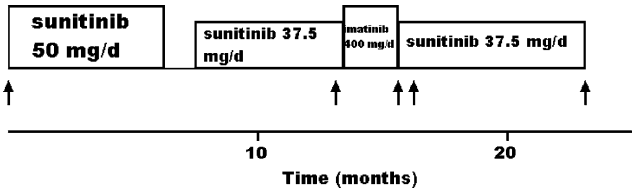

Fig. 2 Treatment over time. *Arrows* indicate the time of scans shown in Fig. 3

infero-lateral to both knees and in the right buttock. Flexion of both knees was limited to about 45° and she could not walk on her heels. The initial PET-CT scans revealed multiple FDG-avid nodules in the legs and buttocks with a maximal SUV (SUVmax) of 10.8 in the right gluteal lesion (Figs. 2, 3a, Table 1).

The patient was hesitant to receive more chemotherapy and was begun on sunitinib 50 mg/day orally for 28 days of a 42-day cycle. Her other medications were warfarin 1 mg/day, lexapro and prevacid. Initially, she experienced an increase in pain in the lesions over the first 7 days, but then the pain improved and resolved by 28 days of treatment, though she still had some discomfort in the legs with walking. At day 28, leg flexibility was improved and heel and toe walking were nearly normal. She continued sunitinib on a 42-day cycle, developed an elevated blood pressure, and metoprolol was added. At 4 months, she could flex her knees to about 90° and walk on her heels without pain. PET-CT scans after 5 months of treatment revealed a maximal SUV of 6.3 in the right gluteal lesion and a reduction in tumor size (Fig. 3b, Table 1).

At this point, treatment was delayed due to removal of renal stones. At 7 months after starting sunitinib, she was doing well; however, her insurance carrier denied further coverage for sunitinib for her condition. At 8 months, her pain had markedly increased, requiring opiates, and her flexibility and activity were limited. At this time it was possible to reinstitute sunitinib, this time at 37.5 mg/day to try to decrease mucocutaneous toxicity, having been off therapy for 6 weeks. The pain increased over the first 5–7 days of sunitinib, but over the subsequent 4 days, the pain largely resolved and opiates were no longer needed. At 9 months, she was doing fairly well, though her TSH was now elevated and L-thyroxine was begun. She then generally did well, and the toxicities of the treatment were as expected, including variable mouth and skin soreness, hypertension requiring treatment and graying of scalp

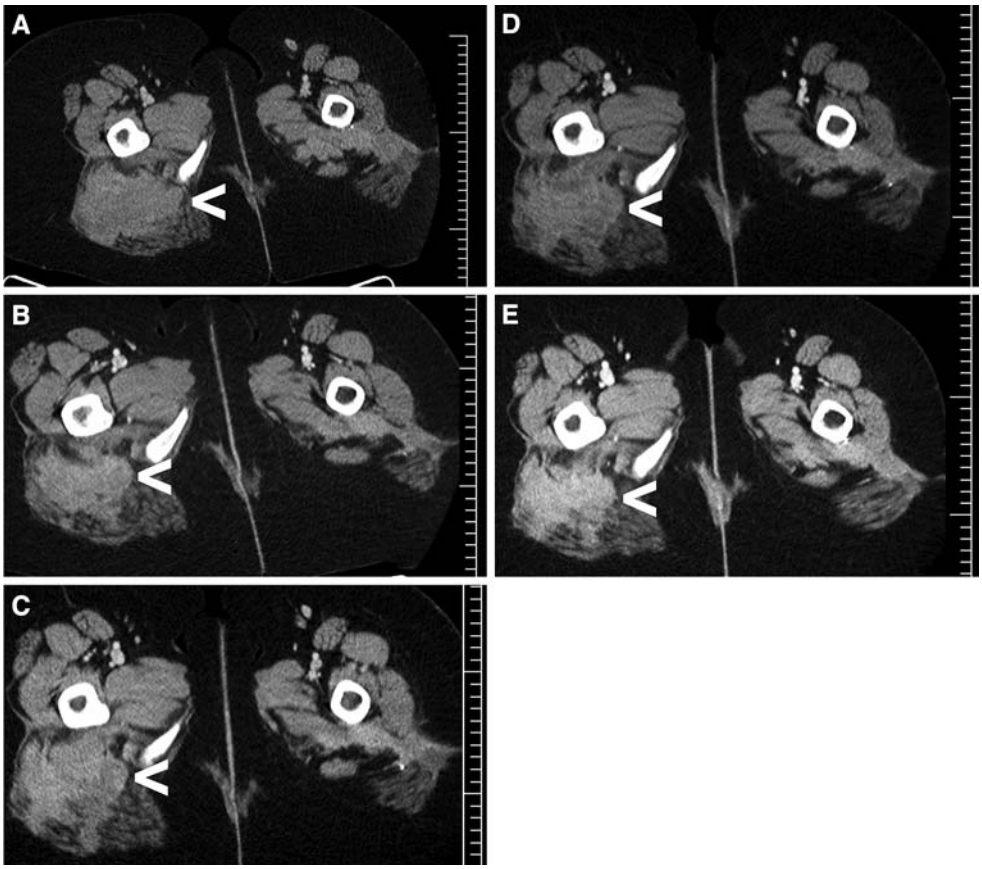

Fig. 3 CT scans at the start of sunitinib (**a**), after 13 months of sunitinib (**b**), after 8 weeks of imatinib (c), after 1 month of sunitinib following imatinib cessation (month 16.5 after first starting sunitinib) (**d**), and 23.6 months after first starting sunitinib (**e**). The tumor is indicated by "<"

Table 1 Tumor measurements during treatment

Time from the beginning of Sunitinib (months)	SUV R gluteal/ size (cm)	SUV R knee/ size (cm)	SUV L knee/ size (cm)
0	10.8/9.8 × 8.1 × 13.4	6.3/5.6 × 9.2 × 16.6	8.0/6.8 × 10.9 × 30.5
5	6.3/6.7 × 8.1 × 4.3	5.4/3.9 × 6.7 × 14.9	5.0/4.9 × 8.3 × 21.4
13	8.2/7.9 × 7.8 × 9.1	5.8/3.3 × 7.6 × 14.6	6.9/6.9 × 5.3 × 27.5
13.5	Beginning of imatinib		
13.8	6.8/7.9 × 8.1 × 7.4	3.8/4.2 × 7.9 × 15.1	4.8/7.6 × 8.8 × 22.9
15.5	3.8/9.2 × 7.5 × 7.8	3.9/3.1 × 6.7 × 8.2	4.6/8.5 × 8.5 × 22.0
15.5	Beginning of sunitinib		
16.5	7.8/8.9 × 9.0 × 9.4	5.9/4.4 ×6.7 × 15.6	5.2/7.2 × 8.6 × 27.5
20.5	5.6/7.7 × 8.0 × 7.4	4.6/2.2 × 5.6 × 6.8	5.3/6.2 × 5.6 × 16.2
23.6	7.8/7.4 × 6.8 × 6.6	3.9/1.5 ×5.0 × 6.3	5.3/3.0 × 4.2 × 10.1

* Dimensions shown are axial/ AP/coronal in cm. PET scans were obtained with the patient on the relevant TKI and not during a rest period

hair. Hydrochlorothiazide was added to metoprolol to control blood pressure at month 12 of sunitinib. Itching at the site of the AF lesion near the left knee was often noted at the end of each 2-week rest period and resolved within a week of starting each sunitinib cycle. After 13.5 months of sunitinib, therapy was changed to imatinib 400 mg orally each day, which has some activity in aggressive fibromatosis [15, 16, 23, 39], in an attempt to find a regimen with less toxicity. However, after 7 days of imatinib, she noticed increasing pain in the AF lesions and decreased knee flexibility. The tumor at the left knee was warm and quite tender. A PET-CT after 10 days of imatinib revealed a decrease in SUVmax of the right gluteal lesion (6.8) (Table 1). Imatinib was continued, and at 1 month of imatinib, the pain was bothersome but stable. Imatinib was continued, but after 8 weeks of imatinib (15.5 months after starting sunitinib) she was much worse and could no longer care for her daughter due to pain in the legs and buttock. She could only walk a few steps due to pain. A PET-CT showed an SUVmax of 3.8 in the right gluteal lesion (Table 1, Fig. 3c). At this point, her symptoms were the most severe at any point in her history. Sunitinib was begun at 37.5 mg/day. Her symptoms improved within 1.5 weeks of restarting sunitinib, and at 1 month she had a marked reduction of symptoms. On examination, the left knee lesion appeared smaller and less warm and she had greater range of motion of her knee. A PET-CT scan at 16.2 months after first beginning sunitinib showed an SUVmax of 7.8 in the right gluteal lesion (Fig. 3d, Table 1). Twenty months after initially beginning sunitinib she was doing very well with a normal activity level. A good functional status continued at 23.6 months and a PET-CT showed an SUVmax of 7.8 in the right gluteal lesion (Fig. 3e, Table 1). In an attempt to further decrease toxicity (primarily loss of taste and mouth soreness), at 25 months the sunitinib was changed to 25 mg/day for 2 weeks on and 1 week off. With the increase in flexibility, she was able to touch her toes for the first time in 7 years. At 29 months the sunitinib was changed to 25 mg/day for 1 week on and 1 week off, and at 30 months it was changed to 1 week on and 2 weeks off. At 32 months, she had a good symptomatic response and limited toxicity, and further tapering of sunitinib was begun.

Discussion

AF or desmoid tumor is a heterogeneous disease in terms of biological behavior, for which the optimal therapy is not well defined. In select cases, chemotherapy is appropriate, but the optimal regimen is not defined. Imatinib has been reported to have activity in some cases of AF and is well tolerated [11, 15, 16, 23, 39]. We report a case of multifocal AF that responded well to sunitinib, but was not responsive to imatinib administered at 400 mg/day.

The spectrum of tyrosine kinases that is inhibited by sunitinib is broader than that inhibited by imatinib, and in particular includes the VEGF receptor. The kinases that are most relevant in the differing effects of imatinib and sunitinib in our patient are unknown. However, this case demonstrates that sunitinib may have efficacy in some AF cases. The expression of genes encoding a set of protein kinases has been reported to identify two broad subsets of AF in patients without Gardner syndrome [36].

Although a decrease in tumor size was evident on CT scan, determination of tumor size by standard criteria such as RECIST, or 2- or 3- dimensional orthogonal dimensions, was not straightforward, because of the irregular dimensions and tendency to extend between muscle planes, and would have been problematic had the patient been enrolled in a trial directed by such measurements. No change in tumor density was noted. PET imaging with FDG was not useful in this case, possibly due to relatively low SUVmax values.

The beta-catenin (CTNNB1) pathway has been strongly implicated in the pathogenesis of AF and desmoid tumors

[2, 4, 7, 8, 30, 38]. In a transgenic mouse model, induction of stabilized beta-catenin leads to the development of AF and hyperplastic cutaneous wounds, suggesting a role of beta-catenin in these fibroproliferative disorders [7]. In a study of sporadic AF, 3 of 12 cases had a mutation in beta-catenin, and the beta-catenin mRNA expression was higher in the beta-catenin mutated group [30]. In another study, 16 of 19 cases of AF had a mutation of the WNT pathway (APC or CTNNB1) [15]. Abnormal growth factor production has also been associated with plantar fibromatosis and hereditary gingival fibromatosis and may play a role in the disease in some cases [1, 9, 24].

AF is known to be a disease with a variable clinical course in different patients. In a series of 12 cases of AF not associated with Gardner syndrome, gene expression studies suggested the existence of at least two distinct subsets of AF [34, 36]. Among the genes differentially expressed between these two groups were ADAM12, WISP-1, SOX-11 and fibroblast activation protein-alpha [34]. A recent report suggests that CTNNB1 mutations can be identified in most cases of sporadic desmoid tumor and that a higher recurrence rate was observed in cases with a mutation in codon 45F of exon 3 than in 41A or wild-type CTNNB1 [18]. In addition, these investigators found that the intensity of nuclear beta-catenin expression was inversely correlated with the incidence of recurrence. In a different study, an increase in nuclear beta-catenin expression, defined as >20% of tumor cells expressing beta-catenin, had a higher recurrence rate than desmoid tumors without beta-catenin expression [12]. Interestingly, in our earlier report suggesting the existence of two general groups of sporadic AF based on gene expression patterns, the group that was suggested to possibly have a higher recurrence rate had a higher level of beta-catenin mRNA expression [34]. Molecular analyses were not performed on the tumor in this case report.

In summary, we report a case of multifocal AF that responded well to sunitinib, but was not responsive to imatinib. The kinases that are most relevant in the differing effects of imatinib and sunitinib in our patient is unknown. However, this case demonstrates that sunitinib may have efficacy in some AF cases. We also found that PET-CT SUVs did not correlate with clinical symptoms in this case. Given the limited response rate to imatinib in AF, and the lack of a standard therapy of high efficacy, trials of sunitinib in imatinib refractory patients are warranted.

Acknowledgments KMS has received research funding from Novartis and Pfizer (makers of imatinib and sunitinib), is on the speakers bureau for Novarits (imatinib in CML and GIST) and Pfizer (sunitinib for renal cancer and GIST), and has been a consultant for Novartis (imatinib in CML).

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