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Imatinib Mesylate as a Preoperative Therapy in Dermatofibrosarcoma: Results of a Multicenter Phase II Study on 25 Patients

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Abstract

Aims: The treatment of dermatofibrosarcoma protuberans (DFSP) involves wide local excision with frequent need for reconstructive surgery. A t(17;22) translocation resulting in *COL1A1-PDGFB* fusion is present in >95% of cases. Certain patient observations and a report on nine patients suggest that imatinib mesylate, targeting platelet-derived growth factor receptor β, has clinical potential in DFSP. The primary aim of this phase II multicenter study was to define the percentage of clinical responders (Response Evaluation Criteria in Solid Tumors) to a 2-month preoperative daily administration of 600 mg of imatinib mesylate before wide local excision. The secondary aims were to determine tolerance, objective response from imaging results (ultrasound and magnetic resonance imaging), and pathologic responses observed in sequential tissue specimens.

Patients and Methods: A two-stage flexible design was used with interim analysis after the recruitment of six patients. Twenty-five adults suffering from primary or recurrent DFSP were included from July 2004 to May 2006.

Results: The *COL1A1-PDGFB* fusion gene was detected in 21 out of 25 patients following fluorescence *in situ* hybridization analysis (two cases were noninformative). A clinical response was achieved in nine (36%) patients (95% confidence interval, 18.9-57.5). The median relative tumoral decrease was 20.0% (range, −12.5 to 100). Apart from expected grade 1 or 2 side effects, we observed one grade 3 neutropenia, one grade 3 maculopapular rash, and one grade 4 transient transaminitis.

Conclusion: Our results support the use of imatinib in a neoadjuvant setting in nonresectable DFSP, or when surgery is difficult or mutilating. These results will be useful for setting hypotheses in the evaluation of new drugs to treat primary or secondary resistance to imatinib. *Clin Cancer Res; 16(12); 3288–95. ©2010 AACR.*

Dermatofibrosarcoma protuberans (DFSP) is a rare soft-tissue sarcoma characterized by progressive local growth of CD34+ spindle cells with a highly infiltrative pattern (1). Approximately 85% to 90% of tumors are low-grade, whereas others contain a high-grade fibrosarcomatous component (1). Wide excision is the standard therapy, but it can be difficult and mutilating (2). In less than 2% of cases, DFSP metastasizes and becomes life-threatening.

More than 95% of DFSP present anomalies on the 17q22 and 22q13 chromosomal regions leading to fusion of *COL1A1* and *PDGFB* genes. Transfection studies suggest that *PDGFB* could act as a mitogen for tumor cells, leading to platelet-derived growth factor (PDGF) receptor activation (3), which thus constitutes a therapeutic target. Indeed, three cases of DFSP with a spectacular response to imatinib mesylate (IM) were reported in 2002 (4, 5). In approximately 5% of cases, *COL1A1-PDGFB* fusion was not found, suggesting that other genes might be involved in DFSP pathogenesis (6).

The aim of this prospective phase II study implemented in 2003 was to provide an estimation of DFSP response to

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This study was presented in ASCO 2007.

This trial was approved by the Paris Saint Louis ethics committee. INSERM was the promoter and did not ask for a registration to the NCI. gov web site.

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Translational Relevance

Dermatofibrosarcoma is a rare disease and thus far only one clinical trial using imatinib has been published. Results were so impressive that the drug was approved in metastatic or nonresectable dermatofibrosarcoma in 2006. We believe that our results are important because they confirm the clinical benefit of imatinib in this indication. They enable the definition of an overall response rate at 2 months and will help to design future trials with short-term end points. We were able to correlate clinical responses to radiologic findings, as well as to cytogenetic and histologic features. We also determined imatinib tolerance and effects in this patient population. However, in certain patients, imatinib does not provide sufficient tumor regression for successful resection. Therefore, other treatments potentially active in the case of primary or secondary resistance to imatinib will be needed.

a neoadjuvant IM short-course therapy to obtain proof of principle and give further insight into tolerance and action mechanisms.

Materials and Methods

Patients

The study population consisted of patients with histologically confirmed primary DFSP or local relapse of DFSP, tumor size ≥2 cm, 18 years of age or older; women that were enrolled into this study were taking contraception. The eligibility criteria also included WHO performance status of 0 or 1, New York Heart Association class >2, adequate hematologic, hepatic, and renal function, no other evolving tumor, no history of hepatitis C/B and/or HIV 1/2 infection, and no previous treatment with tyrosine kinase inhibitor. Patients provided written informed consent before enrollment in the study. The study was approved by the Paris Saint Louis ethics committee.

Study design

This multicenter noncontrolled phase II study was conducted in seven French dermatology centers from June 1, 2004 to September 1, 2006. All eligible patients received neoadjuvant therapy consisting of 600 mg of IM orally once daily for up to 2 months. Treatment was withheld permanently if treatment-related grade 2 or higher cutaneous toxicity or grade 3 or 4 noncutaneous toxicity occurred; two dose reductions (25% and 50%) were allowed in case of grade 2 nondermatologic toxicity. All patients had tumor resection within 1 week of IM withdrawal.

Study end points

The primary outcome of the study was an objective response according to Response Evaluation Criteria in Solid Tumors standards, from clinical measurement of the tumor. Additional end points included the following: objective response using imaging [ultrasound and magnetic resonance imaging (MRI)]; correlation of clinical responses with the presence of a *COL1A-PDGFB* fusion gene using the fluorescence *in situ* hybridization (FISH) technique and karyotyping for tumors larger than 5 cm, with pathologic responses, and with tumor cell apoptosis using terminal nucleotidyl transferase–mediated nick end labeling; tolerance (NIH/NCI toxicity 2003); and quality of life (European Organization for Research and Treatment of Cancer QLQ-C30 version 3.0).

Conventional and molecular cytogenetic analysis

Conventional cytogenetic analysis. For 15 samples from nine patients, a fresh sample was reserved for cell culture and conventional cytogenetic analysis according to standard procedures (7). For each case, 4 to 16 RHG-banded metaphases were analyzed.

FISH analysis. The artificial bacterial chromosome clones RP11-93L18, RP11-89F2, RP11-959K5, and RP11-642F17 were used as probes to detect the *COL1A1-PDGFB* fusion gene as previously described (8, 9). FISH analysis was done on metaphase cell preparations for 1 sample, on interphase cell suspensions for 14 samples, and on formalin-fixed and paraffin-embedded tissue sections for 25 samples (10). FISH analysis could not be performed on four samples that were fixed in Bouin's fluid.

Histologic and immunohistologic analysis

Patients had one histologic evaluation at baseline and one on a specimen taken during surgery performed at the end of IM treatment. Specimens were evaluated blind by one pathologist. Cellular density using standard histology and CD34 staining (scored from 0 to 3), fibrosis (scored from 0 to 3), necrosis, and inflammatory infiltrate were sequentially analyzed. Apoptosis was assessed by *in situ* detection of fragmented DNA, using terminal nucleotidyl transferase–mediated nick end labeling assay as described by Zhao et al. (11).

Statistical analysis

The primary end point was clinical response at 2 months, defined by a decrease in tumor size by at least 30% (Response Evaluation Criteria in Solid Tumors). We estimated the probability of a 30% decrease in tumor size without treatment to be less than 5%. The trial was designed to have a power of 80% to detect a 30% response rate (i.e., clinically promising) versus, at most, 5%, with a one-sided type I error rate of 0.025. It was a two-stage flexible trial (12). The sample size for the first stage was six patients. If no clinical response was observed in the first six patients, the trial would be stopped by reason of futility, and if five or more clinical responses were observed, it would be stopped for reasons of efficacy. Otherwise, it was expected that according to results from stage one, 12 to 22 additional patients would be recruited. The final test would be based on the product of the *P* values obtained at each stage (Fisher's combination test). To avoid a situation

Table 1. Characteristics of patients and tumor at baseline

Variable	*N* (%)	Median (Q1-Q3) [min-max]
Gender		
Male	13 (52)	
Female	12 (48)	
Age	25 (100)	42.4 (35.6-62.1) [23.0-72.5]
Tumor		
Primary	20 (80)	
Recurrent	5 (20)	
Localization		
Trunk	14 (56)	
Head or neck	3 (12)	
Upper limbs	1 (4)	
Lower limbs	5 (20)	
Other	2 (8)	
Tumor presentation		
Plaque	3 (12)	
Nodule	12 (48)	
Plaque + nodule	9 (36)	
Plaque + nodule + ulceration	1 (4)	
Size		
Longest diameter (cm)	25 (100)	4.5 (3.2-7.5) [2.4-16]

Abbreviations: Q1, first quartile; Q3, third quartile.

in which the combination test would reject the null hypothesis whereas the simple test based on all observations would not, we decided that the null hypothesis would be rejected if both the combination test and the fixed sample size test were significant at the prespecified level (13). Although the Bauer-Köhne design does not formally hold in our study, due to the discrete nature of *P* values, numerical simulations showed that the error rates would be preserved. At the interim analysis stage, the independent data monitoring committee advised the inclusion of a total of 25 patients to obtain a sufficiently precise estimate of the response rate. The flexibility features of the design were not used, thus, only results for the whole cohort are presented. Response rates are presented together with their exact 95% confidence interval.

Secondary end points included radiologic response, pathologic response, cytogenetic and FISH analyses, and safety. For radiologic response, agreement between methods (clinical evaluation, ultrasound scans, and MRI) was evaluated using Bland and Altman plots. Factors predictive of clinical response were tested using Fisher's exact tests at a bilateral 0.05 level.

Analyses were done on an intent-to-treat basis. A patient who left the trial after a severe adverse event before study completion and end point evaluation was considered as failed.

Results

Characteristics of patients at baseline

The characteristics of patients at baseline are summarized in Table 1. The gender ratio was ~1, with a slight predominance of men and young adults, a large proportion of trunk, head, and neck locations, and a predominance of the papulo-nodular form. The median tumor size was twice that which was recently reported for a large series of DFSP (2). Thirty-seven percent of patients had recurrent DFSP. No patient had evidence of histologic transformation.

Efficacy

Clinical response. The interim analysis showed a 50% clinical response rate. At final analysis, the response rate was estimated at 36% (95% confidence interval, 18-58; Table 2). Further clinical data are illustrated in Supplementary Fig. S1.

Radiologic responses. Ultrasound and MRI evaluation were done sequentially for 18 and 19 patients, respectively (Table 2). Seven patients had both ultrasound and MRI evaluation. The relative decrease in tumor size was 48.5% as estimated using ultrasound, and 21.6% using MRI. Agreement between methods (clinical, ultrasound, and MRI evaluation), analyzed using Bland-Altman plots,

Table 2. Tumor evaluation over the first 60 d

Variable	*N* (%)	Median (Q1-Q3) [min-max]
Clinical evaluation		
Longest diameter at inclusion (cm)	25 (100)	4.5 (3.2-7.5) [2.4-16]
Longest diameter at day 60 (cm)	24 (96)	4 (2.25-6) [0-15]
Relative decrease (%)	24 (96)	20.0 (6.1-37.7) [–12.5 to 100]
Relative decrease		
<30%	16 (64)	
≥30%	9 (36)	
Ultrasound evaluation		
Longest diameter at inclusion (cm)	18 (72)	5.0 (2.2-7.0) [0.9-12.7]
Longest diameter at day 60 (cm)	15 (60)	1.5 (1.1-3.4) [0-4.6]
Relative decrease (%)	14 (56)	53.3 (32.0-77.8) [8-100]
MRI evaluation		
Longest diameter at inclusion (cm)	19 (76)	3.5 (2.7-6.2) [1.5-13.0]
Longest diameter at day 60 (cm)	16 (64)	2.6 (1.7-3.6) [0.5-7.0]
Relative decrease (%)	15 (60)	21.6 (5.5-30.0) [–5.6 to 82.1]

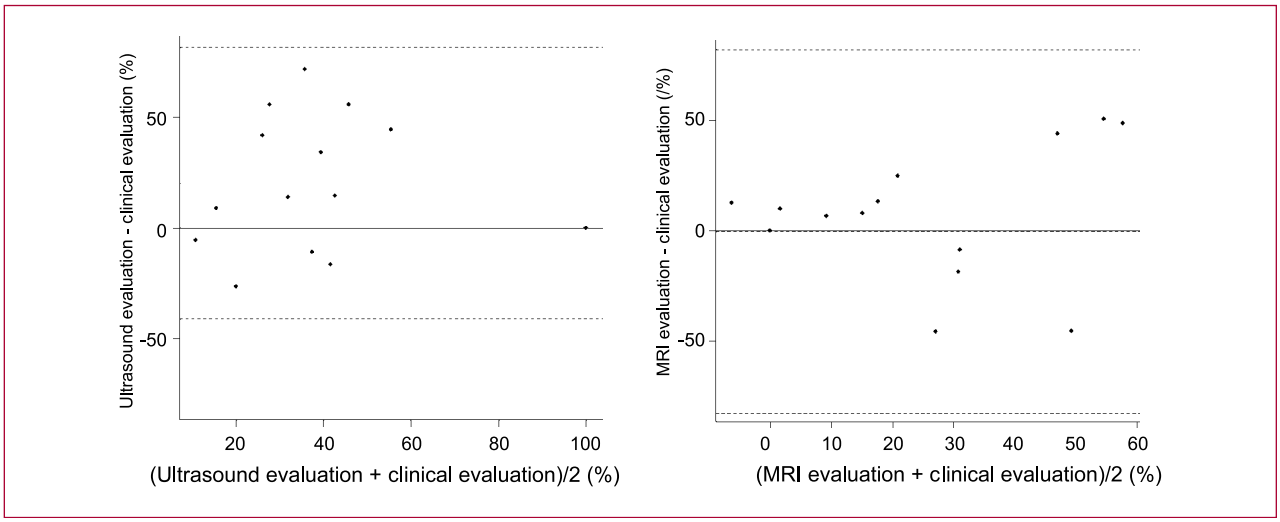

Fig. 1. Agreement between clinical, ultrasound, and MRI evaluation analyzed by means of Bland-Altman plots. This Bland and Altman graph displays a scatter diagram of the differences plotted against the averages of the two measurements. Horizontal lines are drawn at the mean difference, and at the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences.

was poor (Fig. 1). Ultrasound overestimated the relative tumor decrease by 20% as compared with clinical evaluation (P = 0.03 paired Student's test).

Cytogenetic and FISH analysis. An abnormal karyotype was observed in 5 out of 15 cases. In four samples, the presence of a supernumerary ring chromosome was observed. In one sample, the karyotype was complex, showing a supernumerary chromosome thought to be a t(17;22) derivative, and trisomy 8 and 11. The karyotypes of the other 10 samples were apparently normal, probably reflecting the *in vitro* growth of fibroblasts or stromal cells. For these 10 samples, *COL1A1-PDGFB* detection was done on noncultured interphase tumor cells. The *COL1A1-PDGFB* fusion gene was detected by FISH analysis in 32 samples from 21 patients. The detection was negative for two patients and noninformative for two other patients.

Among the 21 patients with the *COL1A1-PDGFB* fusion gene, 8 (38%) achieved partial or complete response, 12 were nonresponders, and 1 discontinued IM prematurely due to toxicity and was considered as failed. Both patients without the *COL1A-PDGFB* fusion gene were nonresponders. The percentage of responding patients was not significantly different according to the presence of *COL1A-PDGFB* translocation (8 out of 21 versus 0 out of 2, P = 0.53). The *COL1A1-PDGFB* fusion gene was detected in all patients analyzed after 2 months of IM therapy (n = 14, among whom 6 patients showed partial tumor response).

Pathologic responses and terminal nucleotidyl transferase–mediated nick end labeling. All 25 cases had histologic and immunohistologic (CD34) sequential analyses of their tumors, comparing features before and after 2 months of therapy. Apoptosis was sequentially evaluated in only eight patients for reasons of quality of specimen fixation.

No necrosis was evidenced before or after treatment, and very little or no inflammatory infiltrate enrichment. However, a modification of extracellular components was noted in 19 of 25 patients with varying degrees of hyalinic fibrosis. In some cases (n = 11), fibrosis was moderate, and hyalinic fibrosis was noted in small patches or small nodules sometimes surrounding vessels. In other cases (n = 8), large areas of hyalinic fibrosis containing sparse tumor cells or nodules of hyalinic fibrosis, sometimes surrounding vessels, were observed. The fibrosis could be observed at the periphery as well as in the center of the tumor (Table 3).

Tumor density decreased in 9 of 25 patients with a major decrease for 6 patients (Fig. 2). A decrease in cellular density score was statistically associated with clinical response (P = 0.022, Fisher's exact test), whereas the occurrence of fibrosis was not (P = 0.095, Fisher's exact test). However, there was a significant association between density and fibrosis scores (P = 0.0015, Fisher's exact test). No variation in cell density was seen in patients with a fibrosis score of 0.

In five out of eight assessable patients, 50% to 75% of cells were apoptotic in the biopsy performed after 2 months of therapy, whereas less than 5% apoptotic cells were detected for the other three patients. Among the eight assessable patients, the two responders had more than 50% apoptotic cells (Table 3).

Safety

Twenty-two patients (88%) had adverse events (Table 4), mainly of grade 1 or 2 severity. These were edema (grade 1 or 2, n = 17), asthenia (grade 1 or 2, n = 7), nausea (grade 1 or 2, n = 6), maculopapular rash (grade 1 or 2, n = 4; grade 3, n = 1), neutropenia (grade 1 or 2, n = 3; grade 3, n = 2), diarrhea (grade 1 or 2, n = 4), transaminitis (grade 1 n = 1,

Table 3. Histologic and immunohistologic analysis

No. of patients	All patients 25	Success 9	Failure 16
Fibrosis score			
0	6 (24)	0 (0)	6 (38)
1	11 (44)	5 (56)	6 (38)
3	8 (32)	4 (44)	4 (25)
Score of cell density decrease			
0	16 (64)	3 (33)	13 (81)
1	3 (12)	3 (33)	0 (0)
3	6 (24)	3 (33)	3 (19)
Occurrence of apoptosis			
Noninterpretable	17 (68)	7 (78)	10 (62.5)
Interpretable	8 (32)	2 (22)	6 (37.5)
Positive	5 (68.5)	2 (100)	3 (50)
Negative	3 (37.5)	0 (0)	3 (50)

grade 4 $n = 1$), cramp with increased Creatine phospho kinase (grade 1 or 2, $n = 1$), anemia (grade 2, $n = 2$), and thrombopenia (grade 4, $n = 1$). IM-related adverse events led to definitive drug withdrawal for three patients, two patients had drug-related rashes, and one patient had grade 3 neutropenia despite dose de-escalation.

Quality of life

Clinically significant decreases (difference in mean values ≥5) from baseline to day 60 of assessment were found for global quality of life status, and for one of the five functional scales (physical). On the nine-item symptom scale, patients reported a significant increase for fatigue compared with baseline.

Discussion

This phase II study yielded a clinical response rate to a 2-month neoadjuvant IM therapy in DFSP of 36.0% (IC95%, 18.0-57.5). The drug was globally well tolerated with a similar toxicity profile to that described in other diseases.

In the literature, IM has been previously evaluated in only one open-label multinational exploratory study. It enrolled patients with a refractory life-threatening malignancy known to be associated with one or more IM-sensitive tyrosine kinases. A subgroup of 12 patients with unresectable ($n = 10$) or metastatic ($n = 2$) DFSP were included and received 400 mg b.i.d. Tumor response was evaluated using Southwest Oncology Group criteria. Evaluation was done using CT scan or MRI ($n = 2$), clinical photography ($n = 4$), clinical examination ($n = 4$), and nonspecified methods for two patients. The authors reported four complete responses, six partial responses, and one progressive disease, whereas status was unknown for one patient. The duration of IM treatment varied from 62 to 698 days. Time to progression was estimated at 23.9 months (7.7 to infinity). Clinical response was observed in nine of nine patients with t(17;22) whereas one patient lacking t(17;22) did not respond (14).

The use of IM has also been reported in 20 isolated cases outside of clinical trials (4, 5, 15–26). Among these, seven patients had fibrosarcoma on DFSP (4, 15, 16, 24) and six patients had metastatic sarcoma (4, 5, 15, 16, 18). Cytogenetic analysis showed the *COL1A-PDGFB* fusion gene in eight out of nine patients studied (4, 5, 15, 17, 24, 25). When all case reports were grouped, tumor size reduction from baseline was achieved for 19 patients, whereas 1 patient with transformed DSFP and a complex karyotype without t(17;22) translocation did not respond (24). In the responding patients, IM dose ranged from 400 mg/d

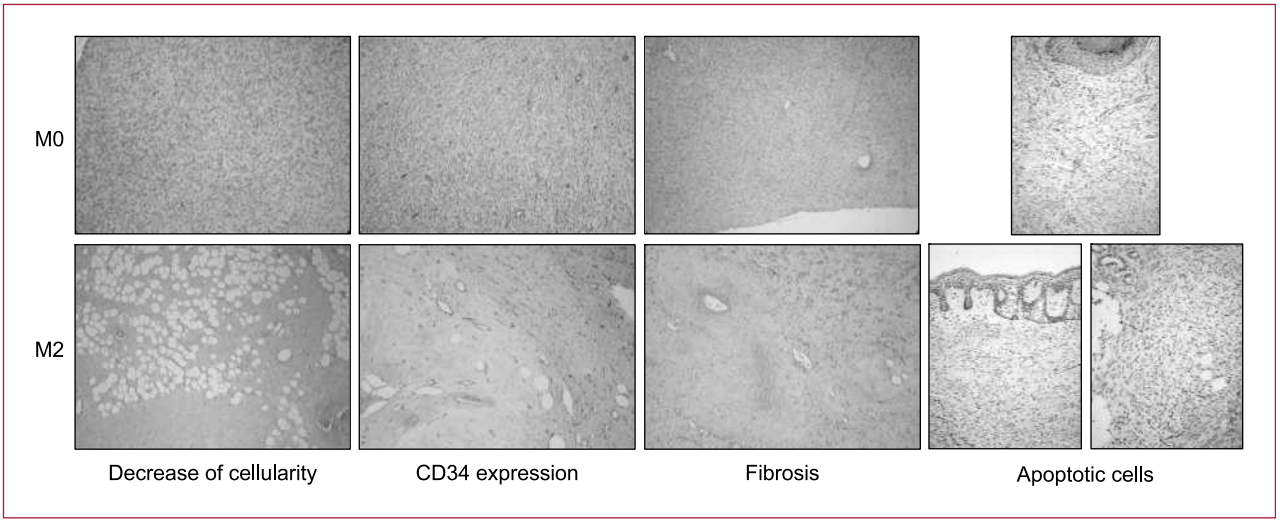

Fig. 2. Decrease of cell density and CD34 expression as well as induction of hyalinic fibrosis and apoptosis in one patient's lesion after 2 months therapy with IM.

Table 4. Side effects in relation to imatinib

Events	No. of patients (%)				
	Total	Grade 1	Grade 2	Grade 3	Grade 4
Edema	17 (68)	13 (52)	4 (16)	0 (0)	0 (0)
Eruption	8 (32)	6 (24)	1 (4)	1 (4)	0 (0)
Asthenia	7 (28)	6 (24)	1 (4)	0 (0)	0 (0)
Nausea	6 (24)	5 (20)	1 (4)	0 (0)	0 (0)
Neutropenia	5 (20)	3 (12)	0 (0)	2 (8)	0 (0)
Thrombopenia	1 (4)	3 (12)	0 (0)	0 (0)	1 (4)
Diarrhea	4 (16)	3 (12)	1 (4)	0 (0)	0 (0)
Gastroesophageal reflux disease	4 (16)	4 (16)	0 (0)	0 (0)	0 (0)
Abdominal pain	3 (12)	2 (8)	1 (4)	0 (0)	0 (0)
Weight gain	3 (12)	2 (8)	1 (4)	0 (0)	0 (0)
Anemia	2 (8)	0 (0)	2 (8)	0 (0)	0 (0)
Headache	2 (8)	1 (4)	1 (4)	0 (0)	0 (0)
Cramp	2 (8)	2 (8)	0 (0)	0 (0)	0 (0)
Dyspnea	2 (8)	2 (8)	0 (0)	0 (0)	0 (0)
Transaminitis	2 (8)	1 (4)	0 (0)	0 (0)	1 (4)
Edema	17 (68)	13 (52)	4 (16)	0 (0)	0 (0)
Conjunctivitis	1 (4)	1 (4)	0 (0)	0 (0)	0 (0)
Decreased libido	1 (4)	0 (0)	1 (4)	0 (0)	0 (0)
Lumbar back pain	1 (4)	1 (4)	0 (0)	0 (0)	0 (0)
Pruritus	1 (4)	1 (4)	0 (0)	0 (0)	0 (0)
Vertigo	1 (4)	1 (4)	0 (0)	0 (0)	0 (0)
CPK increase	1 (4)	0 (0)	1 (4)	0 (0)	0 (0)

(n = 7; refs. 4, 15, 16, 21, 23, 26) to 600 mg/d (n = 1; ref. 26) and 800 mg/d (n = 12; refs. 5, 17–20, 22, 24–26). The time to initial response was 3 months or less in 15 patients for whom this information was available (4, 5, 15, 16, 18–20, 22, 24–26). Treatment exceeded 6 months for seven patients (16, 17, 19, 20, 23, 24, 26), reaching 14, 17, and 20 months for three patients (16, 20, 24).

Our study was designed in 2003 when only three case reports of response in metastatic disease had been published. It was a proof-of-principle trial, specifically designed for DFSP, aiming to define the response rate to a short neoadjuvant IM therapy. We chose a flexible design to obtain an early estimation of the benefit/risk ratio and to adjust initial hypotheses if required. The dosage of 600 mg/d was chosen for the following reasons: (*a*) a phase I to II dose escalation study was difficult to perform in such a rare disease; (*b*) responses had previously been achieved using 400 mg/d; (*c*) using the maximum tolerated dose, 800 mg/d, in a population of non-severe patients seemed unethical; (*d*) in gastrointestinal stromal tumors, 600 mg/d showed acceptable toxicity (27). Our data enabled us to assess the response rate at 2 months as being 36% and not below 18%, in patients suffering from nontransformed DFSP. Such data are very important to generate hypotheses for future trials on DFSP. IM was approved in 2006 for the treatment of unresectable and metastatic disease. However, in certain patients, IM does not provide sufficient tumor regression for successful resection. It is also unlikely to prevent subsequent tumor progression in case of residual tumor if it is withdrawn, as also observed in gastrointestinal stromal tumors (28). Therefore, other treatments potentially active in case of primary or secondary resistance to imatinib will be needed. Our results will help to define future trials with short-term end points. In contrast with the study by McArthur et al. (14, 29), our trial used the same primary end point (clinical evaluation) for all patients. This is important considering the poor agreement of clinical, ultrasound, and MRI assessments evidenced here: the study enabled comparisons of the relative decrease of maximum diameter between clinical assessment and ultrasound or MRI. Ultrasound overestimates the relative decrease compared with clinical assessment. Although the median relative decrease obtained from both clinical assessment and MRI was 20%, the two methods were not correlated. In dermatofibrosarcoma, fast saturation spin echo or short TI inversion recovery (STIR) is useful in distinguishing the tumor signal from that of subcutaneous fat (30). Radiologic centralized review using the same sequence should be done in future multicenter trials.

Cytogenetic and/or FISH analyses were done for all patients. The *COL1A1-PDGFB* fusion gene was detected in 21 patients. The small number of patients in which the *COL1A1-PDGFB* fusion gene was not found prevented any correlation with tumor response to IM. Thirteen out of 21 patients with the fusion gene failed to respond at 2 months, although delayed response could not be excluded in such patients.

Our study is the first to perform a systematic analysis of the effect of IM on histologic parameters and apoptosis. Although apoptosis was evidenced in some responders, it was also observed in patients not considered as responders according to Response Evaluation Criteria in Solid Tumors standards. We cannot exclude the possibility that such patients would have achieved clinical response if IM had been continued. Interestingly, clinical response was correlated with a decrease in cell density, which was itself associated with the score for fibrosis. Hyalinic fibrosis induced by IM has hitherto been reported only in two isolated cases (23, 26) but was observed in 19 of 25 of our patients. The replacement of tumor cells by hyalinized collagen has also been reported in gastrointestinal stromal tumors treated with IM (31). The underlying mechanism is unknown, but might be a specific feature of IM response. Unfortunately, for lack of sufficient initial frozen material, we could not compare the sequential expressions of the target (phosphorylated PDGF receptor).

Side effects have been previously described in other IM clinical trials. A moderate but significant effect was observed on general quality of life after 2 months of therapy in this population with high initial quality of life status. This suggests that other tyrosine kinase inhibitors, such as nilotinib, as efficient as IM on the target but better tolerated, should be evaluated.

In conclusion, IM, already approved for unresectable tumors and rare metastatic disease, is well-targeted for DFSP and could be used as a neoadjuvant therapy in locally advanced tumors when surgery is difficult. Reports in the literature and the experience in gastrointestinal stromal tumors suggests that primary resistance could occur and that the development of secondary resistance can be expected. Resistance mechanisms need to be analyzed to evaluate new drugs.

Disclosure of Potential Conflicts of Interest

C. Lebbe, advisory board organised by Novartis; A. Mathieu-Boue, employee from Novartis. No other potential conflicts of interest were disclosed.

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