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ORIGINAL REPORT

Imatinib Mesylate in Advanced Dermatofibrosarcoma Protuberans: Pooled Analysis of Two Phase II Clinical Trials

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ABSTRACT

Purpose
Dermatofibrosarcoma protuberans (DFSP) is a dermal sarcoma typically carrying a translocation between chromosomes 17 and 22 that generates functional platelet-derived growth factor B (PDGFB).

Patients and Methods
Two distinct phase II trials of imatinib (400 to 800 mg daily) in patients with locally advanced or metastatic DFSP were conducted and closed prematurely, one in Europe (European Organisation for Research and Treatment of Cancer [EORTC]) with 14-week progression-free rate as the primary end point and the other in North America (Southwest Oncology Group [SWOG]) with confirmed objective response rate as the primary end point. In the EORTC trial, confirmation of *PDGFB* rearrangement was required, and surgery was undertaken after 14 weeks if feasible. The SWOG study confirmed t(17;22) after enrollment.

Results
Sixteen and eight patients were enrolled onto the EORTC and SWOG trials, respectively. Tumor size ranged from 1.2 to 49 cm. DFSP was located on head/neck, trunk, and limb in seven, 11, and six patients, respectively, and was classic, pigmented, and fibrosarcomatous DFSP in 13, one, and nine patients, respectively. Metastases were present in seven patients (lung involvement was present six patients). Eleven patients (46%) had partial response as best response, and four patients had progressive disease as best response. Median time to progression (TTP) was 1.7 years. Imatinib was stopped in 11 patients because of progression, one patient because of toxicity, and two patients after complete resection of disease. Median overall survival (OS) time has not been reached; 1-year OS rate was 87.5%.

Conclusion
Imatinib is active in DFSP harboring t(17;22) including fibrosarcomatous DFSP, with objective response rate approaching 50%. Response rates and TTP did not differ between patients taking 400 mg daily versus 400 mg twice a day.

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INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumor (comprising approximately 1% of sarcomas) with typically indolent growth and a less than 5% probability of metastases.[1,2] It is believed that metastases develop more commonly in DFSP harboring areas of fibrosarcoma, known as fibrosarcomatous DFSP (DFSP-FS).[3-6] If metastases occur, they often are localized in the lungs and are less commonly localized in lymph nodes.

The standard treatment of this cutaneous sarcoma is wide local excision. A surgical margin of at least 3 cm has been recommended, and often, reconstructive techniques are needed, which may result in disfigurement or functional impairment.[1,7] However, locoregional recurrence rates ranging from 24% to 90% after complete excision have been reported, and many recurrences can occur late.[1,4,8-13] The majority of authors reported a median time to disease recurrence between 2 and 3 years.[1,4,14] A limited experience with Mohs surgery exists.[15-19]

Radiotherapy is a treatment option for unresectable lesions or in case of margin involvement[20-23] but has limited value as primary therapy of patients who can be cured by surgery. In patients with locally advanced disease, effective use of cytotoxic chemotherapy is anecdotal.[11]

DFSP is characterized by a specific rearrangement of chromosomes 17 and 22, which can be

detected by standard cytogenetics as translocation t(17;22)(q22;q13) or a supernumerary ring chromosome,[24-32] that leads to fusion of collagen type I A1 chain (*COL1A1*) gene to the platelet-derived growth factor B chain (*PDGFB*) gene. This *COL1A1-PDGFB* fusion may be identified in virtually all patients with DFSP by molecular diagnostic testing using fluorescent in situ hybridization (FISH) or multiplex reverse transcription polymerase chain reaction,[33] which is extremely helpful in the differential diagnosis of patients with DFSP-FS without areas of conventional DFSP.[34,35] The result of this rearrangement is upregulation of a COL1A1-PDGFB fusion protein that is processed to a mature PDGF-BB homodimer, which activates the PDGFB receptor (PDGFRB), a protein tyrosine kinase acting as a potent growth factor.[36-38] These mechanisms contribute directly to development and growth of DFSP and also of giant-cell fibroblastoma, which is considered the juvenile form of DFSP.[39-42] Greco et al[43] provided evidence that the rearranged PDGFB could transform NIH3T3 cells by autocrine mechanisms, suggesting that t(17;22) is the inciting pathogenetic event of DFSP.

Advances in the understanding of the molecular mechanisms of DFSP have resulted in the introduction into clinical practice of targeted therapy directed toward PDGFRB. Published case reports demonstrating efficacy of the small-molecule tyrosine kinase inhibitor imatinib in advanced/metastatic DFSP are available, but objective response rates and clinical outcome of imatinib therapy in larger cohorts of advanced DFSP have not been established.[44-46] The aim of present study was to report the combined analysis of two phase II clinical trials performed in parallel by cooperative research groups assessing the activity and safety of imatinib in locally advanced/unresectable and/or metastatic DFSP.

PATIENTS AND METHODS

Design of Studies

At the end of 2004 and the beginning of 2005, the Southwest Oncology Group (SWOG) and the Soft Tissue and Bone Sarcoma Group of the European Organisation for Research and Treatment of Cancer (EORTC) both initiated separate, single-agent, single-arm, open-label, multicenter phase II clinical trials to explore the activity of imatinib therapy in patients with locally advanced/metastatic DFSP. They were registered as trial SWOG-S0345 (NCT00084630) and EORTC 62027 (NCT00085475; EUDRA CT 2004-002538-20). The trials were independently conducted, and each was designed to enroll approximately 40 patients. Two years later, after regulatory body approval of the marketing of imatinib in the treatment of DFSP and subsequent slow accrual rate, both trials were closed early before full enrollment was obtained. The results of the two trials were combined to provide greater numbers for outcome analysis.

Although the two studies had a similar objective, they differed in terms of selection criteria, starting daily dose of imatinib, protocol treatment duration, primary end point, and statistical design. In both trials, eligible patients had to be at least 18 years old with histologically documented diagnosis of DFSP (or giant-cell fibroblastoma in the EORTC trial), at least one site of measurable disease, and adequate organ function and be at least 12 weeks after surgery. Diagnostic tissue could be taken either from the primary tumor or from metastasis. Patients receiving chemotherapy, biologic therapy, or any other investigational drug within 28 days before treatment start were ineligible. For the EORTC trial, selection criteria included advanced or metastatic tumors not amenable to surgery and/or radiotherapy with curative intent as assessed by a multidisciplinary team; in the SWOG trial, the criteria were similar, but in addition, patients in whom R0 resection was not feasible with an acceptable cosmetic or functional result were eligible. Pathology was independently centrally reviewed in both trials (R.S. for EORTC; B.P.R. and A.L. for SWOG). The presence of *PDGFB* rearrangement in trial EORTC 62027 was prospectively confirmed externally by FISH (M.D.-R.), as previously described.[46] In SWOG-S0345, t(17;22)(q22;q13) was confirmed by one laboratory by reverse transcription polymerase chain reaction and/or DNA sequencing (D.L.-T.) after enrollment.

In the EORTC trial, the initial dose of imatinib (Novartis, Basel, Switzerland) was 400 mg twice a day. The minimal treatment duration in the absence of progression was 14 weeks (with disease status evaluated at 2, 4, 6, 10, and 14 weeks); then, if all lesions could be resected and R0 resection was achieved, imatinib was stopped. If complete resection was not possible, imatinib was continued indefinitely until documented disease progression (disease status was assessed every 4 weeks until 6 months and every 3 months thereafter). Dose interruptions and reductions were allowed for prospectively defined toxicities, as previously described.[47]

In the SWOG trial, the initial dose of imatinib was 400 mg daily. Imatinib dose escalation to 400 mg twice a day was allowed in case of disease progression. Disease assessment was performed every 8 weeks. The duration of protocol treatment was 48 weeks; treatment after 48 weeks was not dictated by the trial.

In the EORTC trial, the primary end point was progression-free rate at 14 weeks, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0.[48] A Fleming one-step design was used (P0 = 20%, P1 = 40%, $\alpha = .1$, $\beta = .05$), and 44 patients were planned to be included. Objective response rate, time to progression (TTP), overall survival (OS), duration of response, and safety profile of imatinib (characterized according to National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0) were assessed as secondary end points. In the SWOG trial, the primary end point was confirmed response rate (RECIST1.0). A two-step design was used; 20 patients were to be enrolled onto the first step, and if there was at least one confirmed response, an additional 20 patients were to be enrolled. The design had a 92% power to detect a response rate of at least 20% (P0 = 5%, P1 = 20%, $\alpha = .05$, $\beta = 0.08$). Secondary end points were progression-free survival at 1 year and frequency and severity of adverse events (according to National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0). The protocols were approved by local institutional review boards according to applicable laws in the participating countries. All patients gave written informed consent.

Statistical Methods

The progression status was evaluated at 14 weeks for the EORTC study and 16 weeks for the SWOG trial. Best overall response was determined. Because surgery was allowed after 14 weeks in the EORTC trial, responses have been classified as confirmed or resected residual disease for this trial.

The duration of follow-up, TTP, and OS curves were estimated using the Kaplan-Meier method (alive patients were censored at last follow-up for OS calculations, patients free from disease progression were censored at last follow-up, and patients deceased without disease were censored on the date of death for TTP calculations; TTP was counted for 400-mg dose level in SWOG patients). The TTP and OS estimations have been carried out for all patients (intent to treat [ITT]) and for eligible patients.

RESULTS

Patients

Between December 2004 and March 2007, 17 patients were preregistered onto the EORTC trial. One patient had to be excluded from analysis because neither *PDGFB* rearrangement nor *COL1A1-PDGFB* fusion by FISH was confirmed.

Between February 2005 and October 2006, eight patients were registered onto the SWOG trial. All patients started protocol therapy. The *COL1A1-PDGFB* fusion was not present and DFSP was not centrally confirmed for one patient, who was thus considered ineligible. This patient is included in all tables (ITT), but activity results are also presented for eligible patients only. Two patients in the SWOG trial

were registered for imatinib dose escalation to 400 mg twice a day after progression on 400 mg daily. Patient characteristics at trial entry are listed in Table 1.

Treatment Duration and Intensity

All patients from the SWOG trial are currently off protocol treatment; in this trial, study treatment concluded after 48 weeks, but patients were allowed to continue imatinib therapy using commercially available drug at the discretion of treating physicians. In the EORTC trial, resection of target lesions was allowed after the 14-week evaluation, but patients were allowed to continue therapy; four patients are still on protocol therapy, all of them with more than 1 year of treatment. Progression was the reason for treatment discontinuation in 11 patients (45.8%)—seven patients (43.8%) in the EORTC trial and four patients (50.0%) in the SWOG trial. In one patient, treatment was stopped as a result of toxicity. Median treatment duration was 248.0 days (range, 4.0 to 1,222.0 days) in the EORTC trial and 328.0 days (range, 112.0 to 345.0 days) at the 400-mg daily dose in the SWOG trial.

The dose-intensity (total dose of imatinib/total treatment duration) was greater than 95% in all but one patient in the SWOG study (median, 97.0%) but less than 95% in seven patients from the EORTC study (median, 98.3%). Median dose-intensity was 775.7 mg/d (range, 413.0 to 797.4 mg/d) in the EORTC trial and 392.6 mg/d (range, 298.5 to 400.6 mg/d) for the 400-mg daily dose in the SWOG trial.

Table 1. Patient Demographics and Clinical Characteristics at Trial Entry

Characteristic	Study: EORTC (n = 16) No. of Patients	%	Study: SWOG (n = 8) No. of Patients	%	Total (N = 24) No. of Patients	%
Age, years						
Median	47.4		48.6		47.4	
Range	23.8-69.6		28.9-66.1		23.8-69.6	
Sex						
Male	11	68.8	3	37.5	14	58.3
Female	5	31.3	5	62.5	10	41.7
ECOG performance status						
0	10	62.5	7	87.5	17	70.8
1	5	31.3	1	12.5	6	25.0
2	1	6.3	0	0.0	1	4.2
Prior chemotherapy						
None	16	100.0	6	75.0	22	91.7
1 line	0	0.0	1	12.5	1	4.2
4 lines	0	0.0	1	12.5	1	4.2
Primary location						
Head and neck	4	25.0	3	37.5	7	29.2
Trunk-thorax	7	43.8	4	50.0	11	45.8
Limb	5	31.3	1	12.5	6	25.0
Time since diagnosis, months						
Median	33.9					
Range	0.57-660					
Primary tumor	4	25.0	3	37.5	7	29.2
Local recurrence	8	50.0	4	50.0	12	50.0
Metastases	6	37.5	1	12.5	7	29.2
Lung metastases	5	31.3	1	12.5	6	25.0
Maximum size of the largest lesion, mm						
Median	117.5		45.5		87.5	
Range	12.0-490.0		19.0-279.0		12.0-490.0	
Histology review						
Not DFSP	0	0.0	1	12.5	1	4.2
DFSP classic	8	50.0	5	62.5	13	54.2
DFSP fibrosarcomatous	7	43.8	2	25.0	9	37.5
DFSP pigmented	1	6.3	0	0.0	1	4.2
COL1A1-PDGFB rearrangement						
Absent	0	0.0	1	12.5	1	4.2
Present	16	100.0	7	87.5	23	95.8

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; SWOG, Southwest Oncology Group; ECOG, Eastern Cooperative Oncology Group; DFSP, dermatofibrosarcoma protuberans.

Table 2. Response, Progression, and Survival Status of Patients With Dermatofibrosarcoma Protuberans After Imatinib Therapy in the EORTC and SWOG Trials

Response, Progression, and Survival Status	Study: EORTC (n = 16) No. of Patients	%	Study: SWOG (n = 8) No. of Patients	%	Total (N = 24) No. of Patients	%
Response at 14-16 weeks						
PR	5	31.3	4	50	9	37.5
SD	6	37.5	2	25	8	33.3
PD	3	18.8	1	12.5	4	16.7
Not evaluable	2	12.5	1	12.5	3	12.5
Best overall response						
PR (confirmed)	3	18.8	4	50.0	7	29.2
PR (resected)	4	25.0	0	0.0	4	16.7
SD	4	25.0	2	25.0	6	25.0
PD	3	18.8	1	12.5*	4	16.6
Not evaluable	2	12.5	1	12.5	3	12.5
Progression status						
Progression free	8	50.0	4	50.0	12	50.0
Progression	8	50.0	4	50.0*	12	50.0
Survival status						
Alive	10	62.5	8	100.0*	18	75.0
Dead	6	37.5	0	0.0	6	25.0
Cause of death						
Progression	5	31.3	0	0.0	5	20.8
Cardiovascular (> 30 days after stop of therapy)	1	6.3	0	0.0	1	4.2

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; SWOG, Southwest Oncology Group; PR, partial response; SD, stable disease; PD, progressive disease.
*One ineligible patient.

Responses and Survival

The median follow-up time (for surviving patients) was 2.6 years (range, 2.2 to 2.98 years). Responses to therapy at 14 weeks for the EORTC study (the primary end point) and 16 weeks for the SWOG study and best overall response for all patients are listed in Table 2. Because surgery was allowed after the 14-week evaluation in the EORTC study, some of the responses were not confirmed because target lesions were resected. Altogether, the best overall responses were as follows. Partial responses (PRs) were observed in 11 patients (45.9%; including five patients with DFSP-FS; Table 3); four PRs were

Table 3. DFSP Best Response by Subtype

DFSP Subtype	No. of Patients					
	PR		SD		PD	
	Imatinib 400 mg/d	Imatinib 800 mg/d	Imatinib 400 mg/d	Imatinib 800 mg/d	Imatinib 400 mg/d	Imatinib 800 mg/d
DFSP classic	2	4	3	2		
DFSP fibrosarcomatous	2	3		1		2
DFSP pigmented						1
Not DFSP					1	

Abbreviations: DFSP, dermatofibrosarcoma protuberans; PR, partial response; SD, stable disease; PD, progressive disease.

not confirmed because of resection of residual disease after 14 weeks of therapy, and five of seven patients with primary tumors and four of 12 patients with locally recurrent tumors achieved PR. Stable disease was observed in six patients (25.0%). Progressive disease was observed in four patients (16.6%; including one patient with fibrosarcoma lacking t(17;22) and two patients with DFSP-FS). Three patients (12.5%) were not evaluable (one patient each for toxicity, consent withdrawal, and loss to follow-up). Achieved clinical benefit (PR plus stable disease) from therapy was 70.9%.

A total of 12 progressions have been reported during follow-up (progressions occurred in 50% of patients with DFSP-FS and in six of seven patients with metastases). In the EORTC study, six patients have died, all but one as a result of disease progression.

Median TTP was 1.7 years (range, 0.65 year to not reached; Fig 1A). The 1-year progression-free rate was 57.18% (range, 34.99% to 74.26%) in ITT group and 59.66% (range, 36.71% to 76.63%) in eligible patients. Progression-free rates at 1 year for eligible patients were similar between studies—61.36% (range, 33.25% to 80.53%) in the EORTC study and 57.14% (range, 17.19% to 83.71%) in the SWOG study.

Two patients in the SWOG trial were dose escalated to 800 mg daily. The patient with ineligible fibrosarcoma had progression of disease on the increased dose, and a patient with DFSP-FS initially responding to imatinib 400 mg daily had an unconfirmed PR lasting 6 months after dose escalation. The survival status of all patients is provided in Table 2. Median OS time has not been reached; the 1-year OS rate was 87.5% (range, 66.08% to 95.79%) in the ITT group (Fig 1B) and 86.96% (range, 64.81% to 95.60%) in eligible patients.

Safety

The worst grade of toxic effect recorded during the treatment period is provided in Table 4. Many patients had more than one adverse event; however, adverse events were generally mild to moderate in intensity and easily managed by dose reduction, dose interruption, or standard supportive medical treatment. No treatment-related deaths were recorded. The imatinib safety profile was similar to previous reports,[47,49] and the most common adverse events were anemia, leukopenia, fatigue, edema, rash, and nausea.

DISCUSSION

The introduction of imatinib mesylate, a small-molecule drug rationally developed to inhibit the tyrosine kinase BCR-ABL, but also

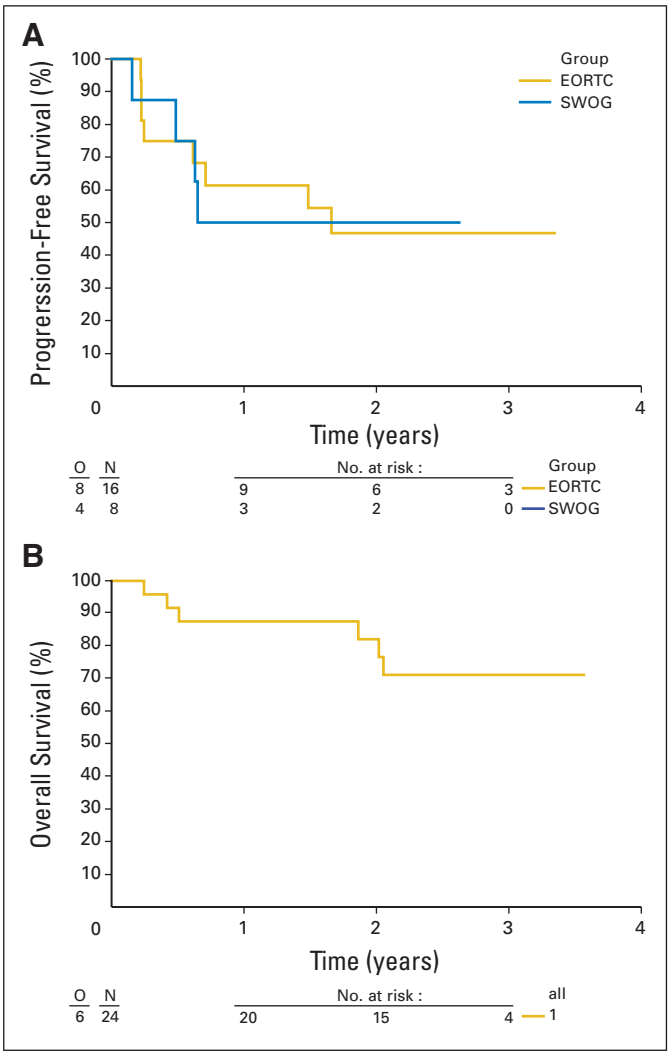

Fig 1. (A) Time to progression curves for European Organisation for Research and Treatment of Cancer (EORTC) and Southwest Oncology Group (SWOG) trials in the intent-to-treat (ITT) patients. (B) Overall survival in ITT patients.

affecting ABL-related kinase, KIT, PDGF receptor α, and PDGFRB, has revolutionized the therapy of advanced GI stromal tumors and chronic myelogenous leukemia.[47,49-53] The spectacular efficacy of imatinib in these neoplasms resulted in a model of targeted therapy in oncology.

The observation that autocrine overproduction of PDGFB as a result of gene rearrangement is a key factor in DFSP pathogenesis[27,36,37] provoked in vitro research that showed inhibition of DFSP cell growth exposed to imatinib.[43] The further demonstration of the inhibitory effect of imatinib on six different DFSP cell lines[38,54] led to the clinical investigation of this new therapeutic approach. Early anecdotal reports suggested significant activity of imatinib in patients with metastatic or advanced DFSP.[44,45,55-60] A subset analysis of 10 patients with locally advanced and/or metastatic DFSP treated in Imatinib Target Exploration Consortium Study B2225 reported a 100% response rate in the nine patients with documented t(17;22); whereas the patients with DFSP lacking t(17;22) experienced progression.[46,61] As a result of these observations, imatinib was registered for therapy of inoperable and/or metastatic DFSP.

Table 4. Adverse Events From Imatinib Reported in Patients With DFSP

Adverse Event	EORTC (n = 16)						SWOG (n = 8)						Total (N = 24)					
	Grade 1		Grade 2		Grade 3		Grade 1		Grade 2		Grade 3		Grade 1		Grade 2		Grade 3	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Leukopenia	4	25.0	2	12.5	1	6.3	2	25.0	0	0	0	0	6	25.0	2	8.3	1	4.2
Neutropenia	2	12.5	1	6.3	2	12.5	0	0	0	0	2	25.0	2	8.3	1	4.2	4	16.7
Thrombocytopenia	1	6.3	0	0	1*	6.3	0	0	0	0	0	0	1	4.2	0	0	1*	4.2
Anemia	11	68.8	4	25.0	0	0	1	12.	0	0	1	12.5	12	50.0	4	16.7	1	4.2
Bilirubin	4	25.0	1	6.3	1	6.3	0	0	0	0	0	0	4	16.7	1	4.2	1	4.2
AST increase	4	25.0	1	6.3	1*	6.3	2	25.0	0	0	0	0	6	25.0	1	4.2	1*	4.2
Arterial hypertension	1	6.3	1	6.3	0	0	0	0	0	0	0	0	1	4.2	1	4.2	0	0
Fatigue	3	18.8	2	12.5	2	12.5	5	62.5	0	0	2	25.0	8	33.3	2	8.3	4	16.7
Rash	4	25.0	1	6.3	1	6.3	3	37.5	0	0	0	0	7	29.2	1	4.2	1	4.2
Anorexia	2	12.5	0	0	0	0	2	25.0	0	0	0	0	4	16.7	0	0	0	0
Diarrhea	3	18.8	3	18.8	0	0	1	12.5	0	0	1	12.5	4	16.7	3	12.5	1	4.2
Nausea	3	18.8	2	12.5	1	6.3	4	50.0	0	0	0	0	7	29.2	2	8.3	1	4.2
Vomiting	1	6.3	0	0	2	12.5	1	12.5	0	0	0	0	2	8.3	0	0	2	8.3
Head and neck edema	6	37.5	0	0	0	0	5	62.5	0	0	0	0	11	45.8	0	0	0	0
Limbs/trunk/visceral edema	6	37.54	1	6.3	1	6.3	5	62.5	0	0	0	0	11	45.8	1	4.2	1	4.2
Pain	3	18.8	0	0	0	0	0	0	0	0	1	12.5	3	12.5	0	0	1	4.2

Abbreviations: DFSP, dermatofibrosarcoma protuberans; EORTC, European Organisation for Research and Treatment of Cancer; SWOG, Southwest Oncology Group.

*Grade 4; two toxic grade 4 events were noted in one patient with pre-existing liver disturbances and alcohol abuse history—thrombocytopenia and AST level increase.

The purpose of our combined analysis of two phase II trials was to provide more statistical power for the evaluation of the objective clinical response rate of locally advanced and/or metastatic DFSP to imatinib and to assess the safety of this therapy. We report here the largest prospectively collected cohort of locally advanced/metastatic DFSP and confirm the excellent activity of imatinib in this selected group of poor-prognosis patients. We have demonstrated a DFSP response rate of 46%, a 1-year progression-free survival rate of 58%, and a median TTP of 1.7 years with treatment with imatinib. Although there were notable differences in trial design, the observed response rate at 14 to 16 weeks and progression-free survival rate at 1 year were remarkably similar between the studies, suggesting that a daily dose of 400 mg has similar efficacy to 800 mg daily. Most of the previously reported patients had been treated with doses of imatinib exceeding 400 mg daily. We have also found that DFSP-FS retains sensitivity to imatinib, although responses may be less durable.[34,62] DFSP-FS tumors lacking t(17;22)[46,63] do not respond to imatinib, suggesting misdiagnosis of disease or loss of tumor dependence on the PDGFR signaling pathway. Therefore, we advocate testing for the presence of t(17;22) in DFSP-FS before therapy with imatinib, especially in the neoadjuvant setting.

Wide surgical excision is the standard curative treatment for localized DFSP but may result in cosmetic disfigurement or functional impairment. Preoperative imatinib therapy to diminish tumor size and decrease surgical morbidity is attractive, in theory, if excellent cure rates can be obtained. Our results demonstrated that some patients with DFSP initially evaluated as having unresectable disease or requiring mutilating surgery were able to undergo resection after imatinib therapy (Fig 2 and Appendix Figs A1 and A2, online only). This rational treatment approach led to complete remission after surgery in four patients and seems to have been curative, although longer follow-up is needed. Lebbé et al[64] presented a preliminary report on 25 patients with resectable DFSP treated in a phase II trial with preoperative imatinib at a dose of 600 mg daily for 2 months. Objective PR was observed in nine patients (36%), which may be inferior to our results but might be explained by the shorter duration of treatment and/or lack of confirmation of PDGFB rearrangement. The optimal duration of preoperative imatinib therapy in patients with DFSP has not been established. Further studies are necessary for elucidating whether imatinib therapy reduces the need for wide surgical margins or whether imatinib has activity as adjuvant therapy in patients with positive margins after excision.

The safety profile in our group of patients was as expected and consistent with that seen in published clinical trials of imatinib in GI stromal tumors.[47,49,52] The majority of patients experienced adverse effects during treatment, but almost all were graded as mild.

Questions remain about the mechanisms of imatinib action and resistance in DFSP, and there is a need to identify additional molecular markers for predicting response to such treatment. It was presumed that the effect of imatinib resulted from inhibition of phosphorylation of PDGFRB. However, clinical activity of imatinib in DFSP is striking even in DFSP expressing relatively low amounts of activated PDGFRB.[38,48] In our trials, we have not studied molecular changes during targeted therapy, but the high clinical benefit rate observed for imatinib in our patients supports the hypothesis of dependence of growth and viability of DFSP cells on aberrant activation of the imatinib-sensitive kinase PDGFRB. It seems that inhibition of low-level receptor tyrosine kinase activity may be effective clinically if tumor cells are dependent on that signaling mechanism. This paradigm may be also operational in

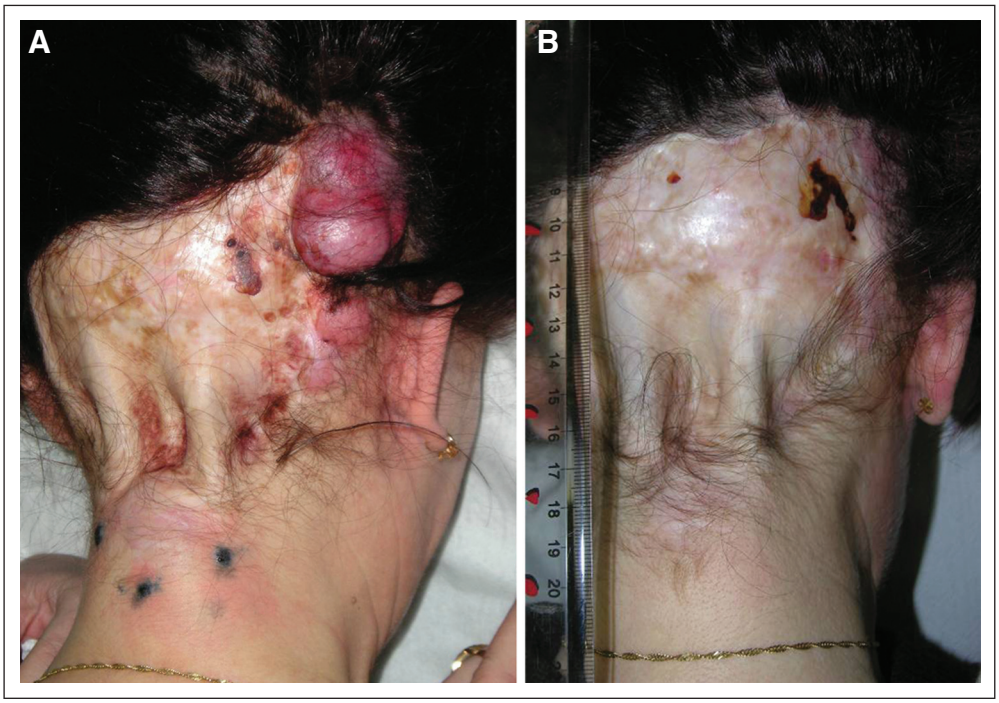

Fig 2. (A) Multiple, recurrent tumors of the scalp, and (B) clinical complete response maintained for more than 3 years on imatinib therapy.

pigmented villonodular synovitis/tenosynovial giant-cell tumor.[65,66] With a clearer understanding of the downstream effects of interactions of imatinib with PDGFRB in DFSP, additional treatment strategies may become evident.

In summary, we have confirmed that therapy with imatinib has profound antitumor effects in advanced DFSP harboring t(17;22), with an objective response rate approaching 50%, and that this therapy is also active in DFSP-FS. The efficacy of imatinib in DFSP seems to be discriminative, in part, to tumor retaining the translocation involving *COL1A1* and *PDGFB*. Although DFSP rarely presents as inoperable, imatinib is an effective treatment in such patients and may allow for complete resection of initially inoperable tumors. Because there was no obvious difference between response rates and TTP in patients receiving imatinib 400 mg versus 800 mg daily, 400 mg daily may be used as a starting dose.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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