Clinical Cancer Research

Efficacy of Imatinib in Aggressive Fibromatosis: Results of a Phase II Multicenter Sarcoma Alliance for Research through Collaboration (SARC) Trial

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Abstract

Purpose: Aggressive fibromatoses (AF; desmoid tumors) are rare clonal neoplastic proliferations of connective tissues that can be locally aggressive despite wide surgical resection and/or radiation therapy. The Sarcoma Alliance for Research through Collaboration (SARC) initiated a prospective phase II trial to investigate the outcome of patients treated with imatinib, a multiple tyrosine kinase inhibitor, in patients with AF, or 1 of 10 sarcoma subtypes. Here, we report specifically on the outcome of patients with AF as well as evaluations undertaken to examine the mechanism of imatinib.

Experimental Design: Patients ≥10 years old with desmoid tumors that were not curable by surgical management or in whom curative surgery would lead to undesirable functional impairment were eligible. Imatinib was prescribed at 300 mg twice daily [body surface area (BSA) ≥ 1.5 m^2], 200 mg twice daily (BSA = 1.0-1.49 m^2), or 100 mg twice daily (BSA < 1.0 m^2). Response outcomes at 2 and 4 months were assessed. Tissue specimens were analyzed by immunohistochemistry for expression of cKIT, platelet-derived growth factor receptor α (PDGFRα), PDGFRβ, AKT, PTEN, FKHR, and β-catenin. Tumor DNA was analyzed for *PDGFRα* exon 18 and *APC* mutations by allelic discrimination PCR.

Results: Fifty-one patients were enrolled. The median number of prior regimens was 1. Kaplan-Meier estimates of 2- and 4-month progression-free survival rates were 94% and 88%, respectively, and 1-year progression-free survival was 66%. Objective response rate was 6% (3 of 51). Expression and polymorphisms of target proteins were identified in tissue samples, but no significant correlation with outcome was observed using the samples available.

Conclusion: Imatinib may have a role in the management of unresectable or difficult to resect desmoid tumors. *Clin Cancer Res; 16(19); 4884–91. ©2010 AACR.*

Aggressive fibromatoses (AF; desmoid tumors) are clonal, neoplastic proliferations of connective tissues. They are rare tumors, occurring in two to four people per million, either sporadically or in association with Gardner's syndrome or familial adenomatous polyposis (FAP; refs. 1–5). Although benign by definition, their propensity to recur locally and invade nearby structures can result in significant morbidity.

The mainstay of therapy for desmoid tumors remains surgery. However, even with wide local excision, recurrence rates as high as 50% have been reported (6–9). Radiotherapy can be a useful primary treatment or complement to surgery, although its true role is unclear (10–12).

When AF recurs or is unresectable, systemic therapy can be effective in controlling disease. Unfortunately, due to the rarity of these tumors, the number of clinical trials done to evaluate the benefit of drugs is limited. The literature consists mainly of case reports, retrospective studies, and small phase II trials. Table 1 summarizes larger studies and case series of various therapeutic strategies for AF. Of note, the largest trial found in the literature to date consists of 30 patients, and no report conducted an independent radiologic review.

Following the Food and Drug Administration approval of the multireceptor tyrosine kinase inhibitor imatinib (Gleevec; Novartis Oncology) for gastrointestinal stromal tumors, Mace and colleagues reported two patients with unresectable AF treated with this agent. Because of progressive disease (PD) and symptoms, amputations were offered in both patients but were avoided due to dramatic responses to imatinib (13). The Sarcoma Alliance for Research through

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doi: 10.1158/1078-0432.CCR-10-1177

Translational Relevance

Because of the rarity as well as the heterogeneous clinical behavior, large prospective trials of aggressive fibromatosis (AF) have been difficult to perform. Based on the expression of platelet-derived growth factor (PDGFRα and PDGFRβ) and cKIT as well as smaller clinical reports, physicians have been using the multityrosine kinase inhibitor imatinib. This study describes the amount of benefit seen in a relatively large group of patients to provide the basis for the future use of imatinib in selected AF patients. This study evaluates some of the proposed mechanisms of action of the drug in these tumors (e.g., PDGFR inhibition) and encourages further investigation into the molecular rationale for this therapy. These findings provide the basis for another potential therapy for AF patients and for further molecular investigation.

Collaboration (SARC) investigators decided to add a subgroup of AF patients to an ongoing trial of imatinib in sarcoma, and here, we report the outcome of this group of patients only. Recognizing the challenges of imaging this disease, both local and central review of images was done as part of this study. Laboratory investigation of possible mechanisms of action was undertaken on available tissue specimens.

Materials and Methods

Patients

Patients >10 years old with a pathologically verified diagnosis of AF with locally advanced disease were eligible. Other key eligibility criteria included adequate hepatic function [as defined by a serum bilirubin ≤1.5 × the institutional upper limit of normal (ULN), and alanine aminotransferase and/or aspartate aminotransferase <2.5 × ULN], adequate bone marrow function (WBC count >2,500 cells/mm^3, hemoglobin >10 g/dL, platelet count >100,000/mm^3), and renal function (serum creatinine ≤1.5 × ULN). There was no limit on the number of previous therapies. The Institutional Review Board of each participating institution approved the protocol, and all patients were required to provide written informed consent.

Treatment plan

Patients were dosed according to body surface area (BSA). Patients with a BSA of ≥1.5 m^2 received 300 mg orally twice daily, BSA from 1.0 to 1.49 m^2 received 200 mg orally twice daily, and BSA of <1.0 m^2 received 100 mg orally twice daily.

Treatment evaluations and dose modifications

Pretreatment evaluation consisted of a history, examination, chemistries, urinalysis, pregnancy test if appropriate, complete blood cell count, and tumor-related imaging. Imaging was done every 8 weeks for 16 weeks and then

Table 1. Select larger case series and trials of systemic therapy in the treatment of AF

Author, year (reference)	Therapy	Patient population	No. patients	Outcome and response criteria
Azzarelli et al., 2001 (23)	Vinblastine/ methotrexate	Patients with primary or recurrent AF	30	12 PRs, 40% ORR (WHO criteria)
Constantinidou et al., 2009 (24)	Pegylated liposomal doxorubicin	Patients with progressive or recurrent AF	12	4 PRs, 36% ORR (RECIST)
Gega et al., 2006 (25)	Doxorubicin/dacarbazine + meloxicam	Patients with FAP and intra-abdominal AF	7	3 CRs, 4 PRs, 100% ORR (>50% decrease in the sum of products of perpendicular axes)
Hansmann et al., 2004 (26)	Tamoxifen or raloxifene (120 mg/d) + sulindac (300 mg/d)	Patients with AF not treated with prior systemic therapy	26	FAP-associated: 4 PR/CR >6 mo, 31% ORR; non–FAP-associated: 1 CR, 13% ORR (>25% reduction in product of perpendicular dimensions)
Heinrich et al., 2006 (22)	Imatinib (800 mg/d)	Patients with primary or metastatic AF	19	3 PRs, 16% ORR (SWOG response criteria)
Patel et al., 1993 (27)	Doxorubicin/dacarbazine	Patients with AF	12	2 CRs, 4 PRs, 67% ORR
Skapek et al., 2007 (28)	Vinblastine/methotrexate	Children with AF not amenable to surgery/ radiation	26	1 CR, 4 PRs, 19% ORR (>50% decrease in product of maximum perpendicular dimensions)
Tsukada et al., 1992 (29)	Sulindac (300 mg/d)	Patients with FAP with recurrent abdominal AF	14	1 CR, 7 PR, 57% ORR

Abbreviations: ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; SWOG, Southwest Oncology Group.

every 12 weeks. National Cancer Institute Common Terminology Criteria of Adverse Events version 2.0 was used to assess toxicity. Patients who experienced grade 3/4 toxicities or intolerable grade 2 toxicities related to drug had imatinib held and then restarted at a reduced dose by 200 mg/d.

Response assessment

Measurable disease was determined by summing the largest diameters of measurable lesions and was assessed at baseline and as above using the same modality. Confirmation of a response was obtained at least 4 weeks later using the same imaging technique. Complete response (CR) was disappearance of evident disease. Partial response (PR) was >30% shrinkage of unidimensional measurable disease and no evidence of progressive or new lesions. Stabilization of disease (SD) was a change in measurable disease too small to meet the requirement for PR or progression and no appearance of new lesions for at least 4 weeks. PD was an unequivocal increase of at least 30% or 3 cm (whichever was smaller) in measurable disease, worsening of evaluable disease, appearance of new lesions, reappearance of a prior lesion, or a significant deterioration in symptoms (unless the deterioration was clearly unrelated to the disease).

Radiology review

Images were retrospectively obtained when available and subjected to a secondary review by an expert local institution radiologist and by a central radiologist. The longest dimension of the tumor was recorded, as well as the cross-sectional dimensions of the largest perpendicular axis. The objective of this portion of the study was to see if local review was adequate for assessment of response, and whether additional central review would be different from conclusions made on local review.

Statistical considerations

The original clinical trial used a Bayesian hierarchical model (BHM) to analyze the various subtypes of sarcoma (14, 15). As AF is not a sarcoma, this group was not included in the BHM and outcomes are reported descriptively and independently. The primary endpoint was tumor response, referred to here as clinical benefit response (CBR), defined as CR or PR within 16 weeks, or SD lasting at least 16 weeks. A Bayesian beta-binomial model was assumed to estimate the CBR rate. The prior distribution was set up to match the estimates that were elicited from the investigators before initiation of the original trial. Specifically, based on the consensus of the SARC clinicians, at the start of the trial, the prior probability that the CBR rate would be >30% was 0.45 and thus a beta(0.5, 1) prior distribution was used. If the data obtained in the study showed that it was likely that the CBR rate was >30%, then the treatment would be considered active.

Laboratory evaluation

Available formalin-fixed, paraffin-embedded tissue blocks obtained from biopsy or resection material from AF patients on trial were obtained with patient consent.

Immunohistochemical staining

Immunohistochemistry was done on the DAKO Autostainer using 3,3′-diaminobenzidine as the chromogen. Deparaffinized sections of formalin-fixed, paraffin-embedded tissue blocks at 5-μm thickness were labeled with antibodies to KIT (DAKO), platelet-derived growth factor receptor α (PDGFRα; Santa Cruz Biotechnology), PDGFRβ (Santa Cruz Biotechnology), PTEN (Novocastra), phospho-AKT (Zymed), AKT, and phospho-FKHR (Cell Signaling). Appropriate negative (no primary antibody) and positive controls were stained in parallel with each set of tumors studied. The immunoreactivity was scored by a four-tier system, which assigns a score of 0 to negative immunoreactivity, 1+ to low or diffusely weak immunoreactivity, 2+ to focally strong immunoreactivity, and 3+ to diffusely strong immunopositivity, a modification of the three-tier grading scheme described by Wang et al. (16).

DNA preparation

Primary tumor tissue blocks were manually microdissected before nucleic acid extraction to ensure that each tumor sample contained at least 70% tumor cells. Genomic DNA was isolated using Nucleon DNA extraction and purification kit (Amersham Lifesciences).

PCR and sequencing

PCR primers to identify mutations within *KIT* (17), *PDGFRα*, *PDGFRβ*, *ck-ras* (18), *bRAF*, *TP53* (19), and *CTNNB1* (encoding β-catenin; ref. 20) were constructed. Reactions were done using Platinum PCR supermix (Invitrogen) and 200 nmol/L primers. After an initial denaturation and Taq DNA polymerase activation at 95°C for 10 minutes, templates were amplified for 35 cycles (94°C, 1 minute, annealing temperature for 1 minute, followed by chain extension at 72°C for 2 minutes), followed by a 10-minute extension at 72°C. PCR products were visualized on 2% agarose gels and purified using a Wizard SV PCR Clean-Up kit (Promega). Amplicons were sequenced directly in both directions using an ABI 377 DNA sequencer (Applied Biosystems). Chromatograms were downloaded directly to CodonCode Aligner software (v1.6.3), and the sequence was compared with reference sequences downloaded from the National Center for Biotechnology Information. All presumptive mutations were reamplified and resequenced from the original tumor DNA and compared with the catalog of somatic mutations in cancer (http://www.sanger.ac.uk/genetics/CGP/cosmic).

Results

Patient characteristics

Fifty-one patients were enrolled at five institutions from October 2002 to December 2005. All patients were assessable for response, and demographic information is summarized in Table 2. The median number of prior therapies was 1 (range, 0-4), and the median age was 34 (range, 12-67). Eight patients carried a known diagnosis of FAP, and 17 patients had multifocal desmoids. Only one patient's tumor was associated with pregnancy.

Table 2. Patient demographics

Characteristic	No. patients
Sex	
Male	14
Female	37
Race	
White	39
Black	9
American Indian or Alaskan Native	1
Asian	1
Other	1
Site of tumor	
Head or neck	5
Abdominal/retroperitoneal	8
Upper extremity	8
Lower extremity	11
Pelvic	2
Trunk	17
Prior radiation therapy	
Yes	17
No	34
Prior surgery	
Yes	40
No	11
Known FAP	
Yes	8
No	43
Multifocal AF	
Yes	17
No	34

Patient outcomes

After 2 months of imatinib treatment, 94% of patients (48 of 51) had SD. At 4 months, 84% of patients (43 of 51) had SD, 5 patients had PD, and 3 patients were not evaluable. Thus, the CBR was 84%. The reasons for patients going off study included progression (n = 19), withdrew consent (n = 13), toxicity (n = 5), noncompliance (n = 3), and lost to follow-up (n = 2).

A plot of the Kaplan-Meier estimates of progression-free survival (PFS) with 95% confidence intervals is provided in Fig. 1. With the available follow-up, the median PFS cannot be estimated. However, the PFS at 2 months, 4 months, 1 year, and 3 years is 94%, 88%, 66%, and 58%, respectively. Five patients remained progression-free after 4+ years of treatment.

Three patients were noted to have a confirmed PR while on study (5.9%). Responses were achieved after 19, 22, and 26 months of treatment. None of the three patients carried a diagnosis of FAP. Figure 2 provides a waterfall plot of the best response in the largest tumor of all patients according to measurements provided by the local reviewer.

Given the observed 43 of 51 CBR rate and the beta(0.5, 1) prior distribution, the resulting posterior distribution is a beta(43.5, 52). Figure 3 provides a plot of the prior (dashed line) and the posterior (solid line) distributions for the CBR rate. The enhancement of the knowledge about the CBR provided by trial data is evident in the figure, which shows that the posterior distribution for the CBR rate is much less variable than the prior distribution. The posterior probability that the CBR rate is >30% is 0.999. That is, it is very likely that the treatment has at least a 30% response rate and the estimated CBR rate is 84%.

Toxicity

In general, imatinib was well tolerated with expected toxicities. Grade 3/4 events occurring with a frequency of >5% included neutropenia (n = 5), rash (n = 5), and fatigue (n = 4). There were no deaths on study, and one patient became pregnant while on study. Seventeen patients were dose reduced by one level (imatinib, 400 mg/d), and three patients were dose reduced by two levels (imatinib, 200 mg/d). Of the 11 patients who remained on study over 2 years, 7 patients were dose reduced by one level.

Laboratory evaluation

Twenty patients had tumor tissue available for ancillary study evaluation. In tested samples, any level of immunohistochemical positivity (1-3+) was seen using the following stains: cKIT (one of seven), PDGFRα (seven of seven), PDGFRβ (seven of seven), AKT (three of seven), phospho-AKT (one of three), PTEN (four of seven), phospho-FKHR (four of five), and β-catenin (five of seven). Mutational analysis of *PDGFRα* exons 12/14/18, *PDGFRβ* exons 11/12/17/18, and *KIT* exons 9/11/13/17 did not reveal any significant findings, except for one deletion in *PDGFRα* exon 12 and two deletions in *PDGFRβ* exon 12. Mutational analysis of *KIT* exon 10 revealed that 2 of 19 specimens sequenced had a single-nucleotide polymorphism. Seven of 19 specimens possessed a single-nucleotide polymorphism in β-catenin in the area responsible for glycogen synthase kinase 3b regulatory domain, similar to mutations seen in Gardner's syndrome. None of the laboratory findings showed any significant correlation with outcome or response that was detectable with the small number of samples available.

Imaging

Patient outcomes were based on investigator report. A local radiologist at each treating institution with expertise in the imaging of AF did a retrospective evaluation of patient imaging. When possible, a second review was done by a radiologist at a different institution. Forty-eight patients had images available for local review, and 35 were reviewed a second time. Twenty tumors were imaged using computed tomography scan, 27 tumors with magnetic resonance imaging, and 1 tumor with ultrasound.

Using a paired t test to compare the local and central review, there was a significant difference in the baseline measurement (P = 0.007) and at the 4-month follow-up (P = 0.011). However, the percent change, which is used to determine CBR, was not significantly different (P = 0.24). Figure 4 provides a graph of the percent change

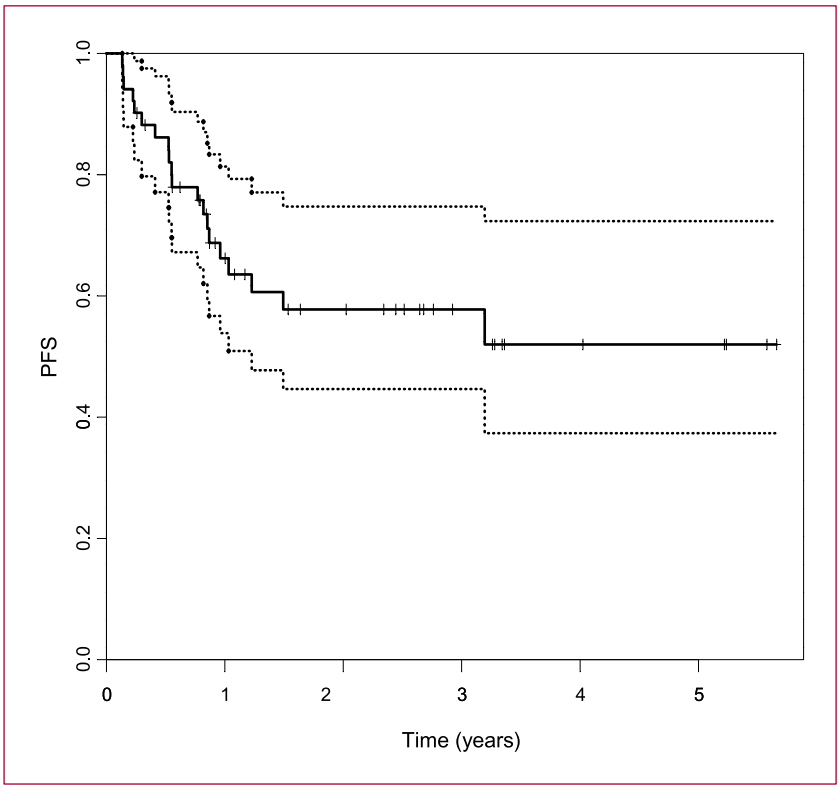

Fig. 1. Kaplan-Meier curves for PFS. Dashed lines represent the 95% confidence interval.

from baseline to 4 months for the central and local review. The dashed line represents perfect agreement between central and local review. The largest discrepancy between local and central review was the patient on the far right of Fig. 4, where the local reviewer measured the tumor as having a 3% decrease and the central reviewer measured a 66% increase. On re-review of these images, the difference in interpretation was in a potential area of artifact on hard copy images. This was the only patient that local and central reviewers would have scored differently in terms of CBR.

Discussion

The natural history of AF is highly variable and unpredictable. Spontaneous regressions (particularly in

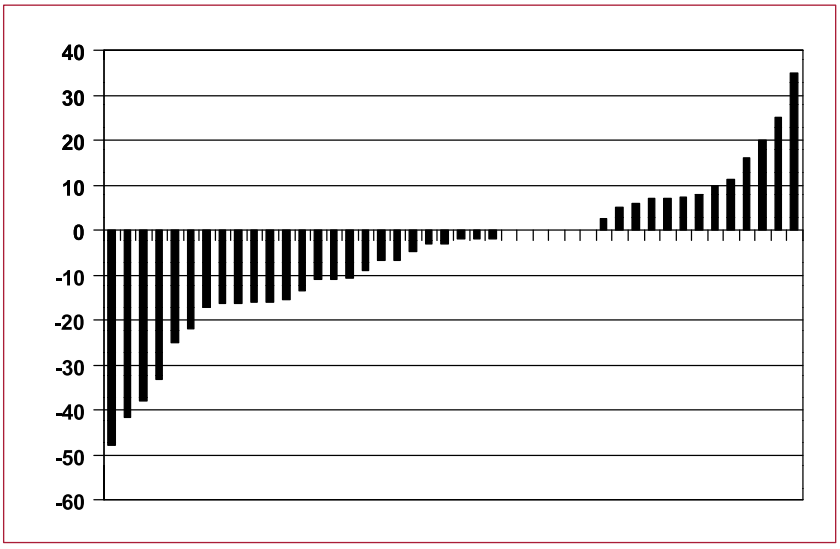

Fig. 2. Best response in longest tumor dimension. Each vertical line represents the best response in a single patient's largest tumor by percentage change from baseline. Measurements were taken from local reviewer interpretation.

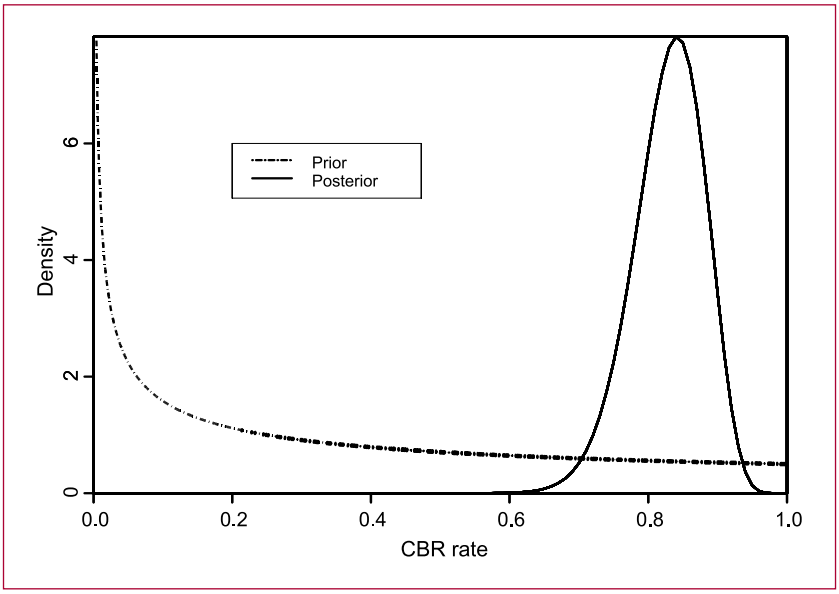

Fig. 3. Prior (dashed) and posterior (solid) density for the CBR rate *P*. The prior Pr($P > 0.3$) = 0.45, and after observing the data in the trial, Pr($P > 0.3$ | data) = 0.999.

pregnancy-associated AF), stability, slow persistent growth, and rapid, rarely fatal progression have all been observed in this "benign" tumor. Similar to other slow-growing neoplasms, unresectable AF often becomes a chronic disease. Thus, it is desirable to have multiple less toxic options for treatment, particularly in the case of primary or secondary tumor resistance or patient intolerance to therapy.

In this phase II trial, imatinib showed efficacy in some patients with AF. Although only three PRs were observed, other patients had minor shrinkage or stability of disease. Nine patients remained progression-free on study for >3 years. Interestingly, patients whose tumors did qualify as having a PR by standard criteria were on treatment from 19 to 26 months before the threshold for response was observed.

The primary endpoint of this study was CBR (CR or PR within 16 weeks or SD for over 16 weeks). In retrospect, given the often indolent growth of AF, the more relevant parameters that are reported here include response rate and PFS rates at longer time intervals. The primary endpoint was chosen as part of the parent study of imatinib in advanced sarcomas. SD at the 16-week time point is more meaningful and is less likely to be achieved without an active therapy in advanced sarcomas compared with AF.

The results of this trial are similar to other studies of imatinib in AF. Heinrich et al. reported a 10% response rate

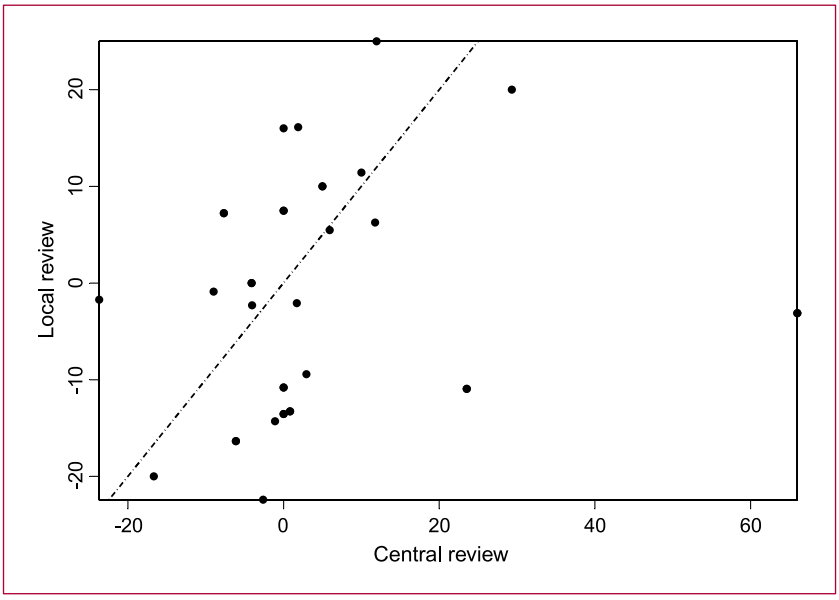

Fig. 4. Plot of percent change from baseline to 4 mo by local and central radiologic review. The dashed line represents the local review equal to central review.

and a 40% stability rate with a median time to progression of 9.1 months (range, 2.9-17) in 20 patients with AF treated with imatinib as part of a larger study of patients with 40 different malignancies. Dufresne et al. reported the preliminary results of a 40-patient trial of imatinib in the treatment of patients with AF in abstract form. Two responders (5%) were identified, and the 2-year PFS rate was 55% at last report (21).

Given the variable natural history of patients with this disease, it is difficult to judge how efficacious imatinib was in patients with SD on treatment, which even prompted some patients and investigators to discontinue imatinib therapy without other therapy. Documentation of progression was not required before study enrollment. Given the variable behavior observed in this disease, and the endpoint of PFS, this is an obvious weakness of the study.

Imatinib is a selective receptor tyrosine kinase inhibitor, which is known to inhibit the Abl, PDGFR, KIT, and ARG tyrosine kinases. Early demonstration of the efficacy of imatinib in AF was thought perhaps related to KIT or PDGFR activation as shown by overexpression by immunohistochemistry. Other pathways that have been investigated include the *PDGFRβ* pathway (22) and *KIT* exon 10 mutations (21). No clear correlation with immunohistochemical or mutational analysis of several candidate molecules was observed in this study. Laboratory studies were done on paraffin-embedded tissue, and only a very small proportion of tissues were available for study. Mandatory tissue evaluation should be considered a priority in future investigations to gain more useful information.

Even compared with many malignant connective tissue tumors, AF imaging interpretation is inherently difficult, as these tumors often do not uniformly grow as a well-circumscribed mass but may extend obliquely through tissue planes. In addition, changes seen in these tumors are often minimal and occur over a long interval of time. In only one case, a discrepancy between local and central review was found to be clinically significant. The differences in measurements may have occurred because different radiologists measured a different axis in the tumor or there was a difference in interpretation of edema versus tumor. Differences seemed to be most apparent when hard copy images were only available for review compared with electronic images. Allowing the same radiologist the opportunity to review tumor imaging electronically, when available, at multiple time points seems to afford the most consistent interpretation and seems to be the best strategy. Regardless, although the imaging of AF is clearly challenging, the addition of central review does not seem to have a significant benefit.

In summary, although the response rate of AF to imatinib is low, the toxicity profile is favorable and some patients had prolonged PFS. Given the variable behavior of AF and our choice of PFS as an endpoint, it is difficult to determine the true benefit of imatinib in patients with AF. The sequencing of imatinib relative to other systemic treatments for AF, which may be associated with higher response rates at the expense of more toxicity, is also debatable. For patients who fail or refuse hormonal or low-dose chemotherapy treatment for AF, it may be reasonable to consider imatinib therapy. For patients in need of rapid shrinkage of their tumor due to disabling symptoms or impending loss of limb or organ damage, aggressive chemotherapy may be preferable. Nevertheless, imatinib is another therapy that should now be included in our armamentarium for use in advanced, recurrent AF.

Disclosure of Potential Conflicts of Interest

R. Chugh, S.M. Schuetze, D.A. Priebat, and B.L. Samuels: commercial research support, Novartis; S.R. Patel, R.G. Maki, S.M. Schuetze, and D.A. Priebat: honoraria from speakers bureau, Novartis; S.M. Schuetze: honoraria from speakers bureau, SARC; R. Chugh: consultant/advisory board (salary support, no direct compensation), SARC; R.G. Maki, D.A. Priebat, and R.S. Benjamin: consultant/advisory board, Novartis.

Grant Support

Novartis Pharmaceuticals.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 05/20/2010; revised 08/05/2010; accepted 08/09/2010.

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