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Phase II prospective study with sorafenib in advanced soft tissue sarcomas after anthracycline-based therapy

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Introduction: We investigated the activity and safety of sorafenib, a multitargeted tyrosine-kinase inhibitor, in patients with advanced soft tissue sarcomas (STS).
Patients and methods: An open-label nonrandomised multicentre phase II study was conducted in advanced STS patients pre-treated with anthracycline-based chemotherapy. Patients received sorafenib 400 mg twice daily for 28 days. The primary end point was the progression-free survival (PFS) rate at 6 months. Toxicity was assessed. Clinical outcomes were evaluated in all histologies and in leiomyosarcoma (L) and angiovascular sarcomas (A).
Results: Between November 2006 and January 2010, 101 patients (36 L, 19 A, and 46 others) were enrolled; 76 patients per-protocol (PP) and 100 per intention-to-treat (ITT) were assessable for the primary end point. In the PP analysis, 11 (14.5%) achieved partial response and 25 (32.9%) stable disease; 6-month PFS rates were all histologies, 34.5%; L, 38.4%; and A, 56.3%. In the ITT analysis, 6-month PFS results were 27.1, 35, and 35.5% in all histologies, L, and A, respectively. When stratified by histology, we observed a better PFS favouring leiomyosarcoma versus other histologies ($P = 0.033$). Treatment was well tolerated.
Conclusions: Sorafenib appears to be a promising option in leiomyosarcoma patients. This finding warrants further evaluation in histology-driven trials.
Key words: angiosarcoma, leiomyosarcoma, soft tissue sarcoma, sorafenib, vascular sarcoma

introduction

Soft tissue sarcomas (STS) are rare heterogeneous mesenchymal neoplasms, accounting for <1% of adult malignancies, with a median survival of ∼1 year. Several studies have been conducted to find an effective systemic therapy, but currently the number of active drugs is very limited. Results of phase II trials with single or combined regimens, including second- and third-generation agents, showed objective response rates of ∼16%–36% [1–3].

Recent advances in the knowledge of molecular characteristics and the prognosis of STS [4, 5] and the

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development of targeted therapies such as imatinib, sunitinib, Cediranib, and crizotinib may lead to better outcomes by long-term control of the disease [6–17]. Sorafenib is one of the most promising multitarget tyrosine-kinase inhibitors, as reported in preclinical and clinical trials [18–22]. It inhibits tumour cell proliferation and angiogenesis by targeting Raf, vascular endothelial growth factor receptor 2 and 3, and platelet-derived growth factor receptor-β. Therefore in 2006, concomitantly with the study by Maki et al. [23], we started a phase II trial with sorafenib in metastatic STS refractory to anthracycline-based therapy, with particular attention to the leiomyosarcoma and angiovascular subtypes.

patients and methods

study design

This was a prospective multicentre open-label nonrandomised phase II trial conducted to evaluate the activity of sorafenib in metastatic STS patients. Beginning in November 2006, patients with progressive STS after an adjuvant and/or first-line anthracycline-based regimen were enrolled. Previous therapy with a Raf-kinase, MEK, or farnesyl transferase inhibitor was an exclusion criterion. Eligible patients were at least 18 years old and had histologically confirmed advanced or metastatic STS with at least one measurable unidimensional target lesion (according to the Response Evaluation Criteria in Solid Tumors [RECIST]), an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤2, a life expectancy of 12 weeks or more, and adequate laboratory parameters. Written informed consent was obtained from all patients. Participating centres received ethics committee and institutional review board approval. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. In 2009, during the recruiting phase of the study and because of the positive results published by Maki et al. [23] on leiomyosarcomas and angiovascular sarcomas, the protocol was extended exclusively to these two histologies to obtain an adequate sample size and confirm these data in our population.

Patients received sorafenib 400 mg orally twice daily on a continuous basis until disease progression, unacceptable toxicity, physician's decision, or withdrawal of patient consent. Every 3 weeks, biochemical and clinical evaluation (with blood pressure measurement using a manual sphygmomanometer) was carried out, and safety and drug accountability were monitored. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0.

Radiologic tumour assessment was carried out at screening (within 28 days before the start of treatment), every 12 weeks, and at 30 days after treatment end. Tumour responses were assessed according to the RECIST criteria (Version 1.0). Every 12 weeks, patients with stable disease and patients classified as responders continued sorafenib until disease progression, death, toxicity, consent withdrawal, or they were lost to follow-up. At the discretion of the investigator, patients with progressive disease could continue treatment, in case of clinical evidence of benefit.

According to the criteria by Van Glabbeke et al. [24], the primary end point was the activity of sorafenib in terms of the progression-free survival (PFS) rate at 6 months, although with an arbitrarily defined higher cut-off (40%) within a biologic therapy setting. To have more clinically relevant results, the cut-off of 40% at 3 months was delayed at 6 months. Secondary end points were overall response rate, overall survival (OS), and toxicity. Patients were considered eligible for analysis if they had received at least 30 days of treatment.

statistical methods

The original study design was planned to enrol STS patients regardless of histotype. During the accrual phase, some studies reported different clinical outcomes in a few histologic STS subtypes, with a greater benefit in patients with angiovascular sarcoma and leiomyosarcoma. On the basis of these considerations, we amended the protocol to obtain an adequate sample size of leiomyosarcomas and angiovascular sarcomas to assess the primary end point separately. A Fleming-Hern single-stage study design for phase II clinical trials was used. Considering an α error of 0.10 and a power of 0.90, it was assumed that a 6-month PFS rate of ≥40%would be of definite clinical value; a PFS rate of ≤25% would indicate the drug should be considered clinically irrelevant. If 10 or more of 30 patients were progression free at 6 months in each histologic subgroup, the hypothesis of inactivity of the treatment would be rejected.

All analyses were carried out assessing all patients who either started treatment with sorafenib (intention to treat [ITT]) or were treated for at least 30 days (per-protocol [PP]). All data were described by descriptive statistics, as numbers and percentages for categorical data, or as median and range for continuous data.

Overall disease control rate was assessed as the proportion of patients who had a complete response, a partial response (PR), or stable disease (SD) as the best response. PFS was defined as the time between the beginning of therapy and disease progression or death, whichever occurred first, or the last visit date for patients alive and disease free. OS was measured from the date of the beginning of therapy until the date of death or last contact date for patients alive. Survival curves for PFS and OS were computed using a Kaplan–Meier analysis. A P value <0.05 was considered the limit of statistical significance for all secondary evaluations. All statistical analyses were carried out using R Package Version 2.0.

Table 1. Baseline patient characteristics

Characteristics	*N* of patients
Patients enrolled	101
Screening failure	1
Assessable patients	100
Histology	
Leiomyosarcoma	35
Angio-/vascular sarcoma	19
Other histologies	46
Fibrosarcoma	5
Liposarcoma	11
MPNST	3
Epithelioid sarcoma	3
Synovial sarcoma	7
Not otherwise specified (NOS)	16
Age median (range), years	54 (21–86)
Gender	
Female	54
Male	46
ECOG performance status	
0	53
1	38
2	9
Prior chemotherapy	
1 line	40
2 lines	23
3 lines	37

MPNST, malignancy peripheral nerve sheath tumor.

results

patient characteristics

Between November 2006 and January 2010, 101 advanced STS patients were accrued in the study. One leiomyosarcoma patient was found to be ineligible (screening failure). Thus, 100 patients were assessable for survival in an ITT analysis, and 76 patients who received sorafenib for at least 30 days were assessable in a PP analysis. Table 1 and Figure 1 summarise the patient characteristics. Of the 100 ITT patients, the leiomyosarcoma group included 35 patients and the angiovascular sarcoma group included 19 patients. For the latter, the expected sample size of 30 patients was not reached due to slow accrual and premature closure of the study. Other histologies (46 patients) were fibrosarcoma, liposarcoma, malignant peripheral nerve sheath tumour, epithelioid sarcoma, and synovial sarcoma. Median age was 54 (range: 21–86) years. Median ECOG PS was 1 (range: 0–2). Nearly a third of all patients had received at least three chemotherapy lines before sorafenib treatment.

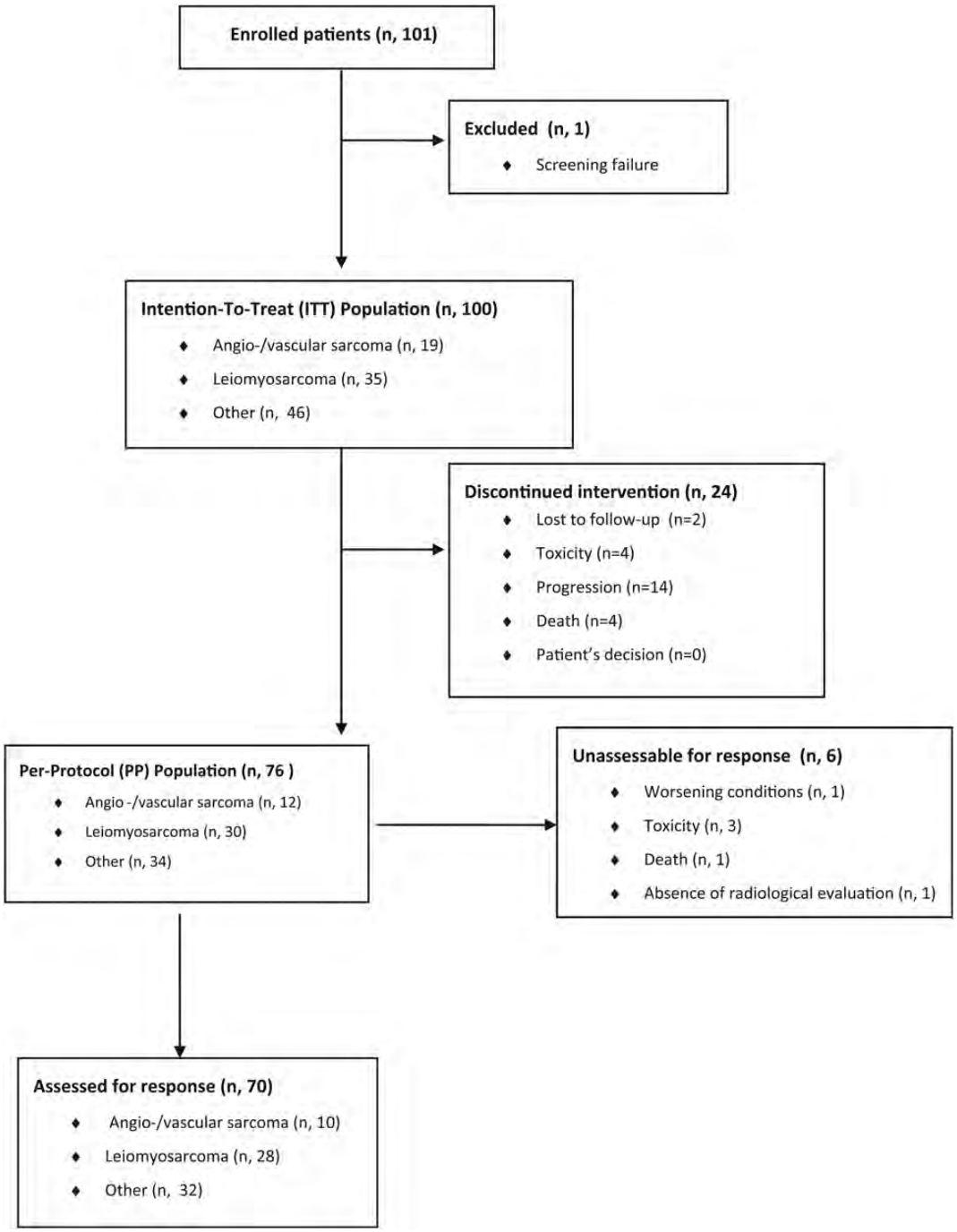

Figure 1. CONSORT flow diagram for STS patients enrolled in the study.

tumour response

Of the 76 PP patients, 11 (14.5%) presented PR, 25 SD (32.9%), and 34 progressive disease (PD) (48.6%); 6 patients (4%) were not assessed for response (clinical deterioration: 1; toxicity: 3; death: 1; absence of radiologic evaluation: 1). In the leiomyosarcoma group, 2 patients (6.7%) presented PR, 15 SD (50%), and 11 PD (36.7%); 2 patients (6.7%) were not assessed. In the angiovascular sarcoma group, 4 patients (33.3%) presented PR, 4 SD (33.3%), and 2 PD (16.7%); 2 patients (16.7%) were not assessable. Finally, in all the other histologies, 5 patients (14.7%) presented PR (2 with fibrosarcoma, 2 with synovial sarcoma, and 1 not otherwise specified), 6 SD (17.6%), and 21 PD (61.8%); 2 patients (5.9%) were not assessed.

survival analysis

per-protocol analysis

In the 76 analysed patients, we observed a 6-month PFS of 34.5%, with median PFS and OS of 4.2 and 11.9 months, respectively. Thus, the primary end point was not reached in the entire population, regardless of histologic type (Figure 2A and B; Table 4).

Considering histologic subtypes, leiomyosarcoma patients achieved a 6-month PFS rate of 38.4% (Table 2). In particular, the primary end point was achieved in the leiomyosarcoma group with 10 of 30 patients achieving PFS at 6 months. However, in the angiovascular sarcoma patients, the primary end point was not met (5 of 12 patients were progression free at 6 months), mainly due to the incomplete recruitment. There were no statistically significant differences among the histologic subgroups in median PFS and OS ($P = 0.145$ and $P = 0.351$). The number of prior therapies did not influence the likelihood of achieving long-term PFS and OS (Table 2).

intention-to-treat analysis

The results according to ITT analysis on all series of 100 patients were mostly superimposable on those of the PP analysis. The 6-month PFS rate was 27.1%, with median PFS and OS of 2.8 and 10.2 months, respectively. The 6-month PFS in leiomyosarcoma was 35% with a median PFS and OS of 4.9 and 12.5 months, respectively. As shown in Figure 2C and D, a statistically significant benefit was observed in PFS favouring the leiomyosarcoma group ($P = 0.033$) compared with the other histologies. However, this trend did not reach statistical significance in OS analysis ($P = 0.103$).

safety

A total of 100 patients were assessable for adverse events. Toxicity data are shown in Table 3. The most frequently reported side-effects were skin toxicity (42%), fatigue (39%), anorexia (31%), hand-foot skin reaction (28%), and diarrhoea (27%). Most of the reported events were of grade 1 or 2 severity. Grade 3 or higher adverse events included diarrhoea (7%), fatigue (5%), hand-foot syndrome (4%), rash (4%), anorexia (2%), emesis (2%), hypophosphataemia (1%), and

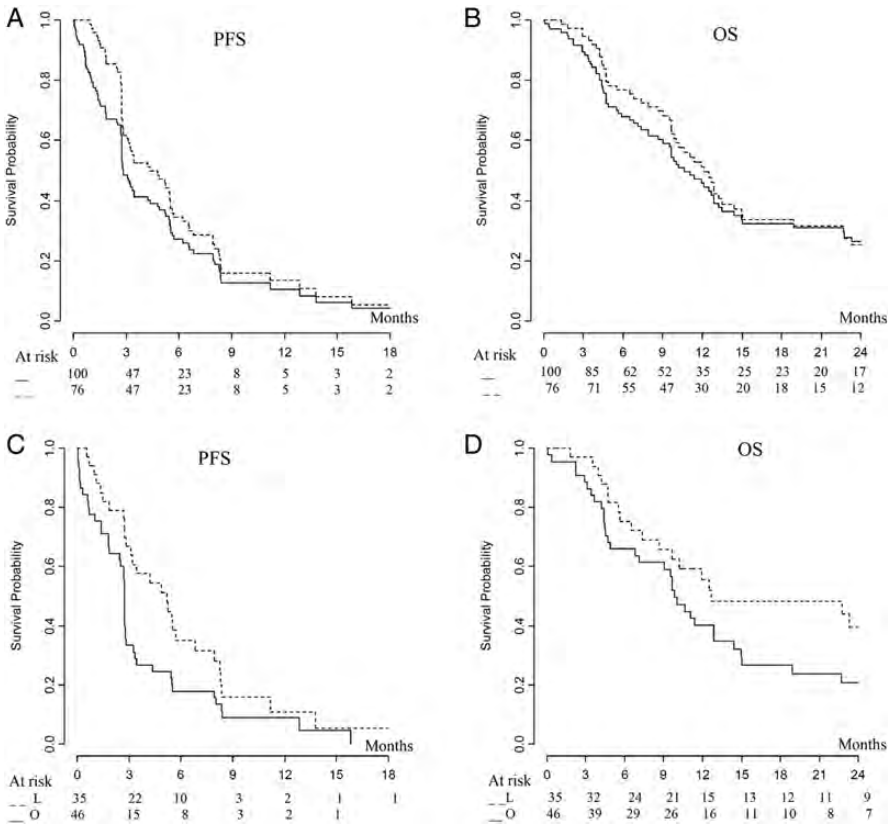

Figure 2. Progression-free survival (A and C) and overall survival (B and D) of the entire population according to PP (dashed line) and ITT (continuous line) analysis and of patients with leiomyosarcoma (L) and advanced soft tissue sarcoma of other histologies (O) receiving sorafenib.

Table 2. Primary end point evaluation and survival data in STS patients according to histology and previous treatment in the ITT (enrolled) and PP (assessable) population[a,b]

	6-mPFS		mPFS		mOS	
	ITT	PP	ITT	PP	ITT	PP
HISTOLOGY						
Angio-/vascular sarcoma	35.5[c]	56.3[c]	1.5	5.6	5.9	12.2
Leiomyosarcoma	35	38.4	4.9	5.2	12.5	12.5
Other	–	–	2.7	2.8	9.6	10.1
P-value	*na*	*na*	*0.033*[d]	*0.145*	*0.119*	*0.351*
CT LINES						
1	–	–	3.2	4.7	10.0	12.2
2	–	–	2.7	2.7	9.5	9.5
≥3	–	–	2.7	3.4	10.2	10.6
P-value	*na*	*na*	*0.654*	*0.497*	*0.883*	*0.397*

[a]ITT, intention-to-treat population (*n*, 100), constituted by 19 angio-/vascular sarcoma, 35 leiomyosarcoma, 46 patients of other histologies.
[b]PP, per-protocol population (*n*, 76): 12 angio-/vascular sarcoma, 30 leiomyosarcoma, 34 other.
[c]Actuarial value (inadequate recruitment).
[d]Refers to leiomyosarcoma versus other histologies comparison.
6-mPFS, 6-month PFS rate; mPFS, median PFS; mOS, median OS; na, not applicable. CT lines, previous chemotherapy lines.

Table 3. Incidence and severity of adverse events in patients with advanced or metastatic soft tissue sarcomas receiving sorafenib 400 mg twice daily

Adverse events	Grade, *N*				Total, *N*
N = 100 patients starting treatment	1	2	3	4	
Alopecia	11	2	0	0	13
Anorexia	21	8	2	0	31
Fatigue	21	13	5	0	39
Hand-foot Syndrome	13	11	4	0	28
Hypertension	4	3	0	0	7
Hypophosphataemia	13	1	1	0	15
Myalgia	6	3	0	1	10
Nausea and vomiting	5	5	2	0	12
Skin toxicity	26	12	4	0	42
Diarrhea	13	7	7	0	27

myalgia (1%). Four patients (4%) had first dose reduction, 12 (12%) a second dose reduction, and 3 (3%) a third one.

discussion

STS is a malignancy cluster of >50 histologic subtypes, each one with a distinct underlying biology, natural history, and response to treatment. Overall, STS responds poorly to chemotherapy. Following initial experiences with antiangiogenic agents in STS (sunitinib, imatinib, and bevacizumab), we conducted a phase II study to evaluate the activity of sorafenib. We began by recruiting all STS histologies. Because of the positive results published by Maki et al. on angiovascular sarcoma and leiomyosarcoma, we extended the protocol to these two more responsive histologies [25].

At the best RECIST response, we observed PRs in leiomyosarcoma (two patients) and angiovascular sarcoma (four patients), but also in fibrosarcoma (two patients) and synovial sarcoma (two patients) [26] with an overall disease control rate (PR plus SD) of 47.4% in both the PP and ITT analyses.

In the leiomyosarcoma group, the primary end point was achieved, confirming the activity of sorafenib in this subset of patients. By contrast, sample size of the angiovascular sarcoma subgroup was too small (12 patients) to define conclusive results. Nonetheless, our results are in line with previous studies [23, 27] showing that sorafenib works in specific histotypes (Table 4). Maki et al. reported a 6-month PFS rate of 31% in 40 angiovascular sarcoma patients, but the French Sarcoma Group recently demonstrated that sorafenib has a limited antitumour activity in this histotype (6- and 9-month PFS rates of 16% and 3.3%, respectively, in 41 patients), with short-term tumour control.

Considering the relatively high number of patients (24 patients) not assessable according to the protocol for inadequate drug intake, we carried out an ITT analysis to more completely understand the therapeutic implications of sorafenib in clinical practice. The ITT analysis underlined the superior efficacy of sorafenib in leiomyosarcomas relative to the other histologies ($P = 0.033$). A disappointing result was observed for median PFS and OS in the angiovascular sarcoma group, probably due to either the limited sample size or the delivery of suboptimal treatment (<30 days) in 37% of patients.

Of note, the outcome did not seem to be related to the number of previous chemotherapy lines. As a matter of fact, although almost half of our patients had received at least three chemotherapy lines, there was no significant between-group difference in PFS and OS.

Like other biologic agents, sorafenib demonstrated a good safety profile with few G3–G4 adverse events, but with continuous G1–G2 toxicity in most patients. For instance,

Table 4. Survival and response data compared with Maki's results (per-protocol analysis)

Outcome measures	All patients		Leiomyosarcoma		Angio-/vascular sarcoma	
	Maki et al.	Santoro et al.	Maki et al.	Santoro et al.	Maki et al.	Santoro et al.
Patients, *n*	122	76	37	30	37	12
6-mPFS, %	22	34.5	30	38.4	31	56.3
mPFS, months	3.2	4.2	3.2	5.2	3.8	5.6
mOS, months	14.3	11.9	22.4	12.5	14.9	12.2
ORR, %	5	14.5	3	6.7	13.5	33.3
DCR, %	56	47.4	51.3	56.7	70	66.7
CR, *n*	1	0	0	0	1	0
PR, *n*	5	11	1	2	4	4
SD, *n*	62	25	18	15	21	4

n, number; 6-mPFS, 6-month progression-free survival; mPFS, median PFS; mOS, median OS; ORR; overall response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

many patients reported anorexia, fatigue, diarrhoea, and weight loss, with a significant impact on the quality of everyday life. Nevertheless, no major toxic effects or toxic deaths were observed [28, 29].

conclusions

The dismal prognosis of advanced STS patients and the poor results achievable with standard chemotherapy strongly suggest the need for developing new drugs and strategies to improve their final outcome. The positive clinical results of sorafenib therapy with its acceptable toxicity profile could represent an appealing treatment alternative at least in some STS histotypes.

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