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Sorafenib in patients with locally advanced and metastatic chordomas: a phase II trial of the French Sarcoma Group (GSF/GETO)[†]

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Background: There is no consensual treatment of locally advanced or metastatic chordomas.

Patients and methods: We conducted a multicenter, open-label, uncontrolled phase II trial of sorafenib (800 mg/day). The primary end point was the 9-month progression-free rate according to RECIST 1.1. All patients had documented progressive disease at the time of study entry.

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Results: Twenty-seven patients were enrolled between May 2011 and January 2014. The median age was 64 (range, 30–86) years. There were 17 men and 10 women. Twelve patients had been previously treated with chemotherapy and molecularly targeted agents. The maximum toxicity grade per patient was grade 3 in 21 cases (77.8%) and grade 4 in 4 cases (14.8%). Sorafenib provided an intent-to-treat best objective response of 1/27 [3.7%; 95% confidence interval (CI) 0.1% to 19.0%], a 9-month progression-free rate of 73.0% (95% CI 46.1–88.0) and a 12-month overall survival rate of 86.5% (95% CI 55.8–96.5). Survival curves were similar in pretreated and not pretreated patients.

Discussion: Additional clinical trials further exploring sorafenib as a treatment of locally advanced or metastatic chordomas are warranted.

Key words: sorafenib, phase II trial, chordoma

introduction

Chordomas are rare primary bone tumors with an incidence of <1 case per million inhabitants. The peak incidence is between 50 and 60 years. The distribution of primary locations is approximately one-third of cases in the skull base, one-third in the mobile spine and one-third in the sacrum [1].

Chordomas are slow-growing tumors but are invasive, spreading between the neural structure and the axial skeleton. At the time of diagnosis, the tumor burden is usually important, making the management of the tumor challenging [1–3]. Large en bloc resection remains the cornerstone of treatment, but this surgery can be deleterious. Adjuvant radiotherapy is largely used to manage chordomas. However, the role and the appropriate technique (intensity-modulated radiation therapy and stereotaxic therapies, both of which use conventional protons, or hadron therapies) are uncertain [2, 4].

Nevertheless, curative-intent surgery is feasible for <50% of sacral chordomas and even fewer clival chordomas. Local relapse and metastatic relapse are frequent. As a consequence, medical treatment of locally advanced or metastatic chordomas is frequently discussed. Chemotherapy is regarded as an inappropriate option [1]. In recent decades, evidence for the use of molecularly targeted therapies has resulted from several phase II trials [5].

Chordomas inconstantly express some actionable targets, mainly stem-cell factor receptor (c-KIT), platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), receptor tyrosine-protein kinase erbB-2 (HER2/neu) and epidermal growth factor receptor (EGFR) [1, 6, 7]. Li et al. [8] and Chen et al. [9] found high levels of VEGF expression in 71% (25/35) and 77.8% (28/36) of chordomas, respectively.

Sorafenib (NSC 724772, BAY 43-9006, Nexavar; Onyx Pharmaceuticals, Inc., Everyville, CA; Bayer Healthcare Pharmaceuticals, Inc., Wayne, NJ) potentially inhibits some actionable targets expressed by chordomas. In *in vitro* biochemical assays, sorafenib potently inhibits the proangiogenic vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3 and PDGFR-β) tyrosine kinases. In cellular assays, sorafenib inhibits the VEGF-mediated autophosphorylation of VEGFR-2 (human endothelial cells and NIH 3T3 fibroblasts expressing VEGFR-2) and VEGFR-3, as well as PDGF-mediated autophosphorylation of PDGFR-β in HAoSMCs [10, 11]. Sorafenib has also demonstrated activity against the human SKOV-3 ovarian tumor cell line with overexpression of EGFR and HER2/neu [10, 11].

For these reasons, sorafenib was considered a logical candidate for the treatment of chordomas.

patients and methods

study population and eligibility criteria

Patients considered for this study were required to be 18 years of age and older. All had histologically proven metastatic or locally advanced chordoma not amenable to radiotherapy or curative-intent surgery after multidisciplinary decision making. Prior systemic treatment of chordoma was allowed. Disease that was measurable or assessable by computed tomography scanning was required, as per RECIST 1.1 guidelines [12]. Additional key eligibility criteria were as follows: at least one lesion measurable according to RECIST 1.1; evidence of progression at the time of study entry; no brain or meningeal metastasis; no >2 prior lines of systemic treatment (whatever the indication); WHO performance status ≤2; WBC ≥3000/mm; platelet count ≥100 000/mm^3; hemoglobin ≥9 g/dl; INR and aPTT ≤1.5 times the upper limit of normal (ULN); liver transaminases ≤1.5×ULN; total bilirubin ≤1.5×ULN; serum creatinine ≤1.5×ULN and amylase and lipase ≤1.5×ULN.

treatment

Patients orally received a starting 400 mg dose of sorafenib twice daily for 9 months or until intolerable toxicity occurred, the tumor progressed or the patient withdrew the informed consent. Dose reduction to 400 mg orally daily and then to 200 mg daily was permitted for patients experiencing severe toxicities (grade 3 or recurrent grade 2 toxicities). In case of treatment discontinuation due to toxicity, if the toxicity grade was 1 or 0, then the drug was re-introduced within 3 weeks; if the toxicity grade ≥2, then treatment was definitively discontinued for toxicity.

study end points

For the indolent course of the disease, we chose the 9-month progression-free survival as the primary end point. The secondary end points were as follows: (i) safety and toxicity assessed according to the National Cancer Institute Common Toxicity Criteria (version 3.0); (ii) response rates at 3, 6 and 9 months; (iii) overall survival and (iv) median time to progression.

During the study, the patients underwent clinical and biological evaluations at baseline, day 1, day 7, day 15, day 30, day 60, day 120, day 180 and day 270. The response to treatment was assessed by comparing unidimensional tumor measurements (computed tomography scans) in pre- and per-treatment imaging studies at 2, 4, 6 and 9 months. We assessed the treatment response according to the RECIST 1.1 guidelines. An independent third-party radiologist reviewed selected imaging studies carried out during the treatment period with the study drug to ensure the consistent and unbiased application of RECIST.

sample size calculation and statistical analysis

This study was designed as an exploratory, hypothesis generating, proof-of-concept study. The sample size was chosen ($n = 25$) based on practical considerations, rather than statistical power and type I error rate calculations, with the aim of demonstrating the biological activity of this targeted therapy on a homogenous group of patients with chordomas. Statistical analyses are descriptive.

ethical and regulatory considerations

Study investigations were conducted after approval by the regional Ethics Committee ('Comité de Protection des Patients Nord-Ouest III', date of approval: 16 June 2009) and after declaration to the French Health Products Safety Agency ('Agence Française de Sécurité Sanitaire et des Produits de Santé', date of approval: 1 June 2009). Informed consent was obtained from each patient. This study was registered in the European Clinical Trials Registry (EudraCT No. 2007-004651-10) and on the ClinicalTrial.gov site (Number: NCT 00874874). The study was conducted in agreement with the Declaration of Helsinki and the International Conference on the Harmonization of Good Clinical Practice guidelines. The present manuscript is a part of the AngioNexT study, which included five different strata: superficial angiosarcoma, visceral angiosarcoma [13], epithelioid hemangiopericytoma [14], solitary fibrous tumor or hemangiopericytoma [15] and chordoma (reported here). http://www.cancer.gov/clinicaltrials/search/view?cdrid=633547&version=healthprofessional.

results

patient characteristics

From May 2011 to January 2014, 27 patients (17 men and 10 women) were enrolled in 12 centers of the French Sarcoma Group (GSF/GETO). The median age was 64 (30–86) years. All patients were eligible, with evidence of tumor progression at the time of study entry. Performance status was 0 in 11 cases (40.7%), 1 in 14 cases (51.8%) and 2 in 2 cases (7.5%). The most common primary sites were the sacrum (20; 74.0%), lumbar vertebrae (3; 11.1%), clivus and skull basis (3, 11.1%) and dorsal vertebrae (1, 3.7%). Metastases were present in 14 patients (51.9%); the most common metastatic sites were lung (7/24; 29.2%), bone (5/24; 20.8%) and liver (3/24; 12.5%). The median time between initial diagnosis and study enrollment was 4.5 years (range, 1–12 years). Prior treatments were surgery (18/27; 67.0%), radiotherapy (18/27; 67.0%) and systemic treatments (12/27; 44.4%). Six patients (22.2%), 5 patients (18.5%) and 1 patient (3.7%) had received 1, 2 and 3 line(s) of systemic treatment, respectively. The median interval between the end of the prior systemic treatment and study enrollment was 1.6 months (range, 1.4–33.0 months). Prior systemic treatments were imatinib (nine patients), imatinib plus metronomic cyclophosphamide (three patients), imatinib plus everolimus (one patient), sunitinib (two patients), everolimus plus erlotinib (one patient), doxorubicin (one patient), cisplatin plus epirubicin plus 5-fluoro-uracil (one patient) and thalidomide (one patient).

safety and toxicity

Safety was assessable in 27 patients. The reasons for treatment discontinuation were: treatment completion (per-protocol duration of treatment: 9 months) in 8 cases (29.6%), non-manageable toxicity in 7 cases (25.9%), documented tumor progression in 7 cases (25.9%), clinical tumor progression without radiological

documentation in 2 cases (7.4%) and patient or investigator decision in 3 cases (11.1%). The median duration of treatment was 139 days (range, 15–305 days). Thirteen patients (50.0%) required temporary treatment discontinuation for toxicity management (mainly for management of skin toxicity in 5 cases and diarrhea in 2 cases). Eleven (42.3%) patients required dose reduction for toxicity. Nevertheless, the median relative dose intensity was 100% (range, 43.0%–100.0%). Table 1 depicts the observed toxicities. The maximum toxicity grade per patient was grade 3 in 21 cases (77.8%) and grade 4 in 4 cases (14.8%). During the study, 10 serious adverse events occurred, including 1 SAE associated with sorafenib (grade 3 diarrhea with hypokalemia and acute pancreatitis) and 2 SAE possibly related to sorafenib (1 case of keratoacanthoma and 1 case of tumor necrosis with nerve palsy). No toxic deaths were noted. The safety profile of sorafenib in this study was in agreement with previous reports.

activity

Twenty-seven patients were assessable for intent-to-treat activity end points. The median time of follow-up was 8.7 months (range, 1.3–31 months). We observed one objective response and one delayed partial response at month 6 and confirmed at months 9 and 11. This partial response was observed in a patient suffering from a local relapse of sacral chordoma (previously treated by surgery and radiotherapy) measuring 100 mm at baseline, 56 mm at month 6, 42 mm at month 9 and 37 mm at month 11. The median progression-free and median overall survival were not reached. As per the central radiological review, the 6-month, 9-month and 12-month progression-free rates were 85.3% [95% confidence interval (CI) 60.7–95.1], 73.0% (95% CI 46.1–88.0) and 73.0% (95% CI 46.1–88.0), respectively (11 observed events, Figure 1). The 12-month progression-free rates were not different in patients not previously treated with systemic treatment (77.0%, 95% CI 4.9–92.0) and in those previously treated (66.7%, 95% CI 19.5–90.4, Figure 2, $P = 0.48$). Three patients died from chordoma during the study. The 6-month, 9-month and 12-month overall survival rates were 100%, 86.5% (95% CI 55.8–96.5) and 86.5% (95% CI 55.8–96.5), respectively (Figure 3).

Table 1. Grade 3 and 4 toxicity ($N = 27$)

| Toxicity	Grade 3, no. (%)	Grade 4, no. (%)
Hand–foot syndrome	5 (18.5)	0
Other skin reactions	1 (3.7)	1 (3.7)
Mucositis	2 (7.4)	0
Fatigue	3 (11.1)	1 (3.7)
Loss of appetite	1 (3.7)	0
Weight loss	4 (14.8)	0
Diarrhea	5 (18.5)	0
Arterial hypertension	5 (18.5)	1 (3.7)
Thyrotoxicosis	0	1 (3.7)
Lymphopenia	3 (11.1)	0
Hypokalemia	1 (3.7)	0

NCI-CT version 4 grade 2–4 adverse events in all patients. The incidence of maximal toxicity was considered by the investigator as possibly, most likely or definitely related to sorafenib.
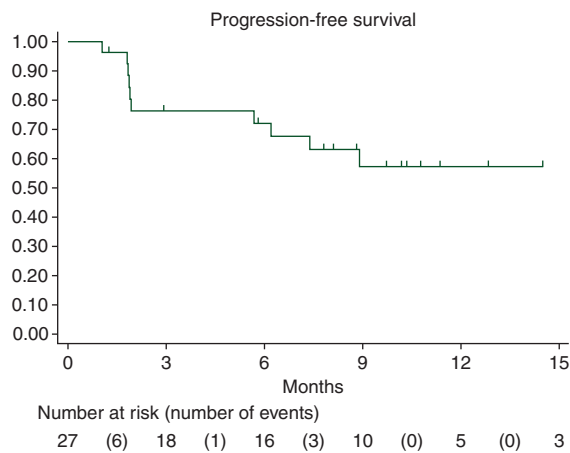
Figure 1. Progression-free survival curves (central radiological review and intent-to-treat analysis).
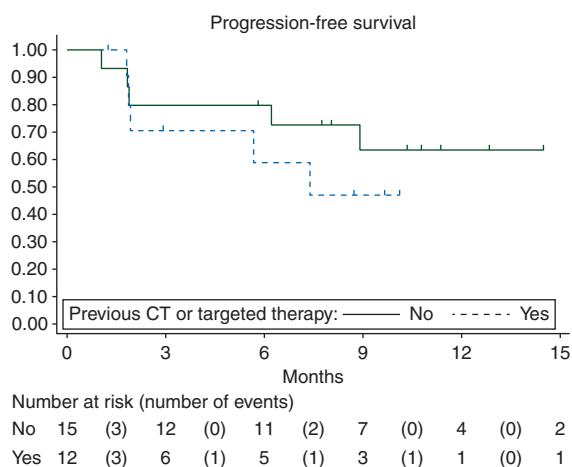
Figure 2. Progression-free survival curves according to prior systemic treatment (yes/no) (central radiological review and intent-to-treat analysis).
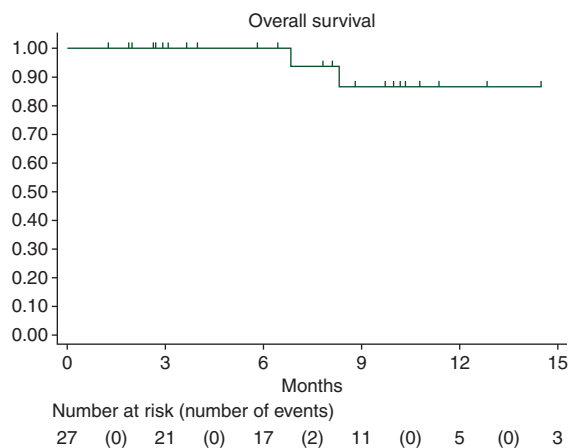
Figure 3. Overall survival curve.

discussion

Sorafenib (400 mg orally twice daily) provides an intent-to-treat best objective response of 1/27 (3.7%; 95% CI 0.1%–19.0%), a 12-month progression-free rate of 73.0% (46.1–88.0) and a

12-month overall survival rate of 86.5% (95% CI 55.8–96.5). The survival curves are similar in pretreated and not pretreated patients. The toxicity profile is as expected.

The activity of several molecularly targeted therapies administered alone or in combination in patients with chordomas has been explored in retrospective studies and expanded cohorts of phase I trials. The limited number of cases and the absence of standardized follow-up make it difficult to draw any clear-cut conclusions [5]. There are two previous phase II trials assessing imatinib [16] and lapatinib [17] in selected chordoma patients. The findings of our trial can be favorably compared with those of the previously published phase II trials (Table 2). In all three trials, the best objective response rate according to RECIST was very low, but these molecularly targeted drugs slowed tumor growth with long-lasting stable disease. For instance, the reported 9-month progression-free rates were 16.6%, 41.0% and 57.4% with lapatinib, imatinib and sorafenib, respectively. However, the study populations were not similar because the rate of pretreated patients widely differed and because patients in the two previous studies had been selected on the basis of a target expression (Table 2).

Our trial has some limitations. The study population was not selected based on the expression of putative targets. However, sorafenib can inhibit several putative targets, and at the time, there was no evidence to pick one driving target for locally advanced or metastatic chordomas. Furthermore, the selection of patients according to the overexpression of some targets is an appealing concept; however, bone tumors, such as chordomas, require decalcification before pathological diagnosis. The decalcification usually alters the capacity to perform immunohistochemical analysis. The evidence for disease progression at study entry was not centrally reviewed, and the clinical and radiological facts justifying the progression were based on the investigator judgment. The median progression-free and overall survivals were not reached in the present trial. Data with longer follow-up would be useful. A simple methodology was applied in this trial. We used RECIST as the metric of tumor response assessment. RECIST is not the best way to measure the activity in bone tumors. However, alternative methods [such as the Choi assessment or [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET)] are not standardized, not validated and are difficult to implement in a multicenter trial. Furthermore, RECIST was used in the two previously published trials. There was no ideal method for tumor response assessment in bone tumors. We centrally reviewed the imaging carried out in the present study to compare the tumor assessment carried out according to RECIST or according to the Choi criteria. In 14 patients, tumor response according to the Choi criteria was not feasible because of the use of MRI or because of inadequate contrast product enhancement. Among the 13 remaining cases, 12 patients experienced stable disease according to RECIST 1.1; among these 12 patients, 7 experienced partial responses according to the Choi criteria and 5 experienced stable disease according to the Choi criteria. We observed a significant decrease in tumor density, as captured by the Choi criteria, reflecting the sorafenib activity in chordomas (Table 3). The use of ^{18}F-FDG PET assessment in this setting appears appealing but warrants additional investigation. Regarding the relatively indolent course of chordomas, some may consider the

Table 2. Results of the phase II trials dedicated to chordomas

Trials	Stachiotti [17]	Stachiotti [16]	Present study
Treatment	Lapatinib 1500 mg/day	Imatinib 800 mg/day	Sorafenib 800 mg/day
Study cohort (n)	18	56	27
Pretreated (n)	18	Unknown	12
Metastatic (n)	13	23	14
Selection	EGFR-positive chordomas	PDGFRB/PDGFB-positive chordomas	Unselected
BORR, % (95% CI)	0.0% (0.0–17.9)	1.7% (0.0–9.4)	3.7% (0.8–18.3)
6-month PFR, % (95% CI)	50.0% (28.8–71.1)	57.1% (44.0–69.1)	85.3% (60.7–95.1)
9-month PFR, % (95% CI)	16.6% (6.0–46.1)	41.0% (29.1–54.1)	73.0% (46.1–88.0)
PFS (months)	8.2	9.0	Not reached[a]
6-month OS, % (95% CI)	–	78.5% (66.1–87.2)	100.0% (87.1–100.0)
9-month OS, % (95% CI)	–	66.1% (52.9–77.1)	86.5% (55.8–96.5)
OS (months)	25.0	34.5	Not reached

[a]PFS was not reached with sorafenib but will be up to 15 months.
BORR, Best objective response according to RECIST; n, number of cases; PFS, median progression-free survival (months); OS, median overall survival (months).

Table 3. Best objective responses according to the RECIST 1.1 and Choi criteria

	Tumor response according to Choi criteria				
	Partial response	Stable disease	Progressive disease	Not assessable	Total
Tumor response according to RECIST 1.1					
Partial response (1)	0	0	0	1	1
Stable disease	7	5	0	12	24
Progressive disease	0	0	1	0	1
Not assessable	0	0	0	1	1
Total	7	5	1	14	27

The partial response documented with RECIST 1.1 was not confirmed by the Choi criteria because the tumor assessment was carried out using MRI.

median follow-up of our trial as limited (8 months); however, our data are mature for the prespecified primary end point, and the previously published trials [17, 18] did not include the description of the median follow-up.

The three previous phase II trials assessing the activity of molecularly targeted drugs in chordoma patients were nonrandomized trials. We recommend that the next trials be randomized to provide stronger conclusions about the impact of drugs on the natural history of this slowly growing tumor. However, direct randomization after inclusion (drug A versus B or drug A versus placebo) is not the ideal design; we think that randomization after a run-in period (drug discontinuation design after tumor stabilization) would be a more appropriate design (e.g. randomization between drug continuation versus drug discontinuation after 6 or 9 months of treatment without progression) [18].

This trial shows that sorafenib is a promising drug in advanced chordomas and warrants further study, especially focusing on the identification of predictive biomarkers.

disclosure

The authors have declared no conflicts of interest.

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Randomized phase II study evaluating veliparib (ABT-888) with temozolomide in patients with metastatic melanoma

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Background: Veliparib (ABT-888) is a potent, orally bioavailable, small-molecule inhibitor of the DNA repair enzymes poly ADP-ribose polymerase-1 and -2. Veliparib enhances the efficacy of temozolomide (TMZ) and other cytotoxic agents in preclinical tumor models.

Patients and methods: In this multicenter, double-blind trial, adults with unresectable stage III or IV metastatic melanoma were randomized 1:1:1 to TMZ plus veliparib 20 or 40 mg, or placebo twice daily. Efficacy end points included progression-free survival (PFS), overall survival (OS), and objective response rate (ORR).

Results: Patients ($N = 346$) were randomized between February 2009 and January 2010. Median [95% confidence interval (CI)] PFS was 3.7 (3.0–5.5), 3.6 (1.9–4.1), and 2 (1.9–3.7) months in the 20-mg, 40-mg, and placebo arms, respectively. Median (95% CI) OS was 10.8 (9.0–13.1), 13.6 (11.4–15.9), and 12.9 (9.8–14.3) months, respectively; ORR was 10.3%, 8.7%, and 7.0%. Exploratory analyses showed patients with low ERCC1 expression had longer PFS when TMZ was combined with veliparib. Toxicities were as expected for TMZ. The frequencies of thrombocytopenia, neutropenia, and leukopenia were significantly increased in the veliparib groups. Grade 3 or 4 adverse events, mainly hematologic toxicities, were seen in 55%, 63%, and 41% of patients in the 20-mg, 40-mg, and placebo arms, respectively.

Conclusions: Median PFS with 20 and 40 mg veliparib almost doubled numerically compared with placebo, but the improvements did not reach statistical significance. OS was not increased with veliparib. Toxicities were similar to TMZ monotherapy, but with increased frequency.

Key words: melanoma, metastasis, poly ADP-ribose polymerase inhibitor

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introduction

The incidence of melanoma has been rising steadily, accounting for nearly 10 000 yearly deaths in the United States alone [1].