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Original Research

Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour

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Abstract ***Background:*** To explore the activity of pazopanib in solitary fibrous tumour (SFT). ***Patients and methods:*** In a preclinical study, we compared the activity of pazopanib, sorafenib, sunitinib, regorafenib, axitinib and bevacizumab in a dedifferentiated-SFT (DSFT) xenotransplanted into Severe Combined Immunodeficiency (SCID) mice. Antiangiogenics were administered at their reported optimal doses when mean tumour volume (TV) was 80 mm^3. Drug activity was assessed as TV inhibition percentage (TVI%). From May 2012, six consecutive patients with advanced SFT received pazopanib, on a national name-based programme. In one case sunitinib was administered after pazopanib failure.

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Results: In the xenograft model, pazopanib showed the lowest antitumour activity (21%TVI), while regorafenib was the most active (95%TVI). Sorafenib, bevacizumab, sunitinib were markedly active (78/70/65%TVI). Axitinib was marginally active (51%TVI).
In the retrospective case-series, three patients carried malignant-SFT (MSFT), three DSFT. Best Response Evaluation Criteria in Solid Tumour (RECIST) responses were: three stable disease (SD), all MSFT, three progressive disease (PD), all DSFT, corresponding to one partial response (PR), two SD, three PD by Choi criteria. Median-progression-free survival was 3 months (range 1–15). In one patient, sunitinib was started after pazopanib failure, with a response.
Conclusions: In dedifferentiated-SFT xenograft pazopanib induced a marginal antitumour activity, while regorafenib appeared the most active and promising agent. When administered in patients, pazopanib showed a modest activity in terms of tumour growth stabilisation, observed only in non-dedifferentiated cases.

1. Introduction

Pazopanib is an inhibitor of vascular endothelial growth factor receptor (VEGFR) 1–3 recently approved for treatment of non-adipocytic advanced soft tissue sarcoma (STS) after failure to front-line chemotherapy [1]. In a Phase 3 study on pazopanib in non-adipocytic STS the median progression-free survival (PFS) was 4.6 months for pazopanib compared with 1.6 months for placebo, with an overall survival (OS) of 12.5 months versus 10.7 months [2].

Very few data are available on the activity of pazopanib in solitary fibrous tumour (SFT), a rare STS subtype [3], the sensitivity of which to antiangiogenics like sorafenib, sunitinib and bevacizumab is reported [4–9]. Antiangiogenics were shown to produce durable disease stabilisation in a proportion of patients by means of tumour responses that were mostly non-dimensional [5,6]. We already reported on the activity of pazopanib in a human high-grade dedifferentiated-SFT xenotransplanted into severe combined immunodeficiency (SCID) mice [10]. When compared to dacarbazine and temozolomide, pazopanib was less active and characterised by a short lasting cytostatic effect. Thus, we decided to expand that experiment to a broader number of antiangiogenic agents (i.e. sorafenib, regorafenib, axitinib in addition to sunitinib and bevacizumab) already applied in the clinical practice. Our findings are reported herein.

Within a name-based protocol following the results of the Phase 3 trial, we treated with pazopanib six patients affected by SFT. We report herein their outcome as well.

2. Patients and methods

2.1. Experimental model and pharmacological studies

A patient-derived human high-grade dedifferentiated-SFT xenograft model [10] was used in the study. The presence of the typical *NAB2-STAT6* rearrangement – recently described in human SFT [12] – was confirmed in xenograft by RT-PCR [10].

The xenograft model was maintained by serial subcutis (s.c.) passages in 6 week-old female SCID mice (Charles River, Calco, IT). Briefly, when tumours reached approximately 500 mm^3, they were removed, aseptically dissected, cut into small fragments ($3 \times 3 \times 3$ mm) and s.c. implanted in the mouse right flank. Twenty-four hours after tumour inoculum, 100 μL of Matrigel Basement Matrix (BD Biosciences) was injected intratumourally. Mice were housed in a pathogen-free facility with free access to food and water. Tumour growth was followed by biweekly measurement of tumour diameters with a Vernier caliper, and tumour volume (TV) was calculated according to the following formula: TV (mm^3) = $d^2 \times D/2$, where d and D are the shortest and the longest diameter, respectively.

2.1.1. Xenograft treatment

Treatment was started when xenotransplanted tumours were approximately 80 mm^3 (day 35). Eight mice for each group were used. Pazopanib, sorafenib, sunitinib, regorafenib and axitinib were all dissolved in 0.5% carboxymethylcellulose and delivered by oral gavage 5 days/week for 4 weeks (qd × 5d/w × 4w) × 2 after a 3-week rest at their reported optimal dose of 100/60/40/30 and 2 × 25 mg/kg, respectively. Bevacizumab was delivered intraperitoneally twice a week for 4 weeks (q3–4d/w × 4w) × 2 after a 3-week rest at its reported optimal dose of 4 mg/kg [12–16]. Control mice were treated with vehicle.

Antitumour activity was assessed as tumour volume inhibition percentage (TVI%) in treated versus control mice (TVI% = 100 − (T/C × 100) × 100, where T and C are the mean tumour volume of treated and control mice, respectively). Drug toxicity was determined as body weight loss and lethal toxicity.

The use of patient material in xenograft and all the experiments were approved by the Ethics Committee for Animal Experimentation of Fondazione IRCCS