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Outcome of uterine sarcoma patients treated with pazopanib: A retrospective analysis based on two European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) clinical trials 62043 and 62072

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ABSTRACT

Background. Uterine sarcomas are a group of mesenchymal tumours comprising several histologies. They have a high recurrence rate following surgery, modest outcome to systemic therapy, and poor overall survival. Pazopanib is a multi-targeted tyrosine kinase inhibitor approved for non-adipocytic advanced soft tissue sarcomas (STS). Here we investigated whether response to pazopanib in patients with uterine sarcomas differs from that of patients with non-uterine sarcomas.

Patients and methods. Uterine sarcoma patients were retrieved from all soft tissue sarcoma patients treated with pazopanib in EORTC Phase II (n = 10) and Phase III (PALETTE) (n = 34) studies. Patient and tumour characteristics, response, progression free and overall survival data were compared.

Results. Forty-four patients with uterine sarcoma were treated with pazopanib. The majority of patients had uterine leiomyosarcoma (LMS) (n = 39, 88.6%) with high grade tumours (n = 37, 84.1%) compared to 54.8% (n = 164) in the non-uterine population. The median age was 55 years (range 33–79) and median follow up was 2.3 years. Uterine patients were heavily pre-treated, 61.3% having ≥2 lines of chemotherapy prior to pazopanib compared to 40.8% in the non-uterine population. Five patients (11%), all LMS, had a partial response (95% CI 3.8–24.6). Median progression free survival (PFS) 3.0 months (95% CI 2.5–4.7) in uterine versus 4.5 (95% CI 3.7–5.1) in non-uterine STS. Median overall survival (OS) was 17.5 months (95% CI 11.1–19.6), longer than the non-uterine population, 11.1 months (95% CI 10.2–12.0) (p = 0.352).

Conclusions. Despite heavy pre-treatment, pazopanib shows signs of activity in patients with uterine sarcoma with the similar outcomes to patients with non-uterine STS.

1. Introduction

Uterine sarcomas are a rare and heterogeneous group of mesenchymal tumours that account for up to 5% of all uterine body malignancies. [1] Leiomyosarcoma (LMS) is the most common histological subtype comprising 63% in one series followed by endometrial stromal sarcoma (ESS) (21%), undifferentiated endometrial

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sarcoma (6%), with adenosarcoma and other rare subtypes making up the remainder. [2]. Surgery is the mainstay of treatment in early stage disease whatever the histological subtype [3]. However, recurrence rates are high. For example, in completely resected FIGO stage 1b uterine LMS 55% of patients relapse [4]. In patients with advanced or locally recurrent disease, palliative systemic treatment can be considered. As holds true for all soft tissue sarcomas, outcomes to systemic treatment greatly differ across the different subtypes. Of all the uterine sarcomas uterine LMS is the most chemo-sensitive [5]. In advanced disease, active agents in uterine LMS include doxorubicin, gemcitabine combined with docetaxel or gemcitabine alone, trabectedin and dacarbazine [6] However, response rates are typically modest, ranging from 10 to 36% and are of relatively short duration, with a median PFS of around 4 months [5]. Patients with low grade ESS exhibit a more indolent disease pattern and are sensitive to hormonal manipulation with aromatase inhibitors [7] [8]. In contrast, those patients with high grade undifferentiated uterine sarcoma have a particularly poor prognosis with a paucity of active agents in this disease type [9] [10]. Given the median overall survival for all patients advanced uterine soft tissue sarcoma (STS) remains in the order of 10 months there is a pressing need for new therapies. [5].

Anti-angiogenic approaches have been explored in patients with uterine LMS. A clinical trial of sunitinib revealed responses in 2 out of 23 patients with uterine LMS, failing to meet pre-defined criteria to warrant further examination [11] [12]. The addition of bevacizumab to gemcitabine and docetaxel chemotherapy was also initially investigated in STS including those with uterine LMS where the toxicity of this regimen was relatively high. [13] Furthermore, a subsequent randomised, placebo controlled Phase III trial of gemcitabine, docetaxel ± bevacizumab in patients with metastatic uterine LMS was stopped early due to futility with no improvement in PFS, OS or response rate (RR) [14]. Pazopanib is another compound thought to exert its anti-tumour activity partially through inhibition of angiogenesis. This drug is a multi-targeted tyrosine kinase inhibitor which targets not only vascular endothelial growth factor (VEGFR)-1, -2, and -3 but also platelet-derived growth factor receptor (PDGFR) -α, -β and KIT. Clinically relevant responses in patients with sarcoma were seen in the initial Phase 1 trial [15]. Subsequently a large stratified EORTC STBSG Phase II trial (62,043) of 142 patients was performed which confirmed activity by progression free rate at 12 weeks in three out of four STS groups including the LMS cohort [16]. The Phase III randomised double blind placebo controlled 62072 (PALETTE) study followed, assigning 369 patients with advanced or metastatic non-adipocytic STS progressing on previous chemotherapy to either pazopanib or placebo and a significant increase in PFS of 4.6 months versus 1.6 months was seen. [17] On the basis of the trial, pazopanib was approved for non-adipocytic STS patients failing prior treatment with doxorubicin- and/or ifosfamide-based chemotherapy. These results were promising for physicians treating uterine sarcoma patients potentially highlighting a novel treatment pathway. This paper investigates in detail the outcome of patients with uterine sarcoma treated with pazopanib in both the Phase II and III EORTC/GSK jointly sponsored studies.

2. Patients and methods

2.1. Patients included

Patients eligible for this retrospective analysis were those with uterine sarcoma, included and treated with pazopanib in the Phase II study (n = 10) or randomised to the pazopanib arm of the Phase III trial (n = 34). Central pathological review was performed as per trial protocols (Fig. 1 Consort diagram).

2.2. Definition of endpoints

PFS was defined from the date of registration/randomization to the first documentation of progression or death, whichever occurred first. The radiological assessment of the principal investigator was used for the definition of progression; clinical progression in the absence of documented objective progression was also taken into account. Patients were censored at the date of last patient visit (before the clinical cut-off date). OS was defined as from the date of registration/randomization to the date of death. Patients alive at the time of the clinical cut-off were censored at the date of last follow-up. Tumour response was measured by RECIST version 1.1 [18].

2.3. Statistical analysis

The characteristics of uterine sarcoma patients were compared to those of the remaining STS patients receiving treatment in the pazopanib studies using descriptive tables (patient characteristics, disease characteristics, treatment exposure, toxicity and post protocol treatment). PFS and OS were estimated by the Kaplan-Meier method. Statistical significance for OS is based on a logrank test of the survival of the two subgroups, stratified by study.

Due to the limited number of patients available for this analysis, only univariate models (logistic regression for best overall response and Cox regression models for PFS and OS) were used to assess the value of selected prognostic factors to predict outcome of uterine sarcoma patients treated with pazopanib.

3. Results

3.1. Characteristics

Out of the 343 eligible patients for this analysis,(ie the total number of patients receiving pazopanib in the Phase II and Phase III trials,) 44 presented with a uterine sarcoma. The median age was 55 years (range 33–79) in the uterine population, similar to that of the non-uterine sarcoma patients; the majority (59.1%) was performance status 1, compared to 48.8% of the non uterine soft tissue sarcoma patients. Patient demographics are summarized in Table 1.

Five patients were treated with pazopanib in the first line metastatic setting having received anthracycline-based neoadjuvant chemotherapy previously, twelve received treatment in the second line, thirteen in the third line, ten in the fourth and four patients in the fifth line. Compared to the other patients included, those with uterine sarcoma were more heavily pre-treated with 61.3% having ≥2 lines of chemotherapy prior to pazopanib compared to 40.8% of non-uterine patients.

Central pathological review was performed for all patients in the Phase III study and for all but 23 patients in the Phase II trial, 9 of whom had uterine sarcoma. Most patients (88.6%) had a diagnosis of uterine LMS and the majority had high grade tumours (84.1%), compared to 54.8% in non-uterine STS. The remaining pathological subtypes in the uterine sarcoma group included one patient with PEComa and one had undifferentiated sarcoma, three could not be classified further due to insufficient material on central histological review. No patients with ESS were treated in these studies.

The clinical cut-off dates for this pooled analysis resulted in an overall median follow-up of 2.3 years (IQR 1.9–2.9).

3.2. Treatment and response.

The median time on treatment for all uterine sarcoma patients was 14.3 weeks (range 03–135.2 weeks) compared to 17.1 weeks (0.1–191.7 weeks) for non-uterine STS patients. Two patients with metastatic uterine sarcoma, both with LMS, one intermediate and one high grade, were still on pazopanib at the cut off dates.