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ORIGINAL ARTICLE

A phase I study on the combination of neoadjuvant radiotherapy plus pazopanib in patients with locally advanced soft tissue sarcoma of the extremities

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ABSTRACT

Accumulating evidence suggests significant synergism combining radiotherapy (RT) with angiogenesis targeted therapies. This multicenter prospective phase I clinical trial established the safety profile and recommended dose for further studies of pazopanib concurrent with preoperative RT in patients with extremity soft tissue sarcomas (ESTS) in curative setting.

Methods. Patients with deep seated intermediate and high grade sarcomas, ≥5 cm, received once daily pazopanib (dose-escalation cohorts 400 mg, 600 mg and 800 mg) for 6 weeks and 50 Gy preoperative RT starting Day 8. Surgery was performed 5–7 weeks later. Toxicity was scored according to CTC criteria 4.0. Dose limiting toxicities (DLT) were divided into two separate sets; DLT-I being toxicities occurring during the 6-week chemoradiotherapy period within the radiation portals until day of surgery (designated as DLT-I) and those occurring perioperatively until Day 21 after surgery (DLT-II).

Results. A total of 12 patients were enrolled, 11 were evaluable (3 females and 8 males, median age 58 years, range 24–78 years, median tumor size 9 cm, range 5–15 cm). Ten underwent surgery. No increased toxicity inside the radiation fields was seen, but two of 10 patients (one each in the 400 mg and 600 mg cohorts) showed delayed wound healing after surgery. None of the patients showed significant volume reductions after RT. Evaluation of the resection specimen showed pathological (near) complete responses (≥95% necrosis rate) in four of 10 cases. Unexpectedly, grade 3 + hepatotoxicity led to premature pazopanib interruption in three of 11 (27%) of cases.

Conclusion. Apart from hepatotoxicity, neoadjuvant pazopanib 800 mg daily in combination with 50 Gy seems tolerable; the regimen appears to demonstrate promising activity in ESTS and is the recommended dose for further studies.

Conservative surgery combined with radiotherapy (RT) results in relatively high local control rates of approximately 85–90% in patients with extremity soft tissue sarcomas (ESTS) [1,2]. In localized ESTS, local control and overall survival do not depend upon the order in which surgery and RT are applied.

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Regarding late functional toxicity and quality of life, preoperative RT (preopRT) is preferred. However, preopRT may result in delayed wound healing, related to the irradiated volume and applied dose. The target volume is dictated by the sarcoma size, the recommended dose is 50 Gy in 1.8–2 Gy once daily fractions in five weeks [2].

For many carcinomas, systemic agents concurrently applied with RT frequently results in increased local control probabilities, sometimes translating into increased survival. Such approaches come at the cost of, usually, temporary increased acute toxicity dependent on the location of the tumor and the type of systemic agent [3].

Neovascularization and angiogenesis are fundamental aspects in tumor initiation, promotion, and the metastatic potential of ESTS [4]. Overexpression of vascular endothelial growth factor (VEGF) and its receptors have been observed as neoplastic phenomena in ESTS. The observation that ESTS overexpress angiogenic factors in both tumor and serum was the basis to explore anti-angiogenic compounds in ESTS [5]. In addition, preclinical studies combining RT with antiangiogenic agents suggest synergistic radiosensitizing effects [6]. A radiosensitizing agent may contribute significantly in the treatment of STS as a complete pathologic responses is shown to result in an improved oncologic outcomes after neoadjuvant therapy [7].

Pazopanib is an oral multikinase inhibitor effecting tumor proliferation and tumor angiogenesis. Following a phase I study, establishing the recommended dose at 800 mg daily, the safety profile and antitumor activity in metastatic ESTS have been examined in phase II and III studies, resulting in approval and registration of pazopanib for patients with advanced, non-adipocytic ESTS failing doxorubicin- or ifosfamide-based regimens [5,8–10]. Given its manageable toxicity profile, potential synergistic effect with RT and evidence of activity in sarcoma patients with metastatic disease, our aim is to establish the toxicity, safety, and recommended dose for further studies of daily pazopanib combined with preopRT in patients presenting with localized ESTS.

Patients and methods

Eligible patients were age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, with pathologically confirmed intermediate or high grade ESTS, ≥ 5 cm in maximal dimension, without evidence of metastases. Routinely, a magnetic resonance imaging (MRI) of the tumor mass and a computed tomography (CT) scan of the chest were performed. Prior to entry, patients were evaluated for adequate hematological-, coagulation-, hepatic-, renal-, cardiac- and thyroid function. In young females a negative pregnancy test just prior to start of pazopanib was obligatory and adequate contraceptive measures were mandatory for both sexes. Patients were checked for prohibited co-medication as per protocol defined. The study was approved by local independent ethics committees, and conducted in accordance with the Declaration of Helsinki. All patients received information regarding the purpose and conduct of this study and provided written informed consent. The study is registered as NCT01985295.

Study design

Two separate sets of dose limiting toxicities (DLT) were scored. Those occurring during the six-week chemoradiotherapy period within the radiation portals until day of surgery (designated as DLT-I) and those occurring perioperatively until Day 21 after surgery (DLT-II). The study evaluated three pazopanib dose levels; once daily 400 mg, 600 mg and 800 mg. As 800 mg is the well established dose for pazopanib monotherapy with antitumor efficacy in the metastatic setting, the study was designed not to escalate above this level even if DLTs would not be observed. Patients were observed for toxicities from start of treatment until three weeks following surgery or until complete wound healing. The systemic toxicity profile of pazopanib is well known [11] and is therefore specifically no part of the DLT analysis of this phase I study. Nevertheless, all toxicities within the radiation portals, perioperatively and systemically were rigorously recorded and acted upon clinically in the patient's best interest. If necessary one or more patients could be added to a cohort to achieve evaluable numbers of cases within that cohort.

Study procedures

Pazopanib was initiated one week prior to RT on Day 1 of study and continued until the last fraction. RT to 50 Gy in 25 fractions of 2 Gy started on Day 8. RT treatment planning was performed according to recent guidelines [2]. The planning CT scan was co-registered to the diagnostic MRI scan in all patients. For this study both intensity modulated RT as well as three-dimensional (3D) conformal techniques were allowed. Surgery was performed 5–7 weeks later. Routine perioperative care was provided, with careful documentation of wound complications as defined by O'Sullivan [1]. Standard surgical approach is a wide resection of the tumor, including the biopsy tract or scar, where the aim is a resection of the tumor with at least about 1 cm of normal tissue covering the

tumor, sparing close but macroscopically normal neurovascular structures, but including when involved. If a large tumor bed cavity is expected, either quilting sutures are used to close the cavity or the reconstructive surgeon is involved in closing the large defect with a muscle/skin transposition flap, or a free vascularized muscle/skin flap. If large skin defect is expected, the reconstructive surgeon is also involved in the closure of the defect. If arterial reconstruction is necessary the vascular surgeon is involved.

Toxicity assessment

Physical examinations, blood pressure monitoring and routine safety laboratory studies were performed at study initiation and repeated weekly during chemoradiation and biweekly prior to surgery. Adverse events were graded according to CTCAE v4.0.

DLT-I and DLT-II definitions

Per protocol, DLT-I was defined as skin toxicity of grades 3–5 during and/or after preopRT until day of surgery. Neutropenia can be a side effect of large field RT, but is rare during RT for ESTS management. Nevertheless, should unexpectedly neutropenia (ANC $< 0.5 \times 10^9$/L) > 7 days and/or neutropenic fever ANC $< 1.0 \times 10^9$/L, fever ≥ 38.5°C) occur, it would also be designated as DLT-I. Importantly, only those toxicities deemed related to the combination of pazopanib and preopRT were taken into account for establishing MTD. For example, hepatotoxicity as a known pazopanib side effect [11] could be a reason to advise the patient to interrupt or stop pazopanib as per protocol described, but it is assumed not to be consequential to the interaction of pazopanib and ESTS irradiation.

DLT-II was defined [1] as a secondary operation under general or regional anesthesia for wound repair (debridement, operative drainage, and secondary wound closure including rotationplasty, free flaps, or skingrafts), or wound management without secondary operation, including invasive procedures without anesthesia (mainly seroma aspiration), readmission for wound care like intravenous antibiotics, or persistent deep packing for 120 days or longer.

Pathological response

All pathology slides were examined in the three participating sarcoma referral centers by sarcoma pathologists. Specimens were examined for determination of percentage tumor necrosis, tumor histology and margin assessment. Near complete or complete pathological response was defined as $\geq 95\%$ and 100% tumor necrosis, respectively [12,13].

Results

Patient and tumor characteristics

Between April 2011 and February 2014, 12 patients were registered in the study, 11 were evaluable. One patient (#2) consented to participate but refused prior to start. Disability to fully comply with the protocol regimen applied to three patients (27%) in all because of grade 3 or 4 hepatotoxicity, defined as isolated transaminase elevations with no concomitant hyperbilirubinemia. These patients had to discontinue pazopanib prematurely (case #6 on Day 24, #8 on Day 36 and #11 on Day 17). Per protocol, it was decided to add one extra patient in the specific dose levels except for #8 because he stopped pazopanib as late as Day 36 of the 40 days chemoradiation period. The baseline patient and tumor characteristics are described in Table I.

Toxicities

Toxicity from combined modality therapy and postsurgical wound complications are shown in Table II. All three cases with hepatotoxicity showed normal liver function tests after stopping pazopanib. We did not observe any significant toxicities within the irradiated volumes (DLT-I) other than grade 1 skin toxicities conform routine clinical practice after RT alone. Other systemic toxicities like fatigue, hair discoloration, hypertension and diarrhea were all mild and transient. In all three cases with grade 3 or 4 hepatotoxicity, the transaminase levels returned to $\leq$ grade 1 within three weeks after stopping of pazopanib.

For perioperative complication analysis (DLT-II), 10 of 11 patients were evaluable; one patient refused surgery. Delayed wound healing after surgery was seen in two of 10 patients (20%), one in the 400 mg and one in the 600 mg cohort. One of these, case #5, in the 600 mg cohort, was a heavy smoker with a myxofibrosarcoma located pretibially. Both factors could have been additive reasons for delayed wound closure.

Pathological response

Pathological response could be evaluated on 10 definitive resection specimens. In 70% of them $> 80\%$ necrosis could be observed and 40% of the resected sarcomas showed (near) complete responses with replacement of the sarcoma by a fibro-inflammatory tissue as defined above (see Table III).

Follow-up

With a median follow-up of 24 months, range 13–48 months, one local recurrence was diagnosed eight

Table I. Patient characteristics.

Patient number	sex	Age (years)	Pathology/grade	Localization of sarcoma	Full regimen compliance	Eligible for analysis	Local failure	Follow-up (months)	Disease status
1	F	45	UPS II	Medial thigh	Yes	Yes	No	48	NED
2	M	63	Dedifferentiated liposarcoma	Upper leg	Never started (A)	No			
3	M	24	MPNST	Upper arm	Yes	Yes	Yes after 8 months	40 (32 since relapse)	NED (B)
4	M	49	UPS III	Lower leg	Yes	Yes	No	21	DOD (C)
5	M	67	Myxofibrosarcoma II	Lower leg	Yes	Yes	No	34	NED
6	M	60	Pleomorphic rhabdomyosarcoma	Axilla/scapula	No (D)	Yes	No	33	NED
7	F	33	Biphasic synoviasarcoma	Knee	Yes	Yes	No	29	NED
8	M	74	UPS III	Lower leg	No (E)	Yes	No	24	NED
9	M	49	UPS III	Lower leg	Yes	Yes	No	16	DOD (G)
10	M	58	UPS III	Dorsal side upper leg	Yes	Yes	NA	19	NED
11	F	78	PEComa	Left gluteal muscle	No (F)	Yes	No	20	NED
12	M	59	UPS II	Medial thigh	Yes	Yes	No	13	NED

DOD, dead of disease; F, female; M, male; M+, metastatic disease; MPNST, malignant peripheral nerve sheet tumor; NA, not applicable; NED, no evidence of disease; UPS, undifferentiated pleomorphic sarcoma.
(A) patient was screened and signed informed consent, but refused the week before start; (B) local relapse after 8 months, salvage surgery and now NED; (C) pulmonary metastases 14 months after start op local treatment, died 7 months later; Pazopanib was stopped on Day 24 (D), 36 (E) and 17 (F) due to grade 3 + hepatotoxicity (see Table II); (G) pulmonary metastases 4 months after start op local treatment, died 12 months later.

months after surgery. This patient was salvaged by surgery and is now without any evidence of disease for 32 months. In case #4 and #9, pulmonary metastatic disease was apparent 14 and 4 months, respectively, after start of therapy. Case #4 died seven months later, case #9 died 12 months later. Otherwise no sarcoma-related events have been seen up to now.

Discussion

Combining once daily pazopanib 800 mg with 25×2 Gy preopRT seems safe and this dose level is the recommended dose to be further explored for its anti-tumor activity.

This phase I study was designed with two separate sets of DLT. The first set (DLT-I) described the tox-

Table II. Toxicities.

		During neoadjuvant pazopanib plus radiotherapy			Perioperative toxicities and wound complications	
Patient number	Pazopanib dose	Any toxicity (highest grade)	≥ Grade 3 toxicity (grade)	DLT I		DLT II
1	400 mg	Fatigue (1) Dermatitis (1)	None	No	None	No
2		Never started[a]		Not evaluable		Not evaluable
3	400 mg	None	None	No	None	No
4	400 mg	ALT (2) AST (1) GGT (2) Hair discoloration (1)	None	No	Delayed wound healing	Yes
5	600 mg	Diarrhea (2)	None	No	Delayed wound healing	Yes
6	600 mg		ALT (3)[a]	No	None	No
7	600 mg	Fatigue (1) Skin rash (1)	None	No	None	No
8	600 mg		ALT (3)[a]	No	None	No
9	800 mg	None	None	No	None	No
10	800 mg	Hypertension (2) Anal mucositis (2)	None	No	Not operated upon	Not evaluable
11	800 mg		ALT (4)[a]	No	None	No
12	800 mg	Fatigue (1) Pain (1)	None	No	None	No

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
[a]for description see text.

Table III. Assessment of radiology and pathology.

Patient characteristics		Maximum size before Radiotherapy	Maximum size before/at surgery	Pathology of definitive resection specimen: percentage of necrosis/ description
Patient number	Pathology/grade			
1	UPS II	8 cm	6 cm	>95%
2	Dedifferentiated liposarcoma II	12 cm	NE	NE
3	MPNST	15 cm	9 cm	100%: complete necrosis
4	UPS III	8 cm	9 cm (with extensive necrosis)	100%: complete necrosis
5	Myxofibrosarcoma II	5 cm	4 cm	>50%
6	Pleomorphic rhabdomyosarcoma	5 cm	4 cm	0%: no response
7	Biphasic synoviasarcoma	5 cm	5 cm	1%: minimal response
8	UPS III	9 cm	8 cm	~90%
9	UPS III	11 cm	9 cm	>95%
10	UPS III	12 cm	14 cm	Refused surgery
11	PEComa	6 cm	5 cm	80–95% necrosis
12	UPS II	9 cm	8 cm	~80% necrosis

DOD, dead of disease; F, female; M, male; M+, metastatic disease; MPNST, malignant peripheral nerve sheet tumor; NA, not applicable; NE, not evaluable; NED, no evidence of disease; UPS, undifferentiated pleomorphic sarcoma.

icities attributable to the combination of pazopanib and RT (e.g. skin toxicity). DLT-I followed traditional dose-escalation definitions to determine the maximal tolerated dose (MTD) of pazopanib in case of side effects in 33% of patients or more. A second set (DLT-II) described toxicities in the perioperative period and was specifically so designed because surgery after preopRT without any systemic agents already results in a 35% wound complication rate [1]. The observed RT side effects and post-surgical morbidities were consistent with those reported in other studies [1,12]. We did not observe any DLT-I in the chemoradiotherapy period. The DLT-II rate of 20% (2 of 10) compares favorably to the 35% rate published [1]. DLT-II was not observed in the three patients receiving 800 mg pazopanib and undergoing resection. Hepatotoxicity is a known side effect of pazopanib. In our study, three cases (27%) were diagnosed with grade 3 hepatotoxicity leading to interruption of pazopanib, on Day 17, 24 and 36, while continuing RT. In a 1478 patient meta-analysis [11] the incidences of all grades of aspartate aminotransferase (AST) and alanine transaminase (ALT) elevations, was 39.6% and 41.4%, respectively. The incidences of grades 3 and 4 AST and ALT were 6.9% and 9.4%. Other than the sample size, we do not have a plausible explanation for our 27% rate of grade 3 or 4 transaminase elevations. We assume that it is not related to the irradiation of extremities, but neither can we rule this out. The next phase II study on this regimen will specifically look into this unexpected high rate of hepatotoxicity especially given the short duration pazopanib was prescribed. Obviously, patients receiving pazopanib (with or without RT) need to be monitored strictly for hepatotoxicity, also in following phase II studies.

The combination of pazopanib with RT has also been explored in other malignancies. Goyal et al. [7] applied once daily pazopanib 800 mg concurrent with RT in 2 Gy per fraction to a total dose of 50–60 Gy in breast cancer. Consistent with our results, they did not observe increased (sub)acute locoregional toxicities compared to RT alone. Overall, treatment was well tolerated.

This phase I study was not designed to evaluate therapeutic response. However, we did observe in 70% of our patients a rate of >80% necrosis and in 40% a pathological complete or near-complete remissions, including three of three patients at the lowest 400 mg dose level. These data compare favorably to published series [13] suggesting a >80% necrosis rate in less than 20% of patients treated with preopRT alone.

Neither was this phase I study intended to investigate biomarkers such as VEGF, as the correlation of these markers with outcome are controversial [14,15]. Nevertheless, the targeted agents sorafenib [16], bevacizumab [17], and pazopanib exert their anti-tumor activity by targeting the tumor vasculature, and are or have been studied in combination with RT. Sunitinib combined with RT is currently under investigation [18] and further discussed below. Bevacizumab in combination with RT resulted in ≥80% necrosis in 45% of tumors, which is over double the historical rate with RT alone. All these data prompt further studies of preopRT combined with anti-angiogenic compounds in localized ESTS to establish the added value of such combinations over RT alone. Obviously, such studies should occur in a randomized setting ideally with stratification for ESTS subtype or performed in specific ESTS subentities alone [19]. However, the group of ESTS comprises more than 50 different subtypes with substantial differences in terms of molecular background, clinical behavior, and sensitivity to systemic agents.

Accordingly, the phase II study of pazopanib in advanced ESTS was explored in four different strata; adipocytic sarcomas, leiomyosarcomas, synovial sarcomas, and a mixed group of other eligible ESTS subtypes [8]. In this study, the predefined criteria for further study of pazopanib was not met in the adipocytic ESTS cohort and this group was therefore not included in the subsequent phase III study. However, in subsequent analyses, no histological subtype could be revealed to be associated with better or worse outcome to pazopanib apart from adipocytic ESTS [9,10]. This observation underlines the heterogeneity in sensitivity to pazopanib across different ESTS subtypes. Like differences in outcome to pazopanib, differences in radiosensitivity among ESTS histological subtypes have also been demonstrated [8,20,21] further stressing the importance of stratification in ESTS studies.

Future clinical trials combining 50 Gy RT with 800 mg pazopanib in ESTS should not only include assays and image modalities providing insight in the underlying (radio)biology, but should also include early stopping rules for futility and unacceptable toxicity, with an emphasis on hepatotoxicity. Especially after 50 Gy, wound healing problems are observed. This risk is related to patient characteristics (e.g. obesitas, diabetes, smoking habits, hypertension and sarcoma location of the sarcoma) as well as RT parameters like dose, volume and skin flap sparing [22–24]. Therefore, the approach of lowering the RT dose by use of systemic agents could be clinically relevant aiming for a reduction in wound complications.

Nevertheless, up to now, the recommended dose of 50 Gy is considered standard for the preoperative management of ESTS [1,2]. However, it is not based upon evidence from randomization between different dose levels. Myxoid liposarcomas (MLS), with their dense vasculature, regress markedly during preopRT. Some suggest that the RT target may not so much be the sarcoma cells but the supplying vasculature [20,21]. In this subtype, de-escalating the preopRT dose is currently under investigation (ClinicalTrials.gov NCT02106312).

To finalize, some issues of serious concern regarding receptor tyrosine kinase inhibitors (RTKI), need further discussion. First, an unexpected toxicity profile has been observed by others as well. Lewin [25] investigated preoperative RT (50.4 Gy in 28 fractions over 51/2 weeks) in combination with sunitinib at dose level 0 ($n = 7$; 50 mg per day for 2 weeks before RT, then 25 mg per day given during RT) and subsequently dose level -1 ($n = 2$; 37.5 mg per day for 2 weeks before RT, then 37.5 mg per day given during RT). This study was prematurely closed due to toxicity. DLTs were seen in four patients at level 0 (G4 liver failure, G4 hyponatremia, G3 hyperglycemia, G3 rash and hyponatremia) leading to dose de-escalation, but despite this reduction, two further DLTs were seen at DL-1 (G3 ALT, G3 neutropenia). Focusing on the liver only, they have observed four of nine (44%) grade 3 + hepatotoxicity and an overall grade 3 + toxicity rate of 78%. A second issue of concern was the observation that patients receiving sunitinib had a higher local failure rate (HR: 8.1; $p = 0.004$). From an efficacy point of view, however, the combination of sunitinib plus RT led to an almost doubling of the median tumor necrosis percentage (40, range 5–100, vs. 75, range 1–95).

Second, both Ebos [26] and Pàez-Ribes [27] describe a phenotype change after RTKIs exhibiting a more invasive and metastatic potential. Ebos [26] showed an acceleration of breast cancer metastasis in mice receiving sunitinib and other RTKI's prior to intravenous implantation of tumor cells, suggesting a metastatic conditioning. Furthermore, mice receiving short-term adjuvant sunitinib therapy after primary tumor removal showed increased spontaneous metastatic tumor burden corresponding with decreased overall survival. Pàez-Ribes [27] showed that in a mouse pancreatic neuroendocrine cancer model increased tumor invasiveness was already evident and significant following one week of antiangiogenic treatment, and the effect persisted and increased during longer term continuous treatment for four weeks. In this model, the incidence of animals with liver micrometastases was two-fold higher in the treated animals than in controls, with a relative risk of 2.0.

For patients with metastatic STS, pazopanib after prior chemotherapy is FDA and EMA approved. In case of response to this second line systemic therapy, continuation of pazopanib is of utmost importance, but can be precluded by the onset of hepatotoxicity. Vlenterie and co-workers have very recently suggested in this journal to add corticosteroids while continuing pazopanib even in case of grade 3 hepatotoxicity with very rapid resolution of transaminase levels [28]. In case of non-metastatic locally advanced disease in the extremities, as investigated in this phase I study, the addition of pazopanib to RT is investigational. Probably the best advice for now, in this neoadjuvant setting, is to stop pazopanib in case of grade 3 + hepatotoxicity and not to add corticosteroids.

In summary, in locally advanced ESTS, neoadjuvant pazopanib to the highest level of once daily 800 mg in combination with 50 Gy preopRT seems tolerable and appears to show a higher tumor response rate than historically observed after RT alone. We did not increase the dose above this registered dose. Twenty-seven percent of the patients could not fully

tolerate the drug because of systemic toxicity. This toxicity profile will be carefully monitored in the following phase II study, aiming to accrue 35 patients to be treated with once daily pazopanib 800 mg in combination with 50 Gy preopRT.

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