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Original Research

Randomised phase II trial of trofosfamide vs. doxorubicin in elderly patients with untreated metastatic soft-tissue sarcoma

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Metronomic;
Safety

Abstract Doxorubicin represents the standard first-line treatment for metastatic soft-tissue sarcoma. We assessed the efficacy and safety of trofosfamide in elderly patients. In this controlled phase II trial, we randomly (1:2) assigned 120 previously untreated patients with soft-tissue sarcoma, older than 60 years, with an Eastern Cooperative Oncology Group score of 0–2, to receive either doxorubicin for 6 cycles (arm A) or oral trofosfamide (arm B). The primary end-point was a 6-month progression-free rate (PFR) in the experimental arm (clinical trial information: NCT00204568). Between August 2004 and October 2012, forty and 80 patients were randomly assigned to arm A and arm B, respectively, in 16 centres. The median age was 70 years (range, 60–89). The primary study end-point (6-month PFR) was exceeded, with 27.6% in arm B (95% confidence interval [CI], 18.0–39.1) and 35.9% in arm A: (95% CI, 21.2–52.8). Survival data in terms of progression-free survival were 4.3 months (95% CI, 2.2–6.3) and 2.8 months (95% CI, 1.7–3.6) and in terms of overall survival were 9.8 months (95% CI, 6.7–11.6) and 12.3 months (95% CI, 9.6–16.2), respectively. The number of serious adverse event (SAE) was 59% in arm A and 30.3% in arm B ($p = 0.005$). Trofosfamide caused more often dyspnoea and low-grade fatigue, whereas with doxorubicin, more often leukocytopenia, neutropenia and mucositis were seen. Discontinuation rates for reasons other than disease progression were 15.4% (arm A) vs. 7.9% (arm B). In an elderly population of patients, oral trofosfamide achieved the estimated primary end-point 6-month PFR and was associated with a favourable toxicity profile compared with doxorubicin.

1. Introduction

Doxorubicin (DOX) as a single agent or in combination is the standard cytostatic drug inducing tumour responses in approximately 9–12% (when given singly) of adult patients with advanced soft-tissue sarcoma (STS) in first-line treatment. However, treatment is limited by cumulative cardiotoxicity and frequent neutropenic episodes, which is especially disadvantageous in the palliative setting [1,2]. Two-drug combinations allow higher response rates, which is useful in patients with symptomatic disease or those in whom resection of limited metastatic disease is considered. However, in an unselected population, there is no significant advantage over single-agent treatment or sequential administration in terms of survival, yet there is a marked increase in toxicity even in younger patients [3]. Toxicity limits the use of the available monotherapies and combination therapies in older patients, who make up a considerable and growing proportion of the total patient population. Drug development should therefore focus on an active treatment that is well tolerated in elderly patients. Trofosfamide (TRO) is an alkylating agent, belonging to the family of the oxazaphosphorine prodrugs, with a bioavailability of nearly 100% after oral application. Similar to other oxazaphosphorines, it is activated by hepatic cytochrome P450 oxidase. TRO has been evaluated in a number of solid tumours and haematological neoplasms. Clinical activity was seen in adult and paediatric patients with STS, with time-to-progression (TTP)/progression-free survival (PFS) ranging from 2.5 to 7.0 months [4–14].

2. Patients and methods

2.1. Patient' selection

The main eligibility criteria were as follows: histologically proven metastatic (stage IV: N+ or M1) or unresectable STS, FNCLCC grading II or III [15], at least one measurable tumour lesion according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria [16], evidence of progression or primary manifestation (except osseous metastases and pleural effusion), no previous radiation therapy of target lesion(s), no previous chemotherapy for metastatic disease (previous adjuvant chemotherapy permitted if there was no progression of the disease within a period of 6 months), age $\geq$60 years, written informed consent, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, granulocytes $\geq 2 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, serum creatinine and bilirubin <1.5 x upper limit of normal, albumin >25 g/l, no severe comorbidity including psychosis or any previous history of uncontrolled cardiovascular disease, normal left ventricular function assessed by echocardiography or a multigated acquisition (MUGA) scan, no symptomatic central nervous system metastases and willingness to receive regular follow-up examinations. The main exclusion

criteria comprised FNCLCC low grade; histology of gastrointestinal stromal tumour, chondrosarcoma, uterine stromal sarcoma, mesothelioma, neuroblastoma, osteosarcoma, Ewing sarcoma/primitiv neuroektodermaler tumor (PNET), desmoplastic small-round-cell tumour, embryonal rhabdomyosarcoma, alveolar soft part sarcoma; and less than 5 years free of secondary malignancy except adequately treated carcinoma in situ of the cervix, the bladder urothelium, basal cell carcinoma or adenoma of the colon including pTIS and pTIN. The study was conducted in accordance with the standards of Good Clinical Practice and in agreement with the Declaration of Helsinki. Study protocol was approved by the local ethics committees of all participating centres.

2.2. Study design

This was an open-label, randomised, multicenter phase II trial. The primary end-point was PFR at 6 months. The secondary end-points were treatment-related adverse events (grade III/IV toxicity according to the National Cancer Institute Common Toxicity Criteria [CTCAE] version 2.0), objective remission rate (ORR) according to RECIST criteria (version 1.0), PFS and overall survival (OS). Randomisation was stratified according to general condition (ECOG PS, 0/1 vs. 2) and liver metastases (yes vs. no). A total of 117 patients (39 in arm A = control, 78 in arm B = study drug) were planned to be recruited into the trial.

2.3. Treatment plan

In the arm A group, patients received 60 mg/m^2 ^{of} DOX 60 mg/m on day 1, repeated every 3 weeks, for a maximum of 6 cycles. For patients between 60 and 70 years of age, a dose escalation to 75 mg/m^2 was allowed. The patients were planned to be treated until disease progression or until unacceptable toxicity occurred. Arm B patients received 300 mg/day of TRO per os (P.O.) on days 1–7, then 150 mg/day per os (P.O.) continuously.

2.4. Statistical analysis

The target criterion 6-month PFR after start of treatment (only arm B) was analysed according to the 2-stage design used by Simon [17] (alpha error of 5% and beta error of 20%), with 43 patients in the first stage and 28 additional patients in the second stage (in total, 71 patients). The study was continued and completed to the estimated full sample of patients as planned since an interim analysis for futility at the first stage revealed a success rate of >6 out of 43 [18]. Thus, the acceptance limit of non-efficacy was ≤14 out of 71. This target criterion was aimed at a success rate of 25%, as described for DOX by the European Organisation for Research and Treatment of Cancer (EORTC) database [1]. A drop-out rate of 10% was calculated. Control arm A using DOX was introduced into the trial to describe the recruited patients in terms of response to standard treatment, thereby to verify the target rate of the design used by Simon [[17]] and identify trends in terms of differences in tolerability among both drugs. Given this objective, control arm A consisted of 39 patients (randomisation at a ratio of 1:2). Comparisons regarding side effects between both arms were carried out using Fisher's exact test. Analysis of the patients' characteristics has been performed descriptively. Explicit p values have been given in case of any explorative statistical tests performed to compare the treatment arms. An adjustment of the significance level with regard to a multiplicity of the analysis was not performed, and therefore, the p values reflect an error related to the individual comparison and not to the overall experiment. A two-sided significance level of 5% was used.

3. Results

3.1. Patient' characteristics

A total of 120 patients were enrolled in the study from 16 oncological practices-as well as hospitals located in Germany and France between 3rd August 2004 and 8th October 2012. Of the 120 patients randomly assigned to each arm, five patients had been randomised but refused treatment or never received the study drug owing to rapid progressive disease (PD). In addition, another patient did not fulfil the inclusion criteria owing to an extensive thoracic skin involvement not enabling implantation of a permanent port catheter. Thus, the per-protocol population consisted of 114 patients (arm A, 39 patients; arm B, 75 patients), the intention-to-treat (ITT) cohort, of 120 patients and the safety population, of 115 patients (Consolidated Standards of Reporting Trials (CONSORT) diagram). No statistical differences in baseline characteristics were found between both arms, with exception of tumour grading (grade II vs. III). The median age was 70 years (range, 60–89 years). Fifty-two percent of patients were males, and 85% had an ECOG PS of 0 or 1. The frequent histologic subtypes were pleomorphic sarcoma, leiomyosarcoma and liposarcoma (33%, 23% and 13%, respectively). Approximately one third of patients have had either 1, 2 or 3 + metastatic sites at study inclusion. Most frequent sites observed had been the lung, liver and bone (Table 1).

3.2. Safety assessment

Safety analyses in 115 patients revealed at least one side-effect in 97.4% vs. 96.1% patients (p = 0.99) (Table 2). The median number of cycles was 5 (range, 1 to 6) and 4 (range, 0 to 60), respectively. TRO has been applied up to a maximum of 60 cycles, corresponding to a

Table 1
Patient characteristics.

Characteristics		DOX (N = 40), N (%)	TRO (N = 80), N (%)
Sex	Male	23 (57.5)	40 (50.0)
	Female	17 (42.5)	40 (50.0)
Age (years)	Median (range)	70.5 (60–84)	70.0 (60–89)
Grading	II/III/n.a.	22/18/0	26/48/6
ECOG	0	16 (40.0)	37 (46.3)
	1	18 (45.0)	31 (38.8)
	2	6 (15.0)	12 (15.0)
Histology	Pleomorphic, NOS	15 (37.5)	24 (30.0)
	LMS	9 (22.5)	19 (23.8)
	LS	7 (17.5)	9 (11.3)
	Angiosarcoma	2 (5.0)	7 (8.8)
	RMS, pleomorphic	–	4 (5.0)
	MPNST	2 (5.0)	2 (2.5)
	Other	5 (12.5)	15 (18.8)
Time to metastasis	NOS	23 (57.5)	40 (50.0)
N of LAD vs. metastatic disease		5 vs 35	7 vs 73
N of metastaticsites	1	12 (30.0)	24 (30.0)
	2	13 (32.5)	30 (37.5)
	3 or more	15 (37.5)	26 (32.5)
Metastatic sites (selected)	Lung	26 (65.0)	52 (65.0)
	Liver	12 (30.0)	16 (20.0)
	Bone	8 (20.0)	14 (17.5)
	CNS	1 (2.5)	1 (1.3)

ECOG, Eastern Cooperative Oncology Group; DOX, doxorubicin; TRO, trofosfamide; N, number; LS, liposarcoma; LMS, leiomyosarcoma; RMS, rhabdomyosarcoma; NOS, not otherwise specified; MPNST, malignant peripheral nerve sheath tumour; CNS, central nervous system; n.a., not available; LAD, locally advanced disease.

treatment period of 41 months. Approximately 10% of patients underwent treatment with TRO for more than 1 year, demonstrating a favourable toxicity profile enabling long-lasting treatment application (Fig. 1). Of note, severe side-effects (grade III or IV) were lower in favour of arm B (59% vs. 30.3%, respectively; $p = 0.005$). TRO caused more often dyspnoea, fatigue (grade I/II), whereas with DOX, more often leukocytopenia and neutropenia as well as mucositis were seen. The discontinuation rate other than PD was higher in arm A, with 15.4% than 7.9% (arm B). The death rate of all causes within 60 days of initiation of the study drug was equal to 7.7% and 8.0%, respectively.

Table 2
Potentially chemotherapy-associated adverse events (whether related or not) assessed in the safety population according to the treatment group.

Adverse event (AE)	Arm A (DOX), n = 39			Arm B (TRO), n = 76			p-value
	All grades	Grade III	Grade IV	All grades	Grade III	Grade IV	
	%	%	%	%	%	%	
Anaemia	76.9	7.7	2.6	69.7	9.2	–	0.5118
Leukocytopenia	66.7	28.2	7.7	60.5	7.9	1.3	0.5485
Nausea	53.8	–	–	44.7	3.9	–	0.4313
Asthenia	38.5	–	–	30.3	2.6	1.3	0.4073
Dyspnoea	7.7	–	2.6	27.6	3.9	1.3	0.0148
Fatigue	7.7	5.1	–	25.0	5.3	–	0.0264
Vomiting	35.9	–	–	21,1	2.6	–	0.1161
Diarrhoea	15.4	2.6	–	19.7	–	–	0.6208
Thrombocytopenia	25.6	–	–	18.4	1.3	–	0.4677
Obstipation	12.8	–	–	17.1	3.9	3.9	0.6014
Neutropenia	56.4	15.4	17.9	14.5	1.3	–	<0.0001
Dizziness	10.3	–	–	11.8	–	–	0.9999
Cough	5.1	–	–	10.5	1.3	–	0.4907
Mucositis	35.9	2.6	–	9.2	–	–	0.0008
Other neurotoxicity	5.1	–	–	1.3	–	–	0.2651
Other	76.9	10.3	2.6	63.2	13.2	3.9	0.1470
Deaths			7.7			8.0	

NCI, National Cancer Institute; DOX, doxorubicin; TRO, trofosfamide; CTCAE, NCI common terminology criteria for adverse events. * Death of all causes within 60 days of initiation of study drug.
Fisher (2-sided, alpha = 0.05). Grade according to NCI-CTCAE version 2.0. A toxicity is counted only once per patient. A patient with several grades of toxicity is counted once with the highest grade.

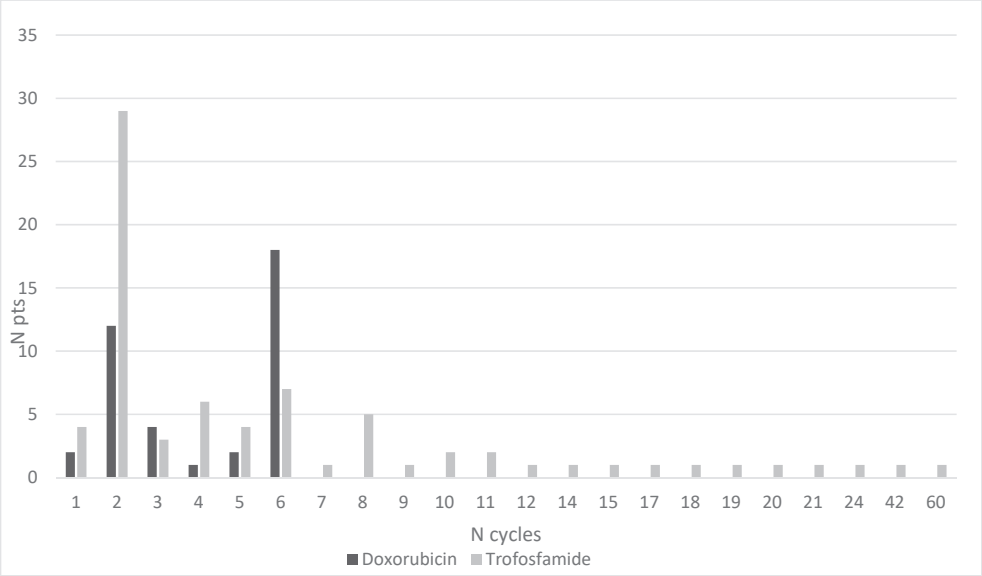

Fig. 1. Comparison of treatment cycles in elderly patients with previously untreated metastatic soft-tissue sarcoma.

3.3. Efficacy assessment

At the time of data capture closure (5th December 2017), the median duration of follow-up of all patients was 10.4 months (range, 0.4–94.7) and 18.4 months (range, 3.8–94.7 months; arm A, 26.0 months; arm B, 15.2 months) for surviving patients. The primary study end-point was met. The 6-month PFR was determined to be 27.6% (95% confidence interval [CI], 18.0–39.1). The median treatment duration was 2.8 months (0–4.6) in arm A and 2.8 months (0.4–41.4) in arm B. The objective response rate was 7.7% (1.6–20.9) in arm A (no complete remission [CR]; 3 partial remissions [PRs]) and 6.6% (2.2–14.7%) in arm B (2 CRs; 3 PRs); the disease control rate (including disease stabilisation) was 53.8% (95% CI, 37.2–69.9%) and 40.8% (95% CI, 29.6–52.7%) (Table 3); the PFS was 4.3 months (95% CI, 2.2–6.3) and 2.8 months (95% CI, 1.7–3.6); the OS was 9.8 months (95% CI, 6.7–11.6) and 12.3 months (95% CI, 9.6–16.2) (Figs. 2 and 3). No difference was found in the ITT and per-protocol population. duration of response (CR/PR/no change (disease stabilisation) (NC)) was 5.0 months in arm A (range, 1.3–8.0) and 4.0 (0–46.6 months) in arm B. In arm B, the two patients achieving a CR with TRO achieved a response duration of 8.8 and 46.6 months. Patients with PR as the best response had a median response duration of 4.3 months in control arm A compared with 8.2 months in arm B with TRO. No CR was seen in arm A (Table 3).

4. Discussion

Oral TRO has a bioavailability of almost 100% after oral intake. It is activated via hepatic cytochrome P450 oxidase; the main metabolites are 4-hydroxy-TRO and 4-hydroxy-ifosfamide. The substance is predominantly eliminated via the kidneys. Until now, only phase II trial experience is available. A Finnish study included 23 patients with metastatic STS with TRO given as first-line treatment in 12 and as salvage treatment in 11 patients. Dosing was a 150-mg flat dose and was escalated to 50-mg increments every 3 weeks up to a maximum tolerable dose (MTD), with dose-limiting toxicity (DLT) defined as leukopenia grade II. The MTD was 200–250 mg. In that study, PR was observed in 3

Table 3
Objective response and response duration.

ORR		Arm A (DOX) (n = 39) (%)			Arm B (TRO) (n = 75) (%)
CR		0			2.6 (2)
PR		7.7 (3)			3.9 (3)
SD		53.8 (21)			40.8 (31)
PD		33.3 (13)			55.3 (42)
missing		12.8 (5)			3.9 (3)
Arm	Duration (months)				
	ORR	No. of patients	Median	Minimum	Maximum
A, DOX	PR	3	4.3	2.2	5.6
	SD	18	5.8	1.3	8.0
	CR/PR/SD	21	5.0	1.3	8.0
B, TRO	CR	2	27.7	8.8	46.6
	PR	3	8.2	1.4	14.9
	SD	26	3.1	0.0	26.9
	CR/PR/SD	31	4.0	0.0	46.6

Month = 30.4375 days, patient 53 (SD as best response) had progression lower than 6 weeks after start of therapy and is included in this table with 0.0 months tumor assessments are based on RECIST 1.0.

RECIST, Response Evaluation Criteria in Solid Tumours; DOX, doxorubicin; TRO, trofosfamide; ORR, objective remission; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

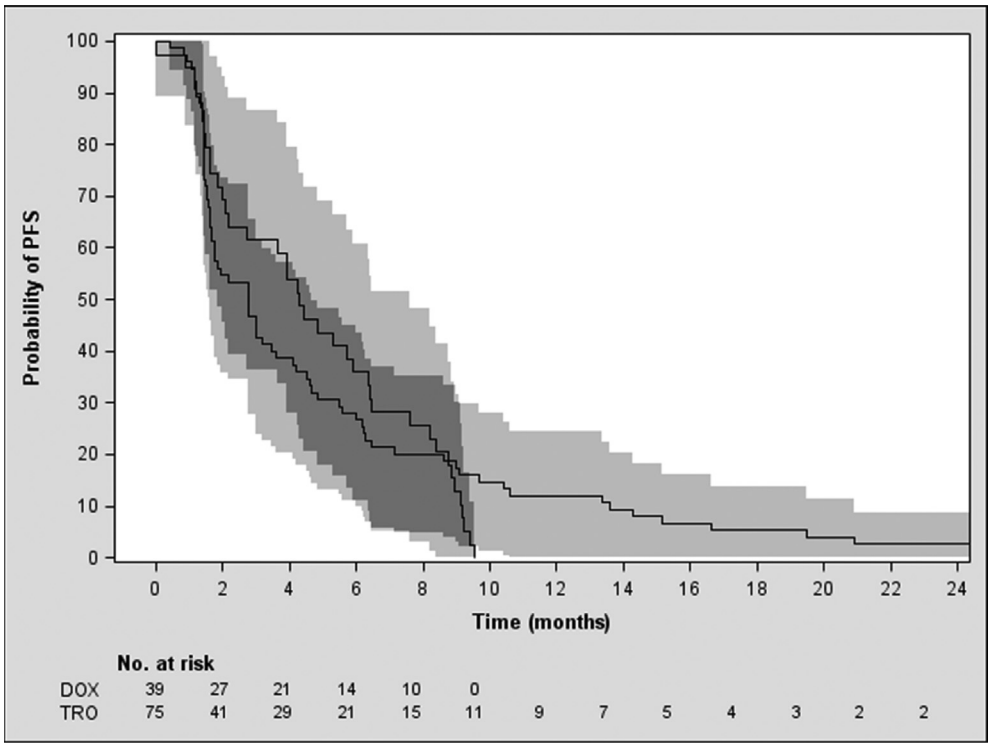

Fig. 2. Progression-free survival in elderly patients with previously untreated metastatic sarcoma in the intention-to-treat population. PFS events: 114 (100% of pts), Median PFS DOX: 4.3 months, Median PFS TRO: 2.8 months. DOX, doxorubicin; TRO, trofosfamide; PFS, progression-free survival.

patients, all of them previously untreated. Stabilisation of the disease was achieved in 6 patients. The median TTP was 3 months (2 weeks–18 months) [10]. Two other phase II trials were conducted on pretreated metastatic STS, treating another 18 patients each [11,12]. In those trials, 300 mg/day of TRO was given for 7 days, and then, the dose was reduced to 150 mg/day continuously until tumour progression. Notably, three PRs were observed in one trial (18% ORR), and a disease stabilisation of approximately 50% was seen in both trials, with a median PFS of 4 and 5.5 months, respectively. Nevertheless, the exact mechanism of action of continuous low-dose TRO, although thought to be antiangiogenic in nature [19], remains unclear. In a published case report, a CR was achieved with single-agent continuous low-dose TRO [19]. All previous trials share a very tolerable toxicity profile, mostly consisting of dose-dependent haematotoxicity, leucopenia and a few cases of gastrointestinal toxicity such as nausea. Haemorrhagic cystitis or a higher grade of nephrotoxicity or neurotoxicity has not been reported for low-dose continuous administration so far compared with intravenous use of other oxazophosphorine alkylating agents such as ifosfamide or cyclophosphamide. No particular toxicity was seen in elderly patients in these trials, given that the convenient oral drug application route prompted this randomised phase II trial. To avoid undertreatment in terms of efficacy, an interim analysis was preplanned and performed [18]. After inclusion of the total number of patients, the trial endpoint PFR at 6 months was met in arm B. The present analysis suggests that TRO might have an activity comparable with DOX in terms of ORR, PFS and OS when treated with palliative intent. A distinct number of long-lasting responses were seen in approximately 10% of patients receiving TRO compared with those in the standard arm, with all patients having progressed after 10 months. Of course, arm A had an inherent drug-specific disadvantage as DOX was given for a maximum of 6 cycles while TRO was allowed to be given continuously. Nonetheless, treatment with DOX is limited owing to a rapid increase in cardiotoxicity when the maximum cumulative dose is exceeded, which precluded the design of such trial. This trial underscores that it is feasible to use TRO continuously even in this elderly population. Notably one patient received treatment for 60 cycles, corresponding to 41 months of treatment. To this end, it is remarkable how the Kaplan–Meier curves cross after 8 months of treatment, resulting in a 12-month PFR of 11.8% (5.6–21.3%) vs 0% (0–9.0%). Apart from the observation in this elderly population, this data underscore the potential value of an oral maintenance therapy with TRO that is used by many centres despite the lack of a proper randomised trial.

Treatment of elderly patients is not free of risk. The 60-day mortality rate was 8% in both arms, meaning

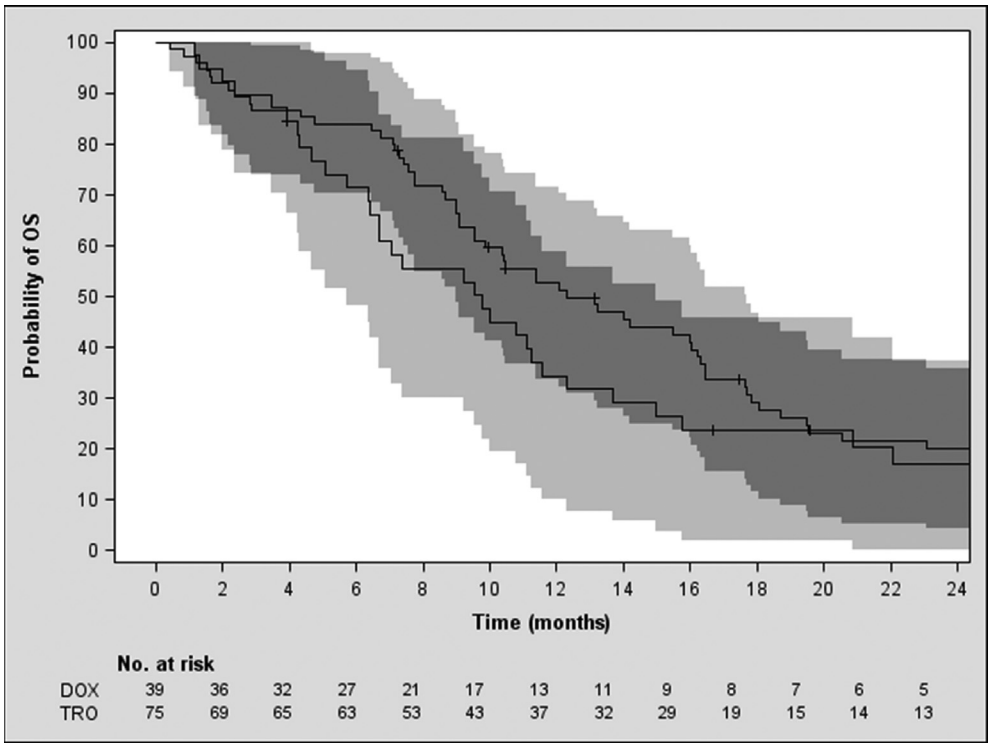

Fig. 3. Overall survival in elderly patients with previously untreated metastatic soft-tissue sarcoma in the intention-to-treat population. 0S events: 100 (88% of pts), Median OS DOX: 9.8 mos, Median OS TRO: 12.3 mos. DOX, doxorubicin; TRO, trofosfamide; OS, overall survival.

that almost every 12th patient is at risk of dying from treatment complication and/or early disease progression. The grade III through IV toxicity level was significantly lower in favour of the experimental drug. In terms of specific toxicity, TRO more often significantly caused grade I/II dyspnoea and fatigue. No unexpected adverse drug reaction occurred during the trial, and discontinuation of treatment due to reasons other than progression was also lower in patients treated with TRO. We still believe that the dire prognosis of untreated metastatic STS justifies the treatment by far, outweighing the risks.

This academic-initiated trial and the analysis are certainly limited by the phase II design, not being a fully powered comparison of both arms with a limited sample size. As with all phase II studies, these results are hypothesis generating and have to be validated in further clinical trials, e.g., comparative phase III studies. It has to be discussed that the threshold level to consider the study as positive was a 25% PFR based on EORTC trial data from the early millennium years. However, the PFR rate of DOX was on the same activity level. In more recent phase III trials, there appears to be a trend to a higher level of activity of DOX when used as a single agent. But it is not proven whether these results are achievable in trials focussing on a strict elderly population because the median age of patients at trial inclusion in age-unrestricted trials was about 55 years with a proportion of the quarter being older than 65 years. Those patients differ considerably in terms of comorbidities, accompanying medications, drug interactions and general health status from the population included within the current trial, with patients with a median age of 70 years. This was also a clear palliative trial setting where an aggressive approach was not part of the treatment concept, and therefore, patients with a chance of secondary resection of metastases were not included in the trial. But the field of geriatric oncology is definitively changing because the general population is getting more and more older, and it is reasonable to weigh out whether a 60-year-old patient is still elderly because the general health of such patients has improved significantly over the last decades in the Western countries, reflected by the larger proportion of people between 60 and 65 years of age still working. This should be considered in further trials by using methods such as geriatric assessments to evaluate those patients appropriately. There is also a constant debate on the appropriate starting dosage of DOX, particularly in the light of a possible dose-response relationship. However, this is unproven and thus speculative. Nowadays, a dose of 75 mg/m^2 is certainly tolerable in a fit 70-year-old patient with modern supportive care and would be an appropriate starting dose. On the other hand, this trial in general identified a higher toxicity level even with a lower dose of 60 mg/m^2 in a context of a treatment with palliative intent and a population being at risk of occurrence of severe toxicity. Central histological review

was undertaken and realised in 64% (77/120) of tumour specimens; however, it cannot be excluded that miscellaneous histological subtypes, as observed in the same degree in other metastatic sarcoma trials with limited case numbers, have influenced the results among both arms. In an elderly population of patients free of symptoms, we consider disease control a sufficient treatment goal of a systemic therapy as shrinkage would not affect quality of life. According to data from the EORTC database [20], achievement of a response is not associated with longer survival than disease stabilisation. Particularly in elderly and unfit patients, avoiding toxicity appears to be paramount to avoid deterioration of PS or frailty. In general, based on previous crossover studies, the majority of patients prefer oral over intravenous treatment [21]. In conclusion, to our knowledge, the current trial is the first randomised trial investigating a drug in an elderly population with metastatic STS. Patients treated with TRO showed comparable survival data and a more favourable safety profile as seen with the current reference drug DOX. However, it should be stressed again that this trial was not powered as an equivalence study and it cannot be concluded that TRO is as active as DOX from the trial results. However, TRO might be a reasonable alternative to DOX in elderly or unfit patients without a chance of curative secondary surgery, who prefer an oral drug with less need for supportive care medications and less toxicity and who like to avoid hospital visits for neutropenic fever and infections due to central catheter devices.

5. Conclusion

In an elderly population of patients with metastatic sarcoma, oral continuous (metronomic) TRO met the protocol predefined end-point. On a basis of a randomised phase II design, trofosfamide was associated with a more favourable toxicity profile than the current standard single-agent DOX.

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Conflict of interest statement

J.T.H. has an advisory and/or speaker role for Roche, Genomic Health, Dres Schlegel & Schmidt, Ipsen Pharma and Excellence in Oncology. He has received research funding from the German Cancer Aid, H.W. & J. Hector Stifung, Federal Ministry of Education and Research and Pfizer. S.B. has an advisory role for Blueprint Medicines, ADC Therapeutics, Lilly, Novartis, Daichii, Plexxikon, Nanobiotix, Deciphera, Exelixis and Janssen-Cilag. He has received continuing medical education (CME) honoraria from Novartis, Pfizer, Bayer, Lilly and PharmaMar and research funding from Blueprint Medicines, Incyte and Novartis. V.G. has an advisory role for AstraZeneca, Bayer, BMS, EUSA Pharm, Ipsen, Pfizer, MSD, Lilly and PharmaMar. Novartis, Merck Serono, Janssen-Cliag, Exelexis, Roche, Eisai, Cerulean and Promedior. He has received research funding from AstraZeneca, BMS, MSD, IKF, Pfizer, Ipsen, Novartis, Janssen-Cliag and Roche. None of these companies are related to or have influenced the work presented here. All other authors stated no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.10.016.

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