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Current Perspective

The fate of new fosfamides in phase III studies in advanced soft tissue sarcoma

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Abstract For decades, doxorubicin alone or in combination with ifosfamide has been used in advanced soft tissue sarcoma (STS). In 2014, a comparison of doxorubicin alone versus the combination with ifosfamide (in the randomised phase III EORTC 62012) showed no difference in overall survival (OS), but a difference in response and progression-free survival (PFS) were observed in favour of the combination but at the expense of increased toxicity. Newer fosfamides, with slightly different modes of action, and potentially less toxicity, namely evofosfamide and palifosfamide have recently been tested in randomised phase III clinical trials in STS. The TH CR-406/SARC021 (June 2017) and the PICASSO III (September 2016) studies compared doxorubicin, as the standard arm, to doxorubicin in combination with evofosfamide and palifosfamide, respectively. In both studies, the combination arm produced increased response rates but at the expense of higher toxicity. However, there was no difference in OS or PFS in favour of the combination. Importantly, the median OS of patients receiving standard of care, doxorubicin, in both studies appeared improved from 12.8 months (95.5% CI 10.5–14·III) in the EORTC 62012 to 16.9 months (95% CI 14.8 to 22.9) in PICASSO III and 19.0 months (95% CI 16.2–22.4) in TH CR-406/SARC021. The results of these three randomised phase III studies highlight several critical issues related to the design and conduct of such trials in STS. We discuss these issues aiming to contribute to the ongoing debate about the optimal approach to perform clinical research in STS.

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Sarcomas are a rare group of heterogeneous mesenchymal tumours comprising over 70 histological subtypes of varying underlying biological and clinical behaviour [1]. Management is challenging because of the rarity and the diversity of the disease. Despite significant advances in the molecular characterisation and classification of sarcomas, effective targeted therapy has only truly influenced the outcomes of patients with gastrointestinal stromal tumours with activating mutations in KIT or PDGFRA after the introduction of multitargeted tyrosine kinase inhibitors [2]. In contrast, for most soft tissue sarcomas (STSs), conventional chemotherapy remains the standard systemic option in the advanced/metastatic setting with two drugs monopolising first-line treatment over the last few decades: doxorubicin [3,4] and ifosfamide [5]. For many years, empirically, doxorubicin was used as monotherapy or in combination with ifosfamide. A head-to-head comparison of the two regimens (EORTC 62012: doxorubicin alone or in combination with ifosfamide) in a randomised controlled phase III trial (RCT) reported in 2014 showed no difference in overall survival (OS), although a difference in progression-free survival (PFS) in favour of the combination was noted at the expense of increased toxicity [6].

Ifosfamide is an alkylating agent undergoing transformation in the liver to become active. The toxicity profile of ifosfamide, primarily the risk of bone marrow suppression, haemorrhagic cystitis and encephalopathy, has provided the rationale for the development of newer analogues with less toxic metabolites. One such agent, palifosfamide, is a tris salt of isophosphoramide mustard, the active metabolite of ifosfamide. Another analogue is evofosfamide, a hypoxia-activated prodrug of bromo-isophosphoramide mustard, which under hypoxic conditions, can function as a DNA cross-linking agent [7]. Tap *et al.* report, in the Lancet Oncology (June 23, 2017 epub ahead of print), the results of TH CR-406/SARC021, a phase III, multicentre, randomised, open-label trial assigning patients with advanced or metastatic STS to receive either doxorubicin alone or in combination with evofosfamide as first-line treatment, with continuation of evofosfamide in non-progressive patients [8]. Evofosfamide had previously demonstrated activity against advanced STS in combination with doxorubicin in a single-arm phase II trial of 91 patients [9], reaching a median OS of 21.5 months (95% CI 16.0–26.2) and a median PFS of 6.5 months (95% CI 5.8–7.7).

One of the main hurdles in clinical research in sarcoma is the difficulty to design and conduct large prospective RCT within reasonable timelines. Given these limitations, the authors of the TH CR-406/SARC021 should be congratulated for performing and completing this phase III study in a timely manner (enrolment of 640 patients between September 2011 and January 2014). Patients were eligible if they were 15 years and older, had advanced or metastatic STS with no standard curative therapy available, measurable disease and performance status of 0–1. The primary objective was OS in the intention-to-treat population. Secondary end-points included PFS and overall response rate. Patients were randomly assigned to a maximum of six cycles of doxorubicin 75 mg/m^2 intravenously on day 1 of every 21 d cycle, or doxorubicin plus evofosfamide 300 mg/m^2 intravenously on days 1 and 8 of every 21 d cycle, plus continuation of single-agent evofosfamide in non-progressive patients. The OS end-point was not reached (Hazard Ratio (HR) 1.06, 95% CI 0.88–1.29; p = 0.527), but the median OS was 18.4 months (95% CI 15.6–22.1) with doxorubicin plus evofosfamide versus 19.0 months (95% CI 16.2–22.4) with doxorubicin alone. Remarkable benefit was seen in the subgroup of 31 synovial sarcoma patients with a HR 0·III2 (95% CI 0.14–0.73III; p = 0.0043) in favour of the combination treatment.

Median PFS was similar in the two groups (6.3 months (95% CI 6.0–7.8) in the combination group versus 6.0 months (95% CI 4.6–6.2) in the doxorubicin alone group). In contrast, the proportion of patients who achieved complete or partial response was significantly higher in the combination group than in the doxorubicin alone group (28% versus 18% of patients; p = 0·0026). A complete and partial response was documented in 2% and 27% of patients treated with the combination, respectively, and in 1% and 17%, respectively, with doxorubicin alone. The proportion of patients achieving disease control (complete response, partial response or stable disease) was 73% in the combination group and 66% in the doxorubicin alone group (odds ratio [OR] 1.49 [95% CI 0.54–1.36], p = 0.0473).

These results raise two critically important points. The first one is that TH CR-406/SARC021 is yet another randomised controlled phase III study in the recent history of clinical trials in advanced STS to show no difference in PFS or OS between the experimental arm and the control arm; potentially rendering the new agent (in this occasion evofosfamide) 'non-interesting' in sarcoma in the eyes of the pharmaceutical industry. The second point is that TH CR-406/SARC021 and other studies reported recently, including PICASSO III (a phase III, multicentre, randomised, double-blind, placebo-controlled trial assigning patients with STS to receive either doxorubicin plus palifosfamide or doxorubicin plus placebo, as first-line treatment) [10], have shown an impressive increase of the median OS in the control arm compared to what studies in the past had shown (EORTC 62012). It appears that the median OS of patients with advanced disease receiving standard of care treatment (doxorubicin) in first-line phase III studies has improved over the last decade from 12.8 months (95.5% CI 10.5–14.3) (EORTC 62012) to 16.9 months (95% CI 14.8–22.9) (PICASSO III) and 19.0 months (95% CI 16.2–22.4) (TH CR-406/SARC021) (Table 1).

Given these two facts, the burning question about TH CR-406/SARC021 is whether the benefit of the novel agent is indeed absent or whether the control arm is too good to allow the detection of any potential benefit. There are now two similar examples of promising ifosfamide-alike agents in sarcoma, palifosfamide and evofosfamide, where phase III trials failed to confirm therapeutic benefits seen in randomised phase II studies [9,11]. Whilst this phenomenon can be attributed to the limitations of study design in randomised trials in heterogeneous diseases like STS, other possible explanations include the incorporation of newer treatments in sarcoma therapeutics, particularly in second-line treatment and beyond, local procedures in metastatic setting, as well as important advances in palliative and supportive care. One should also consider, as a possible contributing factor, the increased emphasis now placed on the accurate histological diagnosis of soft sarcoma subtypes using central pathology review to better specify sarcoma subtypes and to avoid inclusion of non-sarcoma malignancies in clinical trials (with worse prognosis and worse response to doxorubicin), which may have partly masked the true median OS of the standard chemotherapy in the past. This is also illustrated in a second analysis of the EORTC 62012 study based on central pathology review showing an OS benefit for the undifferentiated pleiomorphic subgroup [12].

Setting PFS or OS as the primary end-point in RCT in STS has been under debate for years. Noticeably, in the EORTC 62012 trial, the primary end-point was OS benefit, but this was subsequently criticised as a complex and easily confounded measure of therapeutic efficacy over PFS and response rate in a diverse group of rare diseases such as STS, where perhaps the bar of treatment success was set too high [13]. Interestingly, when PICASSO III was originally designed, the primary end-point was OS, but in order to obtain accelerated approval by the US Food and Drug Administration and following completion of recruitment of all patients, the primary end-point was changed to PFS without altering the sample size or the statistical considerations made at the start. In the TH CR-406/SARC021, PFS was not set as the primary end-point because of concerns that it could have been confounded by inherent weaknesses introduced by the design of the study, such as the absence of placebo or study blind. Data provided by real-life observational studies such as the recently published 'METASARC' [14] highlight the limitations associated with the design and outcomes of clinical trials. Time to next treatment is suggested as a surrogate end-point for OS given their strong correlation.

Table 2
Phenotypical characteristics.

Trial	Progression before study entry	Percentage of female patients Doxorubicin versus combination	Median age (year) Doxorubicin versus combination
SARC021	Not required	53 versus 55	58 versus 50
PICASSO	Not mentioned	47 versus 46	56 versus 58
EORTC 62012	Yes within 6 weeks before start (RECIST 1.0)	55 versus 50	48 versus 47

Despite the lack of OS benefit, the proportion of patients who achieved complete or partial response was significantly higher in the doxorubicin plus evofosfamide group than in the doxorubicin alone group. Similarly in the PICASSO III, there were more objective responses among patients treated with doxorubicin plus palifosfamide than with doxorubicin plus placebo; and interestingly, response rates in both arms were similar to those reported in EORTC 62012. The results of all three studies show that response rate results have limited clinical significance in the absence of survival benefit in STS and, as was shown in the EORTC 62012, absence of progression could be used as a better surrogate for final outcome [15].

Apart from differences in histological subtypes, the biological behaviour and progress of metastases in STS can also differ substantially. Without the requirement of documented progression within a well-defined time period before the start of a study, the risk of introducing

Table 1
Accrual and end-points of the trials.

Trial	Primary end-point	Accrual period	Number of patients	RR (%) doxorubicin versus combination	PFS (months) doxorubicin versus combination	OS (months) doxorubicin (plus placebo) versus combination
SARC021	OS	2011–2014	640	18 versus 28	6.0 versus 6.3 95% CI 4.6–6.2 versus 6.0–7.8	19.0 versus 18.4 95% CI 16.2–22.4 versus 15.6–22.1
PICASSO	PFS	2010–2012	447	20 versus 28	5.2 versus 6.0 95% CI 4.2–6.0 versus 5.4–6.5	16.9 versus 15.9 95% CI 14.8–22.9 versus 13.7–19.4
EORTC 62012	OS	2003–2010	455	14 versus 26	4.6 versus 7.4 95% CI 2.9–5.6 versus 6.6–8.3	12.8 versus 14.3 95% CI 10.5–14.3 versus 12.5–16.5

SARC021: Doxorubicin versus doxorubicin plus evofosfamide.
PICASSO: Doxorubicin plus placebo versus doxorubicin plus palifosfamide.
EORTC 62012: Doxorubicin versus doxorubicin plus ifosfamide.

Table 3
Histology in the different trials.

Trial	Pathology review	Leiomyosarcoma (%) D versus C	Liposarcoma (%) D versus C	Synovial sarcoma (%) D versus C	UPS (%) D versus C	Other (%) D versus C
SARC021	Central	32 versus 36	16 versus 19	3 versus 5	25 versus 21	8 versus 3
PICASSO	Central	31 versus 30	18 versus 12	5 versus 5	29 versus 38	10 versus 7
EORTC 62012	Local	24 versus 26	11 versus 14	17 versus 11	Not mentioned	48 versus 49

C, combination of doxorubicin and evofosfamide (SARC021), palifosfamide (PICASSO III) and ifosfamide (EORTC 62012); D, doxorubicin; UPS, undifferentiated pleiomorphic sarcoma.

unwanted bias is realistic. The attraction to put patients on a competitive clinical study with a new drug may introduce a selection of relatively fit patients with low-volume metastatic disease. Prolongation of median PFS to over 6 months in patients treated with single-agent doxorubicin could be an indirect reflection of this statement. As shown in Table 2, this information is not provided in the TH CR-406/SARC021 or the PICASSO III, although one can appreciate how imbalance in the disease progression status between the groups could have easily affected the survival outcomes in favour of either of the groups. The importance of this observation is lying in the potentially critical role of ensuring homogeneity of clinical/phenotypical data for patients entering clinical trials; in the absence of representative biomarkers and given the biological heterogeneity of the disease, enrolling only patients with the same disease status (i.e. well-defined progressive disease) is important in testing novel agents in STS. The EORTC 62012 study has been the only one requiring documented progression within the last 6 weeks before study entry and as such has probably had patients with more aggressive phenotype on study, leading to the shortest OS of the trials as described.

In recent years, there has been criticism about the 'one-size-fits-all' approach in clinical trials design in STS where a specific drug or regimen is given to various histological subtypes lumped together; it has been clear for some time now that certain STS histologies respond better than others to particular agents [16] and lumping different subtypes together may lead to inaccurate and misleading conclusions. Balancing different subtypes between two treatment arms is extremely challenging in a disease that contains over 70 histological subtypes. In the TH CR-406/SARC021 by and large, this balance was achieved between the two arms (leiomyosarcoma 35% versus 37%, liposarcoma 15% versus 20%), whereas in the PICASSO III trial, some subgroups were less or not balanced (liposarcoma 11.9% versus 18.1% and pleomorphic/undifferentiated/sarcoma, NOS 37.6% versus 28.5%; Table 3). Therefore, to the extent that this is feasible, efforts should be made to focus on specific tumour subtypes.

In terms of safety, in both the PICASSO III and the TH CR-406/SARC021, patients in the combination arms experienced more grade III and IV adverse events compared to single-agent doxorubicin, although the toxicity profile of the newer 'fosfamides' (palifosfamide and evofosfamide) appeared better than that of ifosfamide.

Conclusion

Design and conduct of clinical research in STS is hampered by the rarity and the heterogeneity of the disease. With advances to date, the therapeutic landscape has started to change. Important information derived from RCTs such as the TH CR-406/SARC021 and the PICASSO III should be used to guide future efforts in clinical and translational research. Collaborative efforts are required to ensure that trial design should lead to homogeneous groups to compare as possible within the framework of meaningful statistics. Median OS should be reconsidered in control arms of randomised studies taking the biological behaviour of soft tissues sarcomas into account.

Conflict of interest statement

AC has no conflict of interest to declare. WVG has been in the advisory board of Pharmamar and Bayer, as well as involved in research projects with Novartis and GSK.

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