First-line chemotherapy in advanced intrabdominal well-differentiated/dedifferentiated liposarcoma: an EORTC Soft Tissue and Bone Sarcoma Group retrospective analysis

Stacchiotti, S.; Graaf, W.T.A. van der; Sanfilippo, R.G.; Marreaud, S.I.; Houdt, W.J. van; Judson, I.R.; ... ; Kasper, B.

Original Article

First-line chemotherapy in advanced intra-abdominal well-differentiated/dedifferentiated liposarcoma: An EORTC Soft Tissue and Bone Sarcoma Group retrospective analysis

Silvia Stacchiotti, MD [1]; Winette T. A. Van der Graaf, MD, PhD [2,3]; Roberta G. Sanfilippo, MD[1]; Sandrine I. Marreaud, MD[4]; Winan J. Van Houdt, MD, PhD [5]; Ian R. Judson, MDI[6]; Alessandro Gronchi, MD[7]; Hans Gelderblom, MD, PhD [8]; Saskia Litiere, MSc, PhD[4]; and Bernd Kasper, MD, PhD [9]

BACKGROUND: No prospective trial with anthracycline-based chemotherapy has individually assessed response in a well-differentiated (WD)/dedifferentiated (DD) liposarcoma patient cohort. We conducted a retrospective analysis of first-line chemotherapy in liposarcoma of intra-abdominal origin (IA-LPS) in patients who had entered the European Organisation for Research and Treatment of Cancer (EORTC)/Soft Tissue and Bone Sarcoma Group (STBSG) trials. **METHODS:** We searched for all adult patients treated with first-line chemotherapy for advanced IA-LPS in the EORTC STBSG phase 2 and 3 trials from 1978. Treatment was aggregated into 5 groups: anthracycline alone, ifosfamide alone, doxorubicin plus ifosfamide (D+IFO), doxorubicin/cyclophosphamide/vincristine/dacarbazine, and "other" (brostallicin, trabectedin). Response was assessed prospectively by Response Evaluation Criteria in Solid Tumors or World Health Organization criteria. Progression-free survival (PFS) and overall survival (OS) were computed by Kaplan-Meier method. **RESULTS:** A total of 109 patients with IA-LPS from 13 trials were identified (104 evaluable for response). Overall, there were 10/109 (9.2%) responders: 3/48 (6.3%) in the anthracycline alone group, 2/15 (13%) in the ifosfamide alone group, and 4/18 (22%) in the D+IFO group. At the 10-month median follow-up (interquartile range, 6-24), the median OS was 19 months (95% CI, 15-21) and median PFS 4 months (95% CI, 3-6). D+IFO achieved a not statistically significant longer median PFS (12 months) and median OS (31 months) than observed with other regimens. Univariate/multivariate analysis did not identify prognostic factors. **CONCLUSIONS:** Cytotoxic chemotherapy, in particular anthracycline alone, had marginal activity in advanced IA-LPS. Ifosfamide-containing regimens showed higher activity, although it was not statistically significant and in a small number of cases, with the combination of doxorubicin and ifosfamide appearing to be the more active regimen available in fit patients. This series provides a benchmark for future trials on new drugs in WD/DD liposarcoma. ***Cancer* 2022;128:2932-2938**. © *2022 American Cancer Society*.

KEYWORDS: anthracycline, chemotherapy, doxorubicin, epirubicin, ifosfamide, liposarcoma, sarcoma.

INTRODUCTION

Soft tissue sarcomas (STS) are a rare and heterogeneous group of malignancies of mesenchymal origin.[1] Excluding gastrointestinal stromal tumors and unclassified pleomorphic sarcomas, liposarcoma represents the most frequent histological type of tumor in adults.[2] Based on specific immunohistochemical and molecular features, distinct liposarcoma subtypes can be identified (ie, well-differentiated [WD]/dedifferentiated [DD] liposarcoma, myxoid liposarcoma, and pleomorphic liposarcoma).[1] Initial presentation, clinical behavior, and sensitivity to systemic agents vary with each subtype. In particular, WD/DD liposarcomas are marked by the amplification of proto-oncogenes, mouse double minute 2 homolog (MDM2), and cyclin-dependent kinase 4 (CDK4)[3,4] and can arise anywhere in the body. However, although they have a very indolent course when located in the extremities or superficial trunk, they represent a serious therapeutic challenge when located inside the abdomen or retroperitoneum, where they constitute almost the unique liposarcoma variant. Myxoid liposarcoma almost never arises intra-abdominally and is characterized by unique chromosome rearrangements that result in the *FUS-DDIT3* gene fusion (95% of cases) or, rarely, in the *EWS-DDIT3* fusion.[5,6] Pleomorphic liposarcoma is the rarest variant, also hardly ever arising intrabdominally, and being characterized by a complex karyotype.[2,7]

Corresponding Author: Silvia Stacchiotti, MD, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian 1, Milan, Italy (silvia.stacchiotti@istitutotumori.mi.it).

[1]Adult Mesenchymal Tumor Medical Oncology Unit, Cancer Medicine Department, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy; [2]Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [3]Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; [4]Department of Statistics, EORTC - European Organisation for Research and Treatment of Cancer, Brussels, Belgium; [5]Department of Surgical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [6]The Institute of Cancer Research, London, United Kingdom; [7]Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [8]Department of Medical Oncology, Leids Universitair Medisch Centrum, Leiden, The Netherlands; [9]Mannheim Cancer Center, Sarcoma Unit, University of Heidelberg, Mannheim University Medical Center, Mannheim, Germany

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.34264, **Received:** February 6, 2022; **Revised:** April 19, 2022; **Accepted:** April 25, 2022, **Published online** May 13, 2022 in Wiley Online Library (wileyonlinelibrary.com)

Although surgical resection is the mainstay of treatment for localized disease in all subtypes,[8] many patients with intra-abdominal (IA)/retroperitoneal WD/DD liposarcomas initially present with or ultimately progress to advanced disease and have a poor prognosis.[9] For advanced disease, treatment options consist of standard chemotherapy, including anthracycline-based regimens, with anthracycline being the standard front-line treatment in STS.[8] Other cytotoxic agents available for treating advanced WD/DD liposarcomas are ifosfamide, trabectedin, and eribulin, whereas no targeted agents are currently approved.

In the past decade, a better understanding of the distinct genetic and molecular profile of liposarcomas has led to the development of several new systemic therapies, such as selinexor, MDM2 inhibitors and CDK4 inhibitors, and immune agents. By contrast, no prospective trial with anthracycline-based chemotherapy has individually assessed response in a WD/DD liposarcoma patient cohort alone nor is one ongoing. The knowledge about the activity of anthracyclines in this tumor is based on a very limited number of case reports or retrospective series that have shown marginal activity of this regimen in the disease.[10,11]

On this basis, we decided to conduct a retrospective analysis of the efficacy of cytotoxic regimens administered in first-line clinical trials in adult patients with a diagnosis of IA liposarcoma included in the European Organisation for Research and Treatment of Cancer (EORTC) database to provide more solid information on the efficacy of these systemic treatments in WD/DD liposarcoma and a benchmark for ongoing and future studies for new drug development. We focused on anthracycline-based regimens, but data available on other cytotoxic regimens were also collected.

MATERIALS AND METHODS

We retrospectively searched for all adult patients treated with first-line chemotherapy for advanced (ie, locally advanced unresectable and/or metastatic) IA liposarcoma in EORTC Soft Tissue and Bone Sarcoma Group (STBSG) phase 2 and 3 trials from 1978. Data were extracted from the EORTC STBSG database. Because the database did not always capture the liposarcoma histologic subtype, extra-abdominal liposarcomas were excluded from the present study to focus on WD/DD liposarcoma, and exclude myxoid and pleomorphic liposarcomas, which almost never arise in the abdomen. Liposarcomas included in the database for which the information of the primary site was not available were also excluded. Patients treated for primary resectable disease and/or who received prior (adjuvant or palliative) chemotherapy or were treated from second-line on were also not included.

Written informed consent to treatment was obtained within the context of each study.

Treatment was aggregated into 5 groups: anthracycline alone (doxorubicin 75 mg/m^2; pegylated liposomal doxorubicin [Caelyx] 50 mg/m^2; epirubicin 75 mg/m^2; epirubicin 150 mg/m^2), ifosfamide alone (ifosfamide 5 g/m^2, ifosfamide 9 g/m^2, ifosfamide 12 g/m^2), doxorubicin plus ifosfamide (doxorubicin 50 mg/m^2 plus ifosfamide 5 g/m^2, doxorubicin 75 mg/m^2 plus ifosfamide 5 g/m^2, doxorubicin 75 mg/m^2 plus ifosfamide 10 g/m^2), doxorubicin plus cyclophosphamide plus vincristine plus dacarbazine (CYVADIC), and "other" (brostallicin, trabectedin). Per protocols, treatment was continued until evidence of disease progression or limiting toxicity or until the maximum cumulative dose of anthracyclines and/or the maximum number of cycles was reached.

Statistical Analysis

End points

The end points of interest were progression-free survival (PFS), overall survival (OS), and response to chemotherapy. PFS was the time elapsing from study registration or randomization, depending on study, to first progression or death, whichever occurred first. Patients alive and progression-free at last follow-up were censored. OS was the time between the study registration and reported date of death. Patients alive at the last follow-up were censored. Response to chemotherapy was prospectively evaluated in all trials using World Health Organization (WHO) criteria[12] or Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 or 1.1,[13,14] depending on the study.

Explored covariates

Demographic data included age, sex, and performance status at study entry. Additionally, data on disease primary tumor site and involvement of metastases were collected. Variables related to the history of sarcoma included the time since the first diagnosis of sarcoma. Histological subtype and grade, as reviewed by a panel of reference pathologists, were preferred to the use of local diagnosis to ensure data consistency and homogeneity. The treatment was aggregated in 5 categories: anthracyclines alone (doxorubicin, Caelyx, epirubicin, epirubicin 3 × 50, epirubicin 1 × 150), ifosfamide alone (ifosfamide 5 g/m^2/24 hours, ifosfamide 3 days

3 g/m^2, ifosfamide 9 g/m^2 continuously in 3 days, ifosfamide 12 g/m^2 continuously in 3 days), the combination of doxorubicin and ifosfamide (doxorubicin 50 mg/m^2 plus ifosfamide 5 g/m^2, doxorubicin 75 mg/m^2 plus ifosfamide 5 g/m^2, doxorubicin 75 mg/m^2 plus ifosfamide 10 g/m^2), CYVADIC, and other treatments (brostallicin, trabectedin).

Statistical methods

PFS and OS were visualized through Kaplan-Meier curve. Response to treatment was summarized as percentage, with CI based on the exact binomial distribution. Hazard ratios were calculated for the covariates investigated in the study, including demographic data, information related to the history of the sarcoma and its treatment, the histology characteristics, and treatment received within the context of the aforementioned clinical trials. Because the information on prior radiotherapy or surgery was not collected in the more recent trials (EORTC 62012, 62061, 62091), these variables were not considered in the univariate/multivariate analyses. The potential prognostic value of all other factors was first investigated by univariate analysis using univariate Cox or logistic regression models according to the outcome. The prognostic value of the factors was subsequently assessed in a multivariate model using backward selection. To protect against a considerable loss of information for the multivariate analysis because of the substantial amount of missing data in the assessment of grade and site of primary tumor, we considered these 2 covariates the "missing" as a separate category in all the models. The statistical significance was set at 0.05 for all analyses described in this report. All analyses were performed using SAS v9.4.

TABLE 1. Patients Characteristics

	Patient (N = 109)
	No. (%)
Treatment	
Anthracyclines	48 (44.0)
D+IFO	18 (16.5)
CYVADIC	8 (7.3)
IFO alone	15 (13.8)
Other	20 (18.4)
Sex	
Male	60 (55.1)
Female	49 (45.0)
Age	
Median, y	57
Range	21-80
Q1-Q3	47-62
Performance status	
0	51 (46.8)
1	54 (49.5)
2+	3 (2.8)
Missing	1 (0.9)
Histopathological grade	
1	21 (19.3)
2	34 (31.2)
3	18 (16.5)
Unknown	36 (33.0)
Prior surgery	
No	3 (2.8)
Partial	21 (19.3)
Total	19 (17.4)
Unknown	66 (60.6)
Prior radiotherapy	
No	65 (59.6)
Yes	8 (7.3)
Unknown	36 (33.0)
Time since initial diagnosis	
≤6 mo	41 (37.6)
6-12 mo	15 (13.8)
1-2 y	13 (11.9)
>2 y	40 (36.7)
Median (mo)	11.9
Range	0.1-174.0
Q1-Q3	2.5-46.3

Abbreviations: CYVADIC, doxorubicin plus cyclophosphamide plus vincristine plus dacarbazine; D, doxorubicin; IFO, ifosfamide; Q, quartile.

RESULTS

We retrospectively identified 109 patients with advanced IA liposarcoma treated with front-line chemotherapy from 13 clinical studies between 1978 and 2012 (Supporting Table 1); 104/109 patients were evaluable for response. Table 1 summarizes patient characteristics.

Of the 109 patients identified, 44% (48/109) received anthracyclines alone, 17% (18/109) doxorubicin plus ifosfamide, 14% (15/109) ifosfamide alone, 7% (8/109) CYVADIC, and 18% (20/109) other. All patients had completed their treatment at the time of this analysis.

Table 2 summarizes the radiologic response data, overall and for each treatment regimen. The overall response rate (ORR) was 9.2% (10/109), with no complete response, 9.2% (10/109) partial response (PR), 52% (57/109) stable disease (SD), and 34.9% (38/109) progressive disease (PD). Univariate and multivariate analysis of response to chemotherapy did not identify statistically significant prognostic factors (Supporting Table 2).

Figures 1 and 2 show the PFS by RECIST/WHO and the OS curves in each treatment group, respectively. The median (m-) follow-up for the patients who were still alive at the time of their respective study clinical cutoff dates was 10 months (interquartile range, 6-24). m-PFS was 4 months (95% CI, 3-6) (Fig. 1) and m-OS 19 months (95% CI, 15-21) (Fig. 2). Univariate and multivariate analysis did identify performance status, the time since initial diagnosis (between 1 and 2 years), and histopathological grade (grade

TABLE 2. Response Assessment, Overall and for Each Treatment Regimen

Response	Treatment, No. (%)					Total (N = 109)
	A alone (N = 48)	IFO alone (N = 15)	D+IFO (N = 18)	CYVADIC (N = 8)	Other (N = 20)	
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	3 (6.3)	2 (13.3)	4 (22.2)	1 (12.5)	0 (0.0)	10 (9.2)
SD	24 (50.0)	10 (66.7)	5 (27.8)	4 (50.0)	14 (70.0)	57 (52.3)
PD	20 (41.7)	3 (20.0)	6 (33.3)	3 (37.5)	6 (30.0)	38 (34.9)
Not evaluable	1 (2.1)	0 (0.0)	3 (16.7)	0 (0.0)	0 (0.0)	4 (3.7)

Abbreviations: A, anthracycline; CR, complete response; CYVADIC, doxorubicin plus cyclophosphamide plus vincristine plus dacarbazine; D, doxorubicin; IFO, ifosfamide; PD, progressive disease; PR partial response; SD, stable disease.

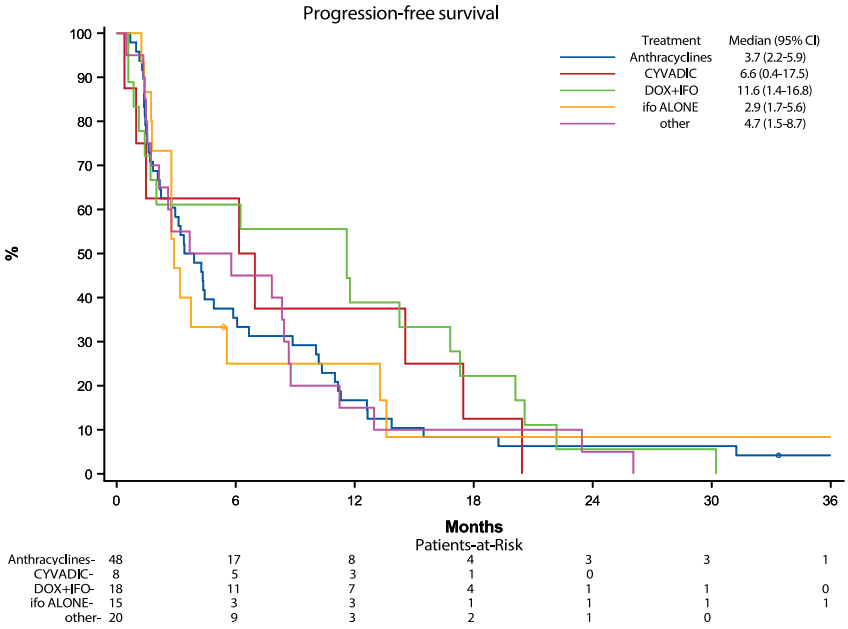

FIGURE 1. Progression-free survival curves by RECIST/WHO in each treatment group. CYVADIC indicates doxorubicin plus cyclophosphamide plus vincristine plus dacarbazine; DOX, doxorubicin; IFO, ifosfamide; RECIST; WHO, World Health Organization.

2/3) as prognostic factors for a worse survival and PFS, whereas there was no significant effect of treatment regimen observed either for PFS or OS (Supporting Tables 3 and 4).

In the anthracycline alone group, 47/48 patients were evaluable for response. All patients received anthracyclines as a first-line treatment. Forty-two patients received doxorubicin 75 mg/m^2, 1 Caelyx 50 mg/m^2, and 5 epirubicin 150 mg/m^2. Best RECIST/WHO response was: 3/48 PR (6.3%), 24/48 SD (50%), and 20/48 PD (41%) for an ORR of 6.3% (95% CI, 1.3-17.2). m-PFS was 4 months (95% CI, 2-6) with 17% of patients progression-free at 1 year; m-OS was 17 months (95% CI, 9-24).

In the doxorubicin plus ifosfamide group, 15/18 patients were evaluable for response. All patients received anthracycline and ifosfamide as a first-line treatment. Best RECIST/WHO response was: 4/15 PR (22.2%), 5/15 SD (66.7%), and 6/15 PD (33.3%) for an ORR of 22.2% (95% CI, 6.4-47.6). m-PFS was 12 months (95% CI, 1-17) with 39% of patients progression-free at 1 year, whereas m-OS was 31 months (95% CI, 6-48).

In the ifosfamide alone group, all 15 patients were evaluable for response. All patients received ifosfamide alone as a first-line treatment. No patient received ifosfamide 5 g/m^2, whereas 8 patients received ifosfamide 9 g/m^2 and 7 ifosfamide 12 mg/m^2. The best RECIST/WHO response was: 2/15 PR (13.3%), 10/15 SD (66.7%), and 3/15 PD (20%) for an ORR of 13.3% (95% CI, 1.6-40.5). m-PFS was 3 months (95% CI, 2-6) with 25% of patients progression-free at 1 year, whereas m-OS was 19 months (95% CI, 11-44).

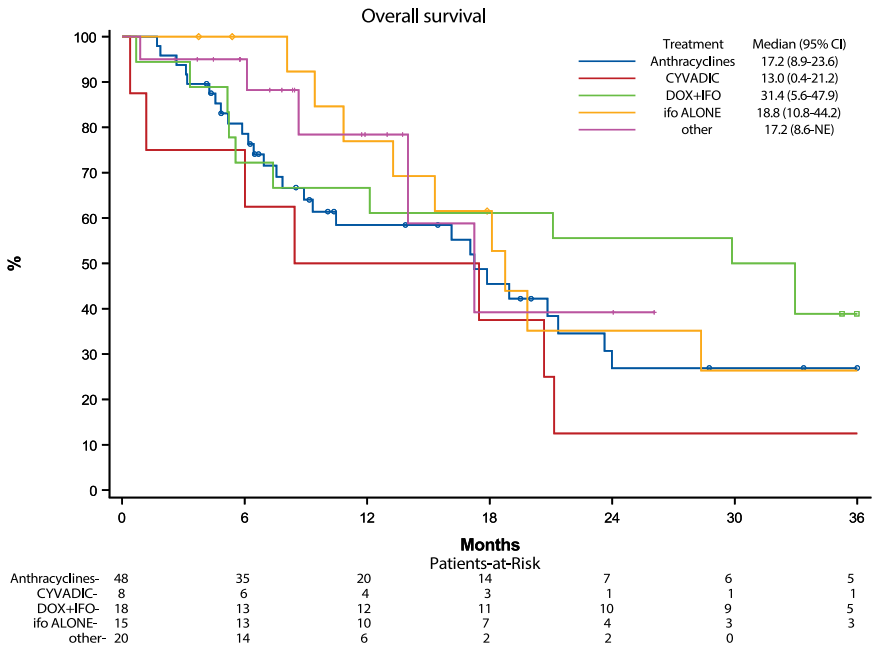

FIGURE 2. Overall survival curves by treatment group. CYVADIC indicates doxorubicin plus cyclophosphamide; DOX, doxorubicin; IFO, ifosfamide.

In the CYVADIC group, all 8 patients were evaluable for response. The best RECIST/WHO response was 1/8 PR (12.5%), 4/8 SD (50%), and 3/8 PD (37.5%) for an ORR of 12.5% (95% CI, 0-52.7). m-PFS was 6.6 months (95% CI, 0.4-17) with 50% of patients progression-free at 1 year, whereas m-OS was 13 months (95% CI, 0.4-21).

In the "other" group (trabectedin, brostallicin), all 20 patients were evaluable for response; however, no responses were detected. m-PFS was 4.7 months (95% CI, 1.5-8.7) with 15% of patients progression-free at 1 year, whereas m-OS was 17 months (95% CI, 8.6-not assessable).

DISCUSSION

Because of the lack of prospective data on the efficacy of conventional first-line chemotherapy in WD/DD liposarcoma, we decided to take advantage of the EORTC STBSG database to conduct a retrospective analysis of the activity of front-line cytotoxic chemotherapy in adult patients with liposarcoma of IA origin who had entered EORTC STBSG phase 2 and 3 trials from 1978. Our analysis confirmed a marginal activity of chemotherapy in this setting, in particular of regimens including single-agent anthracycline, with an ORR of 6.3% (3/47 patients) and an m-PFS of 4 months. Ifosfamide-containing regimens showed higher activity, although not statistically significant, with 22% ORR (4/15 cases) and an m-PFS of 12 months observed with the combination of doxorubicin/ifosfamide, whereas the ORR to ifosfamide alone regimens was 13% (2/15 patients) with an m-PFS of 3 months. The ORR was 12.5% with CYVADIC.

The results of this analysis are limited by its retrospective nature. In addition, patients included in this study were treated in different trials with different regimens and with a degree of variability in patients' follow-up and imaging assessment, according to each study protocol. Unfortunately, the small numbers did not allow an adjusted analysis, stratified by study. Moreover, the assessment of response in IA WD/DD liposarcoma is particularly challenging because of the presence of an abundant WD component that does not shrink with cytotoxic chemotherapy. It is therefore possible that response in this study was somewhat underestimated. Finally, because of the lack of pathologic details on the histologic subtype, we had to select the IA location of the primary tumor as an entry criterion to exclude liposarcoma subtypes other than WD/DD liposarcoma. It is therefore possible that a few cases of pleomorphic/myxoid liposarcoma are still included in the analysis, even though they are exceedingly rare in the abdomen.

With these limitations, this retrospective series of prospectively assessed cases contributes to the limited data in the literature because no prospective studies specifically focusing on anthracycline-based chemotherapy, which is the standard front-line treatment in advanced STS,[8] have ever been conducted in WD/DD liposarcoma nor are likely to happen. Compared with other series, our study has the advantage that response was assessed prospectively and, although based on a small number of patients, provides a result of m-PFS for the combination of anthracycline and ifosfamide.

Our results are comparable to what has been observed in other series, showing that the combination of anthracycline and ifosfamide provides the best disease control in terms of ORR (doxorubicin plus ifosfamide = 22% vs doxorubicin alone = 6.3% and ifosfamide alone = 13%) and also of m-PFS (12 months vs 4 and 3 months, respectively), although we could not show a statistical difference. English colleagues reported for the first time in 2005 a retrospective study of 12 WD/DD liposarcoma with 2 responses (ORR, 17%) to front-line doxorubicin plus ifosfamide, whereas the m-PFS for this specific regimen was not presented.[11] The French colleagues published in 2012 a retrospective series of 171 WD/DD liposarcoma patients treated across 11 sites (10 French institutions and the Memorial Sloan Kettering Cancer Center in the United States), with an anthracycline-based regimen. Ninety-two patients received anthracyclines alone (72 patients had doxorubicin 60-75 mg/m^2, 20 pegylated liposomal doxorubicin, 40-50 mg/m^2), 79 doxorubicin in combination with other agents (25 patients received doxorubicin 60-75 mg/m^2 plus ifosfamide 7.5-9 g/m^2; 14 doxorubicin 60 mg/m^2 plus ifosfamide 2.5 g/m^2 plus dacarbazine 300 mg/m^2; 40 doxorubicin plus miscellaneous cytotoxic or investigational agents). Results were comparable to what we observed, with 7.5% RECIST ORR in patients treated with anthracyclines alone versus 18% in patients treated with an anthracycline-containing combination.[10] No details were presented about m-PFS for each treatment group, whereas a 4.6-month m-PFS was reported for the entire series of patients treated with different regimens at a 28-month median follow-up.

Single-agent ifosfamide is also considered for treatment of WD/DD liposarcoma, usually in second-line treatment. Our study, although based on a very limited number of patients, showed that ifosfamide monotherapy was not inferior to single-agent doxorubicin. Small-cohort retrospective studies have shown the potential role of high-dose prolonged infusion ifosfamide specifically in WD/DD liposarcoma, with an ORR ranging between 20% and 30% and an m-PFS ranging between 3.7 and 7 months.[15,16] This regimen was never prospectively tested in any EORTC STBSG trials, but overall data are consistent with a selective activity of ifosfamide in WD/DD liposarcoma.

The univariate analysis for OS and PFS demonstrated a negative prognostic impact of histopathological grade (grade 2/3 vs grade 1) and time since initial diagnosis. This was confirmed by the multivariate analysis. However, the clinical relevance of these variables in defininig the prognosis of WD/DD liposarcoma treated with chemotherapy for advanced disease is difficult to interpret, because grade assessment in WD/DD liposarcoma presents several challenges and has changed greatly over the years, whereas the time from initial diagnosis can be affected by several aspects that cannot be investigated retrospectively. On the other hand, unfortunately, both univariate analysis and multivariate logistic regression analysis of response to chemotherapy using backward selection could not identify statistically significant predictors of response.

In the past few years, trabectedin and eribulin have been also prospectively investigated in liposarcomas, showing some activity in the WD/DD liposarcoma subtypes and are now available for treatment of WD/DD liposarcoma from second-line treatment.[17,18] Unfortunately, the antitumor effect seen with these agents in the registration trials (2.0-month m-PFS and no objective responses with eribulin in DD liposarcoma[19]; 2.2-month m-PFS to trabectedin[17]) is inferior to what we have observed with doxorubicin plus ifosfamide, which still appears to be the more effective systemic approach among those available for advanced WD/DD liposarcoma in fit patients. An exception seems to be trabectedin in WD/low-grade DD liposarcoma (defined according to the 2020 WHO classification[1]), as recently reported from a retrospective analysis showing a 47% ORR and 13.7-month m-PFS in these subtypes.[20] Clearly, treatment options for patients affected by advanced liposarcoma are limited and there is a strong need for new active agents. New potential strategies currently under investigations are CDK4 inhibitors, selinexor, MDM2 inhibitors, and PD1 inhibitors alone and in combination.[21-26] At present, the ORR and m-PFS observed with these new compounds are limited and this makes it even more important to increase the evidence on the efficacy of standard chemotherapy for comparison. In this regard, our analysis provides a benchmark for ongoing and future studies for new drug development in advanced WD/DD liposarcoma, starting from first-line treatment.

FUNDING SUPPORT

This publication was supported by the EORTC Cancer Research Fund (ECRF).

CONFLICT OF INTEREST DISCLOSURES

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article. Silvia Stacchiotti reports institutional research funding from Amgen Dompe, Advenchen, Bayer, Blueprint Medicines, Deciphera, Eli Lilly, Epizyme, Daiichi Sankyo Pharma, GSK, Karyopharm, Novartis, Pfizer, PharmaMar, SpringWorks, and Hutchinson MediPharma International Inc; honoraria from Bayer, Deciphera, Eli Lilly, Daiichi, Maxivax, and Novartis; invited speaker fees/meeting support from GSK and PharmaMar; fees for expert testimony from Bavarian Nordic and Epizyme; and participation on a Data Safety Monitoring Board or Advisory Board for Astex Pharmaceuticals, Bayer, Bavarian Nordic, Pharmamar, Deciphera, Eli Lilly, Daiichi, GlaxoSmithKline, Maxivax, Ikena, Novartis, and Rain Therapeutics outside the submitted work. Winette T.A. van der Graaf reports research grants from Novartis and Lilly, advisor for Bayer and Springworks, and consultancy for Glaxo Smith Kline, all to her institution. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Silvia Stacchiotti: Conception and design and acquisition and management of clinical data. **Winette T. A. Van der Graaf:** Conception and design and acquisition and management of clinical data. **Roberta G. Sanfilippo:** Acquisition and management of clinical data. **Sandrine I. Marreaud:** Acquisition and management of clinical data. **Winan J. Van Houdt:** Acquisition and management of clinical data. **Ian R. Judson:** Acquisition and management of clinical data. **Alessandro Gronchi:** Acquisition and management of clinical data. **Hans Gelderblom:** Acquisition and management of clinical data. **Saskia Litiere:** Acquisition and management of clinical data and bioinformatic analyses. **Bernd Kasper:** Bioinformatic analyses. All authors contributed to writing the manuscript.

REFERENCES

1. WHO Classification of Tumours Editorial Board. Soft tissue and Bone Tumours. Lyon (France): International Agency for Research on Cancer; 2020 (WHO classification of tumours series, 5th ed.; vol. 3). Accessed May 6, 2022. https://publications.iarc.fr/588
2. Perrier L, Rascle P, Morelle M, et al. The cost-saving effect of centralized histological reviews with soft tissue and visceral sarcomas, GIST, and desmoid tumors: the experiences of the pathologists of the French Sarcoma Group. *PLoS One*. 2018;13:e0193330.
3. Sirvent N, Coindre J-M, Maire G, et al. Detection of MDM2-CDK4 amplification by fluorescence in situ hybridization in 200 paraffin-embedded tumor samples: utility in diagnosing adipocytic lesions and comparison with immunohistochemistry and real-time PCR. *Am J Surg Pathol*. 2007;31:1476-1489.
4. Tap WD, Eilber FC, Ginther C, et al. Evaluation of well-differentiated/de-differentiated liposarcomas by high-resolution oligonucleotide array-based comparative genomic hybridization. *Genes Chromosomes Cancer*. 2011;50:95-112.
5. Rabbitts TH, Forster A, Larson R, Nathan P. Fusion of the dominant negative transcription regulator CHOP with a novel gene FUS by translocation t(12;16) in malig nant liposarcoma. *Nat Genet*. 1993;4:175-180.
6. Powers MP, Wang W, Hernandez VS, et al. Detection of myxoid liposarcoma-associated FUS-DDIT3 rearrangement variants including a newly identified breakpoint using an optimized RT-PCR assay. *Mod Pathol*. 2010;23:1307-1315.
7. Stacchiotti S, Frezza AM, Blay JY, et al. Ultra-rare sarcomas: a consensus paper from the Connective Tissue Oncology Society community of experts on the incidence threshold and the list of entities. *Cancer*. 2021;127:2934-2942.
8. Gronchi A, Miah AB, Dei Tos AP, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32:1348-1365.
9. Gronchi A, Strauss DC, Miceli R, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the multi-institutional collaborative RPS Working Group. *Ann Surg*. 2016;263:1002-1009.
10. Italiano A, Toulmonde M, Cioffi A, et al. Advanced well-differentiated/dedifferentiated liposarcomas: role of chemotherapy and survival. *Ann Oncol*. 2012;23:1601-1607.
11. Jones R, Fisher C, Al-Muderis O, Judson I. Differential sensitivity of liposarcoma subtypes to chemotherapy. *Eur J Cancer*. 2005;41:2853-2860.
12. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981;47:207-214.
13. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205-216.
14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.
15. Martin-Liberal J, Alam S, Constantinidou A, et al. Clinical activity and tolerability of a 14-day infusional ifosfamide schedule in soft tissue sarcoma. *Sarcoma*. 2013;2013:868973.
16. Sanfilippo R, Bertulli R, Marrari A, et al. High-dose continuous-infusion ifosfamide in advanced well-differentiated/dedifferentiated liposarcoma. *Clin Sarcoma Res*. 2014;4:16.
17. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34:786-793.
18. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016;387:1629-1637.
19. Demetri GD, Schöffski P, Grignani G, et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase III study of eribulin versus dacarbazine. *J Clin Oncol*. 2017;5:3433-3439.
20. Fabbroni C, Fucà G, Ligorio F, et al. Impact of pathological stratification on the clinical outcomes of advanced well-differentiated/dedifferentiated liposarcoma treated with trabectedin. *Cancers*. 2021;13:1453.
21. Dickson MA, Tap WD, Keohan ML, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. *J Clin Oncol*. 2013;31:2024-2028.
22. Dickson MA, Schwartz GK, Keohan ML, et al. Progression-free survival among patients with well-differentiated or dedifferentiated liposarcoma treated with CDK4 inhibitor palbociclib: a phase 2 clinical trial. *JAMA Oncol*. 2016;2:937-940.
23. Gounder MM, Bauer TM, Schwartz GK, et al. Milademetan, an oral MDM2 inhibitor, in well-differentiated/dedifferentiated liposarcoma: results from a phase 1 study in patients with solid tumors or lymphomas. *Eur J Cancer*. 2020;138:S3-S4.
24. Gounder M, Razak AA, Somaiah N, et al. Selinexor in advanced, metastatic dedifferentiated Liposarcoma: a multinational, randomized, double-Blind, placebo-controlled trial. *J Clin Oncol*. Published online April 8, 2022. doi:10.1200/JCO.21.01829
25. Zuco V, Pasquali S, Tortoreto M, et al. Selinexor versus doxorubicin in dedifferentiated liposarcoma PDXs: evidence of greater activity and apoptotic response dependent on p53 nuclear accumulation and survivin down-regulation. *J Exp Clin Cancer Res*. 2021;40:83.
26. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017;18:1493-1501.