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Clinical Trial

Outcome in dedifferentiated chondrosarcoma for patients treated with multimodal therapy: Results from the EUROpean Bone Over 40 Sarcoma Study

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Survival

Abstract ***Introduction:*** The role of chemotherapy for patients with dedifferentiated chondrosarcoma (DDCS) is still under discussion. Here, we present the outcome in patients with DDCS treated with intensive chemotherapy from the EUROpean Bone Over 40 Sarcoma Study.

Materials and methods: The chemotherapy regimen included doxorubicin, ifosfamide and cisplatin. Postoperative methotrexate was added in case of poor histological response. Toxicity was graded based on the National Cancer Institute expanded common toxicity criteria, version 2.0, and survival was analysed using Kaplan-Meier curves, log-rank tests and univariate Cox regression models.

Results: Fifty-seven patients with DDCS (localised, 34 [60%]; metastatic, 23 [40%]) aged 42–65 years were included. Surgical complete remission (SCR) was achieved in 36 (63%) patients. The median overall survival (OS) was 24 months (95% confidence interval, 22–25), and the 5-year OS was 39%. Patients with extremity localisation had a 5-year OS of 49% compared with 29% in patients with a central tumour ($P = 0.08$). Patients with localised disease had a 5-year OS of 46%, whereas patients with metastatic disease had a 5-year OS of 29% ($P = 0.12$). Patients in SCR had a 5-year OS of 49%, whereas patients not in SCR had a 5-year OS of 23% ($P = 0.004$). Chemotherapy toxicity was considerable but manageable. There was no treatment-related death, and 39 (70%) patients received ≥6 cycles of the planned nine chemotherapy cycles.

Conclusions: Adding intensive chemotherapy to surgery for treatment of DDCS is feasible and shows favourable survival data compared with previous reports. With the limitations of data from a non-controlled trial, we conclude that chemotherapy could be considered in the management of patients aged >40 years.

1. Introduction

Chondrosarcomas are considered to be chemotherapy-insensitive tumours [1]. In dedifferentiated chondrosarcoma (DDCS), a high-grade dedifferentiated component is seen within the chondrosarcoma [2]. This component frequently has the characteristics of an undifferentiated pleomorphic sarcoma (UPS) or osteosarcoma, is more aggressive and has a more malignant behaviour [2]. The incidence of chondrosarcoma is about 2.85 per million per year, and dedifferentiation develops in 10–15% of these patients [3]. The feasibility of DDCS-specific studies in this ultrarare entity is hence limited. The median age of patients with DDCS is 59 years [4]. Wide surgical resection is the main option for DDCS [4], but distant metastases may have already developed or evolved shortly after the surgery [4,5]. Thus, the prognosis is dismal, and clinical management is challenging. With a 5-year overall survival (OS) <25% and a median survival <1 year [4–8], effective adjuvant therapy for patients with DDCS is highly needed. However, the value of chemotherapy is still under discussion, and several retrospective studies have revealed no benefit regarding OS [4,6,9,10]. To date, there are no reports from prospective clinical trials to discern further on this issue. The European over 40 Bone Sarcoma

Study (EURO-B.O.S.S., ClinicalTrials.gov ID: NCT02986503), a joint effort of the Italian Sarcoma Group (ISG), the Cooperative Osteosarcoma Study Group (COSS) and the Scandinavian Sarcoma Group (SSG), aimed to prospectively evaluate the activity and toxicity of chemotherapy in patients with different types of high-grade spindle cell or pleomorphic bone sarcoma in patients aged >40 years. We have previously reported the data for patients with osteosarcoma [11]. Here, we present data on survival and chemotherapy toxicity in the subgroup of patients with DDCS.

2. Materials and methods

2.1. Patients

The study included patients aged between 41 and 65 years with a diagnosis of DDCS [11]. Patients with localised and metastatic disease were eligible for the trial. The observational nature of the trial allowed enrolment of patients who met the inclusion criteria and who were to receive other systemic treatments as per institutional preference. The study was approved by the institutional review board of each participating group and/or centre as per national and local rules, and patients signed an informed consent before entering the trial.

2.2. Treatment

The protocol included chemotherapy with doxorubicin (60 mg/m^2), ifosfamide (6 g/m^2) and cisplatin (100 mg/m^2); addition of methotrexate (8 g/m^2) was proposed in patients with poor histologic response after surgery (Fig. 1). Depending on clinical features, patients underwent immediate surgery and adjuvant chemotherapy

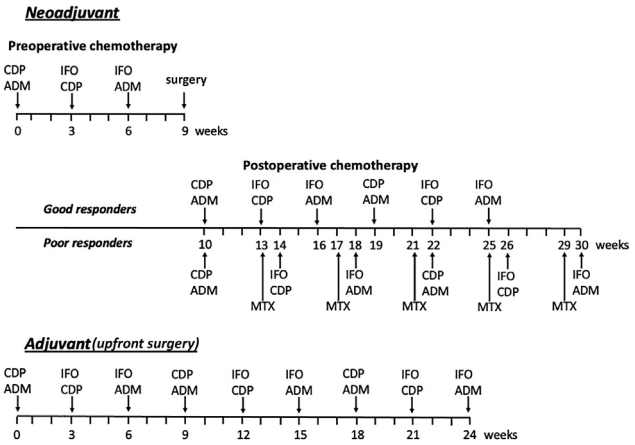

Fig. 1. Treatment schedule. ADM = 60 mg/m^2 of doxorubicin, 24-h intravenous (i.v.) infusion; CDP = 100 mg/m^2 of cisplatin, 48- to 72-h i.v. infusion; IFO = 3 g/m^2 ifosfamide per day. 1- to 2-h infusions, 2 days, dose per cycle: 6 g/m^2; MTX = 8 g/m^2 of methotrexate, 4-h i.v. infusion.

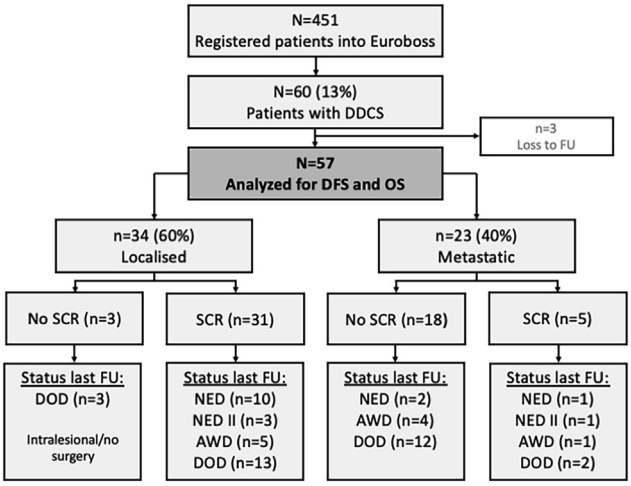

Fig. 2. Consort diagram. DDCS = dedifferentiated chondrosarcoma; DFS = disease-free survival; OS = overall survival; FU = follow-up; SCR = surgical complete remission; NED = no evidence of disease; NED II = no evidence of disease after a second SCR; AWD = alive with disease; DOD = died of disease.

(9 cycles) or received primary chemotherapy (3 cycles), surgery and postoperative chemotherapy (6 cycles for good histological responders or 11 cycles including five methotrexate cycles for patients with poor response).

In patients who received preoperative chemotherapy, the pathological response to primary chemotherapy was evaluated based on the grading systems chosen by the participating groups: Huvos system for the SSG [12], Salzer-Kuntschik system for the COSS [13] and percentage of necrosis for the ISG [14]. Poor pathological response was defined as graded Huvos I, Salzer-Kuntschik 5–6 or for ISG <50% necrosis).

Complete surgical removal of all clinically detectable sites of the disease (primary tumour and all metastases, if metastatic disease) was attempted. If achieved, the patients were registered for surgical complete remission (SCR).

2.3. Chemotherapy toxicity

Haematologic and non-haematologic toxicity (stomatitis, renal toxicity and neurotoxicity) were graded as per National Cancer Institute expanded common toxicity criteria, version 2.0 [15]. The incidence of red blood cell and platelet transfusions, use of granulocyte colony-stimulating factors, episodes of neutropenic fever and number of hospitalisations were also registered.

2.4. Statistics

All analyses were performed using SPSS 25.0 (SPSS, Chicago, IL). For the survival analysis, the Kaplan-Meier estimator was used with the log-rank test for categorical comparisons and the Cox regression model for continuous variables. OS was calculated from the

date of diagnostic biopsy to the date of death from any cause or last follow-up. For patients in SCR, disease-free survival (DFS) and metastasis-free survival (MFS) were calculated from the date of surgery to the date of distant and/or local recurrence or last follow-up. Differences were considered statistically significant if the p-values were <0.05.

3. Results

3.1. Patients

Of the 451 patients included in the EURO-B.O.S.S. study, 60 (13%) had DDCS. Three patients were lost to follow-up, and 57 were available for analysis (Fig. 2). One patient included in this analysis did not start chemotherapy owing to progression and a reduced performance status not allowing intensive chemotherapy. Clinical characteristics are summarised in Table 1. There were 23 men and 34 women, and the median age was 52 years (range, 42–65). The majority of the primary tumours were located in the extremities (37 patients; 65%), whereas the rest had central tumours. Thirty-four patients (60%) had localised disease, whereas 23 (40%) had metastatic disease at presentation. The metastases were localised mainly in the lungs (14 patients; 61%) and skeletal system (4 patients; 17%). The remaining (5 patients; 22%) had metastases to several organs.

3.2. Treatment

Fifty-four of 57 patients underwent surgical resection of the primary tumour; of whom, 33 (58%) patients underwent primary resection and 21 (37%) received neoadjuvant chemotherapy followed by tumour resection (Table 1). Thirty-six (63%) patients achieved SCR. Only four patients (6%) received radiotherapy postoperatively.

Thirty-eight patients (67%) received chemotherapy, as specified in Fig. 1. Fourteen patients (25%) received a modified protocol using the same drugs—cisplatin, doxorubicin and ifosfamide—but they were administered as a single agent sequentially and not in combinations. Four patients (7%) had other deviations to the protocol: carboplatin was substituted for cisplatin in two patients, one patient received epirubicin instead of doxorubicin and one patient had preoperative chemotherapy as specified by the protocol but was treated with three cycles of carboplatin/etoposide postoperatively. Twenty-one (37%) patients completed full protocol of chemotherapy, 40 (71%) patients received $\geq$6 cycles and 16 (29%) received $<$6 cycles. The median number of cycles was 8 (range, 1–14). Of the 21 patients who received neoadjuvant chemotherapy, histological response was reported in 19 patients. Four (21%) patients had a good response as per protocol, whereas 15 (79%) had a poor response; of whom, only six patients received methotrexate.

Table 1
Baseline clinical and treatment characteristics of patients included in the study (N = 57).

Median age, years (range)	52 (42–65)
Sex (male: female)	23:34
Centre	
Cooperative Osteosarcoma Study Group (Germany)	23 (40)
Italian Sarcoma Group	30 (53)
Scandinavian Sarcoma Group	4 (7)
Tumour location	
Extremity	37 (65)
Central	20 (35)
Disease status	
Localised	34 (60)
Metastatic	23 (40)
Metastatic organ (n = 23)	
Lung	14 (61)
Skeletal	4 (17)
Lung, skeletal and/or other	5 (22)
Serum lactate dehydrogenase	
Normal	38 (67)
High	8 (14)
Not available	11 (29)
Serum alkaline phosphatase	
Normal	35 (61)
High	12 (21)
Not available	10 (18)
Surgery	
Primary surgery	33 (58)
After neoadjuvant chemotherapy	21 (37)
No surgery	3 (5)
Type of surgery (n = 54)	
Amputation	8 (14)
Resection	46 (81)
Surgical margins	
Radical	2 (4)
Wide	35 (61)
Marginal	5 (8)
Intralesional	9 (16)
Not available	6 (11)
Surgical complete remission	
Yes	36 (63)
No	21 (37)
Radiotherapy	
Yes	4 (7)
No	53 (93)
Chemotherapy (n = 56)	
Neoadjuvant	21 (37)
Adjuvant	35 (61)
Number of chemotherapy cycles (median = 8 cycles)	
$<$6	16 (29)
$\geq$6	40 (71)

3.3. Outcome

The median follow-up time was 20 months (range, 4–128) for all patients and 40 months (range, 5–128) for patients alive at the last follow-up.

For the whole cohort, the median OS was 24 months (95% confidence interval [CI], 22–25) and the 5-year survival was 39% (95% CI, 37–41; Fig. 3A). At the end

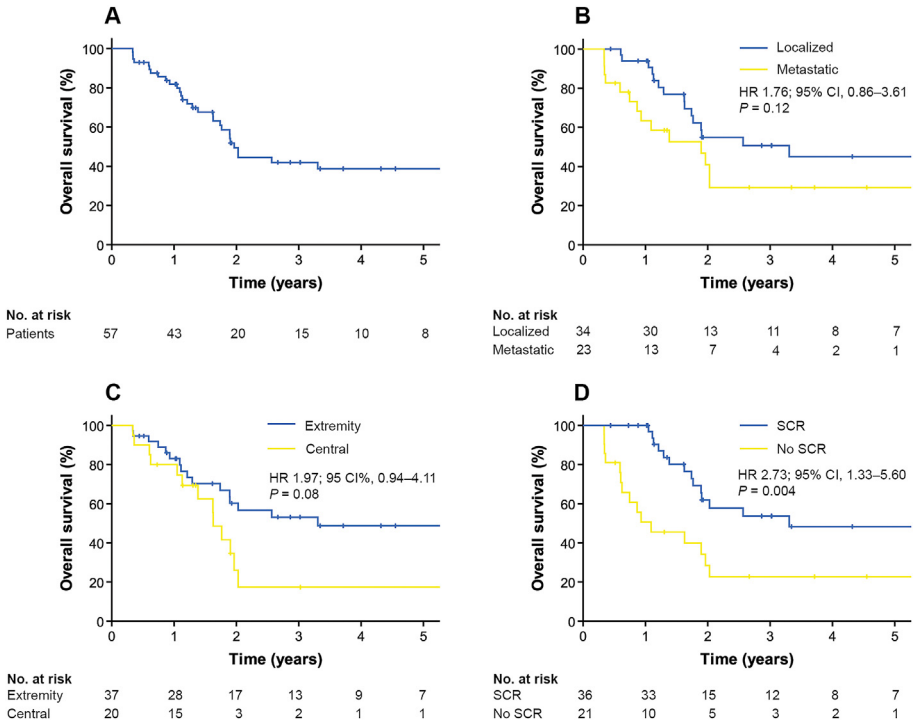

Fig. 3. Kaplan-Meier survival curves. (A) For the complete cohort, (B) stratified based on disease status, (C) stratified based on the location of the primary tumour; (D) stratified based on surgical complete remission (SCR) or not. HR = hazard ratio; CI = confidence interval.

of follow-up (4–128 months), 27 patients were alive; 13 patients had no evidence of disease (NED), four had NED after a second complete surgery and 10 were alive with disease (Fig. 2). Thirty patients were dead of sarcoma. Patients with localised disease had a 5-year OS of 46% compared with patients with primary metastatic disease who had a 5-year OS of 29% (hazard ratio [HR], 1.76; 95% CI, 0.86–3.61; $P = 0.12$; Fig. 3B). Comparing extremity localisation with central localisation, patients with extremity localisation had a 5-year OS of 49% versus 19% for non-extremity localisation (HR, 1.97; 95 CI%, 0.94–4.11; $P = 0.08$; Fig. 3C). For patients in SCR, the 5-year OS was 49% compared with 23% for patients who did not obtain SCR (HR, 2.73; 95% CI, 1.33–5.60; $P = 0.004$; Fig. 3D).

Univariate analysis showed that only SCR was statistically significant for improved OS (Table 2). Owing to the small number of patients, a multivariable analysis was not performed.

When analysing the 36 patients who obtained SCR, 22 (61%) patients had relapse: 15 had a distant relapse, 5 had a local relapse and 2 had a combination as primary event. Most patients with a distant relapse had lung metastases (14 patients, 82%). For the 36 patients in SCR, the median DFS was 18 months (95% CI, 9–29) and the 5-year DFS was 23%, whereas the median MFS was 25 months (95% CI, 21–28) and the 5-year MFS was 32%.

A subanalysis was performed to compare OS in the 38 patients who followed the preplanned treatment to the 14 patients who had sequential therapy or other deviations to the protocol. The cohort that followed the preplanned treatment had better OS, albeit not statistically significant (median OS = 25 months vs. 15 months; HR, 1.76; 95% CI, 0.81–3.84; P = 0.17; Fig. A1, Appendix).

Table 2
Univariate analyses for overall survival.

Parameter	HR (95% CI)	*P* value
Gender		0.98
Female	1.00	
Male	0.99 (0.48–2.10)	
Age	0.98 (0.92–1.04)	0.42
Site of primary tumour		0.08
Extremity	1.00	
Central	1.97 (0.94–4.11)	
Disease status		0.13
Localised	1.00	
Metastatic	1.76 (0.86–3.61)	
Surgical complete remission		
Yes	1.00	
No	*2.73 (1.33–5.60)*	*0.004*
Serum alkaline phosphate		
Normal	1.00	0.36
High	1.53 (0.64–3.64)	
Serum lactate dehydrogenase		0.15
Normal	1.00	
High	2.20 (0.81–5.97)	

HR = hazard ratio; CI = confidence interval.
Significant parameters are presented in italics.

3.4. Chemotherapy feasibility and toxicity

Detailed data on chemotherapy characteristics and toxicity were available for 46 (82%) patients who received a total number of 353 cycles. Thirty-three patients (72%) experienced delays of one or more cycles, and in 17 (37%) patients, toxicity resulted in dose reductions of further cycles. In 13 patients (28%), chemotherapy was stopped early owing to toxicity. No treatment-related deaths were reported, but all patients experienced some adverse events, 36 (78%) had at least one grade III–IV toxicity event, mostly haematological (Table 3). In nine (20%) patients, ≥1 episode of neurotoxicity was reported. Eight had grade I–II peripheral neurotoxicity, whereas in one patient, the depressed level of consciousness (grade IV) was reported after ifosfamide therapy. Regarding nephrotoxicity, 8 (17%) patients had at least 1 episode, mostly grade I or II. Four of the six patients who received methotrexate experienced delayed excretion in the first cycle. Of these, three patients stopped further methotrexate therapy, and the fourth patient received the four remaining cycles with 50% dose reduction (4000 mg/m^2). Two patients received four cycles without any reported toxicity but for unknown reasons did not receive the last cycle. Toxicity by cycles is presented in Table A1 (Appendix).

4. Discussion

To the best of our knowledge, this is the first study to prospectively explore the benefit of adding chemotherapy to the treatment of patients with DDCS. The estimated 5-year OS was 39%, which is better than that previously reported from retrospective studies (range = 10–24%) [4–8]. The chemotherapy toxicity was considerable but manageable, and no toxic deaths were reported.

Owing to the rarity of DDCS, proper prospective randomised clinical trials have not been performed. Retrospective studies on DDCS have consistently reported a dismal prognosis [4–8]. These previous reports have included patients diagnosed over a long period, with different regimens and inconsistent use of chemotherapy regimens and without systematic toxicity reporting. The present study presents a more favourable outcome than previous reports, and with the limitation of a non-controlled study, this could be attributed to the consistent use of more intensive, age-adjusted chemotherapy with drugs known to be effective in younger patients with primary bone sarcomas. Chondrosarcomas are considered unresponsive to antineoplastic drugs [1]. Nevertheless, in clinical practice for DDCS, many experts would consider attacking the dedifferentiated component with chemotherapy. The European Society for Medical Oncology guidelines do not formulate any recommendations, but state that "*DDCS is often treated as a high-grade bone sarcoma, with systemic treatment and local therapies that need to be adapted to patient's age*" [16]. Usually, the treatment has been based on drugs active against the dedifferentiated component (osteosarcoma or UPS)—doxorubicin, ifosfamide and cisplatin—but the evidence of benefit is limited. The results from the present study are supported by a few other studies: a retrospective study including 41 patients indicated survival advantage for 16 patients treated with ifosfamide-based chemotherapy [17], another study reported activity and benefit of doxorubicin in 34 patients with advanced DDCS [18] and a third study on 18 patients with DDCS arising in osteochondromas showed beneficial survival for patients treated with a combination regimen as in the present study [19]. A recent report comparing patients with chondrosarcoma from the SEER database with patients treated at an Italian reference centre found that in the subgroup of patients with DDCS, the 5-year OS was higher (37% versus 21%) for Italian patients [20], although there were no differences in baseline characteristics between the groups. The reason for the higher survival was attributed to the difference in the use of chemotherapy in patients with localised DDCS. In the Italian centre, patients were treated with surgery combined with neoadjuvant and/or adjuvant chemotherapy, similar to the regimen in the present study. Other larger retrospective studies have not shown improved outcomes for patients receiving chemotherapy [4–6]. In the largest series of DDCS reported, a subanalysis of the selected 98 patients of <60 years of age at the time of diagnosis and who had operable tumours showed that the 5-year OS in the 51 patients who had chemotherapy were 45% compared with 25% for the 47 patients who did not receive chemotherapy [4]. This was not statistically significant and was interpreted by the authors accordingly. However, the 5-year OS in the chemotherapy group is comparable with the reported 49% 5-year OS in patients who obtained SCR in the present study.

Some observations from the present study point towards the effect of chemotherapy. First, about one-third of patients achieved long-term SCR (median = 36

Table 3
Chemotherapy toxicity (n = 46).

Dose reduction needed	17 (37)
Hospitalisation	10 (22)
Febrile neutropenia	10 (22)
Granulocyte colony-stimulating factor	36 (78)
Red blood cell transfusion	24 (52)
Platelet transfusion	19 (41)
White blood cells (grade III or IV)	25 (54)
Haemoglobin (grade III or IV)	26 (57)
Platelet (grade III or IV)	27 (59)
Nephrotoxicity (all grades)	8 (17)
Neurotoxicity (all grades)	9 (20)
Stomatitis (all grades)	16 (35)

months of follow-up). Second, 22% of patients with metastatic disease were in the first SCR 8–40 months from diagnosis.

The good histological response rate to preoperative chemotherapy was 21%; this is inferior as compared with studies on younger patients with osteosarcoma receiving more intensive chemotherapy and with other response criteria. This argues against a strong effect of chemotherapy; however, this finding is consistent with that of other studies on DDCS [4,21] and also for patients with osteosarcoma in the same age group treated with same protocol [11].

A few studies of other systemic treatments than chemotherapy in DDCS have been performed. A recent phase II study on patients with chondrosarcoma also recruiting those with DDCS showed activity of the tyrosine kinase inhibitor pazopanib [22], and a partial and durable response to the immunotherapy agent nivolumab was reported [23]. Further studies on these drugs are needed to draw any conclusions with regard to their efficacies.

A finding in the present study was that patients achieving an SCR had a significantly better OS than patients who did not obtain SCR. This is consistent with the findings from other bone sarcomas trials indicating that radical surgical resection of all macroscopic tumour sites combined with intensive polyagent chemotherapy is mandatory for cure and even a significant proportion of patients with primary metastatic disease may obtain long-term remission [16,24]. The estimated OS for patients who achieved SCR in our trial was 49%. Moreover, in some of the relapsed patients, a second SCR was achievable. Thus, the prevailing conception that patients with DDCS uniformly have a poor prognosis should be reassessed. Long-term survival is feasible for selected patients with DDCS, even in the metastatic setting, if surgical remission at all sites is achieved.

The median age of the included patients was 53 years, which is less than the age reported in other large studies (approximately 60 years) [4–6]. The present study introduced a selection bias including only patients aged 41–65 years and patients assumed to tolerate intensive chemotherapy. Thus, the beneficial OS could be ascribed to selection of a prognostically favourable study population.

Consistent with a previous report from the EURO-B.O.S.S. [11], the chemotherapy-related toxicity was considerable but manageable. No toxic death was recorded, and the majority of the patients received $\geq$6 cycles. Although 15 patients had a poor response to preoperative chemotherapy qualifying for additional 5 cycles of methotrexate, only 6 patients received methotrexate. The reason why methotrexate was omitted was not reported, but probably, the known higher toxicity risk and limited experience in this age group and tumour type probably influenced the investigators' decision. Owing to the limited addition, the present study could not discern the added benefit of methotrexate to the other three drug regimens in patients with poor histological response. Thus, use of methotrexate in patients with DDCS needs further documentation, and methotrexate should only be given in a clinical study.

There are some limitations to the present study. First, difficulty in data collection was encountered, especially regarding chemotherapy toxicity. Second, owing to the observational characteristic of the study, some patients were treated with modified regimens. However, all patients' treatment was based on the same drug combination with approximately the same cumulative doses of cisplatin, doxorubicin and ifosfamide. Third, the radiological response rates to chemotherapy for macroscopic disease were not registered. Finally, the study did not include a comparator arm. The present study recruited patients from a population of approximately 200 million. From January 2003 to July 2014, only 60 patients with DDCS were included. Owing to the rarity of the disease, a randomised trial including ten times the number of patients is probably not feasible to conduct within a realistic time frame even with an extended international collaboration.

In conclusion, adding intensive chemotherapy to surgery for treatment of DDCS is feasible and shows favourable survival data compared with previous reports. With the limitations of data from a non-controlled trial, we conclude that chemotherapy could be considered in the management of patients aged >40 years.

Author contributions

Ivar Hompland, Writing - Original Draf, Formal analysis, Resources, Visualisation. Stefano Ferrari, Conceptualisation, Resources, Writing – review & editing. Stefan Bielack, Conceptualisation, Resources, Writing – review & editing. Emanuela Palmerini, Resources, Writing – review & editing. Kirsten Sundby Hall, Resources, Writing – review & editing. Pierro Picci, Resources, Writing – review & editing. Stefanie Hecker-Noltinger, Resources, Writing – review & editing. Davide Maria Donati, Resources, Writing – review & editing. Claudia Blattermann, Resources, Writing – review & editing. Bodil Bjerkehagen, Resources, Writing – review & editing. Eric Staals, Resources, Writing – review & editing. Leo Kager, Resources, Writing – review & editing. Marco Gambarotti, Resources, Writing – review & editing. Thomas Kühne, Resources, Writing – review & editing. Mikael Eriksson, Resources, Writing – review & editing. Virginia Ferraresi, Resources, Writing – review & editing. Matthias Kevric, Resources, Writing – review & editing. Roberto Biagini, Resources, Writing – review & editing. Daniel Baumhoer, Resources, Writing – review & editing. Otte Brosjø, Resources, Writing – review & editing. Alessandro Comandone, Resources, Writing – review & editing. Rudolf Schwarz, Resources, Writing – review &

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Conflict of interest statement

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Appendix

Table A1
Toxicity by cycles (N = 350).

	CDP/ADM (n = 88)	IFO/CDP (n = 70)	IFO/ADM (n = 76)	IFO (n = 34)	ADM (n = 31)	CDP (n = 35)	MTX (n = 16)	TOTAL (N = 350)
[a]WBC	48/69 (70)	28/57 (49)	45/60 (75)	18/24 (75)	15/22 (68)	4/22 (18)	1/14 (7)	**159/268 (59)**
[a]PLT	24/69 (45)	29/58 (50)	17/60 (28)	2/24 (13)	7/22 (32)	4/22 (18)	0/14 (0)	**84/269 (31)**
[a]Hemoglobin level	19/69 (28)	20/57 (35)	26/59 (44)	7/24 (29)	7/22 (32)	8/22 (36)	3/14 (21)	**90/267 (34)**
Nephrotoxicity	4/81 (5)	3/64 (5)	2/67 (3)	0/34 (0)	0/31 (0)	0/35 (0)	2/16 (13)	**11/328 (3)**
Neurotoxicity	3/76 (4)	6/54 (11)	7/66 (11)	1/28 (4)	0/25 (0)	0/29 (0)	0/16 (0)	**17/303 (6)**
Stomatitis	9/88 (10)	4/70 (6)	8/76 (11)	4/34 (12)	4/31 (13)	1/35 (39)	7/16 (44)	**38/353 (11)**
Hospitalization	15/83 (18)	7/64 (11)	10/68 (15)	0/34 (0)	1/31 (3)	3/35 (9)	2/16 (13)	**38/335 (11)**
Febrile neutropenia	7/82 (9)	4/64 (6)	5/66 (8)	0/34 (0)	0/31 (0)	0/35 (0)	0/16 (0)	**16/328 (5)**
RBC transfusion	16/82 (20)	21/64 (33)	22/67 (33)	5/34 (15)	8/31 (26)	4/35 (11)	1/16 (6)	**77/329 (23)**
PLT transfusion	7/82 (9)	11/64 (17)	6/66 (9)	2/34 (6)	1/30 (3)	2/30 (6)	1/16 (6)	**30/325 (9)**
Growth factor	57/80 (71)	49/64 (77)	51/67 (76)	30/34 (88)	26/31 (84)	13/34 (38)	1/16 (6)	**227/326 (70)**

Toxicity from three cycles with carboplatin and etoposide is not reported.
[a] Grade III and IV; WBC = White blood cell count; PLT = Platelet count; RBC = Red blood cell; ADM = Doxorubicin; CDP = cisplatin; IFO = ifosfamide; MTX = methotrexate.

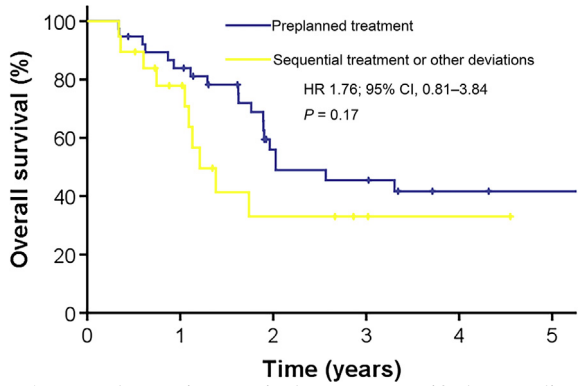

Fig. A1. Kaplan-Meier survival curves stratified according to whether or not the patient followed the preplanned treatment.

References

[1] Italiano A, Mir O, Cioffi A, Palmerini E, Piperno-Neumann S, Perrin C, et al. Advanced chondrosarcomas: role of chemotherapy and survival. Ann Oncol 2013;24:2916–22.

[2] The WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2020.

[3] Thorkildsen J, Taksdal I, Bjerkehagen B, Haugland HK, Johannesen TB, Viset T, et al. Chondrosarcoma in Norway 1990–2013; an epidemiological and prognostic observational study of a complete national cohort. Acta Oncol 2019;58(3):273–82.

[4] Grimer RJ, Gosheger G, Taminiau A, Biau D, Matejovsky Z, Kollender Y, et al. Dedifferentiated chondrosarcoma: prognostic factors and outcome from a European group. Eur J Canc 2007;43:2060–5.

[5] Strotman PK, Reif TJ, Kliethermes SA, Sandhu JK, Nystrom LM. Dedifferentiated chondrosarcoma: a survival analysis of 159 cases from the SEER database (2001-2011). J Surg Oncol 2017;116:252–7.

[6] Staals EL, Bacchini P, Bertoni F. Dedifferentiated central chondrosarcoma. Cancer 2006;106:2682–91.

[7] Miao R, Choy E, Raskin KA, Schwab JH, Nielsen GP, Deshpande V, et al. Prognostic factors in dedifferentiated chondrosarcoma: a retrospective analysis of a large series treated at a single institution. Sarcoma 2019:9069272.

[8] Amer KM, Munn M, Congiusta D, Abraham JA, Basu Mallick A. Survival and prognosis of chondrosarcoma subtypes: SEER database analysis. J Orthop Res 2020;38:311–9.

[9] Dickey ID, Rose PS, Fuchs B, Wold LE, Okuno SH, Sim FH, et al. Dedifferentiated chondrosarcoma: the role of chemotherapy with updated outcomes. J Bone Joint Surg Am 2004;86:2412–8.

[10] Nooij MA, Whelan J, Bramwell VHC, Taminiau AT, Cannon S, Hogendoorn PCW, et al. Doxorubicin and cisplatin chemotherapy in high-grade spindle cell sarcomas of the bone, other than osteosarcoma or malignant fibrous histiocytoma: a European Osteosarcoma Intergroup Study. Eur J Canc 2005;41:225–30.

[11] Ferrari S, Bielack SS, Smeland S, Longhi A, Egerer G, Sundby Hall K, et al. EURO-B.O.S.S.: a European study on chemotherapy in bone-sarcoma patients aged over 40: outcome in primary high-grade osteosarcoma. Tumori 2018;104:30–6.

[12] Rosen G, Marcove RC, Caparros B, Nirenberg A, Kosloff C, Huvos AG. Primary osteogenic sarcoma: the rationale for preoperative chemotherapy and delayed surgery. Cancer 1979;43:2163–77.

[13] Salzer-Kuntschik M, Delling G, Beron G, Sigmund R. Morphological grades of regression in osteosarcoma after polychemotherapy - study COSS 80. J Canc Res Clin Oncol 1983;106(Suppl):21–4.

[14] Picci P, Bacci G, Campanacci M, Gasparini M, Pilotti S, Cerasoli S, et al. Histologic evaluation of necrosis in osteosarcoma induced by chemotherapy. Regional mapping of viable and nonviable tumor. Cancer 1985;56:1515–21.

[15] National Cancer Institute common toxicity criteria, version 2.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdf. Accessed May 2021.

[16] Casali PG, Bielack S, Abecassis N, Aro HT, Bauer S, Biagini R, et al. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv79–95.

[17] Kawaguchi S, Sun T, Lin PP, Deavers M, Harun N, Lewis VO. Does ifosfamide therapy improve survival of patients with dedifferentiated chondrosarcoma? Clin Orthop Relat Res 2014;472:983–9.

[18] van Maldegem A, Conley AP, Rutkowski P, Patel SR, Lugowska I, Desar IME, et al. Outcome of first-line systemic treatment for unresectable conventional, dedifferentiated, mesenchymal, and clear cell chondrosarcoma. Oncol 2019;24:110–6.

[19] Staals EL, Bacchini P, Mercuri M, Bertoni F. Dedifferentiated chondrosarcomas arising in preexisting osteochondromas. J Bone Joint Surg Am 2007;89:987–93.

[20] Bongers MER, Karhade AV, Setola E, Gambarotti M, Groot OQ, Erdoğan KE, et al. How does the skeletal Oncology research group Algorithm's prediction of 5-year survival in patients with chondrosarcoma perform on international validation? Clin Orthop Relat Res 2020;478(10):2300–8.

[21] Mitchell AD, Ayoub K, Mangham DC, Grimer RJ, Carter SR, Tillman RM. Experience in the treatment of dedifferentiated chondrosarcoma. J Bone Joint Surg Br 2000;82:55–61.

[22] Chow W, Frankel P, Ruel C, Araujo DM, Milhem M, Okuno S, et al. Results of a prospective phase 2 study of pazopanib in patients with surgically unresectable or metastatic chondrosarcoma. Cancer 2020;126:105–11.

[23] Paoluzzi L, Cacavio A, Ghesani M, Karambelkar A, Rapkiewicz A, Weber J, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res 2016;6:24–7.

[24] Ferrari S, Briccoli A, Mercuri M, Bertoni F, Picci P, Tienghi A, et al. Postrelapse survival in osteosarcoma of the extremities: prognostic factors for long-term survival. J Clin Oncol 2003;21:710–5.