Clinical features of Ewing and chondrosarcoma

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Chapter 8

Outcome of first-line systemic treatment for unresectable conventional, dedifferentiated, mesenchymal and clear cell chondrosarcoma

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Abstract

Background

Chondrosarcoma is a heterogeneous group of primary bone sarcoma with an excellent overall survival after local therapy. However the small percentage of patients who have no surgical treatment options, have a very poor prognosis. We retrospectively collected data from these patients in four sarcoma centers and compared the progression free survival (PFS) for the different treatment regimens used for the four chondrosarcoma subtypes.

Material and method

Patients diagnosed with unresectable chondrosarcoma in one of four major sarcoma centres were included and data on first line systemic therapy were retrospectively collected for analysis.

Results

A total of 112 patients were enrolled in this retrospective analysis, 50 conventional, 25 mesenchymal, 34 dedifferentiated and 3 clear cell chondrosarcoma patients. In conventional chondrosarcoma patients the longest mean PFS (6.7 months) was found in the group treated with anti-hormonal therapy. Patients diagnosed with mesenchymal chondrosarcoma were all treated with multidrug chemotherapy and the mean PFS was 6.7 months. Doxorubicin monotherapy seems to have an unexplained better PFS than doxorubicin based combination therapy in patients with dedifferentiated chondrosarcoma (5.5 versus 2.8 months respectively, p=0.275).

Conclusion

Prospective studies need to be conducted based on preclinical work to develop a uniform regimen to treat advanced chondrosarcoma patients according to the diagnosed subtype and improve survival.

Background

Chondrosarcoma consists of a heterogeneous group of tumours that share the common feature of cartilage matrix production [1]. Conventional chondrosarcoma is the most common (90%) subtype, the remaining 10% are mesenchymal, dedifferentiated and clear cell chondrosarcoma. For conventional chondrosarcoma metastatic disease is rare and most patients can be cured with surgical interventions. Overall survival (OS) depends on the subtype with dedifferentiated and mesenchymal chondrosarcoma being the more aggressive with a worse overall survival [2-5]. Retrospective studies have shown that these patients may benefit from (neo-) adjuvant chemotherapy or radiotherapy, but large prospective studies still need to be conducted [2, 5-7] The small percentage of patients who present or develop metastatic disease for which no surgical options are available, still have a very poor prognosis and limited treatment options [8]. First line of treatment for any chondrosarcoma is surgery, as this is currently the only treatment option to cure a patient. For patients with metastatic disease it remains unclear what the best chemotherapy regimen is and if chemotherapy has any benefit on overall survival. Recent data on mesenchymal chondrosarcoma patients with localised disease show a significant reduction in local disease recurrence with (neo) adjuvant chemotherapy [9]. For patients with metastatic disease the numbers were too small for the authors to make any recommendations. The data from another retrospective study including advanced chondrosarcoma patients suggest that chemotherapy results in a better progression free survival for patients with mesenchymal and dedifferentiated chondrosarcoma. No effect on overall survival was seen [10].

Here we retrospectively collected the data from patients diagnosed with unresectable chondrosarcoma in four major sarcoma treatment centers. The data was shown separately for the four chondrosarcoma subtypes, conventional, mesenchymal, dedifferentiated and clear cell. The progression free survival after different treatment regimens was calculated and compared.

Materials and method

Patients diagnosed with unresectable chondrosarcoma in one of four centers (Leiden University Medical Centre, the Netherlands; University of Texas MD Anderson Cancer Center, USA; Maria Sklodowska-Curie Institute – Oncology Center Warsaw, Poland; Radboud University Medical Centre Nijmegen, the Netherlands) receiving palliative systemic treatment between 1980 and 2016 were selected. Information was collected retrospectively regarding date of birth, gender, date of last contact or death, histological subtype, grade, tumour location at onset, tumour location of unresectable disease,

received treatments, overall survival and progression free survival. Patients were regarded unresectable if complete resection of the primary tumour and/or metastatic sites was viewed as technically not possible due to the size or (multiple) location(s) of the tumour or if complete resection would lead to unacceptable morbidity for the patient as assessed in multidisciplinary team meetings in centers of expertise.

The progression free survival (PFS) after the first treatment line is compared between the different treatment regimens for each chondrosarcoma subtype.

The PFS was calculated from start of first treatment line until disease progression, death or the last follow-up examination. The survival curves were calculated according to the Kaplan and Meier method and compared using the log-rank test.

Results

Patients

A total of 112 patients were enrolled in this study of which 50 (45%) had conventional, 25 (22%) mesenchymal, 34 (30%) dedifferentiated and 3 (3%) clear cell chondrosarcoma. The patient's characteristics are described in Table 8.1. All patient data is shown in Supplementary Table S8.1.

Table 8.1 Patient characteristics

	Conventional*	Mesenchymal	Dedifferentiated	Clear cell
Total patients number	50 (45%)	25 (22%)	34 (30%)	3 (3%)
Gender				
Male	30 (60%)	9 (36%)	17 (50%)	3 (100%)
Female	20 (40%)	16 (64%)	17 (50%)	0 (0%)
Primary tumour location				
Axial	35 (70%)	16 (64%)	18 (53%)	1 (33%)
Extremity	15 (30%)	9 (36%)	16 (47%)	2 (67%)
Unresectable at diagnosis				
Yes	10 (20%)	17 (68%)	11 (32%)	0 (0%)
No	40 (80%)	8 (32%)	23 (68%)	3 (100%)
Alive				
Yes	15 (30%)	11 (44%)	7 (21%)	2 (67%)
No	35 (70%)	14 (56%)	27 (79%)	1 (33%)

* Six of these patients were also included in the study published by Meijer et al [11].

Of the conventional chondrosarcoma patients four had atypical cartilaginous tumours/ chondrosarcoma grade 1 at time of diagnosis. Three had biopsy proven progression to grade 2 at disease recurrence/progression. Of the fourth patient no new biopsy was performed to establish progression to a higher grade tumour. Thus, except this one patient, all patients in the analysis had a high grade chondrosarcoma at time of unresectability.

Treatment

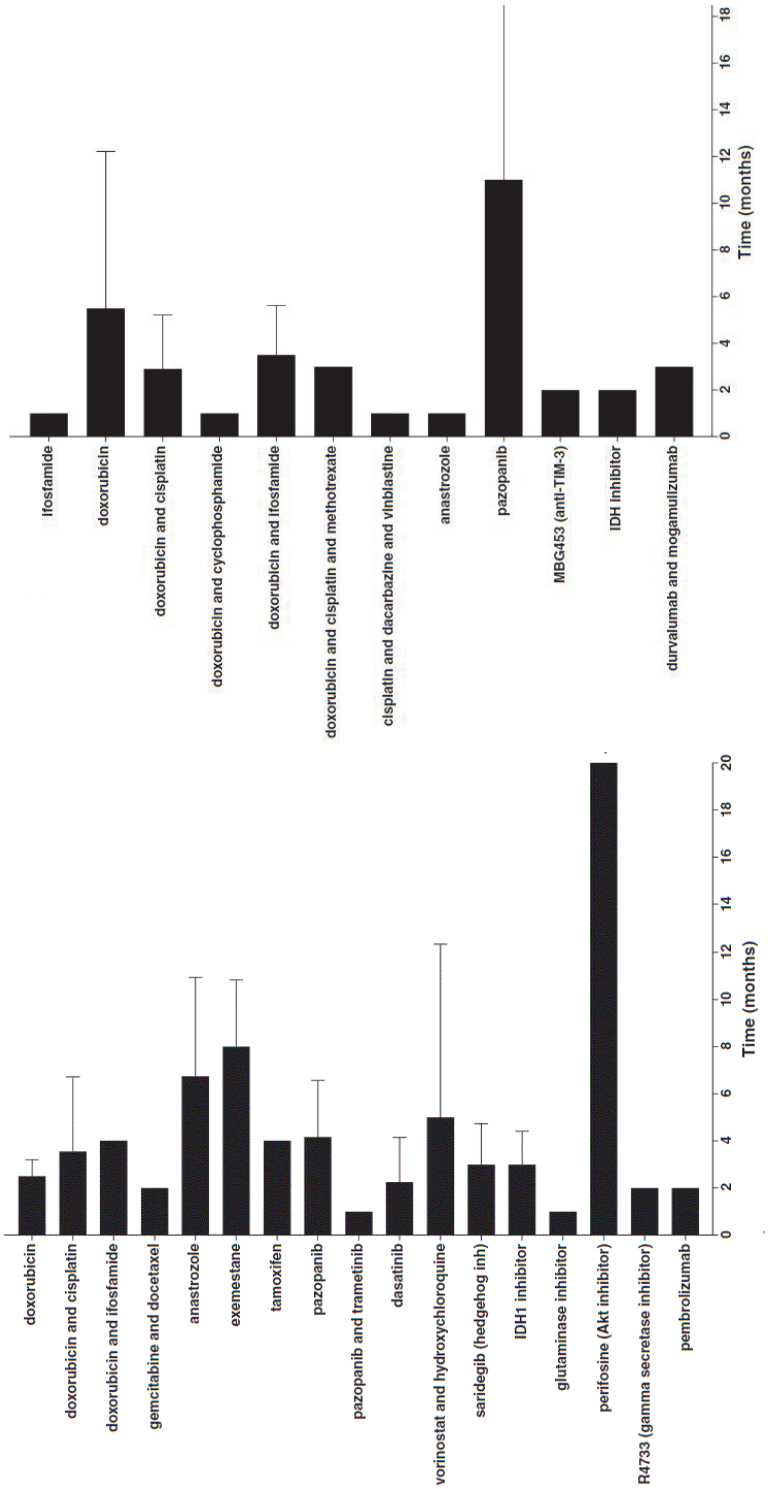
The specific treatment regimens that patients received were compared using a swimmer plot for each chondrosarcoma subtype (Figure 8.1). The numbers of different treatment regimens were too small for a statistical analysis but trends can be observed.

For the conventional chondrosarcoma the patients treated with doxorubicin monotherapy (n=2) had a mean PFS on first treatment line of 2.5 months (Figure 8.1A). Patients treated with a combination of doxorubicin with either cisplatin or ifosfamide (n=10) had a mean PFS of 3.6 months. The combination of gemcitabine and docetaxel has a mean PFS of 2 months (n=3). Seven patients, six males and one female patient, treated with anti-hormonal therapy, aromatase-inhibitors and anti-oestrogen drugs, had a mean PFS of 6.7 months. Six of these were also included in the study published by Meijer et al [11]. Pazopanib and the combination of pazopanib with trametinib had a mean PFS of 3.7 months (n=7) and dasatinib treatment 2.2 months (n=4), these patients were treated in clinical trials. Patients treated with the combination of vorinostat and hydroxychloroquine (n=4) had a mean PFS of 5 months. Hedgehog inhibitors (saridegib) and IDH1 inhibitors had a mean PFS of 3 months (n=5).

For dedifferentiated chondrosarcoma, six patients treated with doxorubicin monotherapy had a mean PFS of 5.5 months (Figure 8.1B). The combination of doxorubicin with cisplatin and doxorubicin with cisplatin and methotrexate had a mean PFS of 2.9 months (n=13).

The 25 patients diagnosed with mesenchymal chondrosarcoma were all treated with chemotherapy based combination regimens (Figure 8.1C). The mean PFS for all chemotherapy regimens is 6.7 months. Patients treated with the combination of ifosfamide and doxorubicin (n=4) had a PFS of 3.7 months, the combination of cisplatin and doxorubicin (n=4) had a PFS of 7.7 months (p=0.04).

The three patients diagnosed with clear cell chondrosarcoma were either treated with sunitinib (n=2) or the combination of pazopanib and denosumab (n=1) and on average their PFS is the same (Figure 8.1D).


doxorubicin
doxorubicin and cisplatin
doxorubicin and ifosfamide
gemcitabine and docetaxel
anastrozole
exemestane
tamoxifen
pazopanib
pazopanib and trametinib
dasatinib
vorinostat and hydroxychloroquine
saridegib (hedgehog inh)
IDH1 inhibitor
glutaminase inhibitor
perifosine (Akt inhibitor)
R4733 (gamma secretase inhibitor)
pembrolizumab
0 2 4 6 8 10 12 14 16 18 20
Time (months)
A
ifosfamide
doxorubicin
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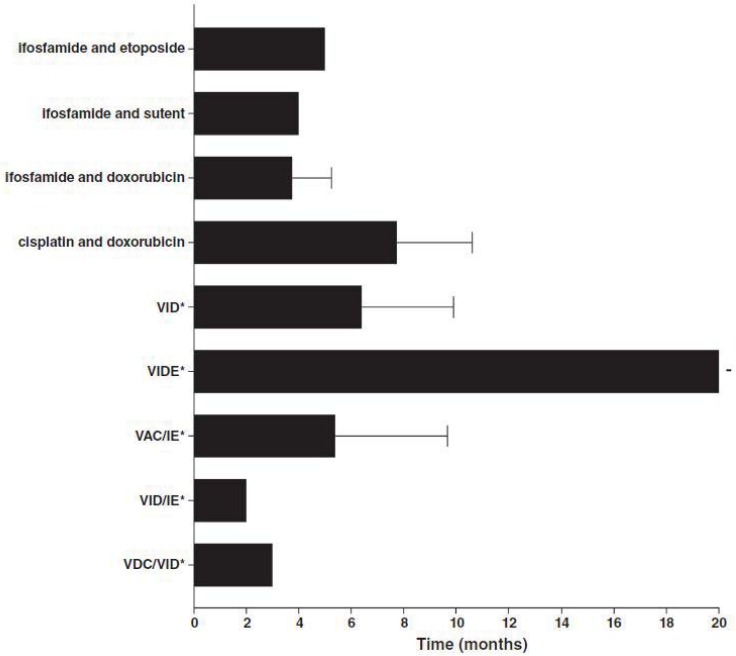
doxorubicin and cyclophosphamide
doxorubicin and ifosfamide
doxorubicin and cisplatin and methotrexate
cisplatin and dacarbazine and vinblastine
anastrozole
pazopanib
MBG453 (anti-TIM-3)
IDH inhibitor
durvalumab and mogamulizumab
0 2 4 6 8 10 12 14 16 18
Time (months)
B



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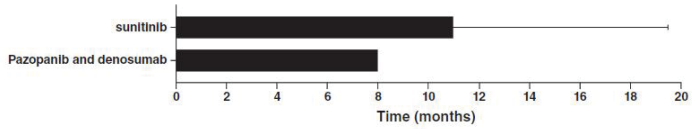

D

Figure 8.1 Swimmer plot of the different treatment regimens used after unresectability comparing the PFS for conventional (A), dedifferentiated (B), mesenchymal (C) and clear cell (D) subtype.
VID, vincristine, ifosfamide, doxorubicin; VIDE, vincristine, ifosfamide, doxorubicin, etoposide; VAC / IE, vincristine, doxorubicin, cyclofosfamide / ifosfamide, etoposide; VID / IE, vincristine, ifosfamide, doxorubicin / ifosfamide, etoposide; VDC / VID, vincristine, doxorubicin, cyclophosphamide / vincristine, doxorubicin, ifosfamide.

Response

No complete responses according to RECIST criteria were seen after the first treatment line. Seven patients had a partial response, one patient diagnosed with conventional CS, four with mesenchymal CS and two dedifferentiated CS patients. The patient diagnosed with conventional CS was treated with the combination of doxorubicin and cisplatin. Of the four mesenchymal CS patients three were treated with VAC/IE (vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide) and one with VID (vincristine, doxorubicin, ifosfamide). The two dedifferentiated CS patients were treated with doxorubicin monotherapy and doxorubicin in combination with cisplatin, respectively.

Survival

The mean progression free survival (PFS) as calculated using the Kaplan and Meier method for the first systemic treatment line after patients became unresectable was 11 months for patients diagnosed with conventional chondrosarcoma, 16 months for mesenchymal, 15 months for dedifferentiated and 10 months for clear cell chondrosarcoma. The differences in outcome for PFS of first systemic treatment line between the histological subtypes were not significant (Figure 8.2).

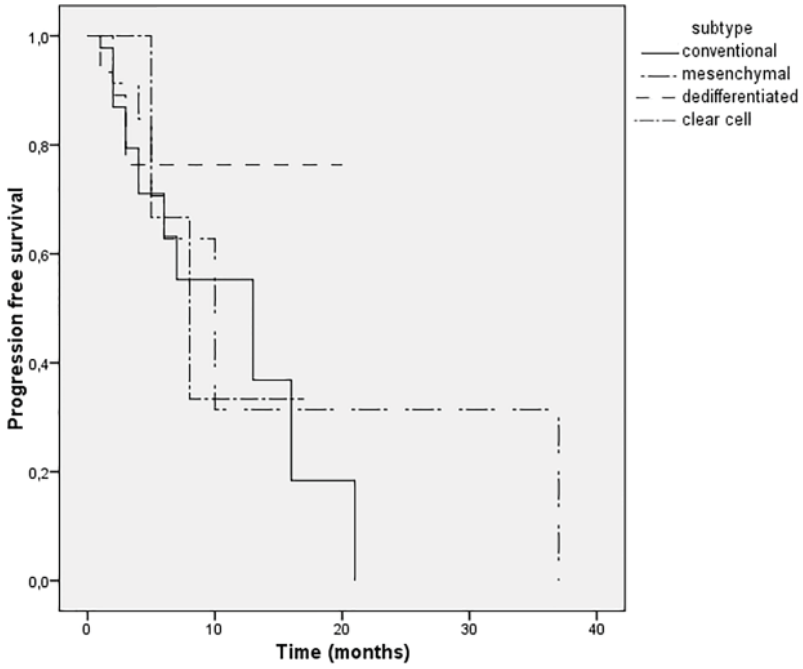

Figure 8.2 Progression free survival for first treatment regimen after unresectability for patients divided in the different chondrosarcoma subtypes.

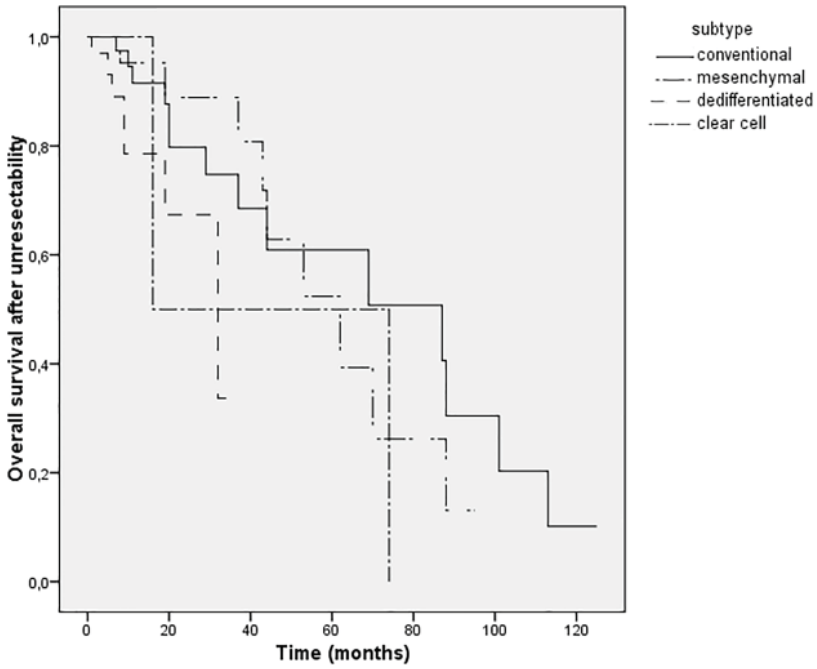

Figure 8.3 Overall survival after unresectability for all patients subdivided in chondrosarcoma subtypes.

At the time of data collection 35 (31%) of the 112 patients were still alive. The OS after unresectability was 87 months for conventional, 62 for mesenchymal, 32 for dedifferentiated and 16 for clear cell chondrosarcoma patients (Figure 8.3). The patients diagnosed with conventional chondrosarcoma or mesenchymal chondrosarcoma show a trend towards having a significant better OS than patients diagnosed with dedifferentiated chondrosarcoma (p=0.53 and p=0.26 respectively).

Prognostic markers

Different prognostic markers were tested for significance for PFS after unresectability. For dedifferentiated chondrosarcoma male patients had a significant better PFS (p=0.042). For the other subtypes no difference in PFS between genders was found. Age (≤50 versus >50 years) and tumour localization showed no significant difference (data not shown). There is no difference in PFS between the different treatment centers (p=0.443).

Discussion

Patients with unresectable chondrosarcoma still have a very poor prognosis with an overall 2-year survival around 24 to 37% [8, 10]. The conventional, mesenchymal, dedifferentiated and clear cell subtypes should not be considered the same disease and should not be treated equally. Even within the different subtypes there is a wide range of clinical and biological heterogeneity. But to make clinical research feasible for this rare disease, patients with the same subtype are considered to have comparable disease.

Conventional chondrosarcoma is the most common form and the low-grade form (now called atypical cartilaginous tumor) infrequently develops metastases. Dedifferentiated CS is a high grade chondrosarcoma with a worse prognosis. From previous studies we know that the overall survival depends on the histological subtype of chondrosarcoma [10, 12]. In line with these previous studies, the patients in our study diagnosed with conventional or mesenchymal chondrosarcoma also seem to have a better, non-significant, OS than patients diagnosed with dedifferentiated chondrosarcoma (Figure 8.3).

In our cohort several conventional chondrosarcoma patients (n=7) were treated with hormonal based therapies and had a mean PFS of 6.7 months compared to 3.1 months for the patients treated with chemotherapy. Six of these patients were included in a previously published study [11]. In previous preclinical work the presence of the estrogen receptor alpha and activity of aromatase in chondrosarcoma cell lines was confirmed providing rationale for inhibition of estrogen and aromatase as a treatment strategy for chondrosarcoma [13, 14]. However, a beneficial effect could not be convincingly and reproducibly shown *in vitro*, and an *in vivo* pilot study in 6 patients showed no clear therapeutic benefit for advanced conventional or dedifferentiated chondrosarcoma patients treated with an aromatase inhibitor [11]. It is interesting though, that in the current study that includes six of these patients, anti-hormonal therapy gave the longest PFS with a mean of 6.7 months among the different treatment regimens. So far we cannot explain the benefit in PFS for the conventional CS patients treated with these treatment regimens. Further preclinical and clinical studies need to be conducted to clarify if anti-hormonal therapy is a possible therapeutic strategy for CS patients.

In our cohort three patients diagnosed with conventional CS were treated with saridegib. The mean PFS for these three patients was 3.6 months. Preclinical studies suggest that hedgehog signaling plays an important role in the pathogenesis of chondrosarcoma. The hedgehog pathway regulates chondrocyte proliferation and differentiation during endochondral bone development. In chondrosarcoma hedgehog signaling is dysregulated. In previous preclinical work only one out of six chondrosarcoma cell cultures was responsive

to the Hh inhibitor cyclopamine [15]. However, in primary human chondrosarcoma tissue xenotransplanted in mice, treatment with the hedgehog inhibitor IPI-926 results in down-regulation of the hedgehog pathway and inhibition of tumour growth [16]. In addition, chondrosarcoma xenografts responded to the hedgehog inhibitor triparanol with a 60% decrease in tumor volume [17]. Preclinical evidence suggests that maybe a small subset of chondrosarcoma patients may benefit from hedgehog inhibition, currently there are no biomarkers to predict which patients will respond. In a phase 2, randomized, placebo controlled trial inoperable chondrosarcoma patients were treated with the hedgehog inhibitor saridegib. The results of the study showed no improvement in PFS when compared to placebo and the study was stopped [18]. Future studies should be performed to investigate whether the subgroup of patients with mutations in hedgehog pathway genes may benefit from hedgehog inhibitors.

In our study, the median PFS for patients with conventional chondrosarcoma treated with dasatinib was 2.2 months. Using kinome profiling the Src pathway was identified as a possible therapeutic target for chondrosarcoma [19]. Inhibition of the Src pathway with dasatinib, a tyrosine kinase inhibitor, resulted in a decrease of cell growth. Combination treatment of dasatinib with the chemotherapeutic agent doxorubicin results in a synergistic effect on inhibition of cell viability and inducing apoptosis in chondrosarcoma cell lines [20]. This may suggest that blocking the Src pathway may overcome chemo resistance in chondrosarcoma. A recent phase 2 study with the tyrosine kinase inhibitor dasatinib included patients diagnosed with chondrosarcoma, who were incurable with conventional therapy. The median PFS for the patients in the study, enrolling all different chondrosarcoma subtypes, was 5.5 months [21].

Three conventional CS patients in the current study were treated with inhibitors of mutant isocitrate dehydrogenase (IDH). In ~50% of the conventional and the dedifferentiated chondrosarcomas driver mutations are found in the IDH1 or the IDH2 gene [22, 23] providing a strong rationale to treat chondrosarcomas with inihibitors of the mutant enzyme. Promising results have been obtained in other IDH mutant tumours including glioma and leukemia [24]. Preclinical data have shown that while IDH mutations are important for the development of the benign precursor lesion enchondroma [25, 26], however after progression to malignant chondrosarcoma the cells do not depend on the IDH mutation anymore for survival [27, 28]. This would imply that chondrosarcoma patients will not benefit from these inhibitors as single agent therapy, which is in line with the poor PFS in the three patients in the current study. Several clinical trials are currently investigating the effect of IDH inhibition for patients with solid tumors with an IDH1 or IDH2 mutation (ClinicalTrials.gov Identifier: NCT02746081, NCT02481154, NCT02073994, NCT02273739.

All patients diagnosed with mesenchymal chondrosarcoma were treated with chemotherapy. The combination of doxorubicin with cisplatin (n=4) seems to have a better PFS than the regimens that contain 3 or more different chemotherapy agents (n=13). Although numbers are small, one may – with reservation - conclude that the need for regimens with multiple different chemotherapy agents are doubtful.

The fusion gene HEY1-NCOA2 is considered a diagnostic molecular marker [29]. Data on HEY1-NCOA2 translocations, described in 73% of mesenchymal chondrosarcomas, and for IDH1 or -2 mutations, described in ~50% of conventional and dedifferentiated chondrosarcoma were not available for our patients. However, the IDH1 or -2 molecular alterations have no known prognostic value [30], for HEY-NCOA2 translocation it is still unclear.

Patients diagnosed with dedifferentiated chondrosarcoma had a wide range of PFS when comparing the outcome with the same treatment regimens. Doxorubicin monotherapy seems to have a better outcome than treatment with the different combination regimens of doxorubicin. This difference in PFS is notable, however non-significant (p=0.275) and thus far unexplained. No difference in toxicity as a reason for discontinuing the treatment was seen, 16.6% in the monotherapy group versus 12.5% for the combination regimens.

From this database we observed that there was a wide variation in effect of the same treatment between patients with the same subtype of CS. This may be related to the low number of patients per subgroup. This makes it hard to draw firm conclusions and propagate one treatment over the other. On the other hand this is still one of the largest series of systemic treatment outcome in chondrosarcoma and the only study taking into account both: line of systemic therapy and CS subtype.

Currently there are no uniform treatment guidelines for advanced chondrosarcoma patients, which results in very diverse treatment regimens being used. In this study we collected the data of 112 patients, but the numbers were still too small to do a statistical analysis on the different systemic treatments. Within the limitations of this study, with low numbers and a retrospective nature causing a selection bias, we can conclude that some treatment regimens seem to have a better PFS as compared to others, and that these results differ between the chondrosarcoma subtypes. Because of the retrospective nature of this study we were not able to do a central pathological review of all the tumours, this may have affected the results. However, all diagnoses were established in a multidisciplinary setting in a center of expertise. Prospective studies need to be conducted based on preclinical work to develop a uniform regimen to treat advanced chondrosarcoma patients according to the histological subtype in order to improve their survival.

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Supplementary Table S8.1 The patient data used for the analysis

Center	Subtype	Gender	Age	Localization	Treatment	PFS first systemic treatment line after unresectability (months)
Netherlands	Conventional	Male	48	Axial	Doxorubicin	2
Netherlands	Conventional	Male	53	Axial	Doxorubicin + cisplatin	5
Netherlands	Conventional	Male	57	Extremity	Doxorubicin + cisplatin	1
Netherlands	Conventional	Female	36	Axial	Doxorubicin + cisplatin	3
Netherlands	Conventional	Male	32	Axial	Doxorubicin + cisplatin	1
Netherlands	Conventional	Female	38	Axial	Ifosfamide	3
Netherlands	Conventional	Male	47	Axial	Arimidex	5
Netherlands	Conventional	Male	31	Extremity	Arimidex	4
Netherlands	Conventional	Male	53	Extremity	Arimidex	5
Netherlands	Conventional	Male	43	Axial	Aromasin	10
Netherlands	Conventional	Male	36	Axial	Aromasin	6
Netherlands	Conventional	Female	58	Axial	Pazopanib	7
Netherlands	Conventional	Female	49	Axial	Dasatinib	5
Netherlands	Conventional	Male	54	Extremity	Dasatinib	1
Netherlands	Conventional	Female	69	Axial	Dasatinib	2
Netherlands	Conventional	Male	47	Axial	Dasatinib	1
Netherlands	Conventional	Female	43	Axial	Dasatinib	2
Netherlands	Conventional	Male	51	Axial	Saridegib	2
Netherlands	Conventional	Male	72	Axial	Saridegib	2
Netherlands	Conventional	Male	55	Axial	Saridegib	5
Netherlands	Mesenchymal	Male	24	Extremity	Doxorubicin + cisplatin	4
Netherlands	Mesenchymal	Female	46	Axial	Doxorubicin + cisplatin	10
Netherlands	Mesenchymal	Male	21	Axial	Doxorubicin + ifosfamide	3
Netherlands	Mesenchymal	Male	45	Extremity	Sutent + ifosfamide	4

Supplementary Table S8.1 continues on next page.

Supplementary Table S8.1 *Continued*

Center	Subtype	Gender	Age	Localization	Treatment	PFS first systemic treatment line after unresectability (months)
Netherlands	Mesenchymal	Female	38	Extremity	Vincristine + ifosfamide + doxorubicin + etoposide	37
Netherlands	Dedifferentiated	Female	29	Axial	Doxorubicin	2
Netherlands	Dedifferentiated	Male	49	Extremity	Doxorubicin	4
Netherlands	Dedifferentiated	Female	45	Axial	Doxorubicin	3
Netherlands	Dedifferentiated	Male	45	Extremity	Doxorubicin	19
Netherlands	Dedifferentiated	Male	51	Axial	Doxorubicin + cisplatin	3
Netherlands	Dedifferentiated	Female	53	Axial	Doxorubicin + cisplatin	1
Netherlands	Dedifferentiated	Female	50	Extremity	Doxorubicin + cisplatin	4
Netherlands	Dedifferentiated	Male	62	Extremity	Doxorubicin + cisplatin	4
Netherlands	Dedifferentiated	Female	41	Axial	Doxorubicin + cisplatin	9
Netherlands	Dedifferentiated	Male	68	Extremity	Arimidex	1
Netherlands	Dedifferentiated	Male	77	Axial	Dasatinib	3
Netherlands	Dedifferentiated	Male	50	Extremity	MBG453	2
Poland	Conventional	Female	32	Axial	Doxorubicin + cisplatin	1
Poland	Conventional	Male	69	Extremity	Doxorubicin + cisplatin	10
Poland	Conventional	Male	56	Extremity	Doxorubicin + cisplatin	2
Poland	Mesenchymal	Male	27	Extremity	Doxorubicin + cisplatin	10
Poland	Mesenchymal	Female	45	Axial	Doxorubicin + cisplatin	7
Poland	Mesenchymal	Female	19	Axial	Vincristine + doxorubicin + cyclofosfamide/ ifosfamide + etoposide	2
Poland	Mesenchymal	Male	21	Axial	Vincristine + doxorubicin + cyclofosfamide/ ifosfamide + etoposide	11
Poland	Mesenchymal	Female	39	Axial	Vincristine + doxorubicin + cyclofosfamide/ ifosfamide + etoposide	2

Supplementary Table S8.1 *Continued*

Center	Subtype	Gender	Age	Localization	Treatment	PFS first systemic treatment line after unresectability (months)
Poland	Mesenchymal	Female	28	Extremity	Vincristine + doxorubicin + cyclofosfamide/ ifosfamide + etoposide	9
Poland	Dedifferentiated	Female	73	Extremity	Cisplatin + dacarbazin + vinblastine	1
USA	Conventional	Male	67	Extremity	Doxorubicin	2
USA	Conventional	Female	41	Axial	Doxorubicin	2
USA	Conventional	Female	62	Axial	Doxorubicin + cisplatin	7
USA	Conventional	Male	25	Extremity	Doxorubicin + cisplatin	2
USA	Conventional	Male	48	Extremity	Gemcitabine + docetaxel	4
USA	Conventional	Male	52	Axial	Gemcitabine + docetaxel	13
USA	Conventional	Female	64	Axial	Gemcitabine + docetaxel	2
USA	Conventional	Male	38	Axial	Aldoxorubicin	2
USA	Conventional	Female	64	Axial	Vincristine + doxorubicin + cyclophosphamide / ifosfamide + etoposide	1
USA	Conventional	Female	53	Extremity	Arimidex	7
USA	Conventional	Female	65	Axial	Tamoxifen	4
USA	Conventional	Male	55	Axial	Pazopanib	3
USA	Conventional	Male	56	Extremity	Pazopanib	1
USA	Conventional	Female	51	Axial	Pazopanib	4
USA	Conventional	Female	32	Extremity	Pazopanib	3
USA	Conventional	Female	32	Axial	Pazopanib + trametinib	1
USA	Conventional	Male	64	Axial	Vorinostat + hydroxychloroquine	2
USA	Conventional	Female	44	Axial	Vorinostat + hydroxychloroquine	16
USA	Conventional	Male	43	Axial	Vorinostat + hydroxychloroquine	3
USA	Conventional	Male	47	Extremity	Perifosine	21
USA	Conventional	Female	44	Axial	R4733	2

Supplementary Table S8.1 continues on next page.

Supplementary Table S8.1 *Continued*

Center	Subtype	Gender	Age	Localization	Treatment	PFS first systemic treatment line after unresectability (months)
USA	Conventional	Female	28	Extremity	Vismodegib	2
USA	Conventional	Male	28	Axial	Pembrolizumab	2
USA	Conventional	Female	47	Axial	CB-839	1
USA	Conventional	Male	40	Extremity	IDH305	2
USA	Conventional	Male	61	Extremity	AG-881	1
USA	Mesenchymal	Female	45	Extremity	Doxorubicin + ifosfamide	3
USA	Mesenchymal	Male	37	Axial	Doxorubicin + ifosfamide	3
USA	Mesenchymal	Female	38	Axial	Doxorubicin + cisplatin	3
USA	Mesenchymal	Female	21	Axial	Ifosfamide + etoposide	5
USA	Mesenchymal	Male	30	Extremity	Gemcitabine + docetaxel	1
USA	Mesenchymal	Female	18	Axial	Vincristine + doxorubicin + ifosfamide	10
USA	Mesenchymal	Female	48	Extremity	Vincristine + doxorubicin + ifosfamide	5
USA	Mesenchymal	Female	45	Axial	Vincristine + doxorubicin + ifosfamide	2
USA	Mesenchymal	Female	18	Axial	Vincristine + doxorubicin + ifsofamide	10
USA	Mesenchymal	Female	48	Axial	Vincristine + doxorubicin + ifosfamide	5
USA	Mesenchymal	Female	24	Extremity	Vincristine + doxorubicin + cyclofosfamide / vincristine + doxorubicin + ifsofamide	3
USA	Mesenchymal	Male	17	Axial	Vincristine + doxorubicin + cyclofosfamide / ifosfamide + etoposide	3
USA	Mesenchymal	Male	16	Axial	Vincristine + ifosfamide + doxorubicin / ifosfamide + etoposide	6
USA	Mesenchymal	Female	7	Extremity	Pazopanib	2
USA	Dedifferentiated	Male	49	Axial	Pazopanib	2
USA	Dedifferentiated	Male	54	Axial	Ddoxorubicin + cisplatin	2

Supplementary Table S8.1 *Continued*

Center	Subtype	Gender	Age	Localization	Treatment	PFS first systemic treatment line after unresectability (months)
USA	Dedifferentiated	Female	78	Extremity	Durvalumab + mogamulizumab	3
USA	Dedifferentiated	Male	63	Axial	Doxorubicin + cisplatin	2
USA	Dedifferentiated	Female	47	Axial	Doxorubicin + cyclofosfamide	1
USA	Dedifferentiated	Female	36	Axial	Doxorubicin + cisplatin + methotrexaat	3
USA	Dedifferentiated	Male	44	Axial	Pazopanib	20
USA	Dedifferentiated	Female	56	Axial	Doxorubicin + cisplatin	2
USA	Dedifferentiated	Male	67	Axial	Doxorubicin + ifosfamide	5
USA	Dedifferentiated	Female	58	Axial	Doxorubicin + cisplatin	4
USA	Dedifferentiated	Male	66	Extremity	Doxorubicin + cisplatin	2
USA	Dedifferentiated	Female	44	Axial	Doxorubicin + cisplatin	1
USA	Dedifferentiated	Female	46	Extremity	Doxorubicin + cisplatin	1
USA	Dedifferentiated	Female	43	Extremity	Doxorubicin + cisplatin + methotrexaat	3
USA	Dedifferentiated	Male	66	Axial	AG-120	1
USA	Dedifferentiated	Female	76	Extremity	Doxorubicin + cisplatin	2
USA	Dedifferentiated	Female	59	Axial	Vorinostat + hydroxychloroquine	3
USA	Dedifferentiated	Male	61	Extremity	Doxorubicin + ifosfamide	2
USA	Dedifferentiated	Female	57	Axial	Doxorubicin + ifosfamide	4
USA	Dedifferentiated	Male	42	Axial	Doxorubicin + ifosfamide	1
USA	Dedifferentiated	Male	53	Extremity	Sunitinib	1
USA	Clear cell	Male	42	Extremity	Ifosfamide	17
USA	Clear cell	Male	43	Axial	Sunitinib	8
USA	Clear cell	Male	42	Extremity	Pazopanib + denosumab	5

PFS, progression free survival; USA, United States of America.