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ORIGINAL ARTICLE

Activity of chemotherapy in mesenchymal chondrosarcoma: a multicentre retrospective analysis within the Italian Sarcoma Group network

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Background: Mesenchymal chondrosarcoma (MCS) is an ultra-rare sarcoma, molecularly defined by the *HEY1::NCOA2* fusion, and characterized by a poor prognosis in the advanced phase. Data on the activity of systemic agents in MCS are only retrospective and limited to case reports or heterogeneous series. We report the results of an Italian, multicentric, retrospective study on the activity of cytotoxic chemotherapy in patients with MCS.

Patients and methods: This retrospective, multicentre Italian Sarcoma Group study included patients with molecularly confirmed MCS, treated with anthracycline-based chemotherapy, high-dose ifosfamide (HD-IFX), or trabectedin between 2000 and 2022. Response to treatment was assessed retrospectively through imaging review. Survival outcomes were estimated by the Kaplan–Meier method.

Results: Thirty-five patients were identified (19 = localized disease, 16 = advanced disease). Anthracycline-based regimens yielded an overall response rate (ORR) of 26% [95% confidence interval (CI) 15% to 50%]. Among patients with localized disease, Ewing-like regimens showed an ORR of 33.3% (95% CI 9.9% to 65.1%), median relapse-free survival (mRFS) of 86.9 months, and 5-year overall survival of 95%; other anthracycline combinations had an ORR of 40% (95% CI 5.3% to 85.3%) and mRFS of 32.6 months. In advanced disease, Ewing-like regimens yielded an ORR of 16.7% (95% CI 0.4% to 64.1%) and median progression-free survival (mPFS) of 13.2 months, while other anthracycline regimens resulted in an ORR of 22.2% (95% CI 15% to 50%) and mPFS of 9.3 months. HD-IFX showed no responses, with early progression in all cases. Trabectedin achieved stable disease in all four treated patients, with a median PFS of 16.9 months.

Conclusions: This multicentre study confirms that anthracycline-based regimens show activity in MCS, with responses more in line with soft tissue sarcoma than Ewing sarcoma. Their benefit in localized disease remains uncertain, but (neo)adjuvant chemotherapy with Ewing-like regimens should be considered for patients eligible for surgery. In advanced disease, trabectedin may provide prolonged disease control after anthracyclines.

Key words: soft-tissue sarcoma, bone sarcoma, chondrosarcoma, anthracyclines, trabectedin, ultra-rare sarcomas

INTRODUCTION

With an incidence of ≤1 in 1 000 000 per year, mesenchymal chondrosarcoma (MCS) belongs to the ultra-rare sarcoma group.[1] It predominantly affects craniofacial bones (particularly the jawbones), followed by ribs, ilium,

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and vertebrae.[2] About one-fifth to one-third of all cases arise from soft tissues, with the meninges being one of the most common extraskeletal primary sites.[2,3]

First described in 1959 by Lichtenstein and Bernstein,[4] MCS exhibits a high-grade and biphasic pattern, characterized by both a cartilaginous and an undifferentiated small blue round cell component.[2] Notably, MCS is molecularly marked by the presence of the *HEY1::NCOA2* fusion.[5] This fusion serves as an important diagnostic marker aiding in differential diagnosis with morphologically similar entities.[2] The chimeric fusion arises from an intrachromosomal deletion between exon 4 of hairy/enhancer-of-split related with YRPW motif 1 (*HEY1*) and exon 13 of nuclear receptor coactivator 2 (*NCOA2*), resulting in the combination of the DNA-binding domain of *HEY1* with the two C-terminal activation domains of *NCOA2*. *HEY1* is located on the long arm of human chromosome 8 and functions as a downstream mediator and effector within the activated Notch signalling pathway, which is crucial for development and stemness. *HEY1* primarily acts as a transcriptional repressor, and its dysregulation can alter the expression of genes involved in musculoskeletal development. *NCOA2*, also located on the long arm of human chromosome 8, interacts with nuclear receptors and recruits histone methyltransferases to specific genomic sequences. This recruitment facilitates chromatin remodelling and transcriptional activation of specific target genes.

The chimeric *HEY1::NCOA2* transcript promotes oncogenesis by activating the Notch signalling pathway, which regulates apoptosis, enhances cellular proliferation, and stimulates epithelial-to-mesenchymal transition. Additionally, this fusion has been associated with effects on chromatin configuration, further contributing to its pathogenetic impact.[6] To date, a single case harbouring an alternative *IRF2BP2::CDX1* fusion has been reported.[7]

Despite a potentially indolent clinical behaviour, MCS shows a strong propensity for metastatic spread.[8] Outcomes remain poor, with a median overall survival (OS) in the advanced setting of ∼3 years, across all the available series.[9-12]

For patients with localized disease, surgery is the mainstay of treatment, often combined with concomitant radiotherapy and anthracycline-based multidrug chemotherapy, resembling regimens used for Ewing sarcoma.[3,9-15]

In locally advanced and/or metastatic disease, treatment options are limited. To date, no prospective studies have specifically evaluated the role of medical therapy in this histological type. Data on the activity of systemic agents in MCS are retrospective and derive mainly from case reports and limited, heterogeneous series.[10-16] These data suggest that MCS could be more sensitive to chemotherapy than the other chondrosarcoma subtypes. Responses were reported to chemotherapy regimens based on doxorubicin, cisplatin, or ifosfamide.[10-16] Historically, Ewing-like chemotherapy regimens, including cyclophosphamide or ifosfamide, and vincristine followed by etoposide and ifosfamide, have typically been commonly offered as a first-line approach, although no formal comparison with other, less intensive regimens are available.[17-21] Among relatively new agents, a longer disease control (mPFS 12 months) was seen in four metastatic patients treated with trabectedin in later-line settings across different series.[22-25]

To improve available evidence, we conducted a collaborative, retrospective study on the activity of cytotoxic chemotherapy in patients with molecularly confirmed MCS treated at the referral sarcoma centres belonging to the Italian Sarcoma Group (ISG), and at the sarcoma reference centre in Cairo, Egypt, between 2000 and 2022, to better inform clinical decision making and the design of future studies. We focused on cytotoxic agents formally approved for treatment of advanced sarcomas, i.e. anthracycline-based regimens, high-dose ifosfamide (HD-IFX), and trabectedin.

PATIENTS AND METHODS

Patient population

Patients of all ages, with a histologically and molecularly confirmed diagnosis of MCS who were treated with anthracycline-based regimens, HD-IFX, and/or trabectedin between January 2000 and April 2022 were retrospectively identified. The study included both patients with localized disease treated with curative intent and with advanced disease (locally advanced not eligible for surgical resection or metastatic), treated in the first or further line. These patients were managed at eight sarcoma reference centres belonging to ISG (Adult and Pediatric Medical Oncology units, Fondazione IRCCS Istituto Nazionale Tumori, Milan; Istituto Ortopedico Rizzoli, IRCCS, Bologna; Azienda Ospedaliera Universitaria Careggi, Florence; Candiolo Cancer Institute FPO-IRCCS, Candiolo-Turin; Campus Bio-Medico University, Rome; Children's Hospital Bambino Gesù IRCCS, Rome; Regina Margherita Children's Hospital, AOU Città della Salute e della Scienza, Turin), and at one centre in Egypt (Ain Shams University, Cairo).

A written informed consent to treatment was obtained from each patient as required by local regulation. Approval of the retrospective study by the institutional review board of each participating institution was required.

Study design and data collection

Data were extracted from patients' medical records or prospectively maintained institutional clinical databases.

In all cases, the diagnosis was either carried out or reviewed by an expert sarcoma pathologist at each participating centre, according to the World Health Organization classification, fifth edition.[2] Molecular confirmation of the *HEY1::NCOA2* fusion was mandatory and only cases that were fusion-positive were included. Cases were tested using real-time polymerase chain reaction (RT—PCR), fluorescent *in situ* hybridization (FISH), or next-generation sequencing (NGS).

Response to treatment was assessed retrospectively through imaging review and categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) based on the determination

of the local radiologist. All participating institutions consistently assessed response through magnetic resonance imaging and/or computed tomography scan, as appropriate, repeated every 2-3 months.

In the anthracycline-based regimens group, chemotherapy was administered every 3 weeks, constituting one cycle. HD-IFX was given at a dose of 14 g/m^2 as a 14-day continuous infusion via an external elastomeric pump and administered every 4 weeks (one cycle). Trabectedin was administered at a dose of 1.3-1.5 mg/m^2 every 3 weeks, corresponding to one cycle.

Statistical analysis

Descriptive statistics and frequency tabulation were used to summarize patient and tumour characteristics.

The primary endpoint of this study was the overall response rate (ORR); secondary endpoints were relapse-free survival (RFS, for patients treated for localized disease with curative intent), progression-free survival (PFS, for patients with advanced disease), OS, and duration of response (DoR).

The association between outcome and the type of chemotherapy regimen administered (Ewing-like approach versus other anthracycline-based regimens) was evaluated.

ORR was defined as the proportion of patients who achieved a CR or a PR according to the local radiologist determination. The corresponding 95% confidence intervals (CIs) were calculated based on the binomial distribution.

RFS, PFS, and OS were estimated using the Kaplan—Meier method.

For patients who were treated for localized disease with curative intent, RFS was calculated as the interval from the start of the upfront treatment to the date of the first evidence of recurrence, death, or the last follow-up; for patients with advanced disease, PFS was calculated as the interval from the start of systemic treatment to the date of PD, death, or the last follow-up; OS was calculated as the interval from the start of the upfront treatment to the date of death or the last follow-up. DoR was calculated from the date of best response to the date of first evidence of progression for patients with CR and PR, or death, or the last follow-up.

A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were carried out with R software (version 4.4.2) (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Thirty-five patients with localized or advanced MCS, all treated with systemic therapies, were retrospectively identified and included in the survival analyses, while 32/35 (91%) were assessable for response (two not assessable because they were treated in an adjuvant setting; one because the patient received concomitant chemoradiotherapy).

All patients had *HEY1::NCOA2* fusion-positive disease, confirmed by RT—PCR in 10 cases, FISH in 15, and NGS in 10. Nineteen out of 35 (54%) patients were treated for localized disease with curative intent and 16/35 (46%) for advanced disease. Among those, 6/16 (37%) had locally advanced disease and 10/16 (63%) had metastatic disease. Thirty-three out of 35 (82%) patients received anthracycline-based chemotherapy, 3/35 (8%) HD-IFX, and 4/35 (10%) trabectedin. Three (8%) patients had more than one line of treatment. The median follow-up for the entire series was 36.5 months (95% CI 25.2-65.5 months).

Tables 1 and 2 summarize the main population and treatment characteristics.

Table 1. Main patients and disease characteristics

	Entire series $N = 35$
Median age at diagnosis, years (range)	31 (8-68)
Sex: M/F	21/14
Primary tumour site, *n* (%)	
Bone	**22 (63)**
Mobile spine	9 (41)
Limbs	5 (23)
Thoracic wall	4 (18)
Head and neck	4 (18)
Soft tissue	**13 (37)**
Limbs	8 (62)
Retroperitoneum	2 (15)
Meninges	1 (8)
Not reported	2 (15)
HEY1::NCOA2 fusion, *n* (%)	
Positive	**35 (100)**
FISH	15 (44)
RT—PCR	10 (28)
NGS	10 (28)
Stage at treatment start, *n* (%)	
Local	**20 (57)**
Advanced	**15 (43)**
Locally advanced	5 (14)
Metastatic	10 (29)

The values were highlighted in bold to distinguish them from the other numbers, which refer to subgroups.
F, female; M, male; NGS, next-generation sequencing; RT—PCR, real-time polymerase chain reaction.

Treatment response and outcome

Anthracycline-based regimens. Thirty-tree patients were included in this group; 30 were assessable for response. Nineteen out of 33 (58%) patients were treated for localized disease with curative intent, while 14/33 (42%) were treated for advanced disease.

In the advanced disease cohort, anthracyclines were used as a first-line treatment in 12/14 (86%) patients, and as a second-line treatment and in further lines in one patient, respectively.

Overall, all patients had completed their treatment at the time of this analysis: 11/30 (37%) for reaching the maximum cumulative dose of anthracycline, 3/30 (10%) for PD, 2/30 (7%) for grade 3 haematological toxicity, 13/30 (43%) for surgery after neoadjuvant chemotherapy, while one patient discontinued treatment by personal choice.

Among patients treated with anthracycline-based regimens overall, best response according to local radiological

Table 2. Main treatment characteristics

	Localized disease *N* (%)	Advanced disease *N* (%)
Anthracycline-based regimens	19/33 (58)	14/33 (42)
Ewing-like regimens	13/19 (68)	6/14 (43)
VAC/VID→ IE	8/13 (62)	3/6 (50)
VAC → IE	3/13 (23)	1/6 (17)
VAI/VAC	2/13 (15)	1/6 (17)
VAI→EC	—	1/6 (17)
(Neo)adjuvant RT		
Yes	5/13 (38)	—
No	8/13 (62)	—
Surgery for local disease		
Yes	13/13 (100)	5/6 (83)
No	—	1/6 (17)
Other anthracycline-based regimens	6/19 (32)	8/14 (57)
AI	6/6 (100)	6/8 (75)
Acis	—	1/8 (12)
A	—	1/8 (12)
(Neo)adjuvant RT		
Yes	3/6 (50)	—
No	3/6 (50)	—
Surgery for local disease		
Yes	6/6 (100)	5/8 (62)
No	—	3/8 (38)
HD-IFX	1/3 (33)	2/3 (67)
(Neo)adjuvant RT		
Yes	—	—
No	1/3 (33)	—
Surgery for local disease		
Yes	1/3 (33)	1/3 (33)
No	—	1/3 (33)
Trabectedin	—	4/4 (100)
(Neo)adjuvant RT		
Yes	—	—
No	—	—
Surgery for local disease		
Yes	—	4/4 (100)
No	—	—

A, anthracycline alone; Acis, anthracycline and cisplatin; AI, anthracycline and ifosfamide; EC, etoposide and cyclophosphamide; HD-IFX, high-dose ifosfamide; IE, etoposide and ifosfamide; RT, radiotherapy; VAC, vincristine, actinomycin D and cyclophosphamide; VAI, vincristine, actinomycin D and ifosfamide; VID, vincristine, ifosfamide and doxorubicin.

review was 8/30 PR (26%), 17/30 SD (56%), and 4/30 PD (13%). The ORR was 26% (95% CI 15% to 50%).

At a median follow-up of 46.6 months (95% CI, 36.4—104), 12 of 19 patients (63%) were alive and relapse-free, while 7/19 (36%) experienced disease progression, all with development of distant metastases. The median RFS (mRFS) was 86.9 months [95% CI 46.2 months-not estimated (NE)]. The median OS (mOS) in patients with localized disease could not be estimated, as only one event occurred.

For patients with advanced disease (14), at a median follow-up of 14.4 months (95% CI 9.05 months-NE), 6/14 (43%) patients were alive and progression free, with a median PFS (mPFS) of 10.2 months (95% CI 6.6 months-NE) (Figure 1) and a median DoR of 10.2 months (range 5.62-11.5 months), while the mOS was 25 months (95% CI 18.8 months-NE).

Among 19 patients with localized disease treated with anthracycline-based therapy, 13/19 (68%) were treated with a multidrug regimen, using an Ewing-like approach (e.g. anthracycline with cyclophosphamide or ifosfamide and vincristine followed by or alternated with etoposide and ifosfamide), while 6/19 (32%) received anthracycline in combination with ifosfamide.

Best response according to local radiological review in patients with localized disease treated with an Ewing-like approach ($n = 12$ assessable for response) was 1/12 CR (8.3%), 3/12 PR (25%), 7/12 SD (58.3%), and 1/12 PD (8.3%). The ORR was 33.3% (95% CI 9.9% to 65.1%).

Best response in patients with localized disease treated with anthracycline in combination with ifosfamide ($n = 5$ assessable for response) was 2/5 PR (40%) and 3/5 SD (60%). The ORR was 40% (95% CI 5.3% to 85.3%).

The median RFS was 86.9 months (95% CI 86.9 months-NE) in patients treated with an Ewing-like approach and 32.6 months (95% CI 11.2 months-NE) in those who received anthracycline in combination with ifosfamide ($P = 0.05$) (Figure 2). The difference in OS between the two groups could not be estimated, as only one event occurred in a patient treated with the Ewing-like approach.

Among the 14 patients with advanced disease treated with anthracycline-based therapy, 6/14 (43%) were treated with an Ewing-like approach, while 8/14 (57%) received anthracycline as a single agent (one patient) or in combination with ifosfamide (six patients) or cisplatin (one patient).

Best response in patients with advanced disease treated with an Ewing-like approach ($n = 6$ assessable for response) was 1/6 PR (16.7%), 4/6 SD (66.6%), and 1/6 PD (16.7%). The ORR was 16.7% (95% CI 0.4% to 64.1%).

Best response, according to local radiological review, in patients with advanced disease treated with other anthracycline-based regimens ($n = 9$ assessable for response) was 2/9 PR (22.2%), 3/9 SD (33.3%), and 2/9 PD (22.2%). The ORR was 22.2% (95% CI 2.8% to 60.0%).

The mPFS was 13.2 months (95% CI 10.2 months-NE) in the six patients with advanced disease treated with an Ewing-like approach and 9.3 months (95% CI 6.5 months-NE) in those who received other anthracycline-based regimens ($P = 0.32$) (Figure 3). Similarly, the mOS was 36.8 months (95% CI 25.3 months-NE) in patients with advanced disease treated with an Ewing-like approach and 19.1 months (95% CI 19.1 months-NE) in those who received other anthracycline-based regimens ($P = 0.9$).

High-dose ifosfamide. Three patients were included, and all were assessable for response. One patient was treated for local disease and two for metastatic disease, both previously treated with ifosfamide in the (neo)adjuvant setting. HD-IFX was administered as a second line in one case and as a later line in the other. At the time of the analysis, all patients discontinued treatment for PD. The median number of cycles was 3 (range 1-3). Best response was 1/3 SD and 2/3 PD. PFS in the two patients with advanced disease was 3.2 and 3.9 months, respectively.

Trabectedin group. Four patients with advanced disease were included, all assessable for response. Three had a primary soft-tissue tumour, while one had a primary bone

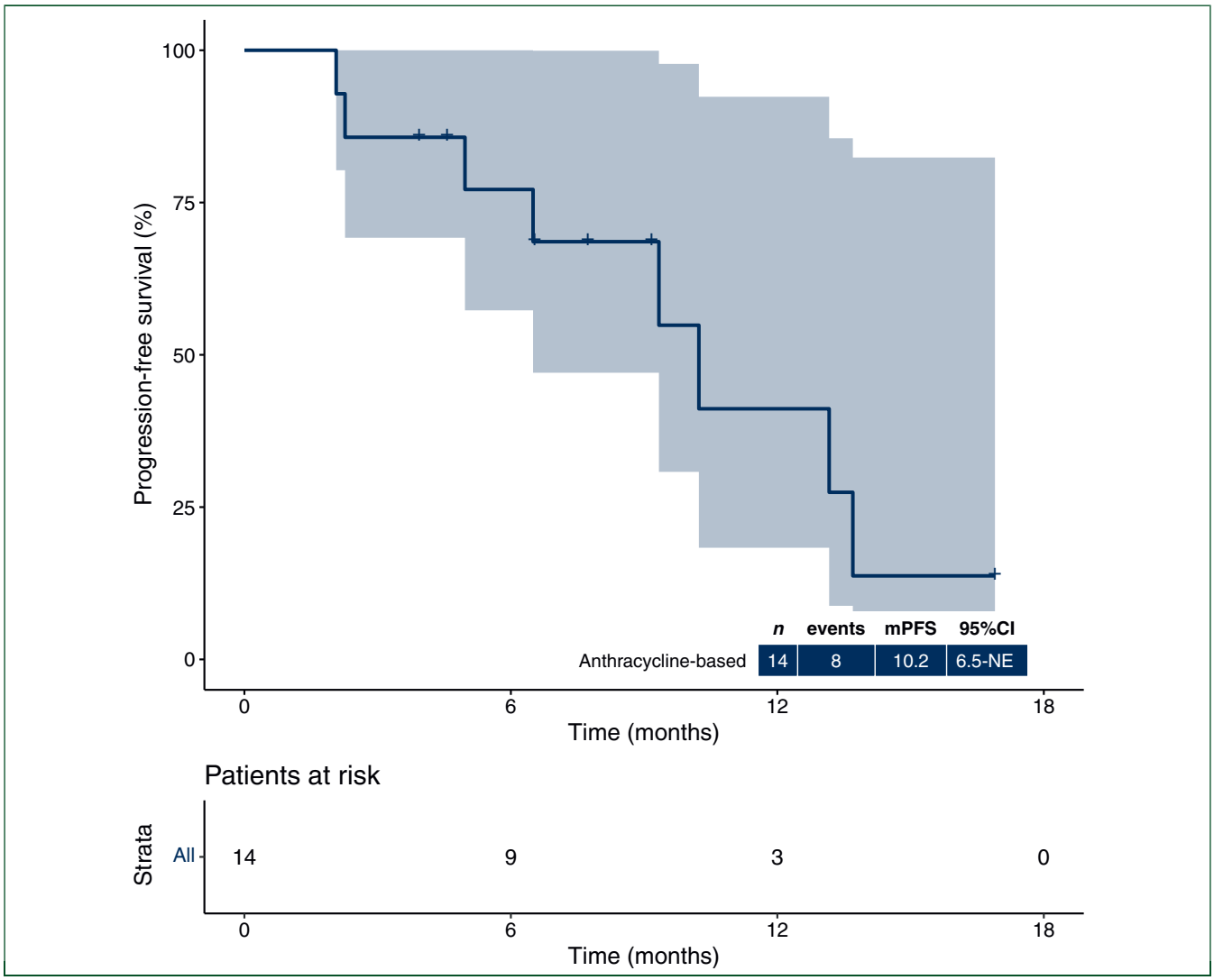

Figure 1. Kaplan–Meier curve showing progression-free survival (PFS) in patients with advanced disease treated with anthracycline-based regimens.
CI, confidence interval; NE, not estimated.

tumour. All patients in this group had PD before starting treatment. Trabectedin was administered as a second-line treatment in three out of four cases and as a further line in one out of four cases. At the time of the analysis, all patients had discontinued treatment: 3/4 (75%) for PD and 1/4 (25%) for toxicity. The median number of cycles was 20 (range 8-25). Best response according to local radiological review was SD in all cases. At a median follow-up of 53.9 months, the mPFS was 16.9 months (CI 9.7 months-NE), with three patients remaining on therapy for >2 years. The mOS was 34.3 months (CI 11.4 months-NE).

DISCUSSION

This retrospective study conducted within the ISG network analysed a cohort of 35 patients with molecularly confirmed MCS treated with systemic therapies. Anthracycline-based regimens achieved a radiological response in slightly >25% of the patients, with an mPFS of 10 months in patients treated for advanced disease. The responses observed with both Ewing-like and anthracycline-based regimens were comparable in both localized (ORR 33.3% versus 40%) and advanced disease (ORR 16.7% versus 22.2%). Overall, these response rates are more consistent with those typically seen in soft-tissue sarcomas, rather than with the higher response rates usually observed in Ewing sarcoma. In the few cases treated with trabectedin, tumour shrinkage or dimensional responses were not reported but all patients experienced a stabilization of the disease with prolonged disease control and an mPFS of 16.7 months. No responses were seen with HD-IFX monotherapy when used in further lines and all patients progressed within 4 months.

While the interpretation of our results is limited by the small population included, this series is the largest available for *HEY1::NOCA2*-positive MCS treated with conventional chemotherapy. Given the retrospective design and the contribution of different institutions, there has been a degree of variability in treatment regimens and follow-up

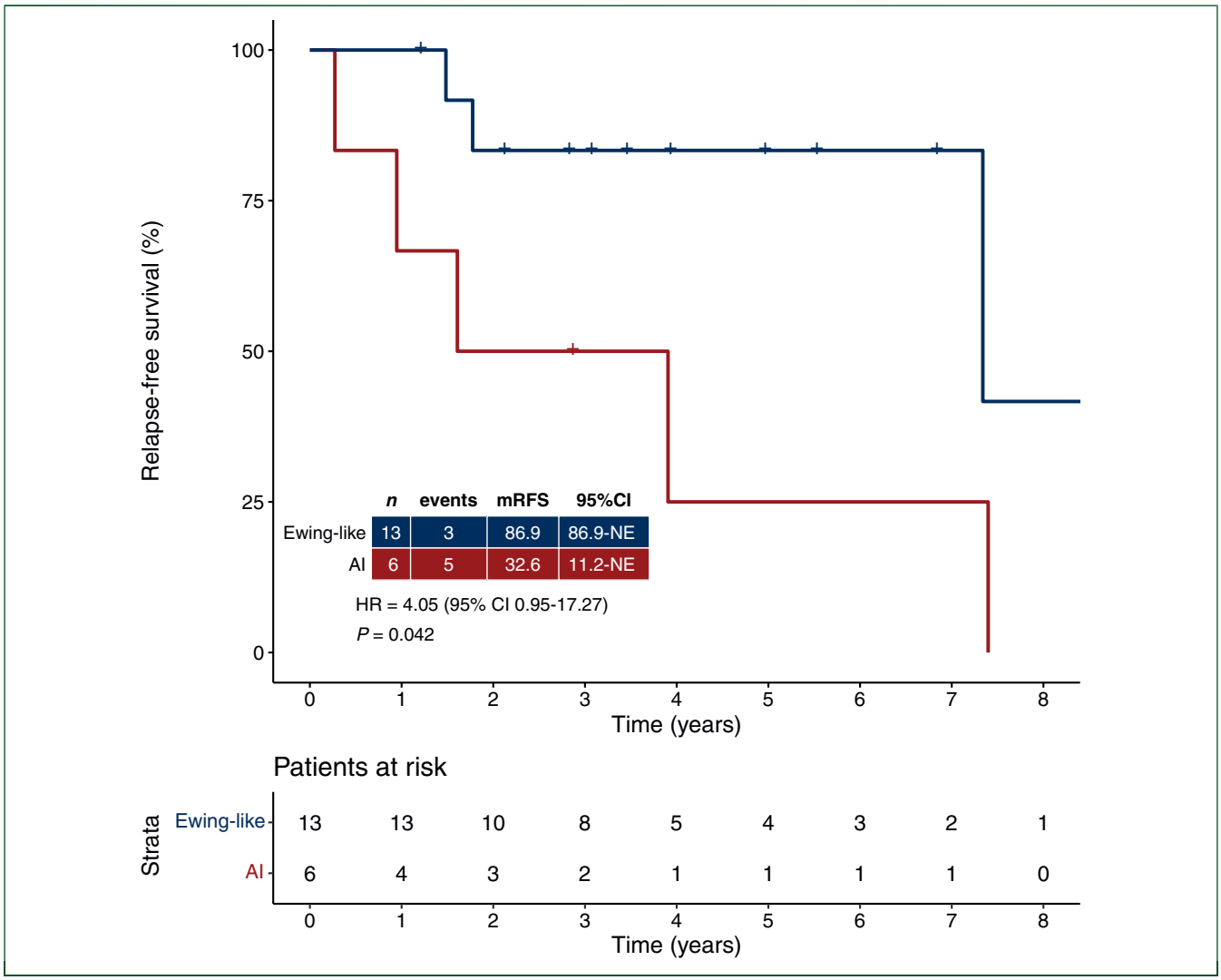

Figure 2. Kaplan–Meier curve showing relapse-free survival (RFS) in patients with localized disease treated with an Ewing-like approach and AI. AI, anthracycline and ifosfamide;
CI, confidence interval; HR, hazard ratio; NE, not estimated.

schedules. This study reflects real-world practice within the ISG network, where only standard cytotoxic regimens are used in routine care; as off-label agents (including immunotherapy) cannot be prescribed in Italy, data on treatments not formally approved were not collected. Finally, given the retrospective design and the long time span covered by this study, pathological response in patients treated in the neoadjuvant setting could not be reliably retrieved, highlighting the need to include this evaluation in future prospective studies.

MCS is an ultra-rare sarcoma, with peak of incidence in the second to third decade of life, no gender predominance, and primary origin from the skeleton in approximately two-thirds of all cases.

For patients with localized disease, surgery, possibly in association with radiotherapy, is the standard of care. Based on the high metastatic risk, the young age of patients, and retrospective results suggesting a higher activity of chemotherapy in MCS compared with other chondrosarcomas, and reporting a benefit in survival, the use of (neo)adjuvant chemotherapy in the therapeutic strategy is often considered.[17] The retrospective series reported by the European Musculoskeletal Oncology Society, based on data from 113 MCS patients, demonstrated that chemotherapy administration (mostly anthracycline-based chemotherapy, although specific details were not provided) in patients with localized disease was associated with a reduced risk of recurrence [hazard ratio (HR) 0.482, 95% CI 0.213-0.996, $P = 0.046$] and death (HR 0.445, 95% CI 0.256-0.774, $P = 0.004$).[13] Similarly, in the retrospective series by Cesari et al., including 26 MCS patients, a better 10-year disease-free survival was reported in patients who achieved a complete surgical remission and underwent chemotherapy (76%) compared with those who underwent surgery alone (17%, $P = 0.008$).[11] In this series, the chemotherapy regimens used were highly heterogeneous, including Ewing-like, osteosarcoma-like, and anthracycline with ifosfamide combinations.

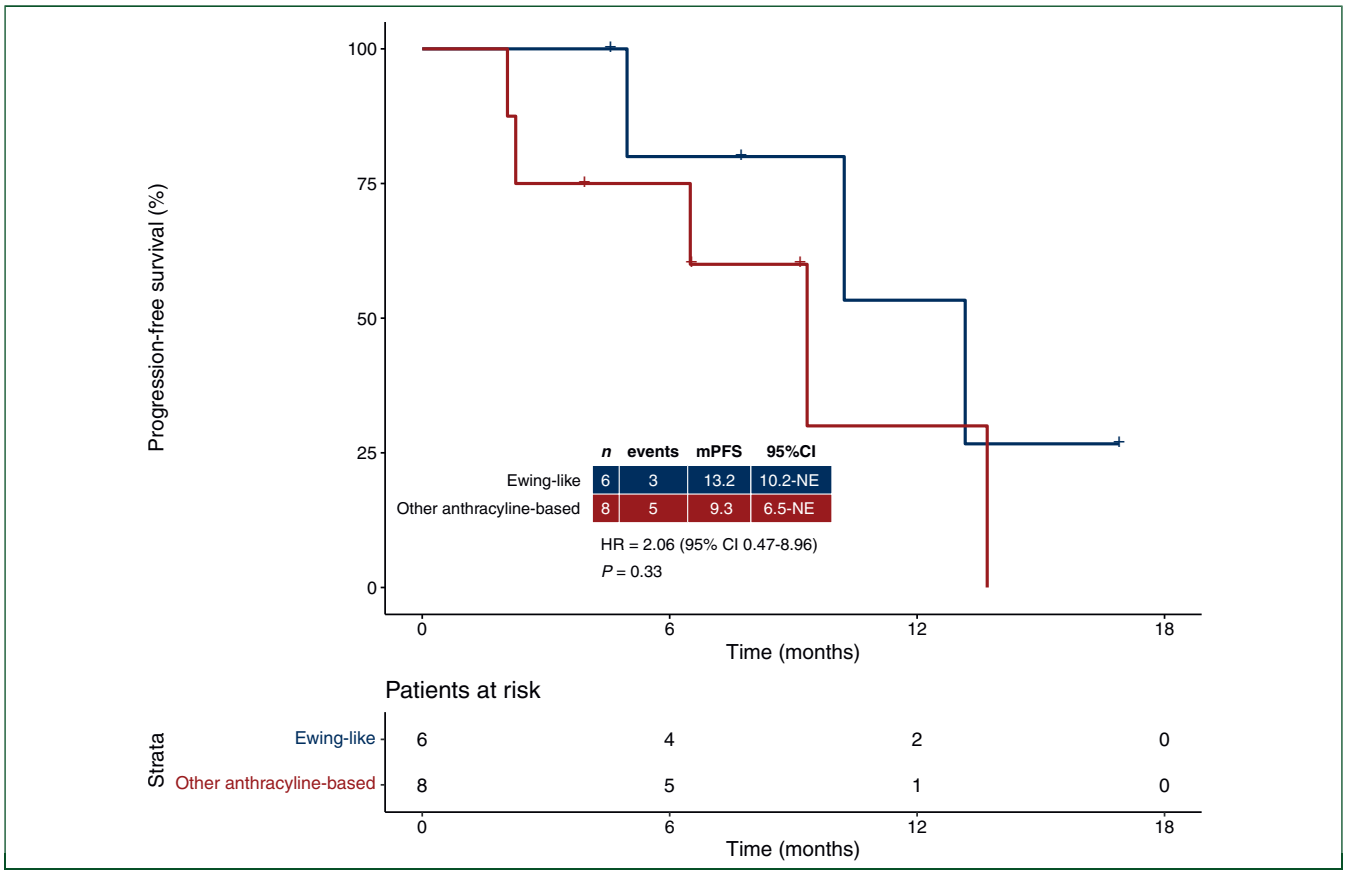

Figure 3. Kaplan–Meier curve showing progression-free survival (PFS) in patients with advanced disease treated with an Ewing-like approach and other anthracycline-based regimens.
CI, confidence interval; HR, hazard ratio; NE, not estimated.

Consistently, in our study patients with localized disease treated with radical surgery and anthracycline-based adjuvant chemotherapy showed an excellent outcome, with an expected OS at 5 years of 95% (only one event over 19 patients included). Interestingly, in this cohort of patients, a positive trend in mRFS (86.9 versus 32.6 months, $P = 0.04$) was noticed in patients who received a prolonged treatment with a multidrug regimen (e.g. anthracycline with cyclophosphamide or ifosfamide and vincristine followed by or alternated with etoposide and ifosfamide) compared with those treated with anthracycline and ifosfamide only. Although no definitive conclusions can be drawn given the limited number of patients in a non-comparative setting, this observation is consistent with some role of adjuvant chemotherapy in the management of localized MCS, particularly in patients fit for prolonged regimens.

The overall outcome for patients with MCS and advanced disease is poor (5-year and 10-year estimated survival rates of ∼70% and ∼50%, approximately).[11,13] In this population, treatment is based on conventional chemotherapy.[15]

In our study, the use of anthracycline-based regimens resulted in an ORR in both localized and metastatic cases of ∼25%, with an mPFS in patients with advanced disease of 10 months. These results are consistent with previous reports, which have shown ORR and mPFS ranging between 20% and 40% and 4 and 8 months, respectively, across different series.[11-15] Our results highlight that MCS exhibits sensitivity to anthracyclines comparable to that of other soft-tissue sarcomas, e.g. higher than that reported for conventional chondrosarcoma (ORR ∼10%),[16] but clearly lower than the response rates typically observed in Ewing sarcoma (ORR 70%-80%).[18-21] Interestingly, in line with that reported by van Maldegem et al.[15] and in contrast to that observed in the cohort of patients with localized disease, no clear advantage was seen in PFS for patients with advanced MCS (13.2 versus 9.3 months, $P = 0.33$) with the use of prolonged, multiagent chemotherapy compared with anthracycline-based doublets.

The activity of trabectedin in advanced MCS was initially noticed in a sub-group analysis of a Japanese, randomized, phase II study testing trabectedin versus best supportive care in translocation-related sarcomas.[22] One of the three MCS patients treated with trabectedin within this study achieved a PR per RECIST and was still receiving trabectedin at the final data cut-off (with a PFS of 2 years).[23] While trabectedin did not achieve objective responses in our study, its correlation with prolonged disease stabilization (mPFS: 16.7 months) in heavily pretreated patients is consistent with previous observations, suggesting a potential role for this agent.[23-25] Based on these findings,

ISG is currently running a phase II clinical trial (NCT04305548) to assess the activity of trabectedin from the second to fourth line, in patients with advanced, *HEY1::NOCA2*-positive MCS progressing on anthracycline-based chemotherapy. The results of this study will provide prospective data on the use of trabectedin in MCS, particularly relevant to primary bone MCS and paediatric patients, since trabectedin in currently not licensed in these indications.

Despite its frequent use in clinical practice, in this series no responses were observed with HD-IFX as monotherapy in further lines and in patients pretreated with this agent in the localized setting.

Our findings emphasize the need for novel therapeutic strategies in advanced MCS, a disease for which, to our knowledge, no targeted agents are currently under clinical investigation. The detection of the *HEY1::NCOA2* fusion, and the resulting activation of the Notch signalling pathway,[5-7] provides the biological rationale for testing agents targeting this mechanism. In particular, it could be worth exploring the activity of γ-secretase inhibitors, such as nirogacestat, recently approved by the Food and Drug Administration and European Medicines Agency for desmoid fibromatosis, and vorinogacestat, currently under evaluation for the same disease, as they are already under development in the field of mesenchymal tumours.[26]

Conclusions

In conclusion, this study shows a degree of activity of anthracycline-based regimens in MCS which is in the range of soft-tissue sarcomas, rather than in the range of Ewing sarcoma. However, it is impossible to state as to which extent it may improve prognosis in the localized disease setting. Nonetheless, anthracycline-based (neo)adjuvant chemotherapy should be considered for patients with chances of a complete surgical remission, and the use of prolonged, multiagent regimens following an Ewing-like approach could be an option in conditions of uncertainty. In advanced MCS progressing on anthracycline-based regimens, the use of trabectedin can prolong disease control in the majority of patients. In the absence of prospective studies, often difficult to conduct in ultra-rare sarcomas like MCS,[27] this multicentre experience provides valuable data to inform everyday clinical practice and might serve as a benchmark for the development of new therapeutic strategies.

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