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ORIGINAL ARTICLE

Outcome of rare primary malignant bone sarcoma treated with multimodal therapy: Results from the EUROpean Bone Over 40 Sarcoma Study (EURO-B.O.S.S.)

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Abstract

Background: Rare primary malignant bone sarcomas (RPMBS) account for 5%–10% of primary high-grade bone tumors and represent a major treatment challenge. The outcome of patients with RPMBS enrolled in the *EUROpean Bone Over 40 Sarcoma Study* (EURO-B.O.S.S) is presented.

Methods: Inclusion criteria were as follows: age from 41 to 65 years and a diagnosis of high-grade spindle cell, pleomorphic, or vascular RPMBS. The chemotherapy regimen included doxorubicin 60 mg/m^2, ifosfamide 9 g/m^2, and cisplatin 90 mg/m^2; postoperative methotrexate 8 g/m^2 was added in case of a poor histologic response.

Version 2.0 of the Common Terminology Criteria for Adverse Events, Kaplan–Meier curves, log-rank tests, and univariate Cox regression models were used.

Results: In total, 113 patients were evaluable for analysis. The median patient age was 52 years (range, 40–66 years), and 67 patients were men. Eighty-eight tumors were categorized as undifferentiated pleomorphic sarcomas (UPS), 20 were categorized as leiomyosarcomas, three were categorized as fibrosarcomas, and two were categorized as angiosarcomas. Eighty-three of 113 tumors were located in the extremities. Ninety-five of 113 patients presented with no evidence of metastases. After a median follow-up of 6.8 years (interquartile range [IQR], 3.5–9.8 years), the 5-year overall survival rate for patients with localized disease was 68.4% (IQR, 56.9%–77.5%), and it was 71.7% (IQR, 58.1%–81.6%) for patients with UPS and 54.9% (IQR, 29.5%–74.5%) for patients with leiomyosarcoma. Grade III–IV hematologic toxicity was reported in 81% patients; 23% had grade II–III neurotoxicity, and 37.5% had grade I–II nephrotoxicity. Five-year overall survival was significantly better for patients with localized disease, for patients who obtained surgical complete remission, and when the primary tumor was located in the extremities.

Conclusions: The survival of patients who had RPMBS in the current series was similar to that of age-matched patients who had high-grade osteosarcoma treated according to the same protocol. An osteosarcoma-like chemotherapy may be proposed in patients who have RPMBS.

KEYWORDS

angiosarcoma, bone sarcoma, chemotherapy, fibrosarcoma, leiomyosarcoma, multimodality treatment, nonosteosarcoma malignant bone tumors, rare primary malignant bone sarcoma (RPMBS), ultra-rare sarcoma, undifferentiated pleomorphic sarcoma

INTRODUCTION

Primary bone sarcomas account for approximately 0.2% of all malignant tumors.[1] Chondrosarcoma, osteosarcoma, and Ewing sarcoma are the most frequent entities and represent 90%–95% of all primary bone sarcomas.[1,2] Rare primary malignant bone sarcomas (RPMBS) that cannot be classified as one of these represent a therapeutic challenge.[3] RPMBS are classified according to their histopathologic characteristics as either spindle cell sarcomas, round cell sarcomas, vascular neoplasms, or other rare entities. The latter group includes other histotypes, such as synovial sarcoma, myxofibrosarcoma, or malignant peripheral nerve sheath tumor, that develop more frequently in soft tissues.[3]

Because of their extreme rarity, there are very limited retrospective studies on RPMBS. Their treatment usually follows high-grade sarcoma principles and may include surgery and chemotherapy. Chemotherapy in particular poses specific challenges because RPMBS usually affect an elderly population compared with other high-grade bone sarcomas.

The European Over 40 Bone Sarcoma Study (EURO-B.O.S.S; ClinicalTrials.gov identifier NCT02986503), a joint effort of the Italian Sarcoma Group, the Cooperative Osteosarcoma Study Group, and the Scandinavian Sarcoma Group, aimed to prospectively evaluate the activity and toxicity of an intensive chemotherapy combination in patients aged 41–65 years with different types of high-grade spindle cell, pleomorphic, and vascular bone sarcomas. The use of chemotherapy in such a cohort was derived from previous reports about the aggressiveness of these tumors and the potential benefits achievable with a combination of cisplatin and doxorubicin.[4]

The objective of this trial was to assess the use of an osteosarcoma-like chemotherapy regimen, including high-dose methotrexate in case of a poor histologic response, in patients with RPMBS. For this entity, no standard systemic treatment has yet been established.

We previously reported the outcomes of patients who had osteosarcoma and de-differentiated chondrosarcoma[5] treated on the EURO-B.O.S.S. protocol. Here, we present data on survival and chemotherapy toxicity for the subgroup of patients with high-grade spindle cell, pleomorphic, or vascular RPMBS.

MATERIALS AND METHODS

This prospective, noncontrolled study included patients who were between ages 41 and 65 years at diagnosis of a primary high-grade bone sarcoma.[5] Patients with either localized or metastatic disease

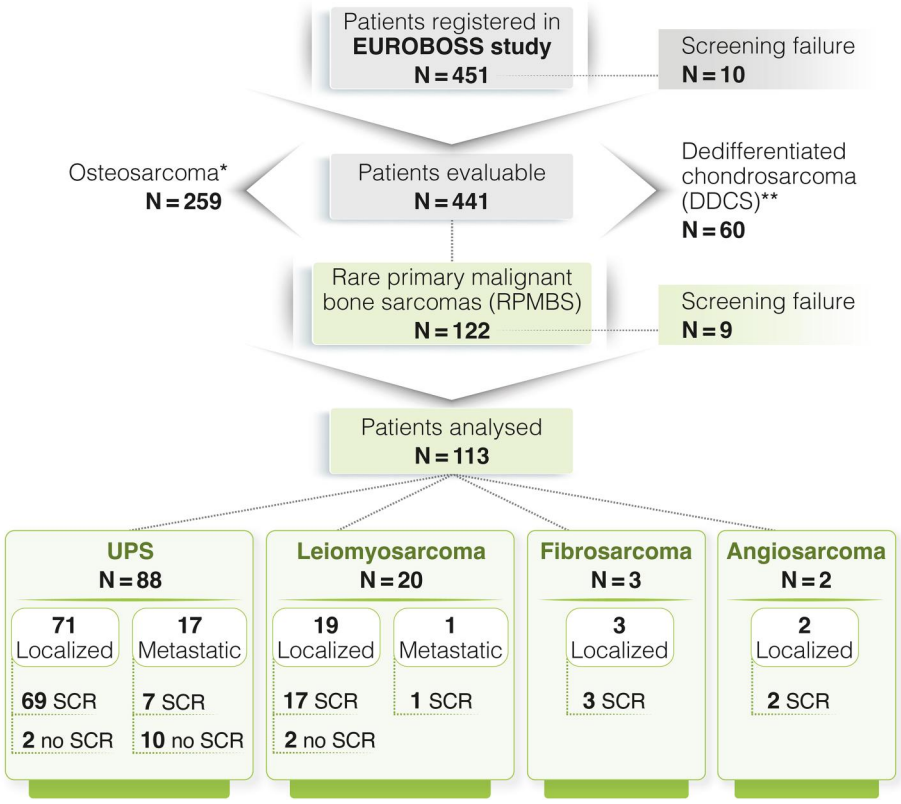

FIGURE 1 Study diagram. SCR indicates surgical complete remission; UPS, undifferentiated pleomorphic sarcoma. [Corrections added on 06 September 2023, after first online publication: Figure 1 has been replaced]

were eligible. The study was approved by the institutional review board or ethics committee of each participating group and/or center, according to national and local requirements. Informed consent was provided by all registered patients.

Patients with the following histologic diagnoses were eligible for the RPMBS cohort: undifferentiated pleomorphic sarcoma (UPS) (also including the entity previously called malignant fibrous histiocytoma), sarcoma not otherwise specified, spindle cell sarcoma (or undifferentiated sarcoma), leiomyosarcoma, fibrosarcoma, or angiosarcoma (Figure 1). A central pathology review of all cases was not required.

The recommended treatment strategy consisted of wide surgical removal of the primary tumor and all metastatic sites, if present, plus multiagent chemotherapy preoperatively and postoperatively or postoperatively only. Blood samples for alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) measurements were taken before the start of treatment. Histologic response to preoperative chemotherapy was assessed on the primary tumor and classified as good (<50% viable tumor) or poor (≥50% viable tumor).

Chemotherapy was comprised of doxorubicin, cisplatin, and ifosfamide. Methotrexate was added to the three-drug regimen only in case of a poor histologic response to preoperative treatment, as described in Figures 2 and 3).

Toxicity was graded according to the expanded National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0. The incidence of red blood cell and platelet transfusions, the use of granulocyte-colony–stimulating factors, episodes of neutropenic fever, episodes of neurotoxicity, hospitalizations, and treatment delays were also registered.

Statistical analysis

The demographic and clinical characteristics of the study cohort were summarized using medians and range or absolute and percentage frequencies. Overall survival (OS) was calculated from the date of diagnostic biopsy to the date of death from any cause or last follow-up. Surgical complete remission (SCR) was defined as surgical removal of primary tumor and all eventual sites of distant disease. Disease-free survival (DFS) was calculated from the date of achievement of SCR status to the date of distant and/or local recurrence, or death, or last follow-up. Time-to-event variables were analyzed using the Kaplan–Meier estimator and the log-rank test. Differences were considered statistically significant if the p values were $< .05$. All analyses were performed using SAS software version 9.4 (SAS Institute Inc.).

RESULTS

One-hundred twenty-two patients with high-grade spindle cell, pleomorphic, or vascular RPMBS were registered onto EURO-B.O.S.S. Of these, 113 patients were considered evaluable for analysis

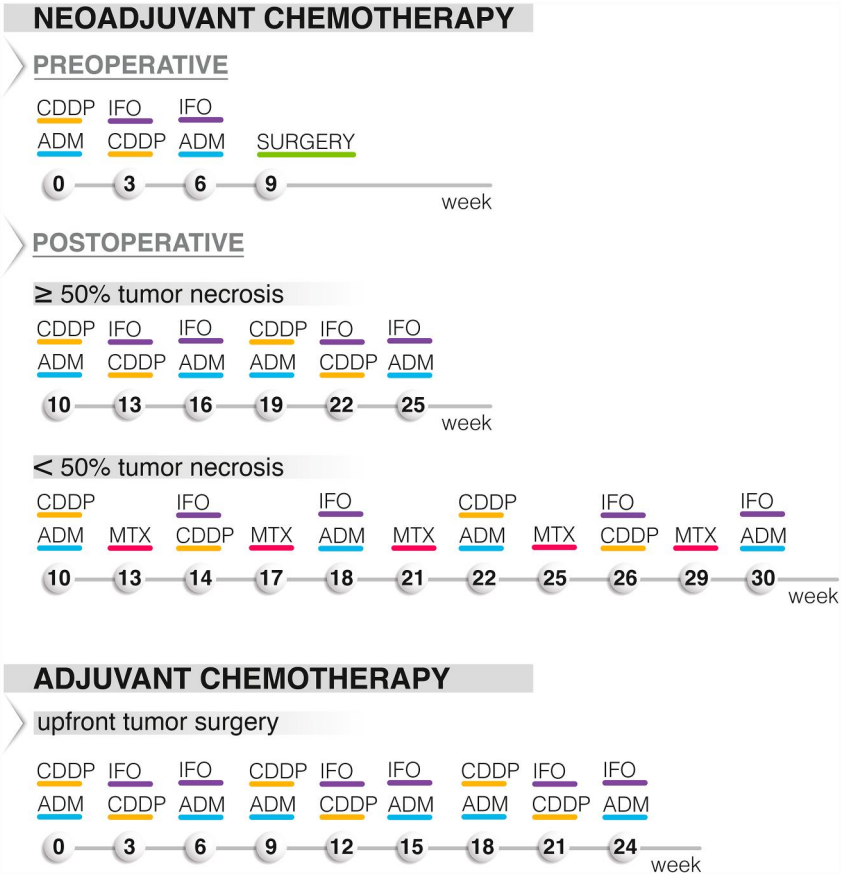

FIGURE 2 Treatment schema and schedule: ADM 60 mg/m^2 (24-hour intravenous infusion); CDDP 100 mg/m^2 (48-hour to 72-hour continuous intravenous infusion; IFO 3 g/m^2 daily (1-hour to 2-hour infusions) for 2 days (dose per cycle, 6 g/m^2); MTX 8 g/m^2 (4-hour intravenous infusion). ADM indicates Adriamycin (doxorubicin); CDDP, cisplatin; IFO, ifosfamide; MTX, methotrexate.

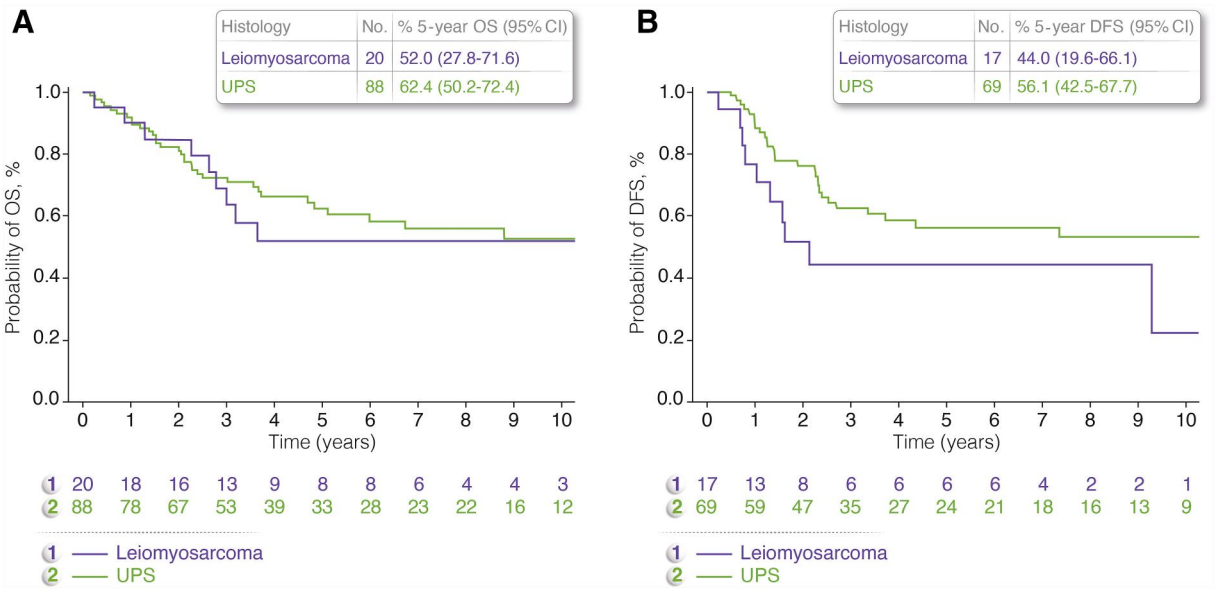

FIGURE 3 Kaplan–Meier survival curves. (A) OS and (B) DFS stratified based on disease histology. CI indicates confidence interval; DFS, disease-free survival; OS, overall survival; UPS, undifferentiated pleomorphic sarcoma.

(Figure 1). Fifty patients (44%) were from the Cooperative Osteosarcoma Study Group, 46 (41%) were from the Italian Sarcoma Group, and 17 (15%) were from the Scandinavian Sarcoma Group.

The median age at diagnosis was 52 years (range, 40–66 years), and 67 patients (59%) were men. Eighty-eight bone sarcomas were grouped as UPS, 20 were grouped as leiomyosarcomas, three were grouped as fibrosarcoma, and two were grouped as angiosarcoma (Figure 1). Eighty-three tumors (73%) were located in an extremity (femur, 54 tumors; tibia, 18 tumors; humerus, seven tumors; ulna, two tumors; radius, one tumor; foot, one tumor), and 30 tumors (27%) involved axial bones (pelvis, 18 tumors; spine, four tumors; scapula, three tumors; clavicle, two tumors; rib, one tumor; craniofacial, one tumor; other axial bones, one tumor). Ninety-five tumors (84%) were considered localized, including 71 of 88 UPS, 19 of 20 leiomyosarcomas, three of three fibrosarcomas. and two of two angiosarcomas (Table 1). Eighteen patients (16%) presented with metastases; in 14 of 18 patients as lung metastases only and in four of 18 patients as other secondary lesions (Table 1).

Chemotherapy according to the EURO-B.O.S.S. schema (Figure 2) was initiated in all patients as planned. In total, 109 patients (96.5%) underwent surgery. Ninety-five patients (87%) patients underwent limb-saving resection, and 14 underwent an amputation. Four patients did not undergo surgery: three had a pelvic lesion, one had a tumor in an axial bone, and two of these four of patients had metastasis at diagnosis.

Among the 109 patients who underwent surgery, 96 (88%) received preoperative chemotherapy (72 patients who had tumors in the extremities and 24 patients in case of an axial location; 83 patients had with localized disease, and 13 presented with metastases at diagnosis) and continued with postoperative chemotherapy, whereas 13 patients (12%), received postoperative chemotherapy only (see Table S1).

Information on the histologic response of primary tumors was available for 76 patients (79%) who received preoperative chemotherapy. A good histologic response (<50% viable tumor) was reported in 24 of 76 patients (22%), including 21 of 60 patients (35%) who had UPS, two of 13 (15%) who had leiomyosarcoma, one of two (50%) who had fibrosarcoma, and zero of one (0%) who had angiosarcoma. SCR was obtained in 91 of the 93 patients (98%) with localized tumors who underwent surgery and in eight of the 16 patients (50%) with metastatic tumors who underwent surgery (Figure 1).

ALP levels were reported as elevated in 13 of 92 patients (14%). LDH elevations were documented in 26 of 96 patients (27%), and no major difference was observed between patients with UPS and those with leiomyosarcoma (Table 1).

At last follow-up, after a median follow-up of 6.8 years (interquartile range [IQR], 3.5–9.8 years), 70 of 113 patients were alive, 62 of those after having achieved SCR (first SCR, $n = 52$; second SCR, $n = 9$; third SCR, $n = 1$). Eight patients were alive with disease. Among

TABLE 1 Characteristics of 113 patients with rare primary malignant bone sarcoma.

	All patients, $N = 113$	UPS, $n = 88$	Leiomyosarcoma, $n = 20$	Fibrosarcoma, $n = 3$	Angiosarcoma, $n = 2$
Age: Median [range], years	52 [40-66]	54 [40–66]	48 [41–62]	47 [43–63]	52 [46–58]
Sex, No. (%)					
Women	46 (40.7)	37 (42.1)	7 (35.0)	1 (33.3)	1 (50.0)
Men	67 (59.3)	51 (57.9)	13 (65.0)	2 (66.7)	1 (50.0)
Tumor site, No. (%)					
Extremity	83 (73.5)	65 (73.9)	16 (80.0)	1 (33.3)	1 (50.0)
Pelvis	18 (15.9)	15 (17.0)	2 (10.0)	1 (33.3)	
Other axial bones	12 (10.6)	8 (9.1)	2 (10.0)	1 (33.3)	1 (50.0)
Tumor stage, No. (%)					
Localized	95 (84.1)	71 (80.7)	19 (95.0)	3 (100.0)	2 (100.0)
Metastatic	18 (15.9)	17 (19.3)	1 (8.0)		
ALP high, No. (%)[a]					
No	79 (85.9)	62 (87.3)	15 (83.3)	1 (50.0)	1 (100.0)
Yes	13 (14.1)	9 (12.7)	3 (16.7)	1 (50.0)	
LDH high, No. (%)[b]					
No	70 (72.9)	55 (74.3)	13 (68.4)	1 (50.0)	1 (100.0)
Yes	26 (27.1)	19 (25.7)	6 (31.6)	1 (50.0)	

Abbreviations: ALP, alkaline phosphatase; LDH, lactate dehydrogenase; UPS, undifferentiated pleomorphic sarcoma.

[a]Available in 92 patients.

[b]Available in 96 patients.

43 patients who had died after a median of 2.1 years (IQR, 0.2–8.8 years), 37 died of progressive disease, two died of other causes (one patient died of neutropenic sepsis and one died of a second malignancy [multiple myeloma]), and four died of unknown causes (two died in complete remission after recurrence and two died with active disease after a first recurrence).

The 5-year OS rate was 61.1% (95% confidence interval [CI], 50.5%–70.1%) for all patients. It was 62.4% (95% CI, 50.2%–72.4%) for patients who had UPS and 52.0% (95% CI, 27.8%–71.6%) for those who had leiomyosarcoma (Table 2, Figure 3A). The two patients who had angiosarcoma (aged 46 and 58 years, both with localized disease) underwent wide resection or amputation and received adjuvant chemotherapy (Table 1). They were alive and disease-free at 2.7 and 7.0 years of follow-up, respectively. The three patients who had fibrosarcoma (aged 47, 43 and 63 years, all with localized tumors) underwent resections (marginal in one patient with a pelvic fibrosarcoma) and adjuvant chemotherapy. Two of these patients were alive after 3.3 and 6.1 years of follow-up, and one patient died 0.7 years from diagnosis.

On univariate analyses, a significantly better prognosis was observed for patients with localized disease (5-year OS: localized vs. metastatic, 68.4% vs. 23.3%; $p < .0001$), for those patients who achieving an SCR (5-year OS: SCR vs. no SCR, 68.5% vs. 8.0%; $p < .0001$), and for patients who had primary tumor located in an extremity (5-year OS: extremities vs. pelvis vs. other axial bones, 66.9% vs.44% vs. 50.0%; $p = .01$) (Table 2).

The 5-year DFS rate was 55.3% (95% CI, 43.7%–65.4%). It was 56.1% (95% CI, 42.5%–67.7%) for patients who had UPS and 44.0% (95% CI, 19.6%–66.1%) for those who had leiomyosarcoma (Table 2, Figure 3B). In patients who had leiomyosarcoma both age, and ALP level were prognostic (5-year OS: younger than 52 years vs. 52 years and older, 68.4% vs. 17.1% [$p = .0341$]; normal ALP vs. high ALP, 55.8% vs. 33.3% [$p = .0001$]) (Table 2).

The univariate analysis of DFS for patients achieving SCR showed a significantly improved prognosis for patients with a good histologic response (5-year DFS: good vs. poor histologic response, 73.3% vs. 43.8%; $p = .0340$) (Table 3). Patient outcomes did not correlate with LDH levels at diagnosis.

Toxicity data were available for 64 patients (57%) who received a total of 523 cycles of chemotherapy. Forty-six patients (72%) experienced delays of one or more cycles. Thirty-seven patients (58%) completed the preplanned protocol schedule: 32 patients received nine cycles of cisplatin/doxorubicin, ifosfamide/doxorubicin, and ifosfamide/cisplatin; and five patients who had a poor histologic response, for whom high-dose methotrexate 8.0 g/m^2 was also planned, received nine cycles of cisplatin/doxorubicin, ifosfamide/doxorubicin, and ifosfamide/cisplatin plus five cycles of methotrexate (as shown in Figure 2). Seven patients received only ifosfamide postoperatively instead of ifosfamide/cisplatin or ifosfamide/doxorubicin, two patients received only cisplatin postoperatively, three patients received only doxorubicin postoperatively, and 15 patients did not complete the expected number of cycles.

A treatment-related death was reported in one patient (one patient died of neutropenic sepsis). Fifty-two patients (81%) had at least one grade III/IV toxicity event, mostly hematologic (Table 4). In 15 patients (23%), an episode of neurotoxicity was reported, including grade I or II neurotoxicity in 12 of 15 patients and grade III neurotoxicity in three of 15 patients. In addition, two patients had grade III sensorial neuropathy; whereas, in one patient, a depressed level of consciousness (grade III) was reported after ifosfamide therapy. Regarding nephrotoxicity, 24 patients (37.5%) had at least one such episode, including 21 who had episodes of grade I or II nephrotoxicity, one who had an episode of grade III nephrotoxicity, and two who had episodes of grade IV nephrotoxicity. Three of the 16 patients who received methotrexate experienced delayed excretion, and in one patient creatinine was increased (Table 4).

DISCUSSION

This report represents the largest prospectively collected data set on patients older than 40 years with RPMBS who underwent multimodality treatment. This trial was made possible by an international European Consortium Joint effort.

Patients who were included in this analysis mostly had a diagnosis of UPS or leiomyosarcoma of bone. With an incidence of less than two per 100,000, these are rare diseases, as defined by RARECARE (i.e., incidence less than six per 100,000 per year).[6] A few cases of fibrosarcoma and angiosarcoma of bone were also included, which were recently defined as ultra-rare entities (i.e., one or less per 1,000,000) by Connective Tissue Oncology Society consensus.[7] Although a central pathology review of all cases was not required in this study, most of the patients were accrued in a referral center for sarcomas, with a high-volume load of bone sarcoma and expert pathologists.

RPMBS presented with predominance of male gender and extremities location of the primary tumor, similar to osteosarcoma in the same age group (Table 4).[8] Also similar to osteosarcoma,[8] LDH levels were elevated at diagnosis in approximately one quarter of patients. In contrast, ALP elevation is not frequent in patients with rare primary malignant bone tumors (only 14% compared with 35% in osteosarcoma,[8] most likely reflecting the missing osteoblastic phenotype.[2]

Because all patients were older than 40 years in the current study, comparisons with other large series are not feasible. Nonetheless, metastases at diagnosis were reported in 16% of the cases, less frequent as compared with the 30% rate observed in patients in the same age range with high-grade osteosarcoma[8] and in a series of patients of all age with spindle cell, nonosteogenic bone sarcomas, also including low grade tumors.[9]

A good response to preoperative chemotherapy was only achieved in 22% of patients in this series compared with 53%, which we observed in osteosarcoma counterparts using the same criteria.[8] The overall outcomes of patients with osteosarcoma and RPMBS,

TABLE 2 Univariate analysis of overall survival in 113 patients with rare primary malignant bone sarcoma.

	All patients[a]			UPS			Leiomyosarcoma		
	No.	% 5-year OS (95% CI)	*p*	No.	% 5-year OS (95% CI)	*p*	No.	% 5-year OS (95% CI)	*p*
All patients	113	61.1 (50.5–70.1)		88	62.4 (50.2–72.4)		20	52.0 (27.8–71.6)	
Age			.3257			.6027			.0341
≤52 years	57	66.6 (51.4–77.9)		41	66.4 (47.9–79.6)		13	68.4 (35.9–86.8)	
>52 years	56	55.7 (40.4–68.4)		47	59.2 (42.4–72.6)		7	17.1 (0.8–52.6)	
Sex			.2044			.2243			.9528
Women	46	71.6 (55.3–82.1)		37	73.1 (54.5–85.0)		7	57.1 (17.2–83.7)	
Men	67	54.7 (40.8–66.6)		51	55.4 (39.2–69.0)		13	48.0 (18.4–72.7)	
Tumor site			.0103			.0069			.9294
Extremity	83	66.9 (54.5–76.6)		65	69.4 (55.0–80.0)		16	52.1 (24.7–73.8)	
Pelvis	18	44.0 (19.5–66.1)		15	38.4 (13.2–63.6)		2	50.0 (0.6–91.0)	
Other axial bones	12	50.0 (20.8–73.6)		8	50.0 (15.2–77.5)		2	50.0 (0.6–91.0)	
Tumor stage			< .0001			< .0001			.0914
Localized	95	68.4 (56.9–77.5)		71	71.7 (58.1–81.6)		19	54.9 (29.5–74.5)	
Metastatic	18	23.3 (6.5–46.2)		17	24.7 (6.8–48.3)		1	100.0	
ALP high[b]			.4159			.2896			.0001
No	79	65.7 (53.0–75.7)		62	67.5 (53.0–78.4)		15	55.8 (26.6–77.4)	
Yes	13	59.2 (27.9–80.7)		9	87.5 (38.7–98.1)		3	33.3 (0.9–77.4)	
LDH high[c]			.2914			.2456			.5978
No	70	68.6 (55.5–78.6)		55	74.5 (60.0–84.3)		13	44.0 (16.8–68.4)	
Yes	26	55.2 (31.7–73.5)		19	54.9 (26.3–76.4)		6	62.5 (14.2–89.3)	
Surgical remission			< .0001			< .0001			.1152
No	14	8.0 (0.5–30.2)		12	9.7 (0.6–34.9)		2	50.0 (6.0–91.0)	
Yes	99	68.5 (57.3–77.4)		76	70.4 (57.2–80.2)		18	58.2 (31.5–77.6)	
Response[d]			.1214			.1365			.9935
Good	24	72.9 (45.7–88.1)		21	76.3 (47.5–90.7)		2	50.0 (6.0–91.0)	
Poor	52	57.4 (41.7–70.3)		39	57.0 (38.6–71.8)		11	61.4 (26.6–83.5)	
Chemotherapy[e]			.0987			.1896			.4275
Presurgery	96	65.0 (53.6–74.2)		76	65.7 (52.6–75.9)		15	57.8 (29.0–78.4)	.4275
Postsurgery	13	43.0 (13.8–69.8)		8	56.3 (14.7–84.2)		5	40.0 (5.2–75.3)	

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; LDH, lactate dehydrogenase; OS, overall survival; UPS, undifferentiated pleomorphic sarcoma.

[a]All patients include UPS, leiomyosarcoma, fibrosarcoma, and angiosarcoma.

[b]Available in 92 patients.

[c]Available in 96 patients.

[d]Available in 76 patients.

[e]Available in 109 patients who underwent surgery on primary tumor.

measured as the 5-year OS probability, however, were almost identical (Table 3).

Primary chemotherapy appeared to be safe, and multiagent chemotherapy was feasible in this patient population. The consequent delay in surgery for patients receiving primary chemotherapy was not associated with a worse outcome, and survival was similar among patients receiving only adjuvant treatment compared with those receiving neoadjuvant chemotherapy and adjuvant treatment after surgery.

Favorable outcomes were associated with extremity site of RPMBS and SCR. A good response to primary chemotherapy, with viable cells <50%, translated to better event-free survival, but with

TABLE 3 Univariate analysis of disease-free survival in 91 patients with rare primary malignant bone sarcoma in surgical complete remission.

	All patients[a]			UPS			Leiomyosarcoma		
	No.	% 5-year DFS (95% CI)	*p*	No.	% 5-year DFS (95% CI)	*p*	N	% 5-year DFS (95% CI)	*p*
All patients	91	55.3 (43.7–65.4)		69	56.1 (42.5–67.7)		17	44.0 (19.6–66.1)	
Age			.4504			.4414			.5723
≤52 years	48	53.0 (37.2–66.5)		34	53.8 (34.2–69.8)		11	45.5 (16.7–70.7)	
>52 years	43	58.3 (40.8–72.2)		35	59.1 (40.0–74.0)		6	50.0 (11.1–80.4)	
Sex			.1168			.1111			.8191
Women	37	68.4 (50.2–81.2)		30	71.2 (50.5–84.5)		5	40.0 (0.5–75.3)	
Men	54	47.0 (32.2–60.4)		39	45.6 (28.2–61.3)		12	45.7 (16.0–71.6)	
Tumor site			.0752			.1200			.0345
Extremity	69	58.2 (44.7–69.4)		53	59.5 (43.8–72.2)		14	45.8 (18.3–69.9)	
Pelvis	14	31.0 (6.5–60.4)		11	33.7 (6.4–65.0)		2	50.0 (0.6–91.0)	
Other axial bones	8	62.5 (22.9–86.1)		5	60.0 (12.6–88.2)		1	100.0	
ALP high[b]			.1047			.9898			< .0001
No	65	61.5 (47.3–73.0)		50	63.3 (46.8–75.9		13	49.4 (19.7–73.6)	
Yes	9	44.4 (13.6–71.9)		6	66.7 (19.5–90.4)		2	50.0 (0.6–91.0)	
LDH high[c]			.4059			.6216			.1298
No	58	54.5 (39.7–67.1)		45	60.2 (43.0–73.7)		11	24.2 (4.4–52.5)	
Yes	20	64.1 (36.2–82.3)		14	63.3 (28.6–84.6)		5	80.0 (20.3–96.9)	
Response[d]			.0340			.0748			.7185
Good	24	73.3 (49.6–87.0)		21	74.2 (48.2–88.5)		2	50.0 (0.6–91.4)	
Poor	44	43.8 (28.2–58.3)		31	44.4 (26.0–61.4)		11	43.6 (14.7–69.9)	
Chemotherapy			.9024			.7761			.6173
Presurgery	83	55.7 (43.6–66.1)		63	56.6 (42.5–68.4)		15	44.4 (18.9–67.4)	
Postsurgery	8	43.8 (6.0–78.5)		6	41.7 (1.1–84.3)		2	50.0 (0.6–91.0)	

Abbreviations: ALP, alkaline phosphatase; DFS, disease-free survival; LDH, lactate dehydrogenase; UPS, undifferentiated pleomorphic sarcoma.

[a]All patients include UPS, leiomyosarcoma, fibrosarcoma, and angiosarcoma.

[b]Available in 74 patients.

[c]Available in 78 patients.

[d]Available in 68 patients.

no difference in OS. It might be hypothesized that treatment after progression has a role in this group of patients.

Judging from our results, the use of multimodality treatment should be considered a standard option for patients aged 41–65 years who have high-grade, nonosteosarcoma bone tumors. A small proportion of our patients received methotrexate postoperatively, according to protocol, because of a poor histologic response to induction chemotherapy. Importantly, our study demonstrates that 8.0 g/m^2 methotrexate is feasible in this elderly population.

However, the study design and the small number of patients prevent us from addressing whether this approach is associated with better outcomes compared with a three-drug approach. Furthermore, because of the limited number of patients in each histologic RPMBS subgroup, the relative benefit from chemotherapy for each histotype remains to be defined. Also, we have to take into account that, for soft tissue sarcoma, in the neoadjuvant setting, histology-driven chemotherapy produced inferior activity compared with standard chemotherapy using epirubicin and ifosfamide for the majority of histologic diagnoses.[10]

The data presented here encourage the use of an osteosarcoma-like therapy. Even for leiomyosarcoma, an aggressive tumor for which a very poor outcome is usually reported,[11] the 5-year OS rate was 52% for all patients in this subgroup.

Because UPS are considered even more aggressive than leiomyosarcomas,[12] the inferior survival of patients with leiomyosarcoma in this series underscores the need of drugs that are more active for the leiomyosarcoma histotype. Several combinations demonstrated activity in patients who had leiomyosarcoma arising in the soft tissue,

TABLE 4 Chemotherapy toxicity in patients older than 40 years undergoing treatment in the EUROpean Bone Over 40 Sarcoma Study, $n = 64$.[a]

	No. (%)
Hematologic toxicity	
Leucopenia, grade III or IV	51 (80)
Thrombocytopenia, grade III or IV	40 (62)
Anemia, grade III or IV	35 (55)
PLT transfusions	23 (36)
RBC transfusion	37 (58)
CSF support	54 (84)
Febrile neutropenia	25 (39)
Hospitalization	39 (61)
Other toxicities	
Nephrotoxicity, grade III or IV	3 (7)
Urinary electrolyte wasting, grade I or II	7 (11)
Stomatitis, grade I or II	15 (23)
Neurotoxicity, any grade	14 (22)
Depressed level of consciousness, grade III	1 (2)
Sensorial neuropathy, grade III	2 (3)

Abbreviations: CSF, cerebrospinal fluid; PLT, platelet; RBC, red blood cell.

[a]Reported for each patient.

such as dacarbazine combined with doxorubicin,[13] trabectedin upfront in unfit patients,[14] or trabectedin combined with doxorubicin.[15] Future studies might address whether an histology-driven approach, including gemcitabine[16] or pazopanib,[17] might be justified in leiomyosarcoma of bone or angiosarcoma of bone.[18] Finally, through genomic and transcriptomic analyses, three specific leiomyosarcoma subtypes were identified, and molecular differences specific for each primary tumor site (i.e., uterine vs. soft tissue) were highlighted.[19] A better understanding of molecular features might change the future approach to treating leiomyosarcoma of bone or other RPMBS in the future.

We conclude that multiagent chemotherapy is feasible in this patient population, with a 5-year OS rate of 62.4% for UPS, which is comparable to the 5-year OS rate of patients with high-grade osteosarcoma and the rate of 52.0% in patients with leiomyosarcoma. For the patients who had osteosarcoma, a favorable outcome was associated with extremity site, localized disease, SCR, and a good histologic response (<50% viable cells) to primary chemotherapy. These data are important because they underscore that a 50% chemotherapy-induced histologic response might be a valid tool to stratify patients who have bone tumors, as also shown[20] in the setting of RPMBS. The lower event-free survival rate of poor responders, with no difference in OS, might suggest activity of salvage chemotherapy in certain histotypes. The relative benefit from chemotherapy for each histologic subgroup remains unclear.

CONCLUSION

This study constitutes a reference for further studies in the setting of RPMBS and indicates that UPS and leiomyosarcoma show a pattern of presentation similar to that of osteosarcoma in the elderly (i.e., individuals older than 40 years). With the addition of chemotherapy treatment based on doxorubicin, cisplatin, and ifosfamide to surgery, a survival comparable to that of patients who have osteosarcoma can be expected. The treatment was toxic but feasible. We conclude that an age-adjusted, osteosarcoma-like chemotherapy regimen can be used in patients older than 40 years with RPMBS. These findings might represent a benchmark for future histology-driven approaches.

AUTHOR CONTRIBUTIONS

Emanuela Palmerini: Data curation and methodology. **Peter Reichardt:** Conceptualization and data curation. **Kirsten Sundby Hall:** Conceptualization. **Rossella Bertulli:** Data curation. **Stefan S. Bielack:** Conceptualization and data curation. **Alessandro Comandone:** Data curation. **Gerlinde Egerer:** Data curation. **Anna Hansmeier:** Data curation. **Matthias Kevric:** Data curation. **Elisa Carretta:** Data curation and methodology. **Lina Hansson:** Data curation. **Nina Jebsen:** Data curation. **Mikael Eriksson:** Data curation. **Øyvind S. Bruland:** Data curation. **Davide Maria Donati:** Data curation. **Toni Ibrahim:** Data curation. **Sigbjørn Smeland:** Conceptualization and data curation. **Stefano Ferrari:** Conceptualization and methodology. All coauthors: Writing–original draft and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

Emanuela Palmerini reports personal fees from Daiichi Sankyo Company, Daiichi Sankyo Europe GmbH, Deciphera Pharmaceuticals Inc., EUSA Pharma LLC, and SynOx Therapeutics outside the submitted work. Peter Reichardt reports personal fees from Bayer, Blueprint Medicines Corporation, Boehringer Ingelheim, Deciphera Pharmaceutics Inc., F. Hoffmann-La Roche, GlaxoSmithKline, Mundibiopharma, Novartis, and PharmaMar; and other support from Boehringer Ingelheim, Clinigen Inc., Deciphera Pharmaceutics Inc., and PharmaMar outside the submitted work. Stefan Bielack reports personal fees from Boehringer Ingelheim, Eisai, F. Hoffman-LaRoche, MAP Biopharma, and Ymabs outside the submitted work. Alessandro Comandone reports personal fees as an expert witness from Novartis Pharma outside the submitted work. Gerlinde Egerer reports support from Pfizer Pharma GmbH outside the submitted work. The remaining authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

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