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First-line chemotherapy for malignant peripheral nerve sheath tumor (MPNST) versus other histological soft tissue sarcoma subtypes and as a prognostic factor for MPNST: an EORTC Soft Tissue and Bone Sarcoma Group study

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Background: The role of chemotherapy in advanced malignant peripheral nerve sheath tumor (MPNST) is unclear.
Patients and methods: Chemotherapy-naive soft tissue sarcomas (STS) patients treated on 12 pooled nonrandomized and randomized European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials were retrospectively analyzed. Clinical outcomes, overall survival, progression-free survival (PFS) and response were determined for MPNST and other STS histotypes and compared. Additionally, prognostic factors within the MPNST population were defined. Studied cofactors were demographics, sarcoma history, disease extent and chemotherapy regimen.
Results: After a median follow-up of 4.1 years, 175 MPNST out of 2675 eligible STS patients were analyzed. Outcome was similar for MPNST versus other STS histotypes, with a response rate, median PFS and overall survival of 21% versus 22%, 17 versus 16 weeks and 48 versus 51 weeks, respectively. Performance status was an independent prognostic factor for overall survival. Chemotherapy regimen was an independent prognostic factor for response ($P < 0.0001$) and PFS ($P = 0.009$). Compared with standard first-line doxorubicin, the doxorubicin–ifosfamide regimen had the best response, whereas ifosfamide had the worst prognosis.
Conclusion: This series indicates the role of chemotherapy in treatment of advanced MPNST. This first comparison showed similar outcomes for MPNST and other STS histotypes. The apparent superiority of the doxorubicin–ifosfamide regimen justifies further investigations of this combination in randomized trials.
Key words: adriamycin, chemotherapy, ifosfamide, malignant peripheral nerve sheath tumor, soft tissue sarcoma

introduction

Malignant peripheral nerve sheath tumor (MPNST) is an uncommon sarcoma with an incidence of 1:100 000/year, compromising 5%–10% of all soft tissue sarcomas (STS) [1]. MPNST originates from or recapitulates the phenotype of peripheral nerves cells, such as Schwann cells or perineural cells. Although the histogenesis of MPNST remains unclear, there is a higher incidence in patients with prior radiation exposure and neurofibromatosis type 1 (NF1), who have a lifetime risk of 10% of developing MPNST [2, 3]. MPNST typically arise in the extremities (40%), followed by trunk/retroperitoneal (38%) and head and neck region (21%) [4]. Most MPNSTs are biologically high-grade sarcomas that tend to recur (40%–65%) and metastasize (40%–80%) [5, 6]. MPNST usually metastasize hematogenous, most commonly to the lungs.

Because of the rarity of MPNST, consistent data regarding chemotherapy sensitivity are lacking; no phase II or III trials were carried out specifically in MPNST. As for other unresectable and metastatic STSs, doxorubicin and ifosfamide are generally considered to be the most active chemotherapeutic agents [7]. STSs are a heterogeneous group of tumors with differences in terms of genetic alterations, pathogenesis and clinical behavior [8]. Therefore, general information from STS trials does not necessarily apply to MPNST specifically. Previously, diagnosis of MPNST was

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proposed to be a significant adverse prognostic factor for local recurrence as compared with other STSs [9].

Promising results of two patients at the Leiden University Medical Center (LUMC) treated with neoadjuvant chemotherapy suggested to further analyze the chemotherapy sensitivity in a retrospective study using the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) database. Both patients had unresectable locally advanced retroperitoneal/sacral MPNST and were treated with neoadjuvant doxorubicin plus high dose ifosfamide. One patient had a partial remission and received six chemotherapy cycles. The other patient had stable disease after four cycles and received additional preoperative radiotherapy (50 Gy). Both patients became resectable, had a good histopathological response with less than 10% vital tumor cells left and are still disease free after 50 and 38 months, respectively.

These promising results encouraged us to study the chemosensitivity of advanced MPNST patients in a relative large series and compare these results with other advanced STS histotypes. For more than 30 years, the STBSG of the EORTC has been investigating different chemotherapy regimens for advanced and metastatic STSs. Data from 12 trials, managed at the EORTC headquarters offer the unique opportunity to retrospectively analyze the role of chemotherapy in advanced MPNST as compared with other STS histological subtypes.

The aim of this study was to determine whether patients with advanced MPNST had a better duration of survival and probability of response to chemotherapy than those with advanced STS with other histotypes. Additionally, the following baseline characteristics were investigated as potential prognostic factors within the MPNST population: demographic data (age, gender, and performance status), time since first diagnosis of sarcoma, the extent of the disease (grade, primary tumor site, and metastatic sides), prior radiotherapy and chemotherapy regimen.

patients and methods

patients

A total of 2675 eligible chemotherapy-naive patients of 3002 patients with unresectable or metastatic MPNST treated in 12 EORTC STBSG advanced STS trials (Table 1) were enrolled into the descriptive part of the study. Characteristics of these patients are summarized in Table 2. For the prognostic factor analysis, patients with MPNST only were selected ($n = 175$). For comparison of treatment outcome, all 2675 patients were included in the overall survival (OS) and progression-free survival (PFS) analysis. There were, respectively, 146 and 2092 cases of death as well as 164 and 2358 PFS events, i.e. progression or death, for MPNST and other STS histotypes. The analysis of response to chemotherapy included 2440 cases with 34 and 503 responders to chemotherapy, respectively, for MPNST and other histological subtypes.

end points of the EORTC STBSG analysis

The end points of our study were OS, PFS and response to chemotherapy. The study aim was to compare these outcomes (OS, PFS and response rate) of patients with advanced MPNST with those of patients with other advanced STS histotypes. In addition, prognostic factors within the MPNST population were defined.

Survival time was computed from the date of randomization (in the randomized trials) or the date of prospective registration (in the nonrandomized trials) to the date of death. Patients who were alive at the last follow-up date were censored.

PFS was defined as the time interval between the date of randomization (randomized trials) or the date of prospective registration (nonrandomized trials) and the date of first report of progression or death, whichever comes first. Patients who were alive and without progressive disease at the last follow-up were censored.

Response to chemotherapy was evaluated in all trials according to World Health Organization (WHO) criteria [10] or RECIST [11]. It was analyzed as a binary variable: patients who achieved a complete or partial response were considered ''responders,'' and patients with stable disease or progression were considered as ''failures.''

Table 1. Therapeutic regimens used in 12 EORTC STBSG advanced soft tissue sarcoma trials (3002 patients)

Study	Trt Arm A	Trt Arm B	Trt Arm C
EORTC 62761[a]	CYVADIC FU (191)	CYVADIC Cy (121)	
EORTC 62801[a]	DOX 75 (106)	EPI 75 (104)	
EORTC 62842	DOX 50 + IFO 5 (203)		
EORTC 62851[a]	DOX 75 (295)	DOX 50 + IFO 5 (297)	CYVADIC FU (157)
EORTC 62883	DOX 75 + IFO 5 (111)		
EORTC 62901[a]	DOX 75 (112)	EPI 3 × 50 (111)	EPI 1 × 150 (111)
EORTC 62903[a]	DOX 50 + IFO 5 (157)	DOX 75 + IFO 5 (157)	
EORTC 62912[a]	IFO 5 (93)	IFO 3 × 3 (89)	
EORTC 62941[a]	DOX 75 (42)	Docetaxel (44)[b]	
EORTC 62953	IFO 12 (124)		
EORTC 62962[a]	DOX 75 (45)	PLD (50)	
EORTC 62971[a]	DOX 75 (110)	IFO 3 × 3 (109)	IFO 5 (107)

[a]Randomized.

[b]Patient treated by docetaxel were excluded from the database.

CYVADIC, cyclophosphamide, vincristine, adriamycin and dacarbazine; DOX, doxorubicin; EORTC, European Organization for Research and Treatment of Cancer; EPI, epirubicin; IFO, ifosfamide; PLD, pegylated liposomal doxorubicin; STBSG, Soft Tissue and Bone Sarcoma Group; Trt, treatment.

investigated cofactors

The factors routinely recorded as baseline data in the different trials were investigated as potential prognostic factors (demographic data, history of sarcoma, extent and localization of disease at the time of trial inclusions, and histology). The demographic variables included age, gender and performance status before the start of chemotherapy. Performance status was measured on the WHO scale except for two trials in which it was retrospectively converted from the Karnofsky scale to the WHO scale. Variables related to the history of sarcoma included prior radiotherapy and the time since the first diagnosis of sarcoma (in years). Data on the extent and localization of disease included the presence of locoregional disease or local recurrence, as well as lung, liver and bone metastases. Histotype and grade, as assessed by a panel of reference pathologists, were preferred over the use of local diagnosis, to ensure the consistency and homogeneity of the data. The missing review data (around 40%) were replaced by the

Table 2. Characteristics of patients treated at EORTC STBSG trials

	MPNST ($N = 175$), n (%)	Others types, ($N = 2500$), n (%)	P
Performance status			
WHO 0	64 (36.6)	1050 (42.0)	0.2268[a]
WHO 1	91 (52.0)	1134 (45.4)	
WHO 2+	16 (9.1)	259 (10.4)	
Missing	4 (2.3)	57 (2.3)	
Gender			
Male	100 (57.1)	1236 (49.4)	0.0488[b]
Female	75 (42.9)	1264 (50.6)	
Treatment			
Anthracyclines	61 (34.9)	940 (37.6)	0.8598[b]
DOX+IFO	58 (33.1)	789 (31.6)	
CYVADIC	30 (17.1)	388 (15.5)	
IFO ALONE	26 (14.9)	383 (15.3)	
Prior radiotherapy			
No	110 (62.9)	1825 (73.0)	***0.0037***[b]
Yes	65 (37.1)	675 (27.0)	
Histopathological grade			
Grade I–II	59 (33.7)	841 (33.6)	0.3021[b]
Grade III	67 (38.3)	789 (31.6)	
Missing	49 (28.0)	870 (34.8)	
Site of primary tumor			
Other	64 (36.6)	1088 (43.5)	***0.0289***[b]
Extremities	51 (29.1)	568 (22.7)	
Missing	60 (34.3)	844 (33.8)	
Primary site involved			
No	61 (34.9)	986 (39.4)	0.4527[b]
Yes	79 (45.1)	1119 (44.8)	
Missing	35 (20.0)	395 (15.8)	
Metastatic site involved			
No	40 (22.9)	368 (14.7)	***0.0010***[b]
Yes	100 (57.1)	1739 (69.6)	
Missing	35 (20.0)	393 (15.7)	
Age at registration, years			
Median	42.6	51.5	***<0.0001***[a]
Range	15.6–76.3	10.0–79.5	
No. of observations	170	2455	
Time between the diagnosis and registration			
Median	232 days	192 days	0.0736[a]
Range	1 day–11 years	0.0–28 years	
No. of observations	161	2350	

[a]Kruskal–Wallis test.
[b]Chi-square test.
Bold signifies that the statistical significance is set at 0.05. CYVADIC, cyclophosphamide, vincristine, adriamycin and dacarbazine; DOX, doxorubicin; EORTC, European Organization for Research and Treatment of Cancer; IFO, ifosfamide; MPNST, malignant peripheral nerve sheath tumor; STBSG, Soft Tissue and Bone Sarcoma Group.

local diagnosis (the potential errors of diagnosis from the local pathologists was estimated around 5%). This variable was recorded in two categories: MPNST versus other histotypes.

Treatment was aggregated in four categories: the anthracyclines alone (doxorubicin 75 mg/m^2, pegylated liposomal doxorubicin, epirubicin 75 mg/m^2, epirubicin 3 × 50 mg/m^2, epirubicin 150 mg/m^2), ifosfamide (ifosfamide 5 g/m^2, ifosfamide 3 × 3 g/m^2, ifosfamide 9 g/m^2, ifosfamide 12 g/m^2), the combination of doxorubicin and ifosfamide (doxorubicin 50 mg/m^2–ifosfamide 5 g/m^2, doxorubicin 75 mg/m^2–ifosfamide 5 g/m^2) and combination chemotherapy of cyclophosphamide, vincristine, adriamycin and dacarbazine (CYVADIC).

statistical methods

For the descriptive analysis, the categorical data were summarized by the frequencies and percentages, and the continuous covariates were summarized with median, range, and numbers of observations. Survival data were estimated by the Kaplan–Meier method. Results were presented according to histological subtype (MPNST versus other histotypes).

To identify significant prognostics factors among baseline covariates, a univariate analysis was conducted. For survival time and PFS, a Cox univariate model was used. For the proportion of responders, all covariates were investigated with a logistic univariate model. The statistical significance was set at 0.05. Three multivariate models were built: a Cox model for OS, one for PFS and a logistic model for response to chemotherapy. All factors that presented with a significant prognostic value in the univariate analyses were initially included in the models. Nonsignificant factors were subsequently removed according to a backward selection procedure. Finally, the predictiveness (C index) and the stability (bootstrap methods) of these models were validated.

results

patient characteristics

Characteristics of the identified 175 MPNST patients and of the 2500 patients with other histological STSs treated at the EORTC STBSG are listed in Table 2. The characteristics of the patients with MPNST were generally similar to those with other histological subtypes, except for age (younger patients, median age: 42.6 versus 51), gender (more men, 57% versus 49%) and tumor site (more commonly extremities as primary tumor site, 29% versus 23%). When diagnosed for advanced disease, MPNST patients more frequently had prior radiotherapy and nonmetastatic disease.

clinical outcome

The OS for all 2675 patients treated in the EORTC STBSG trials is given in Figure 1A. After a median follow-up of 4.1 years, the median OS for the MPNST group was 48 weeks [95% confidence interval (CI): 42–54 weeks] and not significantly different from the 51 weeks (95% CI: 49–53 weeks) for the other STS histotypes ($P = 0.483$). In the series of 2675 patients who were assessable for PFS, no difference was observed between the MPNST versus other type of histology STS group with a PFS of 17.0 (95% CI: 14–20) versus 16.1 weeks (95% CI: 15–18 weeks), respectively (Figure 1B; $P = 0.830$). The response rate for the assessable 159 MPNST patients and 2281 other histological type STS patients was 21% versus 22% ($P = 0.84$), respectively.

prognostic factor analysis

The univariate and multivariate analysis of survival time demonstrated that the performance status was a prognostic factor (Figure 2). The risk of death increased significantly with an increase of the performance status to the next highest score.

Results of the multivariate analysis for PFS are described in Table 3. Interestingly, for PFS and response, treatment was a strong independent prognostic factor ($P = 0.009$ and

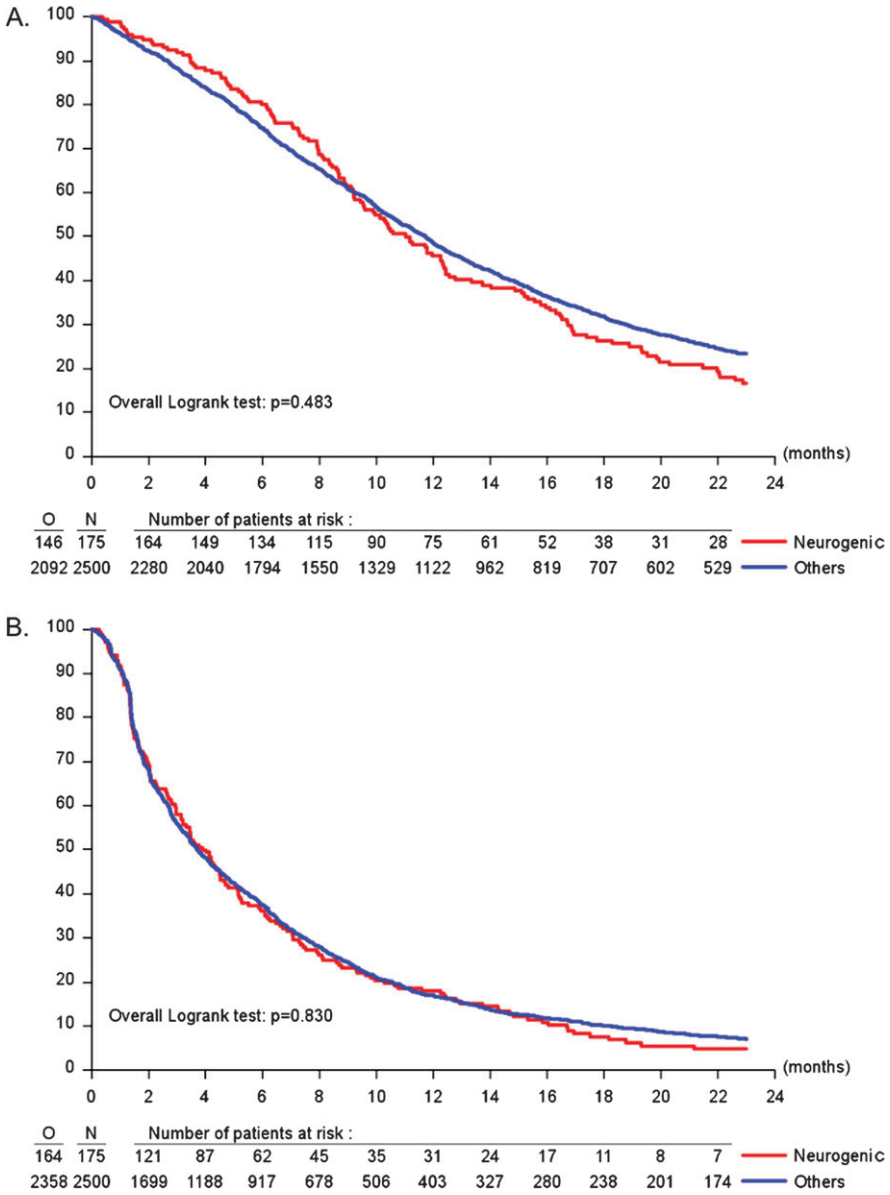

Figure 1. Overall survival (A) and progression-free survival (B) for malignant peripheral nerve sheath tumor and other histological subtype soft tissue sarcoma patients.

$P < 0.0001$, respectively). The median PFS times for the different treatments (Figure 3A) were as follows: for anthracyclines alone: 17 weeks (range 13.7–20.43), for the doxorubicin plus ifosfamide combination: 26.9 weeks (range 22.4–35.1), for CYVADIC combination: 10.4 weeks (range 8.4–41.9) and for ifosfamide: 9.4 weeks (range 7.1–17.0), with an 1-year survival time of 14.8, 25.2, 23.3 and 3.85, respectively. Patients who received doxorubicin combined with ifosfamide tended to have the best PFS [compared with anthracycline monotherapy: hazard ratio (HR) = 0.807, 95% CI: 0.480–1.358], whereas this was the worst for patients who received ifosfamide alone (compared with anthracycline monotherapy: HR = 2.018, 95% CI: 1.155–3.327). In agreement, patients treated with the doxorubicin–ifosfamide combination had the best response rate (HR = 6.283, 95% CI: 2.342–16.852), whereas the worst response was observed for treatment with ifosfamide only (HR = 0.333, 95% CI: 0.038–2.912) as compared with anthracycline monotherapy.

In addition to treatment, for PFS, the performance status and tumor site were independent prognostic factors (Table 3; Figure 3B and C). The risk of progression increased with an increase in the performance status to the next highest score ($P = 0.0108$) and decreased for patients with a tumor localized in the extremities as compared with other sites ($P = 0.0157$). For the response rate, the gender was also an independent prognostic factor. Men had a response rate of 28% as compared with 13% for women ($P = 0.0278$).

The predictiveness and stability of the OS and PFS models were validated and stable, while for response validation was not possible due to a relative low number of events (34 events for 175 patients).

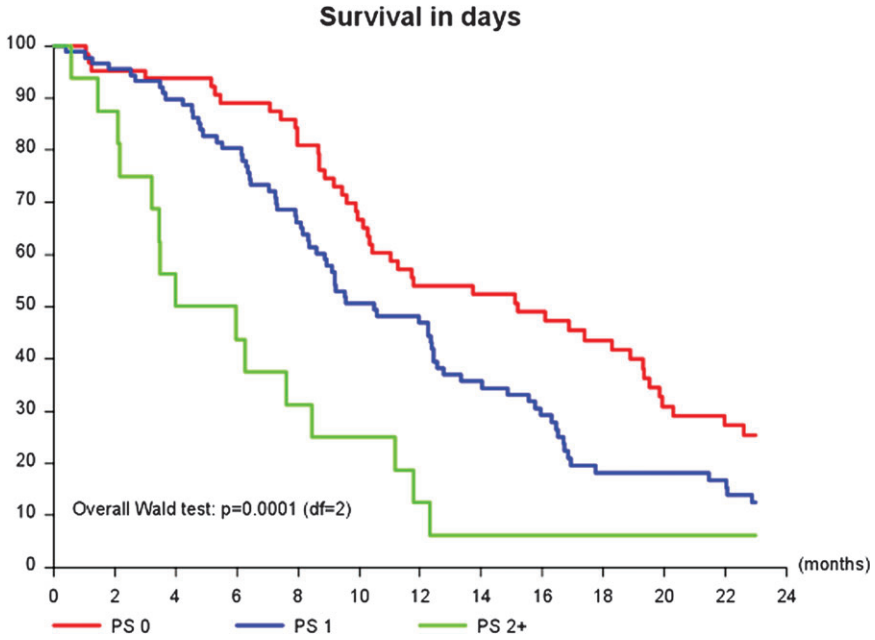

Figure 2. Overall survival by performance status for malignant peripheral nerve sheath tumor patients.

Table 3. Multivariate analysis of progression-free survival for MPNST patients

Factor	Parameter estimate	Hazard ratio	95% lower confidence limit for hazard ratio	95% upper confidence limit for hazard ratio	*P*
Treatment					0.0090
DOX + IFO versus anthracyclines	−0.21387	0.807	0.480	1.358	***0.4199***
CYVADIC versus anthracyclines	0.18785	1.207	0.671	2.171	***0.5306***
IFO alone versus anthracyclines	0.70208	2.018	1.155	3.527	***0.0137***
Primary tumor site	−0.48061	0.618	0.419	0.913	0.0157
Performance status					0.0108
PS 1 versus PS 0	0.35113	1.421	0.900	2.243	***0.1320***
PS 2+ versus PS 0	0.99341	2.700	1.405	5.190	***0.0029***

Bold signifies that the statistical significance is set at 0.05.
CYVADIC, cyclophosphamide, vincristine, adriamycin and dacarbazine; DOX, doxorubicin; IFO, ifosfamide; MPNST, malignant peripheral nerve sheath tumor.

discussion

This is the first study that compares the outcome of patients with advanced MPNST with those with other STS histological subtypes. Soft tissue tumors are a heterogeneous group of clinicopathological and tumor genetically defined entities that too often are lumped together in clinical trials in order to reach pseudo-meaningful numbers [12, 13]. The clinical outcomes of OS, PFS and response rate were similar for both groups. In a previous analysis of the 2185 first patients with advanced STS, treated in seven clinical EORTC-STBSG trials, an overall response rate of 26% and median OS of 51 weeks was found [8]. Although the latter study already demonstrated a prognostic importance of histological subtype, MPNST was not separately tested because of its low incidence.

While most clinical trials on chemotherapy in advanced sarcomas included all histological subtypes, existing differences in biological behavior between STS histotypes seem to result in different chemosensitivity between STS subtypes. For instance, paclitaxel has shown activity against angiosarcoma of the soft tissue [14], gemcitabine plus docetaxel against uterine leiomyosarcoma [15], trabectedin against leiomyosarcoma and liposarcoma [16], and pazopanib against all STS except adipocytic STS [17].

Using the retrospective data of 12 pooled trials, we had the unique opportunity to perform a prognostic factor analysis for this rare subgroup of STS, advanced MPNST. The univariate and multivariate analysis demonstrated the prognostic impact of treatment regimen. For advanced MPNST patients, the doxorubicin–ifosfamide combination tended to have a lower

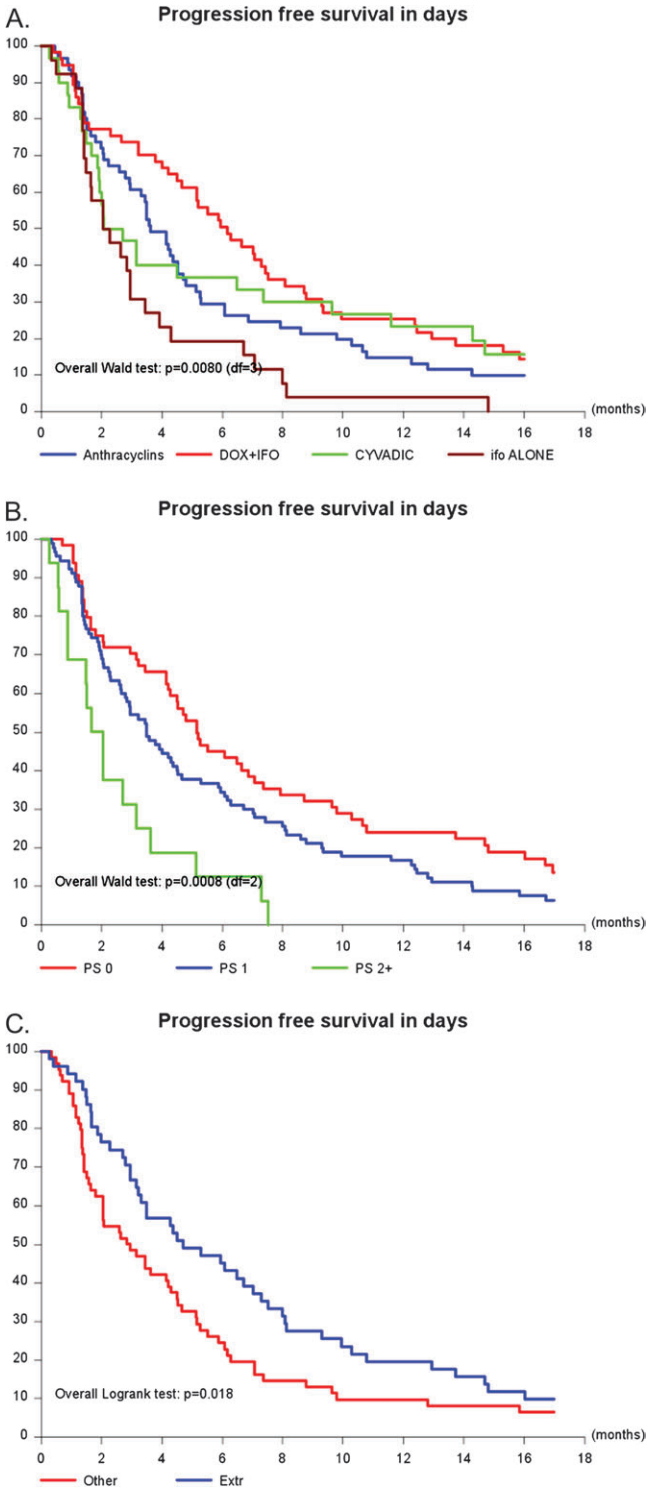

Figure 3. (A) Progression-free survival by treatment of MPNST patients. (B) Progression-free survival by performance status for MPNST patients. (C) Progression-free survival by side of primary tumor for MPNST patients. MPNST, malignant peripheral nerve sheath tumor.

risk of relapse and had a better response rate than the other studied regimens. The previously reported randomized phase III trial comparing a relative low dose ifosfamide (5 g/m^2) plus doxorubicin (50 mg/m^2; $n = 258$) with doxorubicin monotherapy (75 mg/m^2; $n = 263$) did not show significant differences in terms of response rate, PFS and OS between the regimens [18]. No subgroup analysis for MPNST was done. Considering OS data of the current retrospective pooled analysis and the earlier reported prospective randomized trials [18], single-agent doxorubicin is still considered the standard chemotherapy. Results of the EORTC 62012 trial comparing the ifosfamide (10 g/m^2) plus doxorubin (75 mg/m^2) combination with doxorubicin in advanced STS have to be awaited.

With regard to the effect of neoadjuvant chemotherapy on MPNST, only retrospective data in small series are available [4, 19]. Retrospective data of 11 pediatric patients with MPNST considered unresectable at diagnosis showed complete resection after the tumor size was reduced by chemotherapy [4]. Additionally, one case of adult advanced MPNST treated with neoadjuvant systemic chemotherapy, resulting in a histopathological complete response, has been described [20]. Results of an ongoing NCI multicenter phase II trial (NCT00304083) that studies combination chemotherapy with doxorubicin, etoposide and ifosfamide in unresectable (stages III–IV) adult MPNST are awaited.

The weakness of our study is that it concerns retrospective analysis. Not all previously reported prognostic factors for MPNST were available for all 12 pooled trials. Possible prognostic factors that were not studied as cofactors are: association with NF1, rhabdomyoblastic differentiation (triton tumor) and nuclear p53 [3, 4, 6, 21]. The treatment effect should be interpreted with data from randomized trials; nonrandomized trials were added to obtain an acceptable power. The apparent differences of outcome between therapeutic regimens may be explained by selection biases and should be confirmed on the basis of randomized data before they are applied to clinical practice.

The benefit of chemotherapy for metastatic disease should be weighted against the possible side-effects. Previously, the doxorubicin–ifosfamide combination has been shown to be more myelotoxic as compared with doxorubicin alone [18]. It is a challenge to develop new drug combinations with less toxicity and improved antitumor activity. New drug combinations with promising targeted therapies, such as bevacizumab, dasatinib, pazopanib, everolimus, cetuximab, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor-2 agonist, insulin-like growth factor receptor blocker and heat shock protein inhibitor, are currently being studied in advanced STS. Studies in STS subtypes are essential in order to determine the efficacy of treatments for STS, including MPNST.

Although the molecular events leading to MPNST tumorigenesis have not been fully characterized, associations have been made with NF1 mutations, Ras and epidermal growth factor receptor (EGFR) expression, TP53 mutations, heterozygous mutations of ribosomal protein genes and angiogenesis. About one-fourth to one-half of MPNST occur within patients with NF1. NF1 is caused by autosomal dominantly inherited or *de novo* mutations in the NF1 gene leading to nonfunctional proteins. The NF1 gene product, neurofibromin, acts as a negative regulator in the Ras signal transduction pathway. Ras proteins in malignant tumor cell lines from patients with NF1 are in a constitutively activated state [25], suggesting that these Ras proteins would be

appropriate therapeutic targets. However, farnesyl transferase inhibitors, which target Ras, have been disappointing in clinical trials. Furthermore, preclinical evidence has suggested a central role for EGFR in tumorigenesis of MPNST. Although, EGFR expression was found in 63% of MPNST, EGFR phosphorylation was present in only 3.1%, suggesting that this pathway does not appear to be active [26]. This is consistent with the lack of a clinical benefit of erlotinib in a phase II study in metastatic or unresectable MPNST [27]. In addition, tumor angiogenesis in NF1 neurogenic sarcomas has been associated with increased vascular endothelial growth factor receptor (VEGF) expression, implicating VEGF as a potential inducer of tumor angiogenesis in peripheral nerve tumors. VEGF2 inhibition resulted in decreased growth of neurogenic sarcomas [28]. Since malignancy occurs only in a minority of patients with NF1, it is possible that further genetic alterations are required for MPNST to develop. It seems that loss or mutation of the p53 gene might be an obligatory step for malignant transformation. p53 primarily exerts its role as tumor suppressor through the maintenance of genomic integrity after DNA damage by its ability to arrest the cell cycle and induce apoptosis. Mice with both NF1 and p53 mutations have been shown to develop MPNST [29, 30]; and zebrafish, both, carrying heterozygous mutations for 17 different ribosomal protein genes resulting in loss of p53 synthesis as well as p53 mutant zebrafish, develop MPNST [31, 32]. Moreover, the immunohistochemical detection of nuclear p53 is common in the malignant areas as compared with the precursor neurofibroma and related to a worse prognosis in MPNST patients [33]. Trials that explore these biological features are warranted.

In conclusion, analysis of pooled data of 12 trials made it possible to answer the objectives of our study that have not been assessed before in literature. Clinical outcomes were similar for patients with advanced MPNST as compared with patients with other histological subtype STS. In this series, a better outcome was observed for MPNST patients treated with the doxorubicin–ifosfamide combination, which justifies further clinical trials formally comparing this regimen to doxorubicin single-agent treatment.

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disclosures

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