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ORIGINAL ARTICLE

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ABSTRACT

Introduction: As both anti-tumour effects and toxicity are thought to be dose-dependent, patients with the greatest toxicity may also have the best outcome. We assessed whether severity of doxorubicin-induced hematological toxicity is associated with outcome in advanced soft tissue sarcoma (STS) patients. In addition, risk factors for hematological toxicity were explored.

Methods: Worst haematological toxicities (anaemia, leukopenia, neutropenia and thrombocytopenia) seen during treatment were scored according to CTCAE toxicity score. Differences in overall survival (OS), progression free survival (PFS) and response rate (RR) between patients with or without high haematological toxicity (grades 0–2 vs. 3–4) were assessed using conventional statistical tests. Associations between baseline characteristics and hematological toxicity were established using logistic multivariate regression.

Results: In 557 patients eligible for this analysis, 47.2% of the patients received at least six cycles of treatment; 45% stopped treatment early due to progression, 3% because of toxicity. Relative dose intensity (RDI) was constant over the cycles.

OS, PFS, and RR did not differ between patients with grade 3/4 toxicity during treatment versus those with grade 1/2. Risk factors for grade 3/4 haematological toxicity, in particular neutropenia, were age above 60 years, low BMI, and female gender.

Conclusion: In this large series, risk factors for haematological toxicity in STS patients receiving doxorubicin monotherapy were revealed. The finding that there was no association between outcome and haematological toxicity during doxorubicin treatment may be useful to reassure advanced STS patients that failure to experience haematological toxicity during treatment does not equate to under-treatment.

Introduction

Soft tissue sarcomas (STS) are a rare group of tumours consisting of numerous different subtypes displaying great variation in molecular characteristics, clinical behaviour, and sensitivity to anti-tumour agents. Patients with advanced disease not amenable to local treatment options with curative intent have a dismal prognosis, with a median overall survival of approximately 1 year. For these patients, palliative treatment is indicated.

In the first line setting, numerous drugs have been shown to exert anti-tumour activity. Of these, doxorubin and ifosfamide are the most commonly used agents. Given equivalent efficacy of doxorubicin and ifosfamide [1], doxorubicin is preferred, given more convenience for the patients as doxorubicin can be administered once every three weeks in an outpatient setting. Recently, a randomised EORTC study compared doxorubicin monotherapy versus the combination of doxorubicin and ifosfamide [2]. Although response rate and progression-free survival were greater in the patients treated with the combination, overall survival, the primary endpoint in this study, was not statistically different. Consequently, apart from patients whose primary need is tumour shrinkage, have a good clinical condition and adequate organ function and for whom the combination may be preferred, doxorubicin monotherapy is still considered standard for the majority of advanced STS patients [3]. Recently, it was shown in a randomized phase II study that the addition of the anti-platelet-derived growth factor receptor-alpha (PDGFRA) monoclonal antibody, olaratumab, to doxorubicin improved overall survival compared with doxorubicin alone [4] resulting in

approval of this drug in combination with doxorubicin. But given the preliminary nature of these results, in many centres, doxorubicin will remain the mainstay of treatment for many advanced STS patients.

The most commonly used schedule of doxorubicin mono-therapy in advanced STS patients is 75 mg/m^2 every three weeks for a maximum of six cycles. As holds true for all anti-tumour agents, the pharmacokinetics of doxorubicin and its metabolites greatly differs between patients. This large variety in doxorubicin PK between patients may partially account for the great variation in toxicities experienced by patients [5]. Accordingly, a statistically significant association was revealed between systemic doxorubicin blood levels and myelosuppression in a small series of patients with small cell lung cancer [6].

Given this relationship between systemic exposure to doxorubicin and haematological toxicity on one hand and a suggested dose-response association for doxorubicin in advanced STS [7] on the other hand, a relationship between doxorubicin-induced toxicity and outcome may exist in advanced STS. It is important to know whether such a relationship indeed exists in advanced STS for a number of reasons. In daily practice, many patients who do not experience any significant toxicity from doxorubicin are worried about whether or not the treatment 'works', in other words whether the chemotherapy actually exerts anti-tumour effects. Furthermore, if such a relationship does exist, the occurrence and severity of toxicity might be an early marker for response and in principle, could serve to guide treatment, i.e., increasing the dose up to toxicity.

In this study, we retrospectively examined the relationship between the severity of haematological toxicities and efficacy in a large series of advanced STS patients treated with first-line doxorubicin monotherapy. In addition, risk factors for haematological grade 3/4 toxicity were explored.

Patient and methods

Patients

In the EORTC database, nine studies were identified in which advanced STS patients were treated with doxorubicin mono-therapy 75 mg/m^2 every three weeks. No G-CSF, erythropoietin or dexrazoxane was allowed in any of the studies. In case of toxicity, dose reduction had to be applied. This analysis was focused only on patients who received at least one cycle of treatment and with at least one post-baseline laboratory assessment leaving a total of seven eligible EORTC trials conducted between 1990 and 2012 with a total of 557 patients eligible for this analysis (Supplementary Table 1).

Endpoints

The endpoints for outcome considered for this analysis were overall survival (OS), progression-free survival (PFS) and response rate (RR). OS was defined as the time elapsing between the date of randomization (in the randomized trials) or registration (in the non-randomized trials) and the date of death. Patients alive at the last follow-up date were censored.

PFS was defined as the time between date of randomization (in the randomized trials) or registration (in the non-randomized trials) and the date of first progression or death, which-ever came first. Patients who are alive without progression at the last follow-up date are censored. RR was evaluated in all trials using WHO response criteria or RECIST in which patients who achieved a complete or partial response were considered as 'responders', and patients with stable disease or in progression are considered as 'non-responders'. Best responses were used.

Risk factors

This analysis was focused on four hematological toxicities: anaemia, leukopenia, neutropenia and thrombocytopenia. For each of the four toxicities, the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) scoring from grade 0 to grade 4 was used. Patients experiencing grade 0–2 toxicity as the highest toxicity during treatment were considered as patients with 'low toxicity', those patients with grade 3–4 toxicity as most severe toxicity during treatment as patients with 'high toxicity'.

In all but two studies, a full blood count was done weekly. In the two other studies (EORTC 62901 ($N = 112$) and EORTC 62091 ($N = 43$), a full blood count was mandated during the first two cycles and then prior to each subsequent administration of doxorubicin. However, additional analyses (results not shown) showed that many investigators obtained weekly blood counts in these studies as well and that the number of obtained blood samples from these studies did not differ too much from the other studies where weekly blood counts were mandated.

If the laboratory values were measured more than once per cycle, then the worst (minimum) value was considered. When a specific laboratory value was not reported (missing value) but other laboratory data were reported at the same time, it was assumed that the specific toxicity was in the normal range and toxicity grade zero was imputed for that specific toxicity grade.

Several potential confounders for the association of doxorubicin-induced toxicity and outcome were extracted from the database. The relative dose intensity (RDI) was calculated as the ratio of actual doxorubicin dose intensity (administered dose/actual duration of cycle in days) to the intended doxorubicin dose intensity (planned dose/standard cycle duration of 21 days) per cycle. For the calculation of administered dose, BSA was calculated using the weight value reported per patient by cycle and height value reported at baseline. When weight was missing, the last weight available was used for the calculation of RDI.

Other characteristics assessed were demographic factors (age, gender and WHO performance status), and tumour characteristics (STS histological subtype, histopathological grading (low (grade I) versus high grade (grade II and III), time between initial diagnosis and start of chemotherapy, primary site, metastatic sites, and the presence of local recurrence and metastatic disease).

Table 1. Patient characteristics.

	Patient's characteristics by protocol							
	Protocol							
	62901 (N = 101) N (%)	62941 (N = 38) N (%)	62962 (N = 41) N (%)	62971 (N = 99) N (%)	62012 (N = 203) N (%)	62061 (N = 37) N (%)	62091 (N = 38) N (%)	Total (N = 557) N (%)
Gender								
Male	49 (48.5)	22 (57.9)	18 (43.9)	51 (51.5)	95 (46.8)	21 (56.8)	16 (42.1)	272 (48.8)
Female	52 (51.5)	16 (42.1)	23 (56.1)	48 (48.5)	108 (53.2)	16 (43.2)	22 (57.9)	285 (51.2)
Age								
<40 yrs	14 (13.9)	10 (26.3)	5 (12.2)	21 (21.2)	48 (23.6)	0 (0.0)	2 (5.3)	100 (18.0)
40–50 yrs	28 (27.7)	7 (18.4)	14 (34.1)	26 (26.3)	74 (36.5)	0 (0.0)	4 (10.5)	153 (27.5)
50–60 yrs	32 (31.7)	11 (28.9)	11 (26.8)	32 (32.3)	74 (36.5)	9 (24.3)	11 (28.9)	180 (32.3)
>=60 yrs	27 (26.7)	10 (26.3)	11 (26.8)	20 (20.2)	7 (3.4)	28 (75.7)	21 (55.3)	124 (22.3)
Performance status								
PS 0	32 (31.7)	11 (28.9)	10 (24.4)	46 (46.5)	115 (56.7)	20 (54.1)	25 (65.8)	259 (46.5)
PS 1	57 (56.4)	24 (63.2)	26 (63.4)	53 (53.5)	88 (43.3)	17 (45.9)	13 (34.2)	278 (49.9)
PS 2+	12 (11.9)	3 (7.9)	5 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (3.6)
Histopathological aggressivity								
Low	16 (15.8)	9 (23.7)	4 (9.8)	8 (8.1)	13 (6.4)	5 (13.5)	0 (0.0)	55 (9.9)
High	60 (59.4)	14 (36.8)	14 (34.1)	91 (91.9)	190 (93.6)	32 (86.5)	4 (10.5)	405 (72.7)
Missing	25 (24.8)	15 (39.5)	23 (56.1)	0 (0.0)	0 (0.0)	0 (0.0)	34 (89.5)	97 (17.4)
Site of primary tumor								
Other	27 (26.7)	18 (47.4)	29 (70.7)	56 (56.6)	113 (55.7)	26 (70.3)	27 (71.1)	296 (53.1)
Extremities	11 (10.9)	17 (44.7)	12 (29.3)	41 (41.4)	89 (43.8)	10 (27.0)	9 (23.7)	189 (33.9)
Missing	63 (62.4)	3 (7.9)	0 (0.0)	2 (2.0)	1 (0.5)	1 (2.7)	2 (5.3)	72 (12.9)
Histology								
Leiomyosarcoma	43 (42.6)	11 (28.9)	9 (22.0)	21 (21.2)	42 (20.7)	15 (40.5)	12 (31.6)	153 (27.5)
Synovial sarcoma	7 (6.9)	4 (10.5)	4 (9.8)	10 (10.1)	34 (16.7)	1 (2.7)	4 (10.5)	64 (11.5)
Liposarcoma	14 (13.9)	6 (15.8)	7 (17.1)	15 (15.2)	23 (11.3)	8 (21.6)	12 (31.6)	85 (15.3)
Other	34 (34.0)	17 (24.5)	21 (28.3)	52 (54.7)	84 (41.7)	13 (38.8)	10 (30.9)	231 (41.5)
Missing	3 (3.0)	0 (0.0)	0 (0.0)	1 (1.0)	20 (9.9)	0 (0.0)	0 (0.0)	24 (4.3)
Prior Surgery								
No surgery	0 (0.0)	4 (10.5)	4 (9.8)	22 (22.2)	203 (100.0)	37 (100.0)	38 (100.0)	105 (18.9)
Non optimal surgery	0 (0.0)	5 (13.2)	11 (26.8)	13 (13.1)	0 (0.0)	0 (0.0)	0 (0.0)	29 (5.2)
Complete surgery	0 (0.0)	22 (57.9)	20 (48.8)	55 (55.6)	0 (0.0)	0 (0.0)	0 (0.0)	97 (17.4)
Missing	101 (100.0)	7 (18.4)	6 (14.6)	9 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	326 (58.5)
Prior radiotherapy								
No	77 (76.2)	19 (50.0)	29 (70.7)	75 (75.8)	130 (64.0)	37 (100.0)	38 (100.0)	405 (72.7)
Yes	24 (23.8)	19 (50.0)	12 (29.3)	23 (23.2)	73 (36.0)	0 (0.0)	0 (0.0)	151 (27.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Primary site involved								
No	0 (0.0)	25 (65.8)	19 (46.3)	46 (46.5)	110 (54.2)	15 (40.5)	21 (55.3)	236 (42.4)
Yes	0 (0.0)	13 (34.2)	22 (53.7)	53 (53.5)	93 (45.8)	17 (45.9)	17 (44.7)	215 (38.6)
Missing	101 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (13.5)	0 (0.0)	106 (19.0)
Metastatic Site involved								
No	0 (0.0)	3 (7.9)	4 (9.8)	13 (13.1)	0 (0.0)	7 (18.9)	5 (13.2)	32 (5.7)
Yes	0 (0.0)	35 (92.1)	37 (90.2)	86 (86.9)	189 (93.1)	30 (81.1)	33 (86.8)	410 (73.6)
Missing	101 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (6.9)	0 (0.0)	0 (0.0)	115 (20.6)

Statistical analyses

Hematologic toxicity values and grades were summarised by cycle. The time between treatment start and occurrence of first toxicity grade was depicted using a Cumulative Incidence graph to investigate, at which time, higher grades of toxicity occurred.

To compare the PFS and OS between patients with low (grade 0–2) versus those with high haematological toxicities (grade 3–4), Kaplan–Meier methods and the log-rank test were used. To avoid potential bias from patients who received only one, two or three cycles of treatment, landmark analyses were performed to compare the results at the end of cycle 1, cycle 2 and cycle 3. Patients who progressed, died or discontinued before the different landmark analyses were excluded from these analyses.

To explore whether RR differed between patients with or without high hematologic toxicities (0–2 vs. 3–4), the Chi-square test was used for the subgroups of patients still on

treatment at the end of cycle 1, cycle 2 and cycle 3. Patients who stopped treatment before each time point were excluded from these analyses.

Associations between baseline characteristics (gender, body mass index, performance score, and age) and hematological grade 3/4 toxicity were established using logistic multivariate regression modeling.

Results

Patients' characteristics

A total number of 557 sarcoma patients from 7 EORTC trials (conducted between 1990 and 2012) were considered for this analysis. The analysis was based on patients who received at least one cycle of treatment, for a total number of cycles of 2341.

The patients' characteristics per protocol are depicted in Table 1. The majority of patients (32%) were between 50 and
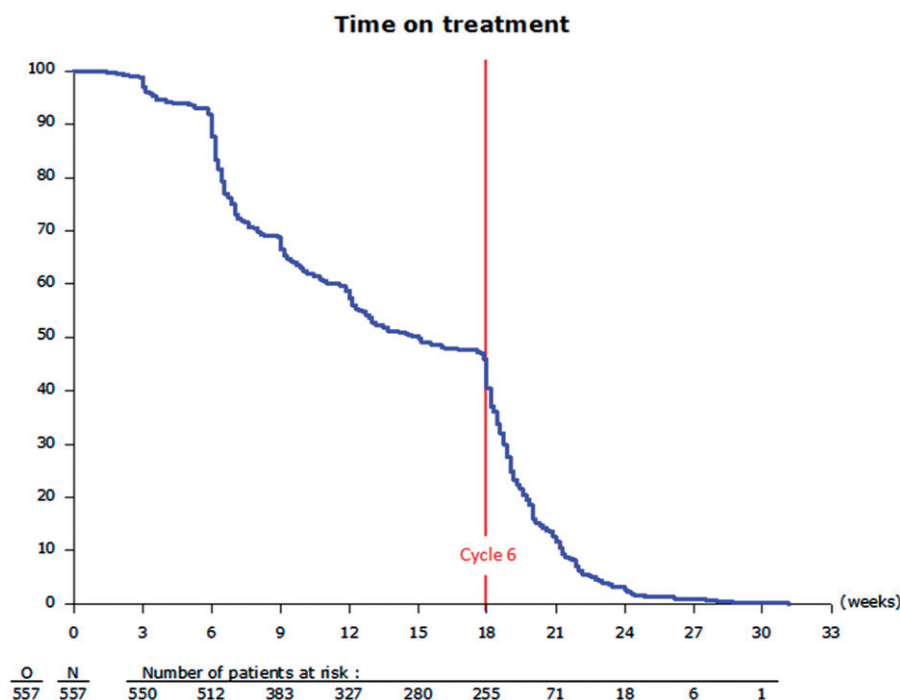
Figure 1. Time on treatment.

60 years old at registration, 51% were female. Almost all patients had a PS of 0 or 1 and 72% had a grade II or III tumor. Leiomyosarcoma (28%) and liposarcoma (15%) were the most frequent STS subtypes entered in these studies.

Treatment exposure

Two hundred sixty three out of 557 (47.2%) patients received at least six cycles of treatment: 220 (39.5%) patients stopped treatment after 6 cycles and 43 (7.8%) received more than 6 cycles. The latter group concerned patients from the two oldest trials (62901 and 62941) in which a maximum of 8 and 7 cycles, respectively, were allowed per protocol whereas in the more recent trials, the maximum number of cycles was set at 6.

The median time on treatment, defined as the time in weeks between the start date of treatment and the end date of the last cycle reported (i.e., the date of administration of the last cycle of doxorubicin +21 days), was 15 weeks (Figure 1) corresponding with a median time on treatment of around five cycles. After 9 weeks of treatment (3 cycles), 63.7% of the patients were still on treatment.

Patients interrupted treatment mainly due to progressive disease (45%), only 19 patients (3%) stopped because of toxicities. Forty percent of patients completed the maximum number of cycles per protocol. The relative dose intensity was constant over cycles and was concentrated around 100% (Figure 2).
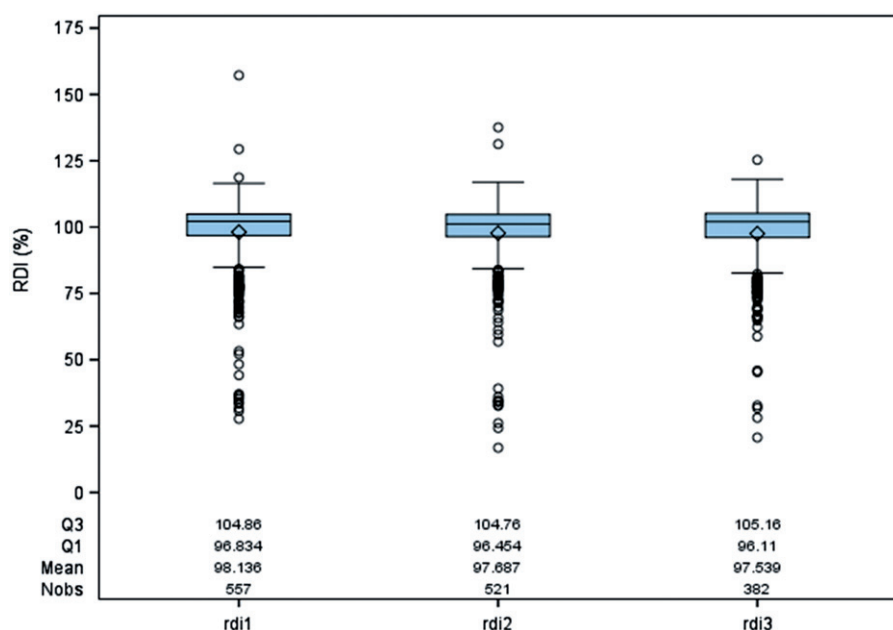
Hematologic toxicity

The distribution of the hematologic laboratory values over the first 6 cycles of chemotherapy is depicted in Figure 3.

The worst toxicity grade per cycle is displayed in Figure 4. At baseline, 90% of the patients had grade 0 or 1 toxicity. The percentage of patients having grade 2 toxicity increased over time from 17% at cycle 1 to 24% at cycle 3. After cycle 1, the percentage of patients experiencing grade 3 toxicity was quite constant over cycle, while the percentage of patients with grade 4 tended to decrease after cycle 1, from 21.0% at cycle 2 to 12% at cycle 3. This tendency was not related to the interruption of the treatment since the majority of patients with grade 3/4 toxicity during cycle 1 did not generally interrupt the treatment after cycle 1. Out of 106 patients with grade 3 and 118 patients with grade 4 at cycle 1, respectively, 93 and 90% continued treatment after cycle 1 and 53 and 42%, respectively, were still on treatment at cycle 6, which is comparable with patients with grade 0–2 toxicity during cycle 1.

Response to treatment and association with toxicity

Ninety one (16.3%) patients had a CR or PR as best response, 453 (81.3%) patients had progression or stable disease. In patients with grade 0–2 toxicity as worst toxicity, the RR was 11.8% (28/238 patients), in patients with grade 3/4 toxicity, the RR was 19.7% (63/319 patients). Since this comparison could be biased by the fact that worst toxicity may have occurred after the best response on treatment, the relationship of response with the worst toxicity was separately done at cycle 1, 2 or 3, considering only patients still on treatment at that cycle. For patients with grade 0–2 toxicity versus those with grade 3/4 toxicity, the respective RRs were 14.9% versus 19.0% at cycle 1 ($p = .44$), 15.1% versus 20.2% at cycle 2 ($p = .264$), and 21.0 versus 25.2% at cycle 3 ($p = .435$).

Figure 2. Relative dose intensity (RDI). RDI (i.e., the actual dose intensity compared to the theoretical one, in %). RDI1 is relative dose intensity during cycle 1, RDI2 during cycle 2, RDI3 during cycle 3.
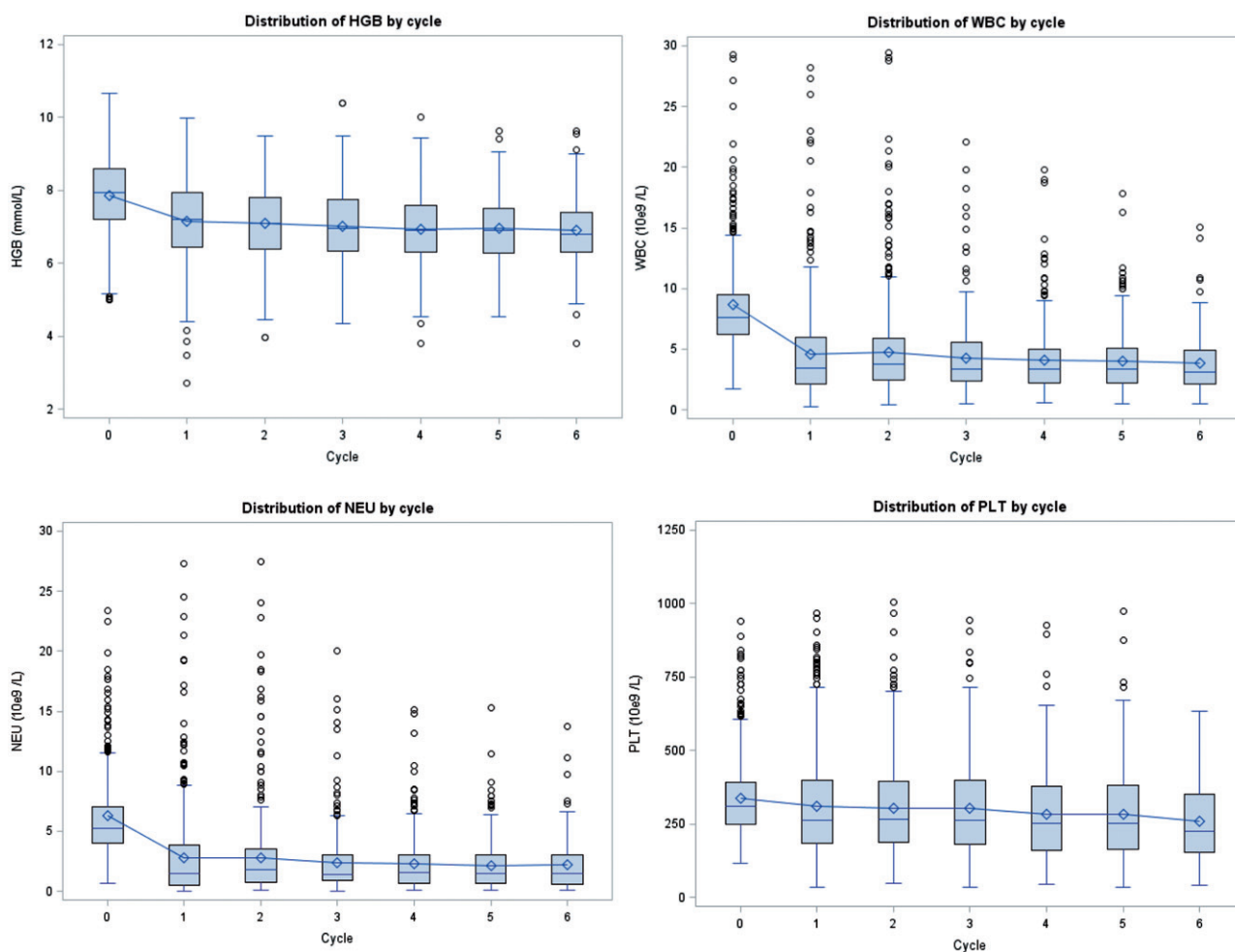
Figure 3. Worst hematological toxicity per cycle. X-axis: '0' refers to values observed at baseline.
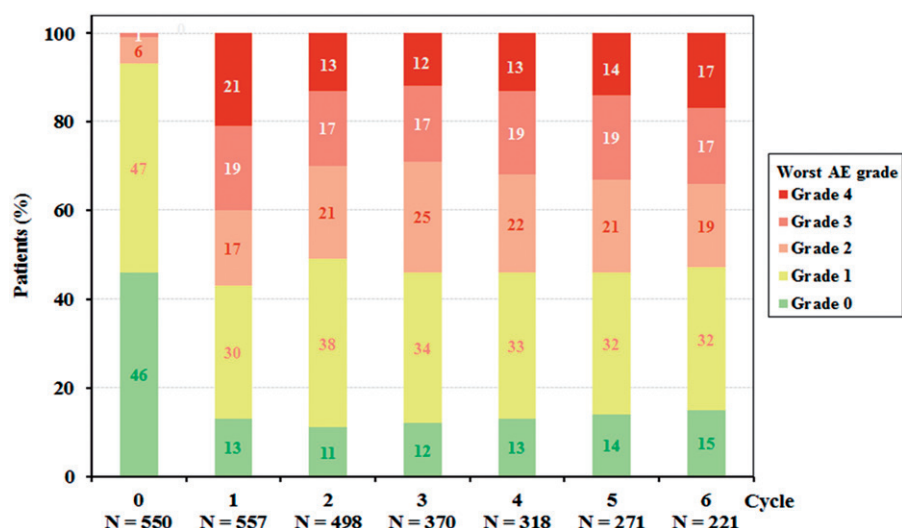
Figure 4. Worst overall toxicity grade per cycle.

Progression free survival and association with toxicity

Five hundred thirty nine (96.8%) patients progressed or died during follow-up; 18 (3.2%) patients were still alive without progression at the last available follow up. To investigate the influence of severity of toxicity on PFS, a landmark analysis was performed. Kaplan–Maier plots to compare the results at the end of cycle 1, 2 and 3 were made in which patients who died, progressed or discontinued treatment before each of those cut-offs were not considered in the analysis.

The median PFS (95% Confidence Interval (CI)) of patients with low hematologic toxicity (grade 0–2) versus those with severe hematological toxicity (grade 3–4) during cycle 1 was 17.7 (12.7–21.1) weeks versus 21.0 (15.0–24.3) weeks (HR 0.85 (0.71–1.01); $p = .066$), during cycle 1–2, 21.2 (19.1–24.6) weeks versus 15.8 (11.4–20.8) weeks (HR 0.91 (0.75–1.10); $p = .316$), and during cycle 1-3, 27.9 (24.1–32.7) weeks versus 30.9 (27.4–32.9) weeks (HR 0.93 (0.75–1.16); $p = .518$).

Also for each specific hematologic toxicity (anemia, thrombocytopenia, leukocytopenia, and neutropenia) landmark analyses were conducted at the end of cycle 1, 2 and 3. Given the low number of patients experiencing thrombocytopenia grade 3/4, the analysis for thrombocytopenia was not possible. For none of the assessments done, was there a statistically significant difference in PFS between patients with low grades of toxicity versus those with high grades of toxicity. To illustrate, the PFS curves for the subgroups of patients with low versus high toxicity occurring during cycle 1–3 are depicted in Figure 5.

Overall survival and association with toxicity

With respect to OS, 437 (78.5%) patients died during follow-up, while 120 (21.5%) patients were still alive at the last available follow up. For the association of hematologic toxicity and OS landmark analyses were also conducted using the same cut-offs as were used in the PFS analyses.

The median OS (95% CI) of patients with low hematologic toxicity (grade 0–2) versus those with severe toxicity (grade 3–4) during cycle 1 was 52.1 (45.1–61.6) weeks versus 54.1 (46.3–63.6) weeks (HR 0.97 (0.80–1.17) $p = .739$), during cycle 1–2, 59.6 (49.7–67.0) weeks versus 55.2 (49.1–65.9) weeks (HR 0.99 (0.81, 1.21); $p = .924$), and during cycle 1–3, 67.0 (57.3–78.7) weeks versus 64.0 (54.1–72.1) weeks (HR 1.04 (0.82, 1.32)); $p = .729$) (Figure 6).

Also for OS, analyses were done for each of the hematologic toxicities separately with the exception of thrombocytopenia, given the low number of patients with greater than grade 3 thromobocytopenia. As for PFS, there were no statistically significant associations between the occurrence of any of the hematologic toxicities assessed and OS. Results are shown for the subset of patients with time on treatment and OS ≥ 63 days ($N = 383$).

Baseline characteristics and grade 3/4 hematological toxicity

The association between the baseline characteristics (age, gender, BMI and performance score) and grade 3/4 hematological toxicity is displayed in Table 2. Female gender, higher age and a low BMI appeared to be associated with grade 3/4 hematological toxicity, in particular grade 3/4 neutropenia.

Discussion

In this large series of advanced STS patients treated with doxorubicin monotherapy, we have identified several predictors for doxorubicin-induced hematological toxicity, but could not demonstrate an association of treatment-induced toxicity with outcome.

After administration, doxorubicin is partially converted into several metabolites with doxorubicinol being the major metabolite [6,8,9]. Like almost all anti-tumour agents, the pharmacokinetics of doxorubicin and its metabolites vary widely between patients with inter-individual coefficients of variation for area under the curve, volume of distribution, and clearance being in the range of 60–90% [6,8]. Several mechanisms may underlie this inter-individual variation including differences in hepatic function [6], gender, BMI [5]
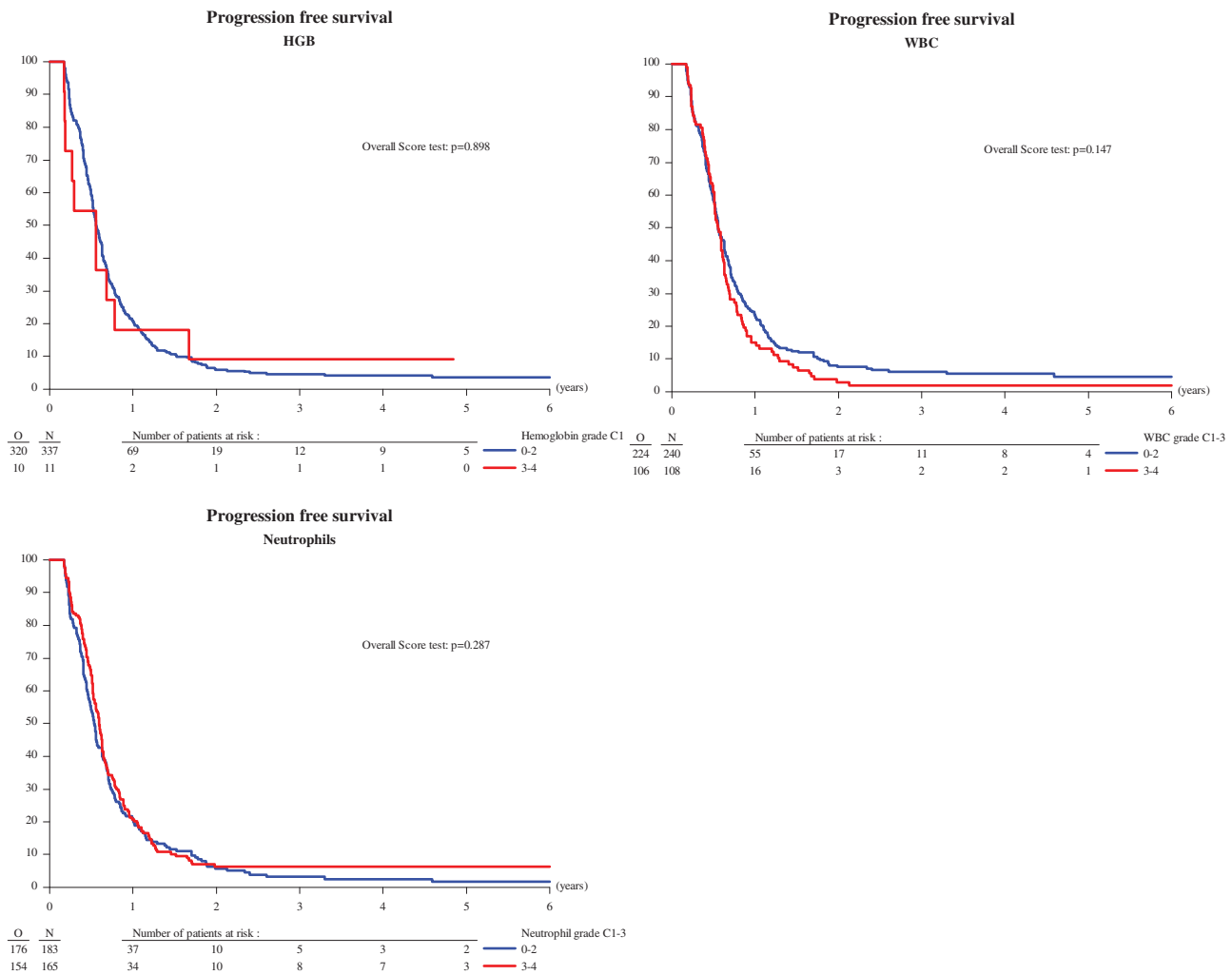
Figure 5. Subgroup of patients with time on treatment and PFS $\geq$63 days ($N = 348$) for each haematological toxicity grade during C1-3.

and genetic variants in genes encoding products involved in the metabolism of doxorubicin [10].

Several previous studies have underlined the importance of pharmacokinetics for doxorubicin-induced adverse events. For example, doxorubicin-induced cardiotoxicity has been suggested to be maximum-concentration dependent, and should in that respect be given as an infusion rather than as a bolus, while leucopenia is more related to the AUC [10]. In a study in patients with small cell lung cancer, there appeared to be a strong correlation between the AUC of doxorubicin and leucocytes, while no relationships were found for hematologic toxicity with levels of doxorubicin's main metabolite, doxorubinicol [6]. In the study, population described here in which 93% of patients had a good WHO performance score (0–1), doxorubicin was generally very well tolerated. The RDI in those patients who did not have to terminate treatment because of progressive disease, remained constant at 100% over treatment and only 3% of the patients had to terminate treatment for reasons of toxicity. To assess the relationship between doxorubicin-induced toxicity and outcome, we focused on hematologic parameters since these are not largely impacted by factors other than the administrated chemotherapy and can be relatively easily captured.

Of the toxicities assessed, leucopenia and neutropenia grade 3/4 occurred most often, grade 3/4 thrombocytopenia was very rare. Importantly, hematologic toxicity appeared not to be cumulative after cycle 1 with occurrence of grade 3 toxicity remaining constant over the diverse cycles while grade 4 toxicity even tended to decrease after cycle 1. Altogether, these data again emphasize the good tolerability of doxorubicin in this group of advanced patients, which is of great importance in the palliative setting.

Compared to toxicity, data on a dose-response relationship for anti-tumor effects of doxorubicin are very scarce. In pre-clinical models, in particular cell line models, there is in general a clear dose-response relationship but to what extent these data can be extrapolated to humans is unknown. One paper suggests that doxorubicin should be given at doses higher than 70 mg/m^2 [7] but the underlying evidence for this is rather weak.

Nevertheless, in view of the assumed dose-response relations for both anti-tumor effects and hematologic toxicity, one could anticipate an association between toxicity and anti-tumor effects. This expectation is also commonly shared by patients. In our experience, many patients can become concerned when they do not experience toxicity during
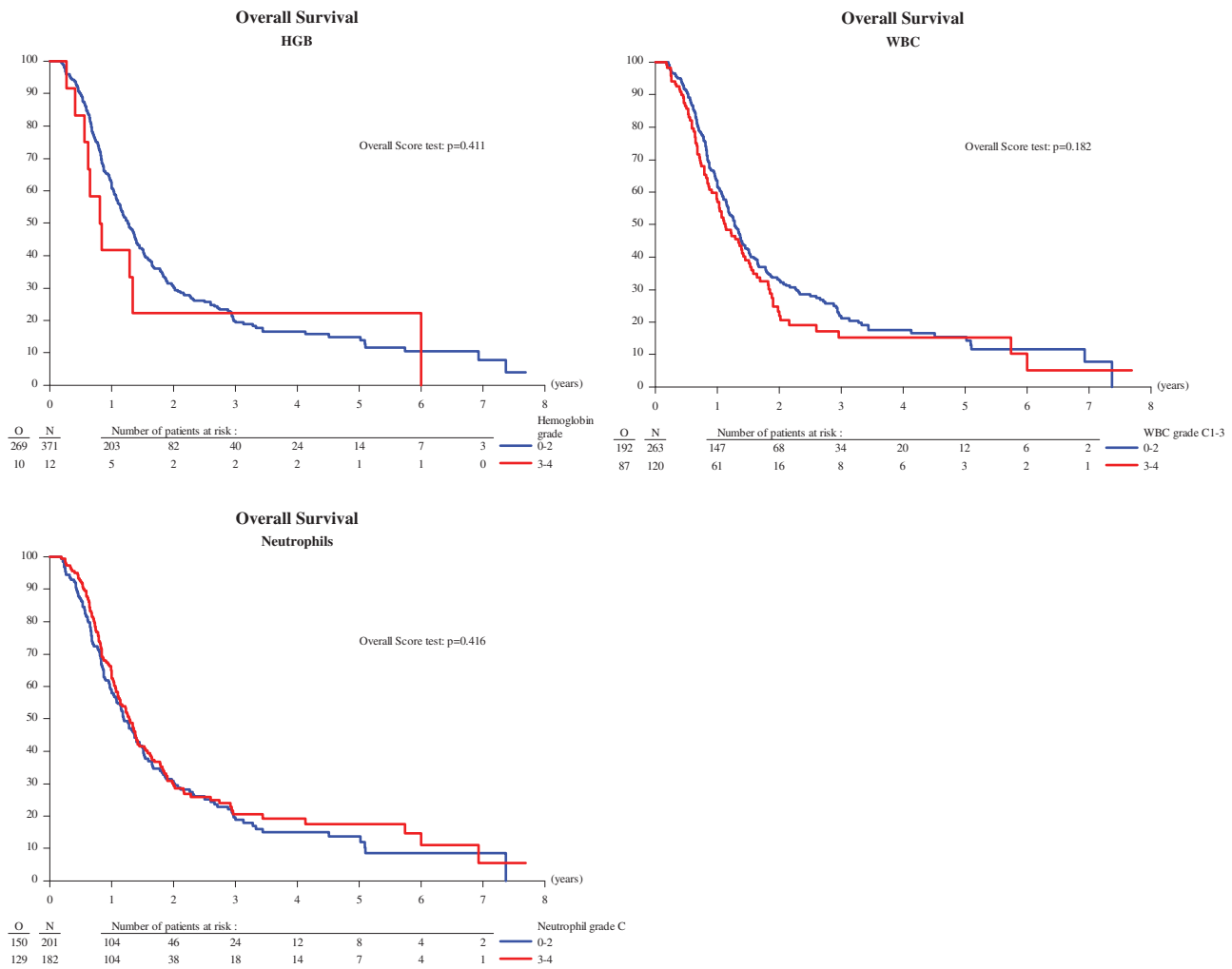
Figure 6. Subgroup of patients with time on treatment and OS ≥63 days (N = 383) for each hematological toxicity grade during C1-3.

Table 2. Association of baseline characteristics and hematological toxicity experienced. (Odds ratio estimates and corresponding 95% CI from a logistic multivariate regression).

Parameter	Any AE grade 3–4	HGB: grade 3–4[a]	WBC: grade 3–4	NEU: grade 3–4
Value at baseline	1.24 (0.93; 1.66)	11.4 (5.34; 24.2)	1.37 (0.59; 3.15)	1.17 (0.58; 2.34)
	$p = .143$	$p < .001$	$p = .464$	$p = .661$
Age				
<40 yrs	0.28 (0.15; 0.51)	0.13 (0.02; 0.71)	0.43 (0.24; 0.76)	0.30 (0.16; 0.54)
40–50 yrs	0.23 (0.13; 0.40)	0.59 (0.21; 1.69)	0.33 (0.20; 0.56)	0.24 (0.14; 0.41)
50–60 yrs	0.32 (0.19; 0.54)	0.60 (0.22; 1.61)	0.31 (0.19; 0.50)	0.33 (0.20; 0.55)
>=60 yrs	1.00	1.00	1.00	1.00
	$p < .001$	$p = .132$	$p < .001$	$p < .001$
BMI				
<18.5	5.49 (1.42; 21.2)	2.36 (0.25; 22.5)	2.93 (0.96; 8.98)	7.60 (1.99; 29.0)
18.5–25	1.86 (1.19; 2.88)	0.94 (0.38; 2.30)	1.49 (0.95; 2.34)	2.31 (1.49; 3.58)
25–30	1.64 (1.03; 2.62)	0.72 (0.26; 2.01)	1.24 (0.77; 2.00)	2.00 (1.26; 3.18)
>=30	1.00	1.00	1.00	1.00
	$p = .007$	$p = .763$	$p = .146$	$p < .001$
PS				
0	0.43 (0.14; 1.34)	1.50 (0.24; 9.25)	0.67 (0.25; 1.83)	0.66 (0.24; 1.83)
1	0.40 (0.13; 1.22)	1.19 (0.21; 6.80)	0.77 (0.28; 2.08)	0.59 (0.21; 1.64)
2+	1.00	1.00	1.00	1.00
	$p = .268$	$p = .826$	$p = .624$	$p = .554$
Gender				
Female	1.91 (1.32; 2.76)	0.75 (0.34; 1.64)	1.51 (1.05; 2.19)	1.69 (1.18; 2.43)
Male	1.00	1.00	1.00	1.00
	$p < .001$	$p = .468$	$p = .028$	$p = .004$

[a]Very few 'events' so results are very unstable.

treatment and ask 'whether or not the chemotherapy actually works, and whether the dose is high enough'. In this study, however, we could not find an association between any of the explored hematologic toxicities and outcome in terms of RR, PFS and OS. This information is important as it may be useful to reassure advanced STS patients that failure to

experience haematological toxicity during treatment does not equate to under-treatment and patients have not to be worried if they do not experience some greater toxicity as it does not reflect their response to therapy.

Apart from the fact that there is indeed no association at all between hematologic toxicity and outcome, there are several reasons to be considered why we could not identify such a relationship. In patients with advanced STS, numerous patients as well as tumor-related factors have been found to determine outcome to doxorubicin, including WHO performance, gender and histologic subtype [11,12]. As a result, a weak to modest association between hematologic toxicity and outcome could therefore be obscured. In this study, sub-analyses to establish whether there was a relationship between doxorubicin-toxicity and outcome in specific histo-pathological subgroups were not additionally performed since it is unlikely that tumor characteristics such as histological subtype or tumor grading impact the toxicity to doxorubicin. In addition, we would end up with relatively small groups of patients hindering to establish robust conclusions.

Another reason underlying the lack of association between toxicity and outcome might be that doxorubicin levels reached in tumors, which are needed to exert anti-tumor effects, could differ from the levels reached in bone marrow causing myelosuppression. Many tumors are characterised by leaky tumor vasculature, which results in a high intra-tumoral interstitial pressure. This can hamper the penetration of drugs from the peripheral circulation into tumors, although this can differ per cytotoxic drug. For example, in studies where simultaneously blood levels as well as intra-tumoural levels were measured, 5FU levels in tumors appeared to be substantially lower in tumors compared to blood whereas for carboplatin, no difference could be revealed [13,14]. To the best of our knowledge, such data have not yet been generated yet for doxorubicin. Further investigations to determine the relationship between both blood drug levels and toxicity, and between blood drug levels, intra-tumoural drug concentrations, and anti-tumor effects are therefore necessary.

In addition to examining the relationship between toxicity and outcome, we explored whether or not the baseline characteristics (age, gender, BMI and performance score) were associated with the occurrence of grade 3/4 hematological toxicity. It revealed that female gender, higher age and a low BMI were associated with an increased risk of grade 3/4 hematological toxicity, in particular grade 3/4 neutropenia. Previous research on the impact of these baseline characteristics on toxicity from doxorubicin-based chemotherapy is rather scarce. In a recent meta-analysis on the effect of obesity on outcome of adjuvant doxorubicin-based chemotherapy in early breast cancer, it was found that in general obese patients experienced less toxicity [15,16]. That the association between body composition and doxorubicin's pharmacokinetics is rather complex, is underlined by a study showing that the systemic clearance of doxorubicin is reduced in obese women, but not in obese men [5]. The effect sizes seen in our study, particularly for the association between age and neutropenia grade 3/4, are substantial taking into account the often-delicate balance between anticipated

benefits versus untoward events when treating elderly advanced STS patients and justify further research in this area.

There are several limitations of this analysis. The retrospective nature of this study renders it prone to all the different sources of bias inherent to retrospective analyses. In addition, we focused on hematological toxicities only and not on other toxicities. Another limitation is the fact that patients included into clinical trials are often not reflective for the populations seen in daily clinical practice. As a consequence, the findings in our study may be generally applicable. Strong points of this study are the large number of patients and the homogeneity in terms of treatment given and patient's and tumor characteristics since the eligibility criteria of the clinical studies used in this analysis changed little over the years.

In conclusion, in this large series of advanced STS patients receiving doxorubicin monotherapy, treatment appeared to be very well tolerated with almost no patients having to stop treatment because of toxicity. This again confirms the tolerability of doxorubicin monotherapy in patients with advanced STS, which is crucial, given the palliative setting of this treatment. Furthermore, a relation between severity of hematologic toxicity and outcome could not be demonstrated, which is reassuring for patients who are concerned they are being undertreated when toxicity fails to occur.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Lorigan P, Verweij J, Papai Z, European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol. 2007;25:3144–3150.

[2] Judson I, Verweij J, Gelderblom H, European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014;15:415–423.

[3] Blay JY, Sleijfer S, Schöffski P, et al. International expert opinion on patient-tailored management of soft tissue sarcomas. Eur J Cancer. 2014;50:679–689.

[4] Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet. 2016;388:488–497.

[5] Sparreboom A, Wolff AC, Mathijssen RH, et al. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. J Clin Oncol. 2007;25:4707–4713.

[6]   Piscitelli SC, Rodvold KA, Rushing DA, et al. Pharmacokinetics and pharmacodynamics of doxorubicin in patients with small cell lung cancer. Clin Pharmacol Ther. 1993;53:555–561.

[7]   O'Bryan RM, Baker LH, Gottlieb JE, et al. Dose-response evaluation of adriamycin in human neoplasia. Cancer. 1977;39:1940–1948.

[8]   Jacquet JM, Bressolle F, Galtier M, et al. Doxorubicin and doxorubicinol: intra- and inter-individual variations of pharmacokinetic parameters. Cancer Chemother Pharmacol. 1990;27:219–225.

[9]   Cummings J, Milstead R, Cunningham D, et al. Marked interpatient variation in adriamycin biotransformation to 7-deoxyaglycones: evidence from metabolites identified in serum. Eur J Cancer Clin Oncol. 1986;22:991–1001.

[10]   Andersen A, Holte H, Slørdal L. Pharmacokinetics and metabolism of doxorubicin after short-term infusions in lymphoma patients. Cancer Chemother Pharmacol. 1999;44:422–426.

[11]   Van Glabbeke M, van Oosterom AT, Oosterhuis JW, et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2185 patients treated with anthracycline-containing first-line regimens–a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol. 1999;17:150–157.

[12]   Sleijfer S, Ouali M, van Glabbeke M, et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). Eur J Cancer. 2010;46:72–83.

[13]   Konings IR, Sleijfer S, Mathijssen RH, et al. Increasing tumoral 5-fluorouracil concentrations during a 5-day continuous infusion: a microdialysis study. Cancer Chemother Pharmacol. 2011;67:1055–1062.

[14]   Konings IR, Engels FK, Sleijfer S, et al. Application of prolonged microdialysis sampling in carboplatin-treated cancer patients. Cancer Chemother Pharmacol. 2009;64:509–516.

[15]   Carroll J, Protani M, Walpole E, et al. Effect of obesity on toxicity in women treated with adjuvant chemotherapy for early-stage breast cancer: a systematic review. Breast Cancer Res Treat. 2012;136:323–330.

[16]   Danesi R, Fogli S, Gennari A, et al. Pharmacokinetic-pharmacodynamic relationships of the anthracycline anticancer drugs. Clin Pharmacokinet. 2002;41:431–444.