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Original Paper

Randomised Study of High-dose Epirubicin Versus High-dose Epirubicin–Cisplatin Chemotherapy for Advanced Soft Tissue Sarcoma

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A randomised study was started in chemotherapy-naive patients with advanced soft tissue sarcomas who received either epirubicin 60 mg/m^2/24 h (total dose for cycle 180 mg/m^2) days 1, 2 and 3, (group A) or epirubicin 60 mg/m^2/24 h days 1, 2 and 3 and cisplatin 30 mg/m^2/24 h days 2, 3, 4 and 5 (group B). The maximal number of cycles foreseen in both groups was eight. Cardiotoxicity of the regimens was monitored by serial LVEF determinations. 106 patients entered this study, 50 (45 evaluable for activity) randomised to group A, and 56 (54 evaluable for activity) to group B. The groups were well balanced for age, sex, performance status and histological type. In group A, there was 1 complete response (CR) and 12 partial responses (PR), the overall response being 13/45 (29%); in group B, there were 7 CRs and 22 PRs, the overall response being 29/54 (54%). The difference between the overall response was statistically significant ($\chi^2 = 6.19$, $P < 0.025$). The epirubicin–cisplatin regimen was found to be more toxic for platelets and more emetogenic, but cardiotoxicity, either acute or cumulative, was not found to be a major problem in both groups. However, a complete responder receiving a cumulative epirubicin dose of 1440 mg/m^2 died from congestive heart failure after a disease-free interval of 27 months. The high response in group B could be the result of the synergism between high-dose epirubicin and cisplatin in patients with advanced soft tissue sarcomas. **© 1997 Elsevier Science Ltd. All rights reserved.**

Key words: epirubicin, cisplatin, chemotherapy, soft tissue sarcoma

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INTRODUCTION

ONLY TWO drugs, doxorubicin and ifosfamide, have consistently demonstrated more than 20% activity in soft tissue sarcoma (STS) [1]. Epirubicin, a doxorubicin analogue, in equimolar dosage has induced the same response rate as doxorubicin in advanced STS [2]. Activities being equal, the use of epirubicin seemed to allow prospective escalation of dosage, a lower incidence of high-grade leucopenia and a higher dose-intensity of the drug administered [3], as this analogue proved to be less haematologically toxic and less cardiotoxic in equimolar doses.

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The dose–effect relationship and the potential superiority of epirubicin in combination chemotherapy regimens in relation to single drug epirubicin has been investigated in advanced STS.

Escalation of epirubicin dosage as monotherapy from 75 mg/m^2, as in the study by Mouridsen and associates [2], to 100–130 mg/m^2, as in the study by Chevalier and associates [4], appeared to bring no benefit, the response rates averaging 20%. Further escalation to 160 mg/m^2 in the study by Carpano and colleagues induced a response rate of 37% [5]; it has been claimed that increasing epirubicin dose to 120 mg/m^2 did not increase the response rate, while further escalation to 140–170 mg/m^2 could improve the percentage of responses [6].

In combination regimens, epirubicin has been studied in advanced STS mostly in combination with ifosfamide. The

study of Frustaci and associates pointed to an increase in response rate obtained by fixed doses of ifosfamide and escalating doses of epirubicin despite relevant haematological toxicity [7]. The study of epirubicin–ifosfamide combination conducted by Chevalier and associates, according to the authors, could not demonstrate whether the combination of epirubicin and ifosfamide was superior to epirubicin alone [8]; within the same setting, the study of Toma and colleagues [9] concluded that the activity of the combination as compared with that of either drugs alone at optimal doses needed to be evaluated in prospective randomised trials. Thus, it appeared that eventual superiority of epirubicin containing combination regimens as compared to single-agent epirubicin was still a topic for prospective studies.

Our previous study of combination chemotherapy in advanced STS, consisting of epirubicin 180 mg/m^2 and cisplatin 120 mg/m^2, yielded an impressive response rate of 57% with a complete response rate of 20% [10, 11]. A subsequent study with single-drug epirubicin 180 mg/m^2 resulted in a response rate of 20% [12], thus not consistent with data claiming dose–response relationship for epirubicin at dosages 140–170 mg/m^2 [6]. These data suggest synergism between high-dose epirubicin and cisplatin in advanced STS, so to test this hypothesis the present prospective randomised study was initiated to compare treatment results (activity and toxicity) of single-drug epirubicin 180 mg/m^2 per cycle with combination chemotherapy comprising epirubicin 180 mg/m^2 and cisplatin 120 mg/m^2 per cycle in patients with advanced STS.

PATIENTS AND METHODS

This prospective randomised study was started in 1992 and closed in 1994. A total of 106 patients entered the study. All patients had advanced STS (surgically unresectable *in toto*, relapsing or metastatic) and were chemotherapy naive. For inclusion in this study, according to the institution's ethical committee's decision, witnessed informed oral consent of the patients was asked for.

Other inclusion criteria were: histologically confirmed STS; presence of at least one bidimensionally measurable lesion (soft tissue masses or skin deposits; pulmonary or pleural metastases measurable on chest X-rays; retroperitoneal, mediastinal, mesenteric or other soft tissue lesions documented on serial CT scans; hepatic metastases measurable on echography or CT scan; metastases in peripheral or other lymph nodes) in addition to subsequently evaluable lesions, performance status ECOG 0–3 and 4 if it was the consequence of a particular sarcoma localisation; age 18 years or over, no cardiac, renal or hepatic contraindications for anthracyclines, and cisplatin administration at entry; and normal serum bilirubin level.

Histological diagnosis and histological type of STS were confirmed by two independent experienced pathologists, one referent, always from the institution, the other an external reviewer. Histological slides were routinely stained with the haematoxylin/eosin technique and for vimentin, desmin, S-100 protein, cytokeratin; less routinely for factor VIII; when necessary for differential diagnosis of disorders not fitting into an STS category in the strict sense, the presence of neural and pan-B/pan-T markers was also assessed. Other markers for subclassification and differential diagnosis of STS were used as needed. A third opinion was asked for if necessary. Two cases were diagnosed as 'sarcoma NOS' for technical reasons due to the quality of material sent for histology (there was an agreement both that it was an STS and that the quality of material did not allow further steps for subclassification), and 2 were diagnosed as "unclassified" as there was an agreement between pathologists for an STS, but not for the exact histological type.

Patients were randomised into two groups, groups A (to receive epirubicin alone) and group B (to be treated with the epirubicin–cisplatin combination chemotherapy). Characteristics of the patients following randomisation are shown in Table 1. Both groups were well balanced according to age, sex and performance status. The histology and localisation of STS in patients evaluable for activity are presented in Table 2.

Treatment schedules were as follows:

Group A: epirubicin 60 mg/m^2/24 h days 1, 2 and 3 (total dose per cycle 180 mg/m^2), as bolus injection through the tube of a running infusion of 500 ml 0.9% NaCl.

Group B: epirubicin 60 mg/m^2/24 h days 1, 2 and 3 (total dose per cycle 180 mg/m^2) applied as in group A, and cisplatin 30 mg/m^2/24 h days 2, 3, 4 and 5 (total dose per cycle 120 mg/m^2) with adequate hydration and mannitol-induced osmotic diuresis.

Cross-over from group A to group B was to be decided individually, for patients who had stable disease after 4 cycles (disease with an increase in individual lesions of less than 25%, suggesting imminent fulfilment of criteria for a progressive disease) whose performance status remained 0 or 1, and who displayed no excessive toxicity with previous chemotherapy cycles.

The intercycle interval was in both groups 4 weeks, with the possibility of postponement for an additional week in case of incomplete haematological recovery. Antiemetics and other supportive treatment were applied as needed.

All examinations relevant to disease extension and size of individual lesions were performed prior to treatment and after each cycle; for localisations necessitating a CT scan, it was performed prior to treatment and following each second cycle. Serum biochemistry was performed on days 1, 6 and

Table 1. Patients' characteristics

Characteristics	Number of patients	
	Group A (single-drug epirubicin)	Group B (epirubicin–cisplatin combination)
Number entered	50	56
Number evaluable		
For activity	45	54
For toxicity	50	56
Age (years)		
Median	55	51
Range	19–72	18–68
Sex		
Males	35	30
Females	15	26
Performance status		
0	12	12
1	23	19
2	13	19
3	2	4
4	0	2

Table 2. Characteristics of advanced soft tissue sarcoma in patients evaluable for activity (n = 99)

	Number of patients		
	Group A (single-drug epirubicin)	Group B (epirubicin–cisplatin combination)	Total
Histology			
Fibrosarcoma	6	5	11
Malignant fibrous histiocytoma	7	9	16
Liposarcoma	5	6	11
Synoviosarcoma	3	6	9
Neurofibrosarcoma	4	3	7
Rhabdomyosarcoma	5	7	12
Leiomyosarcoma	5	7	12
Mesenchymoma	2	0	2
Angiosarcoma	3	4	7
Undifferentiated 'globocellular' STS	1	1	2
Epitheloid sarcoma	1	2	3
Alveolar soft part sarcoma	0	1	1
Clear cell sarcoma	1	1	2
STS, unclassified*	1	1	2
Sarcoma NOS*	1	1	2
Disease localisations			
Soft tissue (primary tumour or local relapse)	8	15	23
Lungs	18	20	38
Liver	4	7	11
Soft tissue (metastases)	19	21	40
Bones	5	5	10
Pleural effusion	1	2	3
Ascites	2	2	4
Mediastinum	3	3	6
Retroperitoneum	19	11	30
Mesenterium	2	3	5
Peripheral lymph nodes	12	19	31

*For explanation, see text.

12 of each cycle and further if needed, while peripheral blood cell count was performed every two days until recovery from the nadir values for granulocytes and/or platelets.

Cardiological monitoring included ECG tracing before and after each epirubicin application and determination of left ventricular ejection fraction (LVEF) by echocardiography before treatment and before each cycle. Although multiple gated image acquisition (MUGA) scan remains the standard procedure for determination of LVEF, echocardiography was chosen as a simpler alternative procedure. This was due to the fact that an extended number of LVEF determinations was necessary for this study, echocardiography being a cheaper procedure which could be, in case of doubt, repeated on the same day or on successive days (or the results could be checked with a MUGA scan).

Exclusion from the study occurred if there was a reduction in LVEF below the lower limit of normal values (50%) or more than 20% in relation to the pretreatment level, even if LVEF remained within normal limits. Patients were also excluded from further treatment if time for complete haematological restoration (for granulocytes and platelets) exceeded 5 weeks. Exclusion criteria for further treatment were also progressive disease (PD) after 2 cycles (even after the first cycle if there was an increase of the pre-existing lesions of more than 50% or appearance of new disease localisations) and stable disease (SD) after 4 cycles (if there was no decision for a cross-over from group A to group B). Patients achieving a complete response (CR) received two more cycles and those with a partial response (PR) received at most 8 cycles, thus fulfilling the maximal epirubicin dose considered safe (1440 mg/m^2) according to results from our previous study [10]. Subsequent exclusion from the study followed if progression of the disease occurred after an initial stabilisation or response, if the patient refused further treatment, or if the investigator considered that further treatment was without additional benefit for the patient.

Standard criteria were used for toxicity grading and response evaluation [13]. A CR was defined as total disappearance of all known disease lasting for at least one month; PR, 50% or more decrease in the tumour size of a measurable lesion, with no appearance of new localisations or progression of any pre-existing lesions; stable disease was defined as a decrease of less than 50% of measurable tumour lesions with no increase in size of more than 25% of any other lesion and no appearance of new localisations; if there was increase in size of more than 25% of any measurable/evaluable lesion, or appearance of a previously absent tumour localisation progressive disease was diagnosed.

Statistical analysis included the χ^2 test for differences in response rates; the Mann–Whitney test for detecting differences in toxicity grades; the Student's *t*-test for difference between mean values; the Wilcoxon test of paired samples for analysis of cardiotoxicity as assessed by serial LVEF determinations; the Kaplan–Meier's curves for estimation of probabilities of remission duration, freedom from progression and overall survival and the log rank test for detecting differences in probabilities between groups A and B.

RESULTS

The overall treatment results are presented in Table 3. 460 chemotherapy cycles were administered to patients (both groups, including the cross-over patients). The complete response rate was 1/45 in group A and 7/54 in group B. The overall response rate (CR + PR) was significantly higher in group B (54%, 95% confidence interval (CI) 41–67%) than in group A (29%, 95% CI 16–42%; $P < 0.025$, $\chi^2 = 6.19$). If cases of rhabdomyosarcoma were excluded

Table 3. Treatment results

Response	Group A (single-drug epirubicin)	Group B (epirubicin–cisplatin combination)
CR (complete response)	1/45 (2%)	7/54 (13%)
PR (partial response)	12/45 (27%)	22/54 (41%)
SD (stable disease)	10/45 (22%)	12/54 (22%)
PD (progressive disease)	22/45 (49%)	13/54 (24%)
RR (response rate)	13/45 (29%)	29/54 (54%)
95% confidence interval	16–42%	41–67%

from the evaluation (as is sometimes done due to a supposed different chemosensitivity pattern of rhabdomyosarcoma in relation to other histological types of STS), the response rates remained approximately the same: 10/40 (25%) in group A and 26/47 (55%) in group B ($P < 0.025$).

5 patients with stable disease following 4 cycles of single-drug epirubicin 180 mg/m^2 underwent cross-over to group B (epirubicin–cisplatin combination). Two had progressive disease after 1 and 2 cycles, respectively, and three achieved a complete response after receiving 4 cycles of the combination.

Regarding the treatment response in relation to histological diagnosis and disease localisations, there is a general, although not substantiated, impression that patients with leiomyosarcoma and neurofibrosarcoma are poor responders to high-dose epirubicin-containing chemotherapy; nearly all histological types appeared to benefit from the epirubicin–cisplatin combination in relation to epirubicin alone, but the number of specific histology types was too small for statistical considerations.

In group A, the only complete response lasted 6 months. In group B, there were 7 complete responses, and an additional 3 complete responses were recruited from patients who underwent cross-over from group A; 3 patients relapsed, respectively, after 11, 11 and 14 months and died after 13, 15 and 18 months from start of treatment; one patient died from delayed toxicity when still disease-free after 27 months, and 6 patients are alive and disease-free with the median disease-free interval of 38+ months (range 25+ to 44+). Kaplan–Meier curves for response duration (i.e. for patients achieving both a complete and a partial response) and freedom from progression are presented on Figure 1. With the log rank test, the difference for both parameters was statistically significant. For patients in group B, on both curves, a plateau effect was observed from the 27th month onwards. The plateau consists exclusively of patients achieving a complete response. At 44 months, estimated probability for duration of response was 19% and for progression-free survival, 13%. As the death registered in the 27th month was not due to disease relapse, but to late toxicity in a patient still in complete response, the strictly disease-related figures would be 26% (the plateau starting at month 17), and 16%, respectively. The overall survival was also significantly longer in group B (Figure 2). The estimated 44 months probability of survival was 11% in group B, but could be somewhat lower, due to the fact that the plateau, starting from the 27th month, consists of 5 complete responders and 1 patient with a partial response (a synoviosarcoma case).

Toxicity data are reported in Table 4. Haematological toxicity grades III/IV for granulocytes, and to a lesser extent platelets, were the most common problem, and nearly all patients, experienced these toxicity grades in at least one cycle. In both groups, the nadir occurred on days 10–12, but complete recovery by day 28 (when the next cycle was to be administered) was the rule. However, no significant haemorrhagic syndrome occurred, and 4 patients (3 from group A and 1 from group B) fulfilled criteria for a febrile neutropenia, designed as infection-toxicity grade III and IV. Clinically significant (grade 2–4) stomatitis was recorded in 14 patients, but was never the reason either to postpone or stop further chemotherapy. With the Mann–Whitney test,

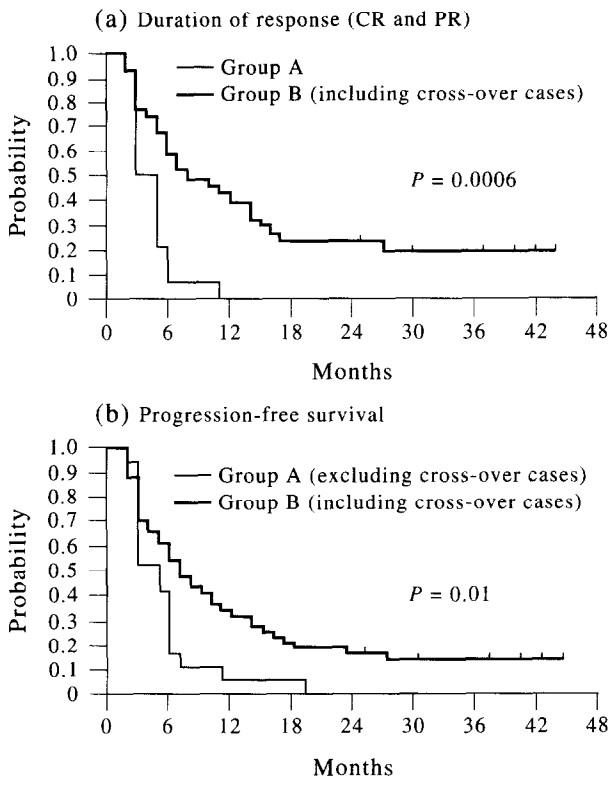

Figure 1. (a) Duration of response and (b) progression-free survival in groups A and B; each vertical line indicates the position of patients with uninterrupted remission ($n = 6$).

combination treatment high-dose epirubicin–cisplatin appeared significantly more toxic for platelets and more emetogenic. From the practical point of view, however, addition of cisplatin to high-dose epirubicin was not associated with significant, additional, clinically important toxicity.

One patient from group B was removed from the study after a cumulative epirubicin dose of 720 mg/m^2 because of recurrent supraventricular tachycardia occurring immediately after epirubicin application. For LVEF, in both groups no statistically significant difference with the Wilcoxon text of paired samples at increasing cumulative epirubicin doses

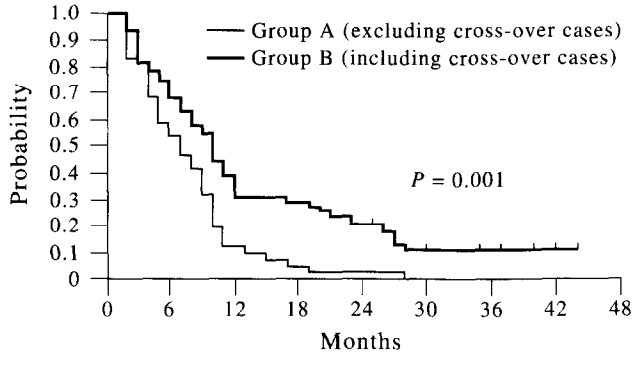

Figure 2. Overall survival in groups A and B; each vertical line indicates the position of patients still alive $n = 7$). Kaplan–Meier probability curves.

Table 4. Toxicity parameters (maximal toxicity grades registered for individual patients)

	Toxicity grade									
	Group A (single-drug epirubicin)					Group B (epirubicin–cisplatin combination)				
Parameter	0	1	2	3	4	0	1	2	3	4
Haemoglobin	10	9	9	14	8	12	12	11	14	7
Leucocytes	0	1	4	16	29	0	0	0	21	35
Granulocytes	1	1	1	10	37	0	0	0	12	44
Platelets	11	5	11	12	11	4	5	4	16	27
Haemorrhage	49	0	1	0	0	51	3	2	0	0
Bilirubin	47	2	1	0	0	56	0	0	0	0
SGOT/SGPT	43	4	3	0	0	56	0	0	0	0
Alk. phosphatase	45	5	0	0	0	55	1	0	0	0
Oral cavity (stomatitis)	36	5	6	2	1	49	2	1	3	1
Nausea/vomiting	32	9	7	2	0	14	8	33	1	0
Diarrhoea	45	3	2	0	0	49	1	2	4	0
Proteinuria	49	1	0	0	0	56	0	0	0	0
BUN	47	1	2	0	0	54	1	1	0	0
Creatinine	47	1	1	1	0	54	1	1	0	0
Hair (alopecia)	5	3	7	35	0	2	7	9	38	0
Infection	36	8	3	1	2	45	2	8	1	0
Heart-rhythm	45	4	1	0	0	50	3	2	1	0
Heart-function*	50	0	0	0	0	56	0	0	0	0

Cross-over cycles are not included in the table for toxicity grading.

* Estimated during treatment; one patient in complete remission died from delayed cardiotoxicity 27 months following start of treatment. Toxicity was significantly more marked (as assessed with the Mann–Whitney test) in group B as compared to group A for platelets ($P < 0.01$), SGOT/SGPT ($P < 0.01$), and nausea/vomiting ($P < 0.01$); there was no difference in other toxicities between the two groups.

was registered in relation to the pretreatment value. With the Student's *t*-test, no difference in LVEFs between groups A and B were registered within the same level of the cumulative epirubicin dose. Figure 3 represents the mean LVEF values up to cumulative epirubicin dosages with the number of samples in each group suitable for the assessment with Wilcoxon test of paired samples. During treatment, no subnormal LVEF values were detected, and no reduction of over 20% from LVEF initial pretreatment value was ever recorded. However, one patient, a complete responder who had normal LVEF values during treatment and who received epirubicin cumulative dose of 1440 mg/m^2 died after a disease-free interval of 27 months from treatment resistant congestive heart failure.

DISCUSSION

To achieve antitumour activity in STS relatively high doses of doxorubicin are required and prospectives of clinical efficacy are hampered by myelosuppression and/or cardiotoxicity [14]. As epirubicin has been shown to be as active as doxorubicin in advanced STS in equimolar dosage, with haematological toxicity becoming a problem only at a substantially higher dose level than with doxorubicin [2], it has been tempting to use the doxorubicin analogue in escalated dosages both as monotherapy and in combination regimens for advanced STS with the prospect of better efficacy.

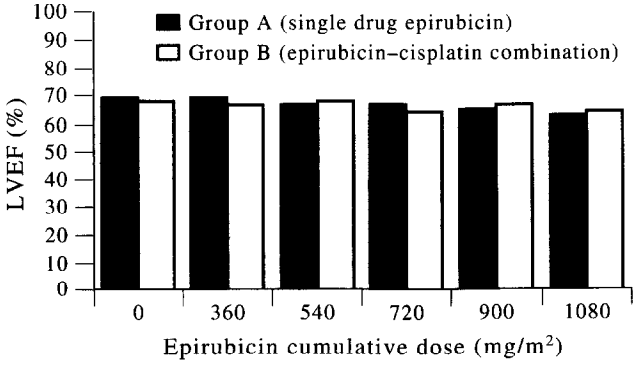

Figure 3. Mean values of left ventricular ejection fractions in relation to cumulative epirubicin dose.

Data concerning combination chemotherapy of advanced STS with epirubicin and cisplatin are scarce. Trial data of the combination of the two drugs appeared as early as 1986 [15] when Sauer and colleagues reported a response rate of 42% in 34 patients treated with epirubicin 90 mg/m^2 per cycle and cisplatin 90 mg/m^2 per cycle. Cisplatin has been used in a multidrug polychemotherapy setting for STS since the late eighties [16], but its activity in advanced STS has been seriously questioned. Although intra-arterial cisplatin has been claimed to induce total necrosis in 50% of malignant fibrous histiocytomas of the bone [17], other authors had reported that cisplatin has minimal activity as a single agent in advanced STS. Minimal activity has been reported both in previously untreated patients [18] and in patients failing to respond to primary chemotherapy [19]. Nevertheless, there have also been reports of activity up to a 24% response rate even in doxorubicin pretreated patients [20].

Our first study of a high-dose epirubicin–cisplatin combination chemotherapy regimen for advanced STS demonstrated a high efficacy of the regimen [10, 11]. The results of the present study also indicate high activity of the high-dose epirubicin (180 mg/m^2 per cycle)–cisplatin combination in advanced STS. The haematological toxicity was clinically significant, although acceptable. The response rate in the present study was 54% with 7/54 complete responses (with an addition of 3/5 cross-over cases achieving CR following cross-over to group B CR rate 10/59, i.e. 17%). These results are practically the same as in our previous

study in which the response rate was 57%, with 20% complete responses [10, 11]. The present study demonstrated a significantly lower response rate to single-drug epirubicin at the dosage of 180 mg/m^2 (as compared for the epirubicin 180 mg/m^2–cisplatin combination), which proved to be 29% in the present study versus 20% in our former study [12]. The response duration, progression-free survival and overall survival were also significantly longer in the combination treatment group as compared to the single-drug epirubicin group. The prospect of a cure could be anticipated for several complete responders from the combination treatment group as a plateau effect was observed on Kaplan–Meier curves for all parameters. Late toxicities should, nevertheless, be a matter of concern.

The haematological toxicity occurred in both groups, although it was less pronounced for platelets in the single-drug epirubicin in comparison to the epirubicin–cisplatin regimen. The toxicity of the single-drug epirubicin 180 mg/m^2 regimen, according to literature data, appeared to be higher than in regimens with epirubicin 75–130 mg/m^2 [2, 4], although the response rate seemed to be only slightly affected by dose escalation of the drug in the single-drug setting.

The present results, apart from confirming the high activity of the high-dose epirubicin–cisplatin combination treatment for advanced STS, also indicate that addition of cisplatin did not add clinically significant toxicity. Cardiotoxicity (although infrequently encountered) of cumulative epirubicin doses appeared as a problem when the dosage reached 1440 mg/m^2. This point has been emphasised before, as congestive heart failures were occasionally reported within this dosage range [21]. Serial LVEF determinations displaying no left ventricular function deterioration during treatment seem not to be a guarantee for the absence of late-appearing cumulative cardiotoxicity.

The dose–effect relationship for epirubicin in escalated doses up to 180 mg/m^2 appears to be only a slight one according to results of the present study. It seems that a synergistic activity of cisplatin and high-dose epirubicin in advanced STS should be seriously considered as indicated by the 3/5 cases displaying no benefit from single-drug epirubicin treatment, who achieved a CR with the epirubicin–cisplatin combination. Whether the same synergistic action might be present with lower doses of epirubicin, such as 150–160 mg/m^2, could be a point of interest for further studies, as within these dosage ranges haematological toxicity might be a less pronounced problem.

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