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Adriamycin Versus Epirubicin in Advanced Soft Tissue Sarcomas. A Randomized Phase II/Phase III Study of the EORTC Soft Tissue and Bone Sarcoma Group

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Abstract—*The objective of this randomized phase II/phase III study was to investigate the efficacy and toxicity of equimolar doses of adriamycin (ADM) and 4-epiadriamycin (EPI) in patients with locally advanced and/or metastatic soft tissue sarcoma.*

Doses of ADM and EPI were 75 mg/m^2 *given as an i.v. bolus injection every* 3 *weeks.*

Two hundred and ten patients were entered into the study by 18 *institutions. Twenty-eight patients were ineligible and* 15 *were non-evaluable, leaving* 167 *evaluable patients. The two treatment groups were well balanced for sex, performance status, age, prior radiotherapy, extent and site of disease.*

Rates of response were similar, 25% *in the ADM group compared to* 18% *in the EPI group* (P = 0.33), *and there were no significant differences between the ADM and EPI groups with respect to median duration of response* (45 *weeks vs.* 77 *weeks,* P = 0.08), *time to progression* (15 *weeks vs.* 12 *weeks,* P = 0.945), *and median survival* (41 *weeks vs.* 48 *weeks,* P = 0.363). *Myelotoxicity as shown by leucopenia was significantly more pronounced in the ADM treated patients* (P = 0.002). *Other toxicities such as alopecia and nausea/vomiting were also more severe in the ADM group* (P = 0.02 *and* 0.06, *respectively*).

In conclusion, the use of equimolar doses of ADM and EPI in advanced soft tissue sarcoma produced response rates which did not differ significantly and were only slightly in favour of ADM. However, this was achieved at the expense of higher toxicity.

INTRODUCTION

In the treatment of advanced soft tissue sarcoma, adriamycin (ADM) remains the most active single agent. The response rate in a cumulative series of more than a thousand patients, not previously treated with chemotherapy, is 23% [1]. More recently, activity in previously treated patients has been suggested in an ongoing EORTC trial (unpublished data). Several drug combinations encorporating ADM have been evaluated. Most frequently the other drugs included have been DTIC, cyclophosphamide and vincristine. Response rates varied from 11% to 51% [2]. The regimen tested most extensively has been CYVADIC (cyclophosphamide, vincristine, adriamycin and DTIC). The initial response rate reported by SWOG was 59% but was later revised to 49% [3, 4]. More recently the EORTC reported a randomized trial [5] comparing CYVADIC with the schedule of ADIC and VCR/

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CTX alternating at 4-week intervals. The overall response rate was 38% for CYVADIC, compared with 14% for the alternating regimen. Taking into account the toxicity and inconvenience of combination chemotherapy, which usually exceeds that normally encountered with single-agent therapy, and based on the available data of response rates from non-randomized trials, the superiority of combination chemotherapy over single agent therapy with ADM has yet to be established.

At the end of 1979, the EORTC Soft Tissue and Bone Sarcoma Group adopted a policy of conducting randomized phase II trials in previously untreated patients with ADM and new anthracyclines. The aim was to identify analogues with less toxicity and equal or even better therapeutic activity. In the initial study carminomycin was demonstrated to be significantly less active than adriamcyin [6].

Other anthracycline analogues have recently been introduced into clinical trials in solid tumours, one of which is 4-epiadriamycin (epirubicin, EPI). EPI has been found to interfere with nucleic acid synthesis as does ADM [7]. Antitumour activity equal to that of ADM was demonstrated in several experimental tumours [8] and in acute and subchronic toxicity studies in normal and tumour-bearing mice EPI was less toxic than ADM, resulting in an increased therapeutic index [9].

Bonfante *et al.* [10] have reported preliminary results from a phase I–II study with EPI. After single doses of 10, 20 and 30 mg/m^2 no side effects were detected. After EPI doses of 50, 60, 75 and 90 mg/m^2 it appeared that the pattern of acute toxicity was similar to that observed after comparable doses of ADM, although incidences of vomiting, stomatitis, alopecia and myelosuppression were lower. Studies to assess cardiac toxicity showed that, like ADM, EPI also produced cumulative asymptomatic myocardial damage although the mean PEP/LVET values after the first dose as well as after cumulative doses were slightly lower than those observed after the same doses of ADM. Although a significant difference was not observed between EPI and ADM the available data would suggest a higher threshold limit for EPI cardiac toxicity. Antitumour activity was documented in 16 of 50 evaluable patients (32%) after doses of 60, 75 and 90 mg/m^2. Among responsive patients eight were previously untreated with chemotherapy. The responses occurred in patients with renal carcinoma (2/6), breast carcinoma (1/5), rectal carcinoma (1/3), Kaposi sarcoma (1/1), thyroid carcinoma (1/2), non-Hodgkin lymphoma (3/3) and chronic haematological malignancies (6/6). Based on these results it was decided to investigate in a randomized phase II study equimolar doses of ADM and EPI in advanced soft tissue sarcomas.

MATERIALS AND METHODS

Eligibility criteria

Patients between the ages of 15 and 80 years with histologically proven, locally advanced and/or metastatic soft tissue sarcoma were eligible for this study. Measurable progressive disease was required as well as a Karnofsky score of at least 50. Recurrent tumour in irradiated areas was not permitted as the sole evaluable lesion and pleural effusion or bone metastases were not considered to be evaluable. Other criteria for non-eligibility were prior chemotherapy, history of another malignant tumour (except for adequately treated carcinoma *in situ* of the cervix and/or carcinoma of the skin), congestive heart failure or central nervous system metastases. Prior to entry patients were required to have adequate hepatic excretory function (serum bilirubin $\leq$ 50 μmol/l) and bone marrow reserve (WBC count $\geq 4 \times 10^3$/l, platelet count $\geq 100 \times 10^3$/l). Informed consent was obtained according to the Helsinki declaration II.

Trial design

Patients were stratified by institution and randomly allocated by the EORTC Data Centre to treatment with either ADM or EPI.

Treatments

Both EDM and EPI were given at 75 mg/m^2 as an i.v. bolus injection. Treatments were repeated every 3 weeks.

Dose modification

The dose was reduced by 50% if serum bilirubin level was between 35 and 50 μmol/l and discontinued if the bilirubin level was above 50 μmol/l. If the WBC count was $\geq 3.0 \times 10^3$/l and platelets $\geq 100 \times 10^3$/l 3 weeks after the previous course, treatment was continued at the 100% dose level. If at this time the WBC count was between 2.0 and 2.9×10^3/l or platelets between 75 and 99×10^3/l doses were reduced to 50%. If the WBC count was $\leq 2.0 \times 10^3$/l or platelets $< 50 \times 10^3$/l treatment was postponed for 1 week and then given with adjustment of dose according to the guidelines mentioned above.

Treatment duration

Patients showing remission or stable disease after two courses were continued on treatment until disease progression. On disease progression patient on EPI having received less than six courses were crossed over to ADM. Other patients with disease progression were considered for second line phase II trials.

Treatment was also discontinued in the event of severe subjective or haematological toxicities

requiring treatment delay for more than 3 weeks. Generally treatment was also discontinued if a maximum cumulative dosage of 550 mg/m^2 had been administered. However, it was left to the discretion of the local investigator whether treatment was continued to a higher cumulative dosage.

Pretreatment and follow-up studies

Baseline studies included history and physical examination, Karnofsky score, tumour measurements, complete blood counts, biochemical profile, chest X-ray and ECG. CT scans or ultrasound scans were done when indicated to measure tumour lesions. Echocardiography and/or radionuclide cardiac scans were performed in some centres. Nadir blood counts between 1 and 2 weeks after treatment were optional. All baseline investigations were repeated after two courses of therapy and thereafter every 6–12 weeks and at the time of progression.

Definition of response

Patients were considered evaluable for response if they had received at least two courses of chemotherapy and if tumour measurements had been repeated at 6 weeks. Assessment of response, duration of response and time to treatment failure were defined according to WHO [11]. All cases were reviewed by an extramural reviewer for both patient eligibility and for response to treatment.

Definition of toxicity

Haematological toxicity were graded according to WHO criteria [11]. Non-haematological toxicities were graded as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, 5 = lethal.

Statistical evaluation

An initial accrual of 29 evaluable patients in each arm was required. The study was to be terminated if three or fewer responses were observed in either arm or if no responses were reported in the first 19 patients entered in either arm. This design ensured that if either drug had a response rate of at least 25%, the probability of rejecting that drug from further study was less than 0.05. After the initial entry of 58 patients, additional patients were added since it was decided at that time to make an actual comparison of the therapeutic effectiveness of the drugs in a phase III trial.

Two different chi-square tests were used to compare the therapeutic results. P is the significance level based on a comparison of the percentage of responders (CR or PR) in the two treatment groups using the chi-square test for comparison of two proportions. P_1 is the significance level resulting from comparison of the degree of response, or equivalently the average response, using a chi-square test for linear trend [12]. This last test was also used to compare the degree of toxicities. All P-values correspond to a two-tailed test. Survival curves and time to progression curves were calculated according to the Kaplan–Meier product limit procedure and were compared by using the log-rank test [13].

Pathology review

Review was carried out by two panels consisting of six members each, one for the northern European institutes, chaired by Professor J. van Unnik, Utrecht, The Netherlands, and one for the southern European institutes, chaired by Dr. G. Contesso, Villejuif, Paris, France. If two members of the panel independently made the same diagnosis as the referring pathologists this diagnosis was accepted. If there was disagreement, other members of the panel examined the histological sections and a consensus diagnosis was reached.

RESULTS

Material

Between December 1980 and June 1983 210 patients were entered into the study by 18 institutions. A total of 28 patients were considered ineligible, due to inadequate histology (16 patients), previous chemotherapy (three patients), Karnofsky index < 50 (two patients), non-measurable disease (four patients), CNS-metastases (one patient), radiotherapy to the measurable lesion (one patient), and previous malignant disease (one patient). Among the 182 eligible patients, 15 were not evaluable for reasons listed in Table 1.

The characteristics of the 167 evaluable patients are given in Table 2. The two treatment groups were well balanced with respect to sex, performance status, age, prior radiotherapy and extent and site of disease.

A central pathology review with grading of the histology was carried out in 145 of 163 patients, of which 32% were leiomyosarcomas and 21% malignant fibrous histiocytomas. The rest of the tumours were equally distributed among 11 groups.

Table 1. *Patient material*

	ADM	EPI	Total
Registered	106	104	210
Ineligible	16	12	28
Non-evaluable	7	8	15
treatment refusal	4	4	8
early death	1	1	2
missing data	1	2	3
protocol violation	1	1	2
Evaluable	83	84	167

Table 2. Patient characteristics

	ADM	EPI
Total number	83	84
Males/females	45/38	42/42
Age		
median (range)	56 (16–80)	51 (18–78)
Karnofsky score		
median (range)	90 (60–100)	90 (50–100)
Prior radiotherapy	23 (28%)	29 (35%)
Extent and site of disease		
local only	23 (28%)	22 (26%)
distant only	41 (49%)	43 (51%)
local and distant	19 (23%)	19 (23%)

Table 3. Response to treatment

	ADM		EPI	
	No.	%	No.	%
PD	25	30	35	42
NC	37	45	34	40
PR	15	18	11	13
CR	6	7	4	5
PR + CR	21	25	15	18
Total	83	100	84	100

Chi-square (CR + R): $P = 0.33$; chi-square for trend $P_1 = 0.11$.

Response

The overall response data in 167 evaluable patients are shown in Table 3. The rate of response (CR + PR) was 25% in the group receiving ADM and 18% in the group treated with EPI. This difference is not significant using the chi-square test ($P = 0.33$). The difference is likewise not significant using a test for linear trend ($P_1 = 0.11$).

The duration of response in each treatment group is presented in Fig. 1. The median duration as measured from the beginning of treatment was 45 weeks for ADM and 77 weeks for EPI. Using the log-rank test there is no significant difference ($P = 0.08$) between the two treatment groups.

Looking at the time to progression for all evaluable patients (Fig. 2) there was no significant difference between the two treatment groups ($P = 0.945$). The median time to progression for patients treated with ADM was 15 weeks and 12 weeks for patients treated with EPI.

The median survival for patients treated with ADM was 41 weeks and for patients treated with EPI 48 weeks (Fig. 3). Using the log-rank test there was no significant difference between the two treatment groups ($P = 0.363$). Likewise there was no difference in survival between the two treatment groups if all eligible cases were included.

A total of 23 patients initially treated with EPI were crossed over to ADM because of progressive disease. Two patients responded to second line ADM. Among 21 patients not responding to second-line ADM treatment, one had responded to prior EPI.

Toxicity

Haematological toxicities expressed as nadirs of leucocyte values achieved on days 7 to 14 after the

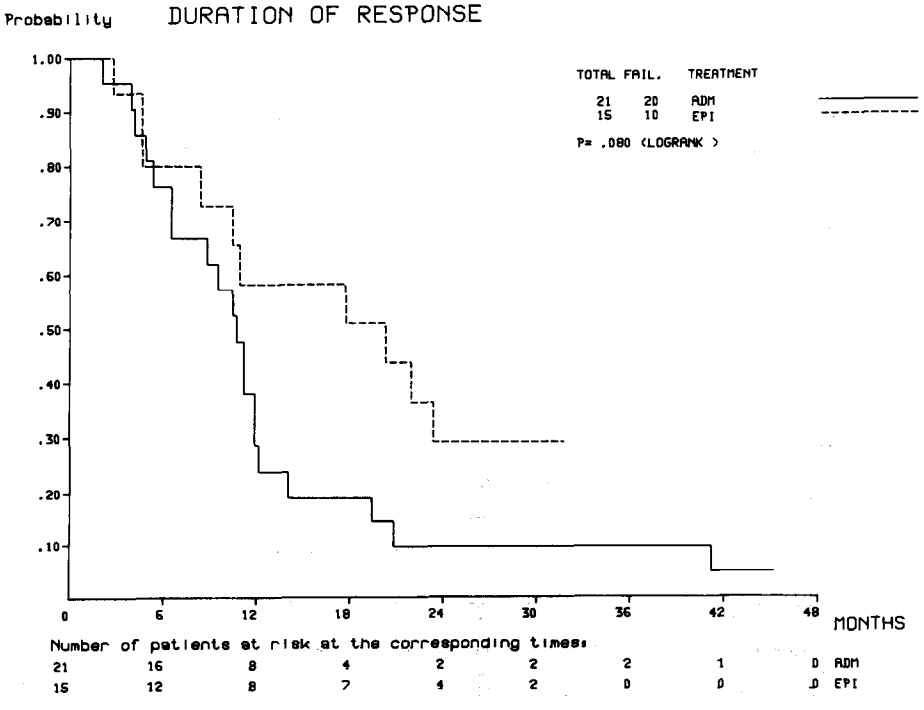

Fig. 1. Duration of response for all evaluable patients. ADM vs. EPI.

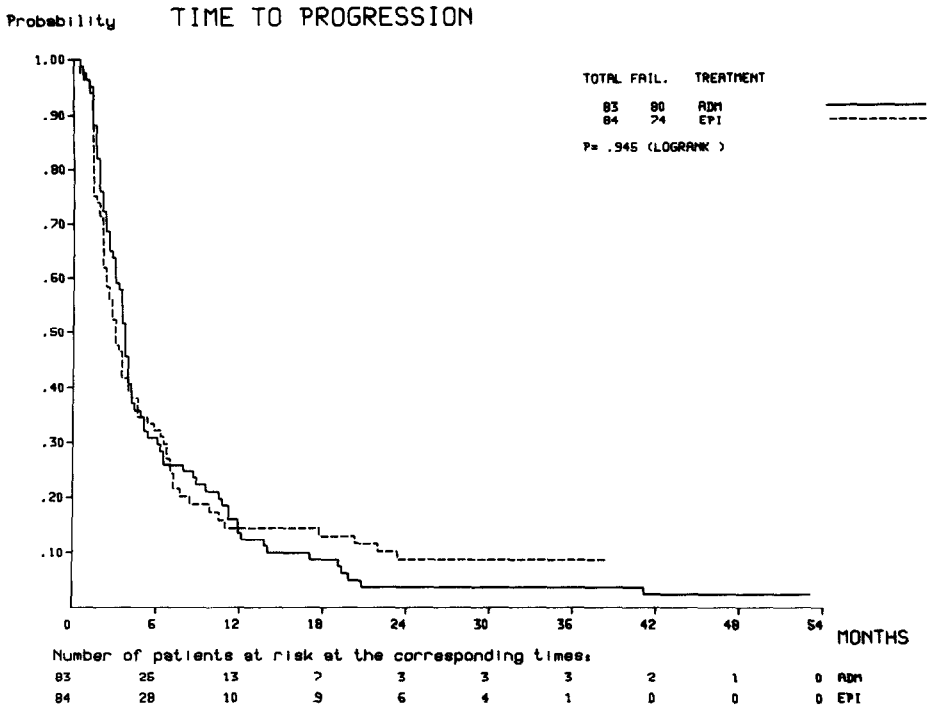

Fig. 2. Time to progression for all evaluable patients. ADM vs.EPI.

first treatment course are presented in Table 4. Among 41 patients treated with ADM and 48 patients treated with EPI, for whom data are available, there is a highly significant difference ($P = 0.002$), with EPI causing less leucopenia.

Non-haematolgical toxicities are summarized in Table 5, which gives the maximum grade of toxicity registered throughout all treatment courses. Among the patients evaluable for toxicity those treated with ADM had received a median of five courses (range 1–13) and those treated with EPI five course (range 1–23). Alopecia was significantly more pronounced in patients treated with ADM than in those treated with EPI.

Data assessing the cardiotoxic potential of these two anthracyclines will be analysed separately,

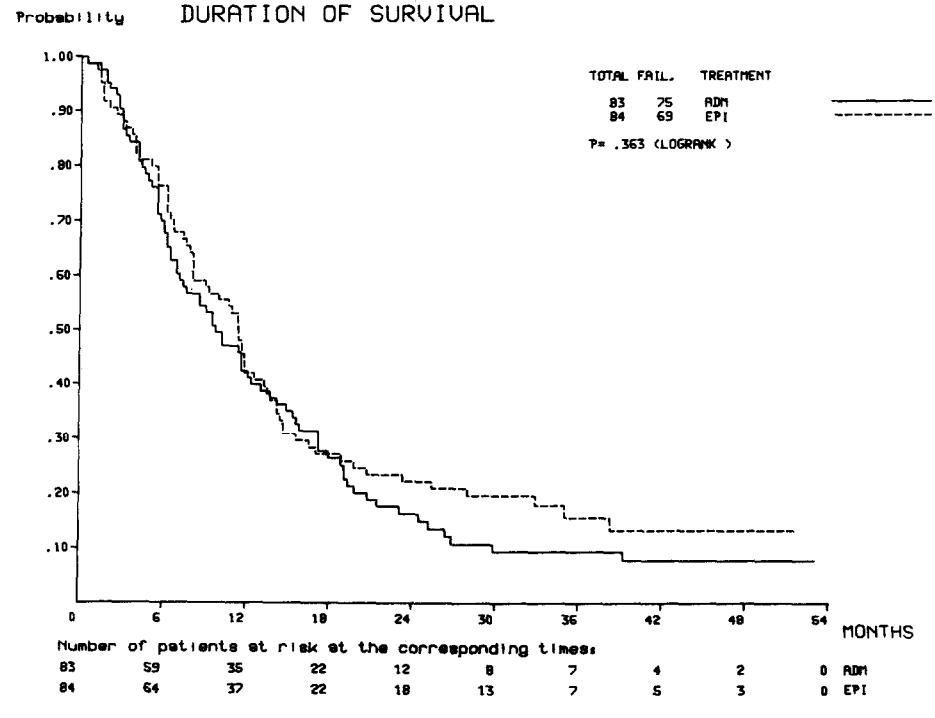

Fig. 3. Survival for all evaluable patients. ADM vs. EPI.

Table 4. Haematologic toxicity: leucocyte nadir after 1st course

WHO grade	ADM n	ADM %	EPI n	EPI %
0	12	29	24	50
1	7	17	12	25
2	10	24	10	21
3	10	24	2	4
4	2	5	0	0
Total	41	100	48	100

Chi-square for trend: $P_1 = 0.002$.

Table 5. Percentage of patients with non-haematologic toxicity over all courses

	ADM	EPI	
Patients evaluable	82	82	
Nausea/vomiting	98 (4)	89 (6)	$P = 0.06$
Diarrhoea	11 (1)	13 (0)	$P = 0.81$
Anorexia	48 (1)	51 (0)	$P = 0.76$
Mucositis	22 (0)	16 (1)	$P = 0.43$
Alopecia	95 (62)	88 (43)	$P = 0.02$

Numbers in brackets indicate percentage with toxicity grade III–IV.

together with data from another EORTC study evaluating the same two drugs in the treatment of advanced breast cancer.

Table 6 summarizes the doses of anthracyclines administered. A median number of five courses were given in each treatment arm, and the dose per course and the cumulative dose administered were similar in the two groups. Nine patients in the ADM group and 15 patients treated with EPI received a cumulative dosage of more than 550 mg/m^2.

Table 6. Doses of adriamycin and epirubicin

	ADM	EPI
Patients evaluable	83	84
No. of courses, median range	5 (1–13)	5 (1–23)
Dose per course (mg/m^2), median (range)	71 (46–84)	74 (52–88)
Cumulative dose (mg/m^2) Median (range)	338 (75–916)	363 (75–1683)
Total dose > 550 mg/m^2 No.	9	15

DISCUSSION

Cytotoxic treatment of advanced soft tissue sarcomas remains palliative. The objective of the present study, therefore, was to increase the response rate and/or to decrease the toxicity with the new anthracycline EPI, compared to ADM.

The use of equimolar doses of ADM and EPI in the treatment of patients with advanced soft tissue sarcoma resulted in a significant difference in toxicity, especially haematological, which was more pronounced in patients treated with ADM. This invalidates to some extent the comparison of therapeutic efficacy between these two drugs. In this study we found a response rate for ADM (25%) comparable to that described in the literature. The response rate for EPI was lower (18%), however not significantly so. No differences in time to progression, duration of response or survival were observed either. Twenty-three of the patients initially treated with EPI were later crossed over to treatment with ADM. Of 22 patients who did not respond to first-line EPI therapy, two patients achieved objective response to subsequent ADM treatment. Although the figures are small this observation indicates that at the dose levels employed there is no complete cross resistance between EPI and ADM.

In conclusion, the use of equimolar doses of ADM and EPI in advanced soft tissue sarcoma produced response rates, which did not differ significantly and were only slightly in favour of ADM. However, this was achieved at the expense of higher toxicity. We recommend that in future comparisons between these two drugs, equally myelosuppressive doses should be administered to enable an adequate comparison of efficacy and toxicity.

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