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Carminomycin vs Adriamycin in Advanced Soft Tissue Sarcomas: an EORTC Randomised Phase II Study*

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Abstract—*Eighty-three patients with advanced soft tissue sarcoma who had received no prior chemotherapy entered a randomised phase II study comparing carminomycin (CMM) 20 mg/m² with adriamycin (ADM) 75 mg/m², both administered i.v. bolus every 3 weeks. Six patients were ineligible and response could not be evaluated in 6 additional patients. Thirty-eight evaluable patients received ADM and 33 received CMM. There was one complete response to ADM and 10 partial responses, an overall response rate of 29%. CMM showed significantly (P = 0.01) lower antitumour activity—one partial response (3%). Stabilisation of disease was similar in both arms (47 and 45%), but fewer patients progressed on ADM (24 compared to 52%). Durations of response dating from the start of chemotherapy were 5 months for complete remission on ADM, a median of 7 months (range 4–17) for partial response on ADM and 14 months for the one partial remission on CMM. Although the median time to progression for all patients receiving CMM (2 months) was significantly (P = 0.001) shorter than for those receiving ADM (5 months), patients on ADM had only a marginally significant longer duration of survival (P = 0.06) than the patients receiving CMM. A leucocyte nadir $<2.0 \times 10^9/l$ occurred in 38% of patients receiving ADM and 43% receiving CMM. Anaemia and thrombocytopoenia were uncommon. Other toxicities such as nausea, vomiting, anorexia and alopecia were more severe in the ADM group. There was one infective death secondary to leucopoenia in the ADM arm, and one patient who had received 109 mg/m² CMM + 255 mg/m² ADM developed progressively fatal cardiomyopathy.*

INTRODUCTION

SOFT tissue sarcomas are sometimes responsive to chemotherapy and many single agents and drug combinations have been tested in these comparatively rare tumours. Adriamycin remains the most active single agent, although the range of response rates, 9–70%, is wide [1]. Variability in the dose and schedule of drug administration and heterogeneity of the patient population with regard to factors such as prior chemotherapy or radiotherapy, performance status and site, volume and histology of the tumour may account for this disparity. In 1975 two literature reviews [2, 3], each with more than 350 patients, found average response rates of 25 and 27%. Collected data from more recent series suggest a slightly lower rate of remission—23% in 154 patients [4, 5]. In most of these series large intermittent doses of adriamycin, in the range 60–75 mg/m² every 3–4 weeks, have produced the highest response rates.

Over the past 7 yr a large number of drug combinations have been evaluated [4–6]. Those lacking adriamycin are rarely active, but the range of response rates (15–74%) for those containing

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adriamycin is wide. The most extensively tested combination is CYVADIC (cyclophosphamide, vincristine, adriamycin and DTIC), but although an earlier study documented an overall response rate as high as 59% [2], re-analysis of the data reduced this to 47% [7], and subsequent experience with this combination has been disappointing [8, 9]. In all series the complete remission rate rarely exceeds 15%. In advanced soft tissue sarcoma chemotherapy is almost invariably palliative, and long-term survivors are rare [10]. As the toxicity of combination chemotherapy usually exceeds that encountered with single-agent adriamycin and there is considerable overlap in response rates, the advantages of multiple drug therapy are far from clear.

Adriamycin has a number of undesirable side-effects, including vomiting, mucositis, myelosuppression, alopecia and, in high cumulative doses, cardiotoxicity. Intensive research has been directed towards the development of analogues lacking some of these toxicities. Carminomycin, isolated from *Actinomadura carminata*, is an interesting analogue which has been developed in Russia. It is chemically related to daunorubicin, but its biochemical activity resembles that of adriamycin [11]. Pre-clinical studies in the Zbinden rat model suggested a lower potential for cardiotoxicity than adriamycin. Myelosuppression was the dose-limiting toxicity and data from Russian studies, which employed two dose schedules (7.5 mg/m^2 twice weekly and 5.5 mg/m^2/day × 5), suggested significant activity in soft tissue sarcomas—13 responses in 48 patients (27%)—as well as in other tumours such as breast carcinoma, lymphomas and leukaemia [12, 13]. Nausea and vomiting seemed less severe and alopecia was not reported. A phase I study in Brussels, conducted by Rozencweig and co-workers using a single dose schedule, found that leucopoenia, with a nadir at day 12, was the dose-limiting toxicity, and the recommended dose for phase II study in good-risk patients was 20 mg/m^2 i.v. every 3 weeks [14].

At the end of 1979 the EORTC Soft Tissue and Bone Sarcoma Group decided to conduct a series of randomised phase II studies in patients who had received no prior chemotherapy, comparing newer anthracyclines with adriamycin. The aim was to identify an analogue with less toxicity but equal or better antitumour activity in soft tissue sarcoma. In a randomised phase II study a true comparison of the relative efficacies of two active analogues cannot be made without considerable expansion of patient numbers, but an inactive drug may be discarded if the response rate in the adriamycin arm indicates a representative patient population. An additional advantage of this policy was that new phase II agents could be evaluated in patients who had only received one or two anthracyclines. The results of the first study assessing carminomycin are reported here, and a second study evaluating 4'-epiadriamycin is currently in progress.

MATERIALS AND METHODS

Criteria for eligibility

Patients, 15–80 yr of age, with histologically proven advanced and/or metastatic soft tissue sarcoma were eligible for this study. Patients were required to have measurable progressive disease and a Karnofsky performance status of at least 50%. Recurrent tumour in irradiated areas was not permitted as the sole evaluable lesion, and pleural effusions or bony metastases were not considered to be measurable. Other criteria for exclusion were prior treatment with cytotoxic agents, a previous or concomitant different malignant tumour, congestive cardiac failure or other serious concurrent disease, and central nervous system metastases. Prior to entry patients were required to have adequate hepatic excretory function (serum bilirubin <50 μmol/l) and bone marrow reserve (leucocytes $<4.0 \times 10^9$/l, platelets $>100 \times 10^9$/l).

Trial design

After stratification by institution, patients were randomised to receive either adriamycin (NSC-123127) or carminomycin (NSC-180024). Patients showing disease progression after two courses of carminomycin were crossed to the adriamycin arm, while those failing on adriamycin went off-study. In the event of disease stabilisation, patients continued therapy until progression or the maximum cumulative dose of the drug was received.

Therapeutic regime

Adriamycin (ADM) 75 mg/m^2 was given as an i.v. bolus once every 3 weeks. Continuation of therapy beyond a cumulative dose of 550 mg/m^2 was not recommended, but was left at the discretion of the individual investigator. Carminomycin (CMM) 20 mg/m^2 was given as an i.v. bolus once every 3 weeks. The potential for cardiotoxicity was unknown and no specific recommendations were made about cumulative dose. (Carminomycin was supplied by Bristol-Myers, New York.)

Dose modifications during treatment

The dose was reduced by 50% if the serum bilirubin was between 35 and 50 μmol/l, and the drug was discontinued if the bilirubin was above

50 μmol/l. If the WBC count was below 3.0×10^9/l or the platelets below 100×10^9/l 3 weeks after the last course, treatment was postponed for 1 week. At this time, if the WBC were between 2.0 and 2.9×10^9/l or platelets $75\text{–}99 \times 10^9$/l, therapy was continued at 50% dose. Counts below these levels precluded treatment. Adjustments for the nadir count in previous courses were: WBC $2.0\text{–}2.9 \times 10^9$/l or platelets $50\text{–}74 \times 10^9$/l, adriamycin 75% dose, carminomycin 90% dose; WBC $<2.0 \times 10^9$/l or platelets $<50 \times 10^9$/l, adriamycin 50% dose, carminomycin 75% dose. Dose escalation was not permitted. Patients went off-study if haematological toxicity delayed retreatment for more than 3 weeks.

Pretreatment and follow-up investigations

Baseline studies included history and physical examination, Karnofsky performance status, tumour measurements, complete blood count including differential white count, biochemical profile, chest radiograph and ECG. Echocardiography and radionucleide cardiac scans were performed in some centres. Nadir blood counts between 1 and 2 weeks after treatment were performed in half of the cases, and all baseline investigations were repeated after two courses of chemotherapy and at the time of discontinuation or cross-over to alternative therapy.

Definition of response

Patients were considered evaluable for response if they had received two courses of chemotherapy and tumour measurements had been repeated at 6 weeks. Response criteria were those defined by WHO [15]. Any demise occurring before 6 weeks was classified as early death.

Toxicity

Haematological and cardiac toxicity were graded according to WHO criteria [15]. Other toxicities were graded according to the following scale: 0 = none; 1 = mild, not requiring modification of treatment; 2 = moderate, requiring modification of treatment; 3 = severe; 4 = life-threatening; 5 = lethal. Alopecia was graded: 0 = none; 1 = minimal; 2 = mild, not requiring a wig; 3 = moderate, requiring a wig; 4 = complete.

Central pathology review

A central pathology review was carried out by 2 panels consisting of 6 members each, one for the Northern European Institutes, chaired by Professor Van Unnik, Utrecht, The Netherlands, and one for the Southern European Institutes, chaired by Dr Contesso, Villejuif, Paris, France. If 2 members of a panel independently made the same diagnosis as the referring pathologist, this diagnosis was accepted. If there was disagreement, other members of the panel examined the histological sections and a consensus diagnosis was reached.

Statistical design

An initial patient entry of 29 evaluable patients in each arm was required, with termination of the study if 3 or fewer responses were observed in either arm. There was provision to stop the study if no responses were reported in the first 19 patients in either arm. This plan ensured that if the anthracycline analogue had a true response rate of at least 25%, the probability of rejecting it from further study was <0.05.

RESULTS

Over a 9-month period from March 1980, 83 patients were entered into this study by 13 European centres. Six patients were considered to be ineligible, five of these after histological review (xanthogranuloma, chondrosarcoma, benign schwannoma, non-Hodgkin's and Hodgkin's lymphomas) and one patient who had a Karnofsky performance status below 50% and no measurable disease. Another six patients were not evaluable for tumour response. These included three early deaths (<6 weeks), two due to malignant disease and one due to toxicity. One patient was lost to follow-up after the second course, prior to evaluation, and in two patients the followed lesion was treated by either surgery or radiotherapy after one course of therapy. The last two patients were considered to be evaluable for toxicity. Thus 71 patients, 38 in ADM and 33 on CMM, could be evaluated for response, and their characteristics are shown in Table 1. Apart from a reversal of the sex ratio, such that females were commoner in the ADM arm, the groups were well balanced. Histological material has been reviewed in 62 of the 71 evaluable cases, and the cell types are shown in Table 2. ADM produced 1 CR and 10 PR, an overall response rate of 29% (Table 3). Disease stabilised in 18 patients (47%) and progressed in 9 (24%). CMM showed minimal antitumour activity—1 PR (3%), disease stabilising in 15 patients (45%) and progressing in 17 (52%). The difference in response rate is significant at $P = 0.01$. Sixteen patients crossed from CMM to ADM, and one patient with progressive disease achieved a PR. Nine of the 11 patients responding to ADM had lung metastases, although one also had lymph node and another had subcutaneous metastases. Two patients had local residual/recurrent disease only. The one patient who responded to CMM had a complete clinical remission of extensive intra-abdominal,

Table 1. Patient characteristics

	ADM (38 patients)	CMM (33 patients)
Sex		
male	15 (39%)	20 (61%)
female	23 (61%)	13 (39%)
Age		
median (yr)	56.5	54
range	22–73	28–74
Karnofsky PS (%)		
median	90	90
range	60–100	50–100
Sites of disease		
locoregional only	7	10
metastases only	19	10
both	12	13
Distribution of disease		
locoregional*		
abdominal	10	13
trunk	1	2
limbs	2	3
metastases†		
lung	25	14
liver	3	6
subcutaneous	1	5
lymph nodes	1	2
intra-abdominal	1	3
No. of courses		
mean	6	4
range	2–11	2–13
Dose per course (mg/m²)		
mean	70	19
range	45–77	15–21

*Previously irradiated lesions not included—followed parameters only.
†Some patients—more than one site.

liver and axillary node metastases from a liposarcoma of the thigh, although residual intra-abdominal disease was evident on CT scan.

Durations of response dating from the start of chemotherapy were 5 months for the 1 CR (1 month from documentation of CR), median 7 months (range 4–17 months) for 6 PR on ADM and 14 months for the 1 PR on CMM. One partial responder to ADM was lost to follow-up after four courses of chemotherapy, but with this exception all responding patients ultimately progressed. A significant difference ($P = 0.001$) in median time to progression (Fig. 1) in favour of ADM (5 vs 2 months) was observed. Based on all eligible patients for whom follow-up data were available, a marginally significant longer duration of survival on ADM was noted ($P = 0.06$), with a median of approximately 9 months in both groups (Fig. 2). If only evaluable patients were analysed, the difference was even less significant ($P = 0.13$). Thirty-one patients on the CMM arm have died and 28 on the ADM arm. There was one toxic death due to anthracycline cardiomyopathy, and apart from the four intercurrent deaths, the remaining patients died of malignant disease.

Haematological toxicity encountered during the first two courses is illustrated in Table 4. Nadir (days 7–14 after chemotherapy) blood counts were available for 21 patients in each arm. Leucopoenia $<2.0 \times 10^9/l$ was noted in 38% of patients receiving ADM and 43% of patients receiving CMM. Thrombocytopaenia and anaemia were uncommon. Data were insufficient to calculate cumulative myelotoxicity. Other toxicities are summarised in Table 5. Nausea/vomiting, anorexia and alopecia were significantly more pronounced in the ADM group. Diarrhoea and mucositis were infrequent and mild in the ADM arm and rare in the CMM arm. Table 6 summarises the cumulative dose of anthracycline. The patient who died of progressive cardiomyopathy had received 109 mg/m² of CMM and 255 mg/m² of ADM. Three other patients had crossed from CMM to ADM and had received high cumulative doses of both drugs. The highest total dose of ADM alone was 772 mg/m²

Table 2. Histological subtypes

	ADM	CMM	Total (%)
Leiomyosarcoma	10	6	16 (23)
Malignant fibrous histiocytoma	5	6	11 (15)
Liposarcoma	2	8	10 (14)
Neurofibrosarcoma	4	2	6 (8)
Fibrosarcoma	3	1	4 (6)
Synovial sarcoma	2	1	3 (4)
Angiosarcoma	0	2	2 (3)
Rhabdomyosarcoma	0	0	0 (0)
Unclassified	4	1	5 (7)
Miscellaneous*	4	1	5 (7)
Not reviewed	4	5	9 (13)
Total	38	33	71 (100)

*Includes: ADM—clear cell, mixed mesodermal, alveolar soft parts, round cell undifferentiated; CMM—endometrial stromal.

Table 3. Response to chemotherapy

	ADM		CMM		Total
	No.	%	No.	%	
CR	1	3	0	0	1
PR	10	26	1	3	11
NC	18	47	15	45	33
PD	9	24	17	52	26
Total evaluable	38	100	33	100	71
Ineligible	2		4		6
Early death	1		2		3
Not evaluable	1		2		3
Total entered	42		41		83

Difference in response rate, 29 vs 3%, $P = 0.01$. Difference in average response, $P = 0.001$.

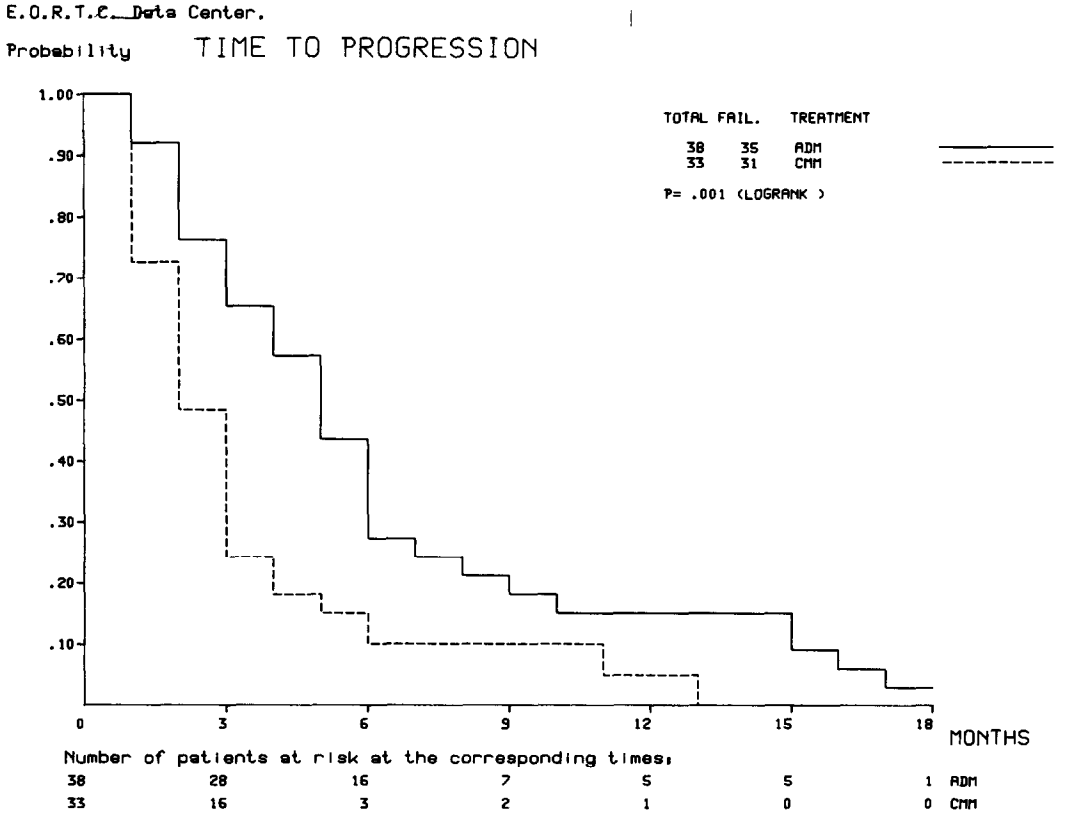

Fig. 1. Time to progression from randomisation, ADM vs CMM.

and of CMM alone 238 mg/m^2—neither patient developed cardiomyopathy. Three patients received >550 mg/m^2 ADM and two received ⩾150 mg/m^2 CMM.

DISCUSSION

The results of this study are in agreement with earlier reports in the literature of a response rate of 25–30% for single-agent adriamycin used at maximally tolerated doses [1–5]. However, in contrast with Russian studies [13], we have shown very little activity for carminomycin used in this dose and schedule. It is possible that a twice weekly schedule, as used by the Russian investigators, is more effective, although this remains to be confirmed. The total dose delivered over a 6-week period does not differ significantly between the two regimens. It is interesting to note

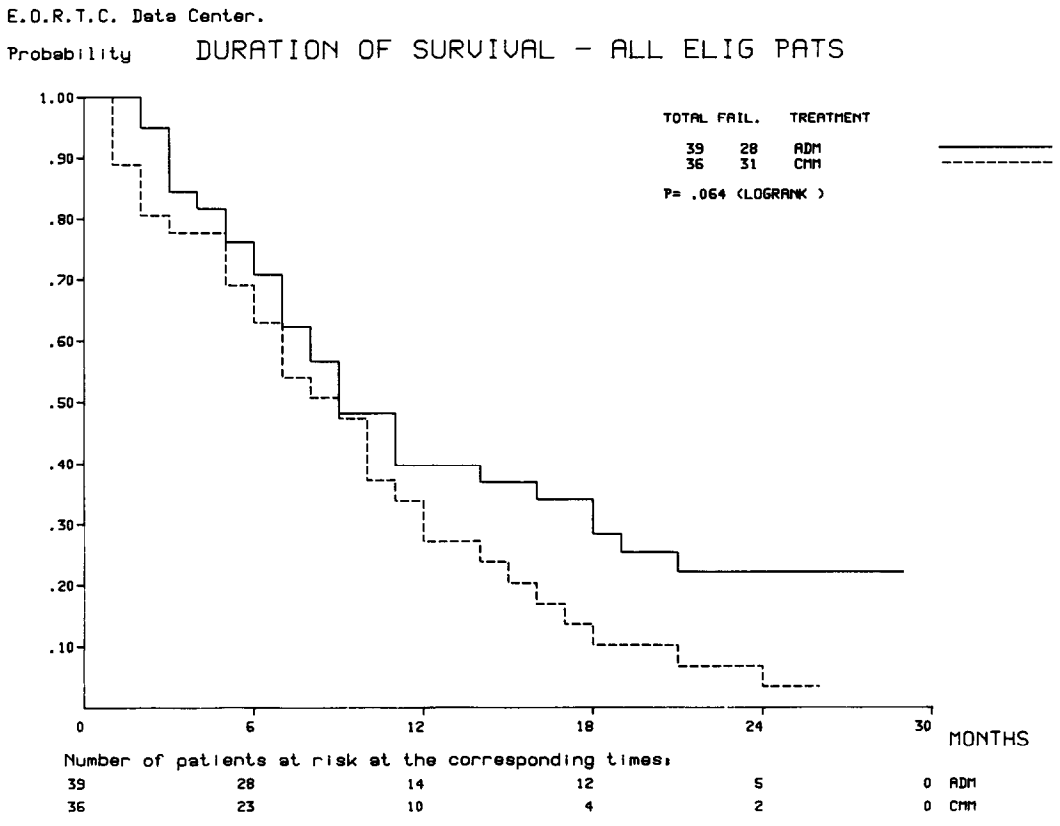

Fig. 2. Survival from randomisation, ADM vs CMM.

that two other EORTC trials have found carminomycin, in a similar dose and schedule, to be inactive in breast cancer [16, 17]. In the present study the median duration of response (7 months) was inferior to that (14 months) on CYVADIC combination chemotherapy in our previous study [9]. Surprisingly, the one patient responding to CMM had the longest duration of response (14 months). In the previous CYVADIC randomised trial and the present study, differences in response rate between the two arms did not translate into significant benefit in terms of overall survival. The low response rate, even in the ADM arm, and the relatively indolent nature of some tumours may account for this discrepancy. In contrast with studies of combination chemotherapy, in which occasional long-term (>3 yr) disease-free survivors have been reported [10, 18], all patients in this study treated by chemotherapy alone have relapsed. Only one partial remission was observed on crossing from CMM to ADR, but the numbers are too small to draw any conclusions.

Although nadir blood counts were only available in just over half of the patients, the distribution of haematological toxicity suggests that both drugs were administered at maximal dose for the schedule chosen. The leucopoenia produced by CMM slightly exceeded that induced by ADM. In contrast, gastrointestinal intolerance and alopecia were significantly less severe with CMM. Cross-over from CMM to ADM was accompanied by a significant deterioration in patient tolerance.

As the majority of patients did not receive doses of ADM in excess of 550 mg/m^2, and few patients received high doses of CMM, very little comment can be made about cardiotoxicity. No patient who received CMM alone developed cardiomyopathy. The one fatal case of cardiomyopathy had only received 225 mg/m^2 of ADM, which alone has low potential for cardiotoxicity. Prior to this he had received the equivalent of 5½ courses of CMM, which may have contributed to the cardiac damage. However, in view of the low activity of CMM, the question of cardiotoxicity is at present academic.

In conclusion, although CMM was better tolerated than ADM, in this dose and schedule it demonstrated minimal antitumour activity in patients with advanced soft tissue sarcoma.

Table 4. Haematological toxicity—first two courses

	WHO grade of toxicity													
	0		1		2		3		4		Grades 1–4 Total			
Type of toxicity	ADM (%)	CMM (%)	ADM (%)	CMM (%)	ADM (%)	CMM (%)	ADM (%)	CMM (%)	ADM (%)	CMM (%)	ADM (%)	CMM (%)	No. evaluable* ADM	CMM
Anaemia	45	47	45	33	10	10	0	10	0	0	55	53	20	21
Leucopoenia	34	5	14	14	14	38	33	33	5	10	66	95	21	21
Granulocytopoenia	55	16	9	17	0	33	18	17	18	17	45	84	11	12
Thrombocytopoenia	81	90	14	0	5	0	0	5	0	5	19	10	21	21

*No. of patients having nadir (days 7–14) blood counts.

Table 5. Non-haematological toxicity—all courses

	Grade of toxicity							
	None 0		Mild 1		Moderate 2		Severe 3	
Type of toxicity	ADM (%)	CMM (%)	ADM (%)	CMM (%)	ADM (%)	CMM (%)	ADM (%)	CMM (%)
Nausea/vomiting	2	20	37	53	45	18	13	9*
Diarrhoea	76	91	21	9	3	0	0	0
Anorexia	34	44	42	50	24	3	0	3
Mucositis	65	97	29	3	3	0	3	0
Weight loss	81	76	11	18	8	6	0	0
Fever with drug	89	94	8	6	3	0	0	0
Bleeding	92	97	5	0	0	0	3	3
Alopecia	0	56	21	41	34	3	45	0
Other	71	71	26†	29	3‡	0	0	0

No. of patients evaluable: ADM, 38; CMM, 34.

*One life-threatening vomiting—patient changed to 6-hr infusion after 2 courses with improvement.

†Mild toxicities with both drugs—mainly psychological, e.g. anxiety/depression, dizzy, tired, watering eyes, hot flushes, headache, dry mouth, constipation.

‡Respiratory—patient had tumour in upper abdomen and liver, but not lungs.

Table 6. Cumulative dose of anthracycline

	Adriamycin alone	
>450 mg/m²	13/38 patients	34%
>550 mg/m²	3/38 patients*	8%
	Carminomycin alone	
≥120 mg/m²	4/33 patients	12%
≥150 mg/m²	2/33 patients†	6%

Both drugs ≡ 8+ courses

	CMM (mg/m²)	ADM (mg/m²)
R.V.	100	546
A.K.	39	546
J.V.‡	109	255
D.B.	56	355

*579, 629, 772 mg/m².

†150, 238 mg/m².

‡Definite cardiotoxicity—progressive heart failure and death. Also, O.P. 520 mg/m² ADM—mild cardiac decompensation; death due to tumour; cardiomyopathy at autopsy.

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