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Phase I-II Evaluation of Carminomycin in Adults with Acute Leukemia*

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Abstract—*Twenty courses of carminomycin were administered to* 18 *evaluable adult patients with acute leukemia* (14 *ANLL*, 2 *ALL*, 2 *CGL-BC*). *All but one received daily doses of* 6-14 mg/m² *for* 5 *consecutive days. Two patients older than* 60 yr *had not prior chemotherapy and the others had refractory or relapsed disease. The median age was* 60 yr. *Three ANLL patients achieved complete remission for* 8, 9 *and* 9 months *respectively, with no maintenance therapy. None of these had proven clinical resistance to daunomycin and/or doxorubicin. Mucositis was dose-related and dose-limiting. Nausea and vomiting were rare. Alopecia was constant. Cardiac arrythmia was ascribed to carminomycin in two patients. One episode of cardiac failure seemed clearly drug-related and recovered with symptomatic treatment. In conclusion, encouraging antileukemic activity was observed with carminomycin in poor-risk patients. At doses up to* 12 mg/m² day × 5, *extramedullary toxicity remained acceptable.*

INTRODUCTION

CARMINOMYCIN (carubicin, NSC-180024) is an anthracycline derivative that was isolated from *Actinomadura carminata* [1]. In the rat the drug produces less cardiac damage than equitoxic doses of doxorubicin [2]. With single administrations of up to 22-25 mg/m² leukopenia is dose-limiting, whereas other toxic effects are mild to moderate [3, 4]. These observations, coupled with reports of favorable findings in acute leukemia [2, 5], led us to carry out a phase I-II study of carminomycin in this disease.

MATERIALS AND METHODS

Nineteen patients were entered in the study (Table 1). There were seven men and 12 women, with a median age of 60 yr (range 24-78 yr). Fifteen had acute non-lymphocytic leukemia (ANLL), two had acute lymphocytic leukemia (ALL) and two had chronic granulocytic leukemia in relapsing lymphoblastic crisis. Among ANLL patients, three who were older than 60 yr had no prior chemotherapy and six had refractory disease. The ten remaining patients had relapsed leukemia. A total of 14 patients had previously received daunomycin and/or doxorubicin at cumulative doses of 100-570 mg/m². All patients had adequate liver and renal functions.

The first patient received carminomycin at a single dose of 30 mg/m². Subsequently, the drug was given once daily for five consecutive days at daily doses of 6 (two courses), 10 (five courses), 12 (12 courses) and 14 mg/m² (one course). One patient was treated with two courses at daily doses of 6 and 10 mg/m² respectively. Another patient, entered at the dose level of 12 mg/m²/day × 5,

Table 1. *Pretreatment characteristics*

No. of patients	19
Age (yr)	
median	60
range	24-78
Sex	
male	7
female	12
Histologic type	
ANLL	15
relapse	6
refractory	6
never treated	3
ALL (relapse)	2
CGL-BC (relapse)	2

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achieved complete remission and received a second consolidation course at the same dose level. None of the other patients had more than one course. One ANLL patient who went off-study for cardiac problems after two daily injections of 12 mg/m² was considered evaluable for toxicity only.

Carminomycin was supplied by Bristol Laboratories in vials containing 10.45 mg carminomycin-HCl equivalent to 10 mg carminomycin base. Carminomycin solutions had to be prepared immediately prior to dosing using 20 ml sterile water for injection per 10 mg vial for a final concentration of 0.5 mg/ml. This solution was administered as a slow i.v. push injection.

Baseline studies included bone marrow examination, complete blood counts, biochemical profile, ECG and chest roentgenogram as well as, at the highest dose levels, radionuclide cardiac scan and/or echocardiography. After treatment complete blood counts were scheduled daily and biochemical profile twice weekly. ECG was performed before and 2 hr after each drug administration. Left ventricular ejection fraction was controlled after 3 weeks of therapy.

Complete response denoted a cellular bone marrow with <5% blasts, hemoglobin >10 g/dl, peripheral white blood cell count ≥3500/mm³ and platelet count ≥100,000/mm³. Failures were classified according to criteria defined by Preisler [6].

RESULTS

Eight ANLL patients received total doses of 30 or 50 mg/m² per course (Table 2). One of these had unchanged bone marrow but was considered as a partial remitter because of a return to normal WBC and platelet counts, as well as a reduction in peripheral blast count from 8000 to 135/mm³ for 4 months. Of the seven other patients, no marrow hypocellularity could be obtained at any time during carminomycin therapy in one (F1 failure), marrow hypocellularity but regrowth of leukemic cells within 4 weeks was seen in four (F2 failure) and death during postchemotherapy aplasia occurred in two (F4 failure). Six ANLL, two ALL and two CGL-BC patients were evaluable for antitumor activity at doses of 12 mg/m²/day × 5. Three women aged from 61 to 67 yr achieved unmaintained complete remission from ANLL for 8, 9 and 9 months respectively. The oldest patient had an M4 FAB-type marrow and received carminomycin as first induction therapy. The two other complete remitters had responded previously to daunomycin and neither had demonstrated resistance to daunomycin or doxorubicin. They had previously received cumulative anthracycline doses amounting to 480 and 510 mg/m² respectively. One was in first relapse after a complete response of 43 months. The other patient was in second relapse after complete responses of 9 and 3 months respectively. Her complete response to a first course of carminomycin was consolidated by a second course at 12 mg/m²/day × 5 and lasted longer than the previous response, which had been achieved with a single course of daunomycin (60 mg/m²/day × 5).

At daily doses of 12 mg/m² four patients had F2 failure and three, one with ANLL, one with ALL and one with CGL-BC, had F4 failure. The single patient who received 14 mg/m²/day × 5 had ANLL and treatment resulted in F1 failure.

Toxicity

Severe myelosuppression was encountered in all patients with median WBC and platelet nadirs of 100/mm³ (100-500/mm³) and 3000/mm³ (50-7000/mm³) respectively. Hematopoietic recovery could be evaluated at doses of 12 mg/m²/day × 5 after three induction courses that elicited complete response and after one consolidation course. PMN counts of 500 and 1000/mm³ were noted after 21-34 days and 23-45 days respectively from initiation of therapy; 28-35

Table 2. Response to carminomycin

Dose level (mg/m²)	Diagnosis	No. of courses evaluable	Effect CR-PR	Effect F_1-F_2-F_4	Response duration (months)
30 × 1	ANLL	1		1	
6 × 5	ANLL	2		2	
10 × 5	ANLL	5	1	1-1-2	4
12 × 5	ANLL	6	3	1-2-1	8-9-9
	ALL	2		1-1	
	CGL-BC	2		1-1	
14 × 5	ANLL	1		1	

CR: complete remission; PR: partial remission. Failures are classified according to Preisler (F_1: absolute resistance; F_2: leukemic regrowth after initial reduction of blast cells; F_4: death during the post-chemotherapy aplasia).

days were necessary to recover to 100,000 platelets/mm^3.

At the highest dosages mucositis was prominent (Table 3). The single course given at 14 mg/m^2/day × 5 was complicated by a massive and lethal necrosis of the gut. Among 11 full courses at 12 mg/m^2/day × 5, five resulted in mucositis, which was severe in three. Nausea and vomiting were never seen at doses below 12 mg/m^2/day × 5. These manifestations occurred in four courses, being mild in three and severe in one. Moderate diarrhea was also observed in four courses but its relation to carminomycin remained uncertain. Hair loss was complete in the three patients who had no alopecia at entry. One patient experienced hypocalcemia on day 4 with serum levels down to 5.4 mg/dl and prompt recovery with calcium supplements. None of the patients had clearly drug-related hepatic or renal function impairment.

Table 3. Non-hematological toxic effects in 20 courses

Toxic effect	Courses with toxic effect
Mucositis	6
Nausea, vomiting	4
Diarrhea	4*
Alopecia	3†
Cardiac arrhythmia	2-2*
Congestive heart failure	1-3*
Hypocalcemia	1

*Doubtful relation to carminomycin administration.
†Out of 3 evaluable.

Cardiac problems were found at daily doses ≥10 mg/m^2 in eight patients who had prior cardiac history, prior anthracycline or both. Arrhythmia was observed in four patients receiving the 12 mg/m^2/day × 5 schedule. A symptomatic attack of atrial fibrillation appearing 4 hr after the second daily injection resulted in treatment discontinuation in a 78-yr-old patient with previous history of moderate hypertensive and degenerative cardiomyopathy and no prior anthracycline therapy. Normal rhythm resumed rapidly with digitalis. A possible relationship between this episode and the sudden death that occurred 14 days later cannot be substantiated. One 46-yr-old patient without any cardiac history but previous treatment with anthracycline and amsacrine had asymptomatic atrial fibrillation of sudden onset 2 hr after the fourth injection of carminomycin with spontaneous recovery. Ectopic supraventricular beats noted in two other patients were unlikely to be related to carminomycin.

Congestive heart failure (CHF) was observed in four patients but it seemed clearly related to carminomycin in only one. She was 66 yr old and had received previously a total anthracycline dose of 610 mg/m^2. Acute left ventricular failure developed on day 15 of a second course of carminomycin at 12 mg/m^2/day × 5. Her cardiac status improved rapidly with conventional treatment. Another 70-yr-old patient had CHF 6 months after one course of carminomycin (10 mg/m^2/day × 5). This patient had also presented CHF 15 months earlier during doxorubicin therapy. In the two remaining patients CHF appeared to be essentially related to complex terminal events. No alterations in the left ventricular ejection fraction were observed in four other patients who had repeated determinations 3 weeks after initiation of carminomycin courses at a dose of 12 mg/m^2/day × 5.

DISCUSSION

Encouraging antileukemic activity was detected despite a selection of high-risk patients as evidenced by older age and relapsed or refractory disease. Of the two evaluable previously untreated elderly patients, one achieved complete remission. Among the 16 previously treated patients, single courses at total doses of 30-70 mg/m^2 yielded complete remission in two and only two showed complete failure to respond (F1). The poor prognosis in the majority of our patients was also reflected by the lack of complete remission with the subsequent regimens that were given for progressive disease under carminomycin.

The extent of cross-resistance between carminomycin and conventional anthracyclines remains to be elucidated. Two of the three patients achieving complete remission with carminomycin had previously responded to daunomycin and/or doxorubicin and none of them had proven acquired resistance to these drugs.

Complete remissions were obtained only in ANLL at 12 mg/m^2/day × 5. Small sample sizes preclude any conclusion concerning a possible selective activity of carminomycin on various types of acute leukemia. Similarly, whether lower doses could elicit complete remissions could not be excluded since only eight patients, of whom two died during marrow aplasia, received carminomycin at doses below 12 mg/m^2/day × 5.

Administration of the effective dose of 12 mg/m^2/day × 5 proved feasible without important extramedullary toxic effects. Significant mucositis was observed in six patients and was dose-limiting at 14 mg/m^2/day × 5. The occurrence of fatal gut necrosis at this dose level prevented further attempts of dose escalation.

Gastro-intestinal tolerance was remarkable, with only rare episodes of nausea and vomiting.

Limited data are available to evaluate the cardiotoxic potential of carminomycin relative to that of daunomycin and doxorubicin [7, 8]. In a large-scale study conducted in the U.S.S.R. there were no CHF episodes but ECG changes were identified in 5.4% of the patients [2]. Comis *et al.* [4] found unexplained decreases in cardiac ejection fraction in three of nine patients who received a total dose of $\geqslant$100 mg/m^2, with one patient developing CHF at a total dose of 160 mg/m^2. A case of fatal CHF was also reported by Bramwell *et al.* after a cumulative dose of 109 mg/m^2 [9]. In our study four episodes of supraventricular arrhythmia were observed and at least two could be ascribed to carminomycin administration. A single patient who was heavily pretreated with anthracyclines (610 mg/m^2) experienced a clearly drug-induced CHF which was reversible with standard therapy. Decreases in cardiac ejection fraction were not seen in the four patients evaluated at 3 weeks after administration of 60 mg/m^2 of carminomycin.

EORTC phase II trials in soft tissue sarcoma [9] and breast cancer [10] failed to confirm stimulating data from initial studies with carminomycin in these malignancies [2]. In contrast, our findings appear to support previous reports of significant antileukemic activity of this drug [2, 5]. Our results in poor-risk patients were noticeable and tolerance at an effective dose level was acceptable. These observations warrant further investigations of the relative value of carminomycin as compared tc other anthracyclines in the treatment of acute leukemia.

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