Europ. J. Cancer Vol. 16, pp. 1555–1559
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0014-2964/80/1201-1555 $02.00/0

Carminomycin (NSC-180024): A Phase I Study*

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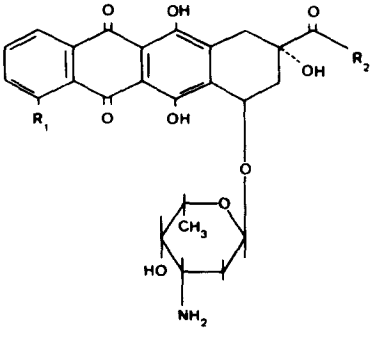
Abstract—*Carminomycin is a new anthracycline derivative. In this phase I trial, the drug was given i.v. every* 3–4 weeks *to* 19 *patients with solid tumors. Thirty-five courses of therapy were given. Leucopenia was dose-related and dose-limiting with a steep dose-effect relationship. Leucopenia appeared to be exacerbated in patients with low performance status and massive liver involvement. Thrombocytopenia was negligible. Mild to moderate alopecia was encountered in less than one-half of the patients. Vomiting and stomatitis were not seen. Transient electrocardiographic changes could be documented in two patients. Drug-induced congestive heart failure was not observed but full evaluation of the cardiac effect of carminomycin requires more prolonged treatments and larger accrual of patients.*

Doses of 20 mg/m^2 *repeated every* 3 weeks *can be recommended for phase II trials with carminomycin in good-risk patients. Relative to leucopenia, other acute toxic manifestations appear to be of minor clinical significance which makes this new anthracycline attractive for further investigation.*

INTRODUCTION

CARMINOMYCIN (Carubicin, NSC-180024) is a new anthracycline analog (Fig. 1) that was initially isolated from mycelia of *Actinomadura carminata* in the USSR [1]. The drug is active against a variety of experimental tumors. Pharmacology studies in animals revealed that the drug bound largely to serum proteins (70–90%) and that it was widely distributed [2]. Excretion as unchanged species occurred mainly via the biliary tract and to a lesser extent in the urine. These studies also demonstrated oral absorption with tissue distribution similar to that achieved with intravenous administration. In the Zbinden rat model [3], carminomycin produced less cardiac damage than adriamycin when both drugs were given at equitoxic doses [4].



	R_1	R_2
adriamycin	OCH_3	CH_2OH
carminomycin	OH	CH_3
daunorubicin	OCH_3	CH_3

Fig. 1.

Initial clinical trials in the USSR used a twice weekly schedule for 3 weeks (total dose 27–40 mg/m^2) or daily × 5 courses repeated at 21–30-day intervals (1.5–5 mg/m^2 per day)

Accepted 11 April 1980.
*This work was presented in part at the 16th Annual Meeting of the American Society of Clinical Oncology, May 1980, San Diego, U.S.A., and partially supported by grant No. 3.4535.79 from the "Fonds de la Recherche Scientifique Médicale" (F.R.S.M.-Belgium).
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[4, 5]. The main toxic effect was myelosuppression but gastrointestinal intolerance and alopecia were also reported. There was no evidence of drug-induced congestive heart failure. Encouraging therapeutic results were seen in acute leukemia, lymphoma, soft tissue sarcoma and breast cancer.

Carminomycin was selected for this phase I trial on the basis of a possibly higher therapeutic index relative to adriamycin and its potential for oral administration. The trial was designed to determine the maximum tolerated dose for intravenous administration in an every 3-week schedule, which is the schedule most commonly employed with adriamycin.

MATERIALS AND METHODS

All patients had histologic confirmation of advanced solid malignancy. Expected survival was longer than 3 months. No patient had received prior anthracycline treatment. All had leucocyte counts of at least $4.0 \times 10^9/l$ and platelet counts of $100 \times 10^9/l$ or more. Bilirubin and creatinine serum levels did not exceed 1.5 mg% in any patient. There was no clinically detectable heart dysfunction prior to entry into the trial.

The starting dose was 12 mg/m^2. The selection of this dose level was based on earlier clinical findings [6]. Dose escalation within the same patient was carried out if no toxicity was encountered in the previous course. Treatments were repeated at 3-week intervals or upon recovery from myelosuppression.

During the study period, three complete blood cell counts and one SMA 12 chemistry panel were scheduled per week. In this analysis, the leucocyte nadir for patients receiving two or more courses at the same dose level represents the lowest cell count among all courses. Electrocardiograms were performed before, 2 and 24 hr after carminomycin treatment. In patients with measurable disease, tumor response was assessed every 3 weeks according to standard criteria of response [7]. The pharmacokinetics of carminomycin was also studied. Blood and urine samples were analyzed with a high pressure liquid chromatographic method using adriamycin as an internal standard [8].

Carminomycin hydrochloride was supplied by Bristol Laboratories, Syracuse, New York, in 10 mg vials, containing 20 mg mannitol. The drug was dissolved in 20 ml of sterile water for injection immediately prior to use. The solution (0.5 mg/ml) was administered as a slow i.v. injection.

RESULTS

Nineteen patients with a large variety of tumor types entered the trial (Table 1). Doses were escalated from 12 to 22 mg/m^2. A total of 35 courses were administered. Only two patients received more than 2 courses.

Table 1. *Patient characteristics*

Total number entered	19
Male: Female	13: 6
Age:	
median	63
range	39–74
Performance status:	
median	70
range	40–90
Primary tumors:	
Lung non-small cell	5
small cell	1
Head and neck	3
Miscellaneous	10
Previous treatment:	
Chemotherapy only	3
Radiotherapy only	6
Chemotherapy + radiotherapy	7

Carminomycin induced dose-related and dose-limiting leucopenia (Table 2). This effect appeared to vary widely within each dose level. No linear relationship could be defined between dose of drug and degree of leucopenia. Of seven patients, two showed slightly more pronounced leucopenia when retreated at the same dose of carminomycin.

At doses of 12–15 mg/m^2, 3 patients had white blood cell counts (WBC) under $4.0 \times 10^9/l$. All of these had massive liver involvement confirmed by computed axial tomography, with altered liver function tests but normal bilirubin value. The dose level of 20 mg/m^2 was explored when it became apparent that the maximum tolerated dose would be 22 mg/m^2. Therefore,only good-risk patients were selected to receive 20 mg/m^2 of carminomycin. Among these, leucocyte counts ranged between 0.5 and $6.8 \times 10^9/l$ but leucopenia under $10^9/l$ was seen in one patient only. At doses below or equal to 20 mg/m^2, median time to nadir was noted between day 10 and 15. Return to normal cell counts of at least $4.0 \times 10^9/l$ was achieved by day 21 in all but two patients.

In this trial, the maximum tolerated dose was considered to be 22 mg/m^2 because of a median leucocyte nadir per patient of $1.1 \times 10^9/l$. Three patients treated at that dose level experienced severe leucopenia with WBC below $10^9/l$. They had either borderline per-

Table 2. Carminomycin-induced leucopenia

Dose (mg/m^2)	No. of evaluable patients/ evaluable courses	Median nadir $\times 10^9/l$		Median No. of days to	
		Leucocytes (range)	Granulocytes (range)	Nadir (range)	Recovery (range)
12	1/2	2.9	1.9	15	—
15	4/5	4.35 (0.5–4.9)	2.8 (0.3–3.6)	11.5 (10–13)	16.5 (14–19)
18	5/6	2.9 (0.7–3.3)	1.8 (0.2–2.5)	10 (9–14)	16 (15–21)
20	6/11	1.75 (0.5–6.8)	1.0 (0.2–4.1)	11 (11–13)	20 (16–36)
22	6/7	1.1 (0.2–5.6)	0.5 (0.1–4.6)	12 (9–18)	22.5 (20–34)

Table 3. Carminomycin-induced thrombocytopenia

Dose (mg/m^2)	No. of evaluable patients	No. of evaluable courses	Platelet nadir $\times 10^9/l$		No. of days to nadir
			Median	Range	
12	1	2	74		12
15	4	5	151	60–440	10
18	5	6	180	170–240	—
20	6	11	162	120–344	—
22	6	7	131	80–149	13

formance status, (Karnofsky scale 40), massive liver involvement, or bone metastases previously treated with radiotherapy. The patient with low performance status had a rapidly progressive disease and died on day 10 of his second course of treatment, with a leucocyte count of $0.2 \times 10^9/l$. No post mortem examination could be obtained in this patient.

Thrombocytopenia under $100 \times 10^9/l$ was rare and occurred only in three patients with massive liver invasion (Table 3). Thrombocytopenia was never of clinical significance.

Non-hematological toxic effects appeared to be minimal (Table 4). Nausea without vomiting was reported in 4 of 35 courses (11%). Stomatitis was not observed. Electrocardiographic monitoring was performed during 19 courses given to 14 patients. Definite but transient electrocardiographic changes consisting of ST-T wave modifications were observed in two courses. These alterations disappeared within 24 hr. Rare supraventricular extrasystoles were also noticed in one of these courses. There was no drug-induced congestive heart failure. Alopecia was seen in 8/19 (42%) patients and was minimal in most cases. It developed only after retreatment or with treatments at doses of 20 mg/m^2 and higher. Phlebitis was produced in one patient after slight drug extravasation, inducing local symptoms for more than 2 months, without tissue sloughing. No 'recall phenomenon' at previous radiation ports was encountered.

Table 4. Non-hematological toxicity of carminomycin

	Dose (mg/m^2)				
	12	15	18	20	22
Number of evaluable patients	1	4	5	6	7
Number of toxic patients	0	2	3	4	6
alopecia		1	1	3	3
nausea		1	1	1	1
EKG changes		0	1	0	1
fever ($t° > 38°C$)		0	0	1	0
phlebitis		0	0	0	1

Patients were closely monitored for possible disease regression. Nine patients had measurable lesions. Seven of these received doses of 18 mg/m^2 or more which were considered as possibly active. No antitumor effect could be detected.

Results of the pharmacokinetic studies of carminomycin were published elsewhere [9].

Preliminary data indicated a biphasic serum elimination with a terminal half-life of approximately 12 hr. The alcohol metabolite carminomycinol appeared rapidly and persisted for at least 24 hr in the serum.

DISCUSSION

The search for analogs represents an important facet of drug development programs [10]. Adriamycin is one of the most active drugs among currently available chemotherapy agents. Several anthracycline derivatives have been recently proposed with possibly higher therapeutic indices or pharmacological advantages. To date, none of these has shown clear superiority over daunorubicin and adriamycin with respect to both antitumor activity and spectrum of toxicity.

Intravenous carminomycin given in an intermittent schedule produces dose-limiting leucopenia with a very steep dose-effect relationship. It occurs at doses under 18 mg/m^2 in poor-risk patients only. The maximum tolerated dose is 22 mg/m^2 as evidenced by the median leucocyte nadir of 1.1×10^9/l seen in our experience. Platelets are minimally affected by the myelosuppressive effect of the drug. Massive liver invasion, low performance score, and probably bone marrow impairment may sharply enhance the drug-induced myelosuppression. Hepatic clearance of carminomycin may be decreased in patients with liver metastases [11]. Pharmacokinetic data are needed to ascertain this point.

Minor non-hematological toxic effects are also encountered within these dose levels. Transient electrocardiographic modifications have been found in two patients. We have not seen any congestive heart failure in our patients. However, our data do not allow a proper evaluation of the possible cumulative cardiac effect of carminomycin [12]. Other toxic manifestations include mild to moderate alopecia and rarely nausea, temperature elevation and phlebitis at the injection side.

Of note, we have also given carminomycin at a dose of 30 mg/m^2 to one patient with acute myeloblastic leukemia refractory to a previous anthracycline-containing regimen. Non-hematological side effects were not observed. Peripheral blood blasts fell from 50 to 2% in this patient but its bone marrow could not be re-examined.

Overall, carminomycin is attractive for further clinical trials. It is much better tolerated than adriamycin when both drugs are given at doses achieving similar leucopenia but drug handling might be easier with adriamycin particularly in poor-risk patients. Assessment of the long-term effect of carminomycin on the heart as well as exploration of its oral administration should probably await results of phase II trials with the intravenous form. Ongoing E.O.R.T.C. trials are evaluating its antitumor activity in breast cancer and soft tissue sarcoma at doses of 18–20 mg/m^2 repeated every 3 weeks. Additional investigation is also warranted in acute leukemia and in tumor types traditionally resistant to conventional anthracyclines.

Acknowledgements—The authors acknowledge the statistical assistance of Dr. M. Buyse, E.O.R.T.C. Data Center, and the secretarial help of Ms. G. Decoster.

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