Eur J Cancer Clin Oncol, Vol. 19, No. 4, pp. 449–454, 1983.
Printed in Great Britain.

0277-5379/83/040449-06$03.00/0

Clinical Phase I Trial of Marcellomycin with a Single-dose Schedule*

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Abstract—*Marcellomycin is a new anthracycline that was proposed for clinical trials on the basis of experimental data suggesting reduced potential for hematologic and cardiac toxicity as compared to conventional anthracyclines. This phase I trial was designed to determine the maximum tolerated dose of marcellomycin at a single-dose schedule. The drug was given as a* 15- *to* 30-*min i.v. injection. Eighteen patients with a variety of solid tumors received a median of* 2 *courses (range:* 1–5*) at doses of* 5–60 mg/m^2. *Myelosuppression was dose-limiting and somewhat unpredictable. It was characterized by early thrombocytopenia and late leukopenia. It occurred at doses* $\geqslant$40 mg/m^2 *and resulted in a few cases of infection and hemorrhage. Nausea, vomiting and stomatitis were frequent and occasionally severe. Other common non-hematological toxic effects consisted of local phlebitis and fatigue. Electrocardiographic changes were also encountered. Hair loss was rare and negligible. No antitumor activity could be detected. It appears that phase II trials should be preferably restricted to ambulatory patients and that a dose schedule of* 50 mg/m^2 *repeated every* 3 weeks *may be proposed for this favorable patient population.*

INTRODUCTION

MARCELLOMYCIN is a pyrromycinone glycoside isolated by fractionation of the bohemic acid complex, an anthracycline mixture obtained from fermentation broth of *Actinosporangium* sp. [1]. Its chemical structure is closely related to that of aclacinomycin A (Fig. 1). The antitumor effect of the drug has been ascribed, at least in part, to its ability to inhibit nucleolar RNA synthesis [2]. In Novikoff hepatoma ascites cells, this inhibition requires concentrations more than 1000-fold lower than those necessary to inhibit DNA synthesis [3].

Marcellomycin was found to be active against various i.p. implanted tumors in mice, i.e. the P388 leukemia, the B-16 melanoma, the Lewis lung carcinoma and the colon 26 carcinoma [4]. Other screening experiments, however, could not confirm the efficacy of marcellomycin against L1210 leukemia and failed to identify antitumor activity against advanced P388 leukemia and i.v. implanted Lewis lung carcinoma [5]. The therapeutic effect obtained with marcellomycin in murine malignancies was generally comparable to that achieved with aclacinomycin A but somewhat lower than that of doxorubicin. No schedule dependency could be detected in the L1210 system with marcellomycin [6]. In this system there was no increase in life span after oral administration [7].

Acute toxicity studies in animals performed at Bristol Laboratories (Syracuse, NY) indicated a steep dose–response relationship. In Swiss Webster mice the LD_{50} and the LD_{10} after i.v. administration were 19.9 and 17.4 mg/kg respectively. In beagle dogs a single i.v. dose resulted in no deaths at 2.87 mg/kg, whereas all animals died at 3.69 mg/kg. Administration of lethal doses to

Accepted 1 December 1982.
*This work was supported in part by contract NIH NO1-CM 53840 from the National Cancer Institute (NCI, Bethesda, MD), grant No. 3.4535.79 of the "Fonds de la Recherche Scientifique Médicale" (FRSM, Brussels, Belgium) and by a grant from the Bristol-Myers Company.
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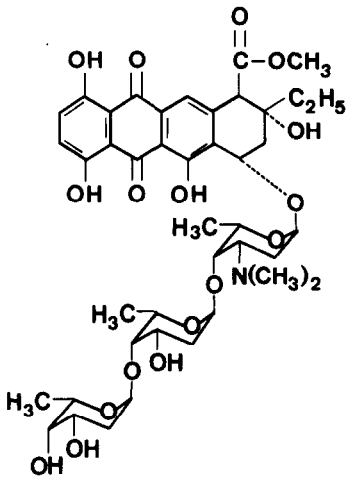

Fig. 1.

dogs produced severe intestinal toxicity, which appeared to be the cause of acute death [8]. In initial experiments minimal leukocyte depression was noted with i.p. marcellomycin in BDF1 mice below the LD_{50}; in beagle dogs leukopenia was mild at non-lethal i.v. doses [7]. The relative cardiotoxicity of doxorubicin and marcellomycin was investigated with inconclusive results by measuring the CPK-MB isoenzyme in mice and by serially recording EKGs in rats [9, 10].

In the agar diffusion chamber precursor cell assay, the sensitivity to marcellomycin of leukocyte-committed colony-forming cells from dogs was found to be similar to those from man [11]. A comparative study on the toxic effect of marcellomycin and aclacinomycin A against normal human myeloid stem cells indicated that significantly higher concentrations of marcellomycin were necessary to inhibit CFU-c [5]. Based on these *in vitro* findings, the clinical maximum tolerated dose of this compound could be expected to be higher than that of aclacinomycin A [12–14] in the event of dose-limiting leukopenia.

This paper summarizes results of a phase I clinical trial of marcellomycin with a single i.v. dose schedule. This work was undertaken as part of the new drug program of the Early Clinical Trials-Group of the EORTC.

MATERIALS AND METHODS

Eighteen patients with histologically confirmed solid tumors, mainly squamous cell carcinomas of the head and neck, were entered in the trial (Table 1). All had diseases not or no longer suitable for conventional therapy. There were 11 men and 7 women with a median age of 67 yr (range: 35–70 yr) and a median performance status on the Karnofsky scale of 60 (range: 40–100). All but one had been previously treated with radiotherapy (3 patients), chemotherapy (5 patients) or both (9 patients). One patient had received prior intravesical administrations of doxorubicin. None of the other patients had prior anthracycline therapy. None had received cytotoxic treatments during the 4 weeks prior to entering the trial. Eligibility criteria included a life expectancy of at least 4 weeks, WBC $\geqslant 4000/\mu l$, platelet counts $\geqslant 100{,}000/\mu l$, serum bilirubin levels <1.5 mg/dl and serum creatinine levels <1.5 mg/dl. Patients with a history of cardiac disease were excluded from the study.

Table 1. *Marcellomycin phase I study: patient characteristics*

Total No. of patients	18
Male:female	11:7
Age	
median	67
range	35–70
Performance status	
median	60
range	40–100
Prior therapy	17
radiotherapy	3
chemotherapy	5
radio- and chemotherapy	9
Tumor types	
head and neck	5
lung	3 (3)
gastrointestinal	2
kidney	2
cervix	1
ovary	1
adenoid cystic carcinoma	1
adrenal gland	1
melanoma	1
bladder	1

( ) = No. of patients with a second primary: head and neck (2), cervix (1).

Initial work-up included complete history and physical examination, complete blood cell counts, SMA-12 chemistries, urinalysis, chest radiograph and 12-lead electrocardiogram. The electrocardiogram was repeated within 2 and 24 hr of drug administration. A majority of patients had also a Holter survey for 24 hr prior to and after marcellomycin administration. Blood cell counts were scheduled 3 times per week and biochemical profiles once weekly. Other investigations were performed and repeated as indicated.

Marcellomycin was supplied by the Bristol-Myers Company, International Division, as a tartrate salt, each vial containing 10 mg of marcellomycin base plus L(+)-tartaric acid for injection. The drug was reconstituted with 10.3 ml of sterile water for injection; each vial yielded 10 mg deliverable dose containing 1 mg/ml of marcellomycin. The solution after reconstitution was stable for at least 24 hr at room

temperature. The drug was given i.v. over 15–30 min. Drug administration was followed by an infusion of fluids for at least 2 hr.

The study was designed to define a maximum tolerated dose for single-dose intermittent treatments. The starting dose was 5 mg/m^2, corresponding to 1/10 of the LD_{10} in mice, as currently recommended [15]. Doses were escalated by increments of 100% up to 40 mg/m^2 and by one increment of 50% thereafter. At the level of 60 mg/m^2 life-threatening toxicity was encountered and dosage in subsequent entries was reduced to 40 or 50 mg/m^2. Up to then retreatment at higher dose levels had been given when no significant toxic effects were encountered in previous courses. One to eight new patients were entered at each dose level from 5 to 50 mg/m^2. Two patients received one course, 9 patients received 2 courses and the remaining patients received 3–5 courses for a total of 45 courses.

Patients were carefully monitored to identify drug efficacy. Response to therapy and non-hematological toxic effects were assessed according to WHO criteria [16].

RESULTS

Of a total of 45 courses, 41 were fully evaluable. In 4 patients who received 2–4 courses of marcellomycin the last course was only partially evaluable: 2 had inadequate follow-up after a dose of 5 and 60 mg/m^2 respectively and 2 had most likely disease-related death on days 12 and 13 after a dose of 40 and 60 mg/m^2 respectively.

Myelosuppression was the main toxic effect encountered in this trial. It was dose-related and dose-limiting (Table 2). It was characterized by early thrombocytopenia with a nadir on days 9–13 and a somewhat delayed leukopenia with a maximum WBC depression between days 14 and 21. Complete recovery from thrombocytopenia could occur before the development of leukopenia. All but two leukopenic patients recovered from leukopenia within 3 weeks of drug administration. Thirteen patients had WBC $<4000/\mu l$ (6 courses), platelets $<100{,}000/\mu l$ (1 course) or both (17 courses). Life-threatening toxicity was encountered at the three highest dose levels; myelosuppression probably contributed to the death of two patients with far-advanced disease who had WBC $\leqslant 400/\mu l$ and platelets $\leqslant 5000/\mu l$ at 40 and 60 mg/m^2 respectively.

Myelosuppression was seen only at doses $\geqslant 40$ mg/m^2, with a considerable range in WBC and platelet nadirs at the same dose levels. This observation could be related, at least to some extent, to variations in pretreatment performance status. A comparison of data obtained at 40 and 50 mg/m^2 indicates, however, little effect of this prognostic feature on the degree of thrombocytopenia, which was more clearly dose-related than leukopenia. Three of the four patients entered at the dose level of 50 mg/m^2 with a

Table 2. Myelosuppression by marcellomycin at each dose level

Dosage (mg/m^2)	Karnofsky score	No. of patients/ No. of courses	Median nadir (cells × $10^3/\mu l$) WBC	PMN	Platelets
5		2/2	8.0 (6.9–9.1)	5.9 (4.2–7.6)	225 (200–250)
10		3/3	11.1 (10.8–13.4)	9.5 (7.2–11.0)	360 (190–490)
20		3/3	9.2 (5.5–11.8)	7.3 (4.2–10.7)	250 (250–330)
40		12/18	2.7 (0.1–14.7)	0.7 (0.1–12.9)	116 (5–418)
	40–60	8/10	1.3 (0.1–14.7)	0.4 (0.1–12.9)	90 (5–418)
	70	4/8	4.3 (1.5–8.4)	3.4 (0.5–6.7)	145 (94–185)
50		8/14	1.7 (0.9–4.2)	0.6 (0.1–1.3)	47 (23–176)
	60	4/5	1.1 (0.9–1.6)	0.4 (0.1–0.8)	47 (25–109)
	70–90	4/9	3.3 (2.0–4.2)	0.7 (0.1–1.3)	49 (23–176)
60		3/3	2.4 (0.4–5.8)	0.8 (0.2–3.4)	35 (1–271)

performance status of 60 and prior radiotherapy were retreated at 40 mg/m^2 because of excessive myelosuppression. Two of these patients had no prior chemotherapy and experienced similar hematologic toxicity at each dose level, whereas the third patient, who had previously received a mitomycin-containing regimen, did not show leukopenia or thrombocytopenia at the lower dose level. The three patients entered at 60 mg/m^2 had a performance status of 50–60; one showed no myelosuppression, one died presumably of septic shock related to leukopenia and one expired with abnormal hematologic values but was considered to have died from disease progression. Also of interest, 5 patients were retreated at the same toxic dose levels for 2–5 courses. Among these patients platelet nadirs varied between 94,000 and 177,000/μl in one, it decreased from 92,000–120,000/μl to 25,000–36,000/μl in three and increased from 62,000 to 155,000/μl in one. Less striking variations in leukopenia were observed in consecutive courses.

Nausea and vomiting occurred frequently and were occasionally severe despite prior i.v. administration of 20 mg of metoclopramide (Table 3). Stomatitis was also common and sometimes dose-limiting. It occurred generally within a few days after drug administration. Phlebitis at the injection site was noted in 14 courses. In one of these severe dermatitis followed extravasation of dextrose 5% in water 2 hr after apparently correct drug administration. Clearly drug-induced fatigue was noticeable in 4 patients at least. Infection and hemorrhage (hematochezia) in relation to myelosuppression were observed in a total of 4 patients, with documented sepsis in two.

EKG abnormalities, consisting of alterations in the ST-T wave, appeared within 24 hr of drug administration in 5 courses given to 4 patients at doses $\geqslant$40mg/m^2. Two of these patients had no Holter monitoring prior to their cardiotoxic course. These EKG changes were generally minor and aspecific. One patient, however, showed profound inverted T waves, suggestive of subendocardial infarction, at the dose of 60 mg/m^2. There was no evidence of cardiac damage on post-mortem examination on day 13 in this patient. None of the patients experienced congestive heart failure.

Negligible alopecia was also encountered. No other toxic effects were found in this trial. Of interest, one patient who had received 2 courses of marcellomycin developed leukonychia with a double transverse streak one week after having entered a subsequent phase I study with *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II (CBDCA).

Only 4 patients with colorectal cancer, ovarian cancer, renal cell cancer or adenoid cystic carcinoma had evaluable or measurable disease, received at least 2 courses of marcellomycin and experienced significant toxicity. All but one had received extensive prior chemotherapy. None of these patients showed evidence of antitumor activity.

DISCUSSION

In this trial marcellomycin produced dose-limiting bone marrow toxicity with early thrombocytopenia and delayed leukopenia. This pattern of myelosuppression is reminiscent of that reported with aclacinomycin A [13]. Hematologic tolerance to marcellomycin appeared to be largely affected by performance status. It could, however, remain highly variable even after adjustment of the data for this prognostic factor. Non-reproducibility of maximum myelosuppression was also evidenced in repeated courses in the same patients. Of note, a

Table 3. Non-hematological toxic effects

	Dosage (mg/m^2)					
	5	10	20	40	50	60
No. of courses	3	3	3	18	14	4
No. of patients	2	3	3	12	8	3
No. of toxic patients	0	1	3	9	8	3
Nausea and vomiting		1	3	7 (3)*	7 (3)	2
Stomatitis				3 (1)	6 (2)	1 (1)
Phlebitis				3	7 (1)	
Fatigue				3	3	
Infection				2 (1)	1 (1)	1 (1)
EKG				3	1	1
Alopecia				1	2	1
Hemorrhage				1	1	1

*No. of patients with severe toxic effects in parentheses.

preliminary report of a phase I trial with a weekly schedule also described erratic myelosuppression of marcellomycin [17].

All non-hematological toxic effects encountered with this new derivative seemed qualitatively similar to what may be observed with conventional anthracyclines. Stomatitis and phlebitis were perhaps unusually frequent, whereas alopecia was rare and minimal. The actual importance of drug-induced fatigue remains to be assessed in good-risk patients. Congestive heart failure was not noted with marcellomycin, but more prolonged treatments and larger patient populations are required to evaluate chronic heart damage clinically.

There was no evidence of anticancer effect in this trial. This fact should not prevent phase II trials from being initiated since it could result from an unfavorable selection of far-advanced malignancies often inadequately treated for proper assessment of antitumor activity. Our results would indicate that such trials should be undertaken with the greatest caution in poor-risk patients. Despite somewhat unpredictable myelosuppression, it appears that a dose schedule of 50 mg/m^2 repeated every 3 weeks would be appropriate for phase II trials in ambulatory patients.

Anthracycline antibiotics play a major role in cancer chemotherapy and represent a wide area of extensive research [18]. Preclinical and clinical experience accumulated with marcellomycin further underline problems encountered with current methods of selecting analogs for clinical trials. The drug was primarily introduced into clinical trials because of its potential for reduced myelosuppression. Minimal or no activity in the L1210 system has been proposed to be predictive for lack of myelosuppression in man [19]. Accordingly, our negative results with marcellomycin in this system were in agreement with the rationale for developing this new anthracycline [5].

Experiments with a cloning assay indicated that marcellomycin was toxic for human myeloid stem cells, and CFU-c inhibition with this drug occurred at significantly higher doses than with aclacinomycin A [5]. The maximum tolerated dose of aclacinomycin A at a single-dose intermittent schedule was 100–120 mg/m^2 in several phase I clinical trials [12–14]. Based on our *in vitro* results, the clinical maximum tolerated dose of marcellomycin could have been expected to be higher in the event of dose-limiting leukopenia. This erroneous prediction must be analyzed in the light of comparative clinical pharmacology investigations, but the pharmacokinetics of marcellomycin remain to be determined. Conclusions regarding the relevance of this cloning assay to assess hematologic tolerance to marcellomycin must also await results of ongoing studies correlating *in vitro* and *in vivo* drug effect in the same patients.

Finally, animal toxicology investigations also failed to predict that myelosuppression would be a major toxic effect in humans. Special sensitivity of the laboratory animals to a non-hematologic adverse reaction might account at least in part for these data. The low predictive value of animal findings must also be considered with toxicologic observations that are uncommonly seen in humans with other chemotherapeutic agents in general and anthracyclines in particular (e.g. lack of myelosuppression) [15].

Acknowledgement—The authors are grateful to Mrs Geneviève Decoster for secretarial assistance.

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