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A Phase I Trial of Marcellomycin with a Weekly Dose Schedule

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Abstract—*Marcellomycin, a new anthracycline antibiotic, was administered intravenously on a weekly schedule to 22 patients with advanced malignant solid tumors. Patients were treated at 6 dosage levels ranging from 5 to 30 mg/m² weekly for 4 weeks. Courses were repeated after a 3-week rest period. Hematologic toxicity was dose-limiting but unpredictable. Of 10 patients treated with weekly doses of 27.5 mg/m², 3 patients exhibited myelosuppression and 2 died in agranulocytosis. Moderate to severe nausea and vomiting occurred in 19 of 22 evaluable patients. Other toxic effects were non-acute and consisted of mild stomatitis, diarrhea, phlebitis and moderate fatigue in 1–3 patients each. In 17 patients evaluable for antitumor activity no partial or complete responses occurred. One patient with advanced breast cancer showed a mixed response. Marcellomycin given on a weekly dose schedule has unpredictable and erratic hematologic toxicity. The maximally tolerated dose appears to be between 27.5 and 30 mg/m² weekly. However, no firm recommendations can be given for a dose level that results in tolerable, predictable and reversible toxicity.*

INTRODUCTION

MARCELLOMYCIN is one of a series of anthracycline antibiotics synthesized in an effort to find agents having a therapeutic index superior to that of the parent compound, adriamycin. Marcellomycin is extracted from fermentation of *Actinosporangium* sp., together with other similar compounds [1]. The chemical structure of marcellomycin is closely related to that of aclacinomycin A. It is a trisaccharide anthracycline differing from adriamycin both in the aglycone (pyrromycinone) and in the glycosidic portions (one rhodosamine and two 2-deoxyfucose sugars in the C-7 position) [2]. Marcellomycin inhibits nucleolar RNA synthesis at concentrations 200-fold lower than whole-cell RNA or DNA [3]. The experimental evaluation of marcellomycin has shown antitumor activity against murine leukemias and solid tumors such as L1210, P388, B-16 melanoma and Lewis lung carcinoma [4]. However, additional screening experiments could not confirm the efficacy of marcellomycin against the L1210 leukemia and failed to identify antitumor activity against advanced P388 leukemia and i.v.-implanted Lewis lung carcinoma [5]. Minimal activity was found against colon 26 carcinoma and Madison 109 lung carcinoma. No schedule dependency was observed in the L1210 system with marcellomycin [2]. Acute toxicity studies in animals showed a steep slope in the dose-response curve. In BDF 1 mice the LD_{50} and LD_{10} values were 6 and 3.5 mg/kg respectively (i.p. route), whereas in Swiss Webster mice the LD_{50} and LD_{10} values were 19.9 and 17.4 mg/kg respectively (i.v. route).

In beagle dogs single i.v. doses resulted in no deaths at 2.87 mg/kg and 100% deaths at 3.69 mg/kg. Deaths occurred in laboratory animals mainly because of overt gastrointestinal toxicity with severe emesis and bloody diarrhea [6]. Preclinical toxicology studies in both rodents and beagle dogs showed minimal or no leucocyte suppression after single sublethal dosages. Moderate thrombocytopenia was noted in rats treated with marcellomycin at doses of 15 and 20 mg/kg [4]. The cardiotoxicity was investigated by measuring the CPK-MB isoenzyme in mice and

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by serially recording electrocardiograms in rats [7, 8]. The enzyme concentrations were elevated to a lesser extent after marcellomycin than to equitoxic doses of adriamycin. Unlike adriamycin, the administration of a maximally tolerated dose of marcellomycin i.p. for 5 days resulted in no appreciable lowering of the QRS voltage during the dosing period. These data are not conclusive but suggest a lower cardiac toxicity of marcellomycin than adriamycin.

These data prompted us to initiate a phase I trial of marcellomycin. This study, using a weekly i.v. schedule, was conducted within the framework of the new drug program of the Early Clinical Trials-Group of the EORTC.

MATERIALS AND METHODS

Twenty-two patients with advanced malignant neoplasms were entered into this phase I study. The patient characteristics are shown in Table 1.

Eligibility requirements for patients entered into this trial included histologic confirmation of a malignant solid neoplasm resistant to conventional therapy or patients with tumors unresponsive to conventional therapy. Furthermore the patients had to fulfill the following criteria: (1) age ≤ 75 yr; (2) a performance status (WHO) ≤ 3; (3) an estimated survival > 4 weeks; (4) complete recovery from toxicity of prior treatment; and (5) no history of congestive heart failure nor any evidence of ischemia or arrhythmias on EKG. A prior total dose of adriamycin of less than 300 mg/m^2 did not preclude from entry into the protocol. An acceptable hematologic status (WBC ≥ 4000/mm^3 and platelet count $\geq 100{,}000$/mm^3), adequate hepatic function (bilirubin ≤ 1.5 mg/dl) and adequate renal function (creatinine ≤ 1.5 mg/dl) were required in all patients.

Table 1. *Patients' characteristics*

Total No. of patients	22
Male:female	16:6
Age (yr)	
median	57
range	30–74
Performance status	
median	2
range	0–3
Prior therapy	22
radiotherapy	1
chemotherapy	18
1–3 drugs	8
> 3 drugs	10
radio- and chemotherapy	3
Tumor types	
nasopharyngeal carcinoma	1
adenocarcinoma of the parotid gland	1
lung cancer	8
squamous cell carcinoma	3
adenocarcinoma	1
anaplastic large cell carcinoma	3
small cell carcinoma	1
breast cancer	1
renal cell carcinoma	1
bladder cancer	2
uterine leiomyosarcoma	1
biliary cancer	1
colon cancer	1
adenocarcinoma of unknown primary origin	1
chondrosarcoma	1
soft tissue sarcoma	1
malignant melanoma	2

Pretreatment evaluation of the patients included a complete history and physical examination, and laboratory evaluation, consisting of a complete blood count, an SMA-12 chemistry panel, serum creatinine, urinalysis, stool test for occult blood, EKG and chest X-ray. Additional scans and radiologic studies as well as a bone marrow examination were obtained when indicated. Follow-up studies included twice weekly determinations of hemoglobin, WBC and platelet counts, a weekly differential white blood count, a weekly 12-channel biochemical profile and an EKG prior to each course of marcellomycin. In patients with measurable disease tumor response was assessed every 3 weeks according to standard criteria of response [9].

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 drug was given i.v. over 15 min. Drug administration was followed by an infusion of isotonic solutions for at least 1 hr.

The study was designed to define a maximum tolerated dose for a weekly dose schedule. The starting dose was 5 mg/m^2 weekly for 4 weeks, corresponding to 1/10 of the LD_{10} in mice, as currently recommended [10]. No dose reduction schema was adopted during the 4-week period of treatment. Doses were escalated as shown in Table 2. One to ten patients were entered at each dose level from 5 to 30 mg/m^2. Three patients were retreated at higher dose levels after a rest period of 4 weeks as no significant toxic effects were encountered in the previous course. Nineteen patients received one course (4 weekly injections), 2 patients received 2 courses and 1 patient received 3 courses.

Twenty-two of 26 courses were fully evaluable. One course was not evaluable as the treatment had to be interrupted after 2 doses because of rapid disease progression, with death on day 26. One patient with bronchogenic carcinoma died on day 4 from a massive pulmonary hemorrhage with normal leucocyte and platelet counts. Two

Table 2. Hematologic toxic effects

Dosage (mg/m^2)	No. of courses/ No. evaluable	Median nadir WBC $\times 10^3/mm^3$	Median day to: nadir (range)	recovery
Drug-induced leucopenia				
5	1/1	8.4	8	—
10	2/2	4.5/7.0	15/15	—
20	5/3	7.1 (5.1-9.3)	12 (4-37)	—
25	6/6	4.4 (1.4-6.5)	30 (10-36)	34
27.5	10/9	6.2 (0.2-9.4)	22 (8-31)	*
30	2/1	0.3	39	42
Drug-induced thrombocytopenia				
Dosage (mg/m^2)	No. of courses/ No. evaluable	Median nadir platelets $\times 10^3/mm^3$	Median day to: nadir (range)	recovery
5	1/1	256	15	—
10	2/2	169/209	15/15	—
20	5/3	218 (148-362)	22 (8-22)	—
25	6/6	188 (75-391)	19 (11-30)	*
27.5	10/9	122 (10-328)	20 (4-31)	*
30	2/1	40	35	39

*See text.

patients refused further treatment after 2 injections of marcellomycin.

RESULTS

The main toxic effect observed during this phase I trial was myelosuppression (see Table 2). Hematologic side-effects were first observed in patients receiving marcellomycin at a weekly dose of 25 mg/m^2. Two of six patients showed after 4 weekly injections leukopenias of 1400/mm^3 and 2100/mm^3 on days 30 and 36 respectively, with a prompt recovery after 4 and 6 days respectively. The patient with the WBC nadir of 1400/mm^3 also had thrombocytopenia, with a platelet count of 75,000/mm^3 on day 28, recovering promptly on day 32. Both patients with hematologic side-effects were fully ambulatory (performance status 0), but had been extensively pretreated with chemotherapy. At the dose level of 27.5 mg/m^2 3 patients exhibited hematologic side-effects and 2 patients died with septicemia during episodes of agranulocytosis. A 57-yr-old man with metastatic anaplastic large-cell carcinoma of the lung had been pretreated with VP 16-213, cisplatin, adriamycin and mitomycin. Upon entry in the trial this patient was partially bedridden, with a performance status of 3. After 2 weekly dosages of marcellomycin the leucocytes dropped to 3200/mm^3 and the platelets to 58,000/mm^3 on day 15. The patient was given a third dose of marcellomycin on day 18. The WBC dropped to 200/mm^3. The patient did not recover from hematologic toxicity, developed pneumonia and septicemia and died of respiratory failure on day 27. The second patient was a 72-yr-old male with a performance status of 1. He suffered from an adenocarcinoma of the lung with liver metastases and had previously been treated with 4'epiadriamycin and 9,10anthracenedicarboxaldehyde. At the time of study entry the alkaline phosphatase was slightly elevated to 64 IU/l (upper limit of normal 47 IU/l). The bilirubin, SGOT and SGPT were normal as well as the serum creatinine, leucocyte and platelet counts. The patient received 3 weekly doses of marcellomycin (27.5 mg/m^2 weekly). On day 15, when given the third injection, the patient exhibited normal hematologic values (WBC 8300/mm^3, platelets 114,000/mm^3). On day 22 the leucocytes had dropped to 1300/mm^3 and the platelets to 17,000/mm^3. The patient became septic the next day and died on day 26 with a WBC count of 400/mm^3 and platelets of 10,000/mm^3. Seven of ten patients treated at the dose level of 27.5 mg/m^2 weekly exhibited no hematologic side-effects whatsoever. Two patients were entered at the 30 mg/m^2 dose level. One patient received only 2 injections. Further therapy was deferred due to

rapid disease progression. This patient exhibited no hematologic toxicity. The second patient was a 38-yr-old man with a metastatic soft tissue sarcoma. The patient had been extensively pretreated with chemotherapy and was known for a fair bone marrow tolerance. He was in good general condition (performance status 1). After three weekly doses of 30 mg/m^2 marcellomycin the patient developed thrombocytopenia (70,000/mm^3 on day 33, 40,000/mm^3 on day 35), with full recovery on day 39. The leucocytes fell on day 37 to 1700/mm^3, with a nadir of 300/mm^3 on day 39. The patient became septic and developed a bilateral pneumonia, but recovered fully from hematologic toxicity on day 42.

The non-hematologic toxic effects are summarized in Table 3. Moderate to severe nausea and vomiting was common, occurring in 10 of 22 evaluable patients. A mild stomatitis lasting for 3 days occurred in one patient. Mild to moderate non-hemorrhagic diarrhea was observed in 3 patients. Two patients exhibited a mild phlebitis and 3 patients complained of moderate fatigue. No patient developed electrocardiographic abnormalities or clinical evidence of congestive heart failure. Only 6 of 22 patients were not bald at the time of study entry. There was no alopecia observed in these 6 patients.

Table 3. Non-hematological toxic effects

	Dosage (mg/m^2)					
	5	10	20	25	27.5	30
No. of evaluable courses	1	2	3	6	9	1
No. of toxic courses	0	2	3	6	8	1
Nausea/vomiting	0	1	3	6	8	1
Stomatitis	0	0	0	1	0	0
Diarrhea	0	0	0	2	1	0
Phlebitis	0	1	0	1	0	0
Fatigue	0	0	1	2	0	0
Infection	0	0	0	0	2	1

The antitumor activity was evaluable in 17 patients. No partial or complete remissions were observed. However, in one patient with advanced breast cancer marcellomycin at the dose level of 25 mg/m^2 induced a mixed response, with decrease in size of supraclavicular lymph-node metastases but progression of pulmonary metastases.

DISCUSSION

In this phase I trial of marcellomycin administered intravenously on a weekly dosage schedule myelosuppression was dose-limiting but unpredictable. Hematologic toxicity was first observed at the 25 mg/m^2 level in 2 patients with good performance status but extensive prior chemotherapy. At the dose levels of 27.5 and 30 mg/m^2 hematologic toxic effects occurred in 4 of 12 patients. Two of three patients with life-threatening or lethal hematologic toxicity had a good performance status but had been heavily pretreated. Four of the six patients with hematologic toxicity had been pretreated with more than 3 cytostatic agents, but only one of these patients had received prior chemotherapy with mitomycin and none was pretreated with nitrosoureas.

High variability of hematologic side-effects was also observed in a phase I trial with a single-dose schedule of marcellomycin, even after adjustment for performance status, which appeared to influence hematologic tolerance [11]. In our trial 4 of 6 patients with hematologic toxicity had a performance status of 0–1 and only 2 patients had a performance status of 2 or 3. Therefore our study does not suggest that performance status has an influence on the hematologic tolerance. In our study myelosuppression seemed, rather, to be related to previous extensive chemotherapy, as outlined above. On the other hand, 5 extensively pretreated patients, including one patient with prior mitomycin treatment, exhibited no hematologic toxicity after marcellomycin at dose levels of 25 and 27.5 mg/m^2 respectively. In summary, myelosuppression was felt to be too unpredictable to allow us to continue the study. We therefore terminated the trial without having clearly reached the maximally tolerated dose of marcellomycin given on a weekly dose schedule.

Non-hematologic toxic effects observed during our trial included moderate to severe gastrointestinal disturbances in the majority of the patients (19 of 22) and mild stomatitis, diarrhea, phlebitis and fatigue in 1–3 patients each. No alopecia was observed, but only 3 patients received more than one month of treatment and the majority of our patients were bald at the time of study entry. Although we did not observe any signs of impaired ventricular function, a full evaluation of the cardiotoxic potential of marcellomycin obviously requires observation of a larger patient population treated with marcellomycin and prolonged follow-up of patients who have received high total doses of the drug.

In conclusion, marcellomycin given on a weekly dose schedule has unpredictable and erratic hematologic toxicity. Further evaluation of the weekly dose schedule should be undertaken with extreme caution. The maximally tolerated dose appears to be between 27.5 and 30 mg/m^2 weekly. However, no firm recommendations can be given for a dose level that results in tolerable, predictable and reversible toxicity.

REFERENCES

1. NETTLETON DD JR, BRADNER WT, BUSCH JA *et al.* New antitumor antibiotics: musettamycin and marcellomycin from bohemic acid complex. *J Antibiot (Tokyo)* 1977, **30**, 525–529.
2. BRADNER WT, MISIEK M. Bohemic acid complex. Biological characterization of the antibiotics musettamycin and marcellomycin. *J Antibiot (Tokyo)* 1977, **30**, 519–522.
3. CROOKE ST, DUVERNAY UH, GALVAN L, PRESTAYKO AW. Structure–activity relationship of anthracyclines relative to effects on macromolecular synthesis. *Mol Pharmacol* 1978, **14**, 290–298.
4. REICH SD, BRADNER WT, ROSE WC *et al.* Marcellomycin. In: CROOKE ST, REICH SD, eds. *Anthracyclines: Current Status and New Developments.* New York, Academic Press, 1980, 343–364.
5. ROZENCWEIG M, NICAISE C, DODION P *et al.* Preliminary experience with marcellomycin: preclinical and clinical aspects. In: MUGGIA FM, ed. *Anthracycline Antibiotics in Cancer Therapy.* New York, Martinus Nijhoff, In press.
6. HIRTH RS. Other toxicities associated with anthracyclines in animal systems. In: CROOKE ST, REICH SD, eds. *Anthracyclines: Current Status and New Developments.* New York, Academic Press, 1980, 221–240.
7. SCHURIG JE, BRADNER WT, HUFTOLEN JB *et al.* Screening anthracyclines for side effects in mice. In: CROOKE ST, REICH SD, eds. *Anthracyclines: Current Status and New Developments.* New York, Academic Press, 1980, 141.
8. BUYINSKI JP, HIRTH RS. Anthracyclines cardiotoxicity in the rat. In: CROOKE ST, REICH SD, eds. *Anthracyclines: Current Status and New Developments.* New York, Academic Press, 1980, 157.
9. *WHO Handbook for Reporting Results of Cancer Treatment.* Geneva, WHO, 1979.
10. ROZENCWEIG M, VON HOFF DD, STAQUET MJ *et al.* Animal toxicology for early clinical trials with anticancer agents. *Cancer Clin Trials* 1981, **4**, 21–28.
11. NICAISE C, ROZENCWEIG M, DE MARNEFFE M *et al.* Clinical phase I trial of marcellomycin with a single-dose schedule. *Eur J Cancer Clin Oncol* 1983, **19**, 449–454.