Cancer Chemother. Pharmacol. 5, 11–15 (1980)

Cancer Chemotherapy and Pharmacology

Phase I Clinical Trial of Mitoxantrone: A New Anthracenedione Anticancer Drug

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Summary. *Mitoxantrone, 1,4-dihydroxy-5,8-bis(((2-[(2-hydroxyethyl)amino]ethyl) amino))-9,10-anthracenedione dihydrochloride, a new antitumor agent was evaluated in nine cancer patients as part of a phase I trial. In general, the drug was well tolerated. Leukopenia was the dose-limiting toxic effect. Mild to moderate leukopenia (but not neutropenia or thrombocytopenia) occurred in four of six patients given 4 mg/m²/week after a mean of 2.75 doses (range, 2–4 doses) and in all three patients given 5 mg/m²/week after three doses. Only one patient had mild nausea and vomiting. No patient experienced alopecia or mucositis, and none showed evidence of any cardiac, renal, hepatic, or pulmonary abnormality. Mitoxantrone treatment induced two partial remissions (patients with metastatic squamous cell carcinomas of the hypopharynx and rectum) and one mixed response (patient with gastric carcinoma). For phase II studies the starting dose, when used on a weekly schedule, should be 5 mg/m² in patients who are known to have adequate bone marrow reserve.*

Introduction

The compound 1,4-dihydroxy-5,8 bis(((2-[(2-hydroxyethyl)amino] ethyl)amino))-9,10-anthracenedione dihydrochloride (NSC 301739) (mitoxantrone) is a new anthracenedione derivative [1–5], which has superior or equal antitumor activity to doxorubicin in a number of animal tumor systems but no proven cardiotoxicity [5].

Pre-clinical toxicology showed that mitoxantrone caused dose-related but reversible leukopenia, anemia, and bone marrow hypoplasia in Beagle dogs and cynomolgus monkeys. Other toxicities included vomiting and diarrhea, which were associated with histologically demonstrable enterocolitis. Light and electron microscopy studies of left ventricular papillary muscles and intraventricular septa showed no evidence of drug-induced cardiotoxicity.

Von Hoff et al. have recently completed a phase I clinical trial of mitoxantrone which showed dose-limiting but rapidly reversible leukopenia and thrombocytopenia at a dose of 12 mg/m² as an IV infusion (over 30 min) every 4 weeks [6]. Nausea, vomiting, and diarrhea were uncommon (i.e., about a 10% incidence). There was no evidence of alopecia, azotemia, or cardiotoxicity. Of the 25 patients treated in this phase I study one patient with an adenocarcinoma of the lung responded to mitoxantrone with a partial remission.

We have carried out a phase I clinical trial of mitoxantrone, administered on a once-weekly schedule. At 4–5 mg/m² mitoxantrone caused dose-limiting leukopenia; we recorded two partial responses in patients with squamous cell carcinomas of the hypopharynx and rectum and a mixed response in a patient with gastric adenocarcinoma.

Materials and Methods

Patient Characteristics

The characteristics of the nine cancer patients who received mitoxantrone are listed in Table 1. All patients had histologically confirmed malignancies, an estimated survival of greater than 6 weeks and prior treatment with multiple chemotherapeutic agents (an average of five different drugs). Six of the nine patients had received prior radiotherapy, but all patients had far-advanced, measurable cancers at the time of mitoxantrone treatment. All patients had adequate blood cell counts (WBC > 3000/mm³ and platelets > 100 000/mm³) and normal renal and liver function tests. Informed consent was obtained prior to treatment.

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0344-5704/80/0005/0011/$ 01.00

Table 1. Patient characteristics

Patient	Sex	Age (yrs)	Type of cancer	Cancer sites and size	Prior chemotherapy
1	F	70	Melanoma	Multiple skin metastases on vulva and thighs (1.5 cm); multiple pulmonary nodules	BCNU, hydroxyurea, DTIC Melphalan Adriamycin, actinomycin-D Retinyl palmitate *cis*-Platinum mAMSA
2	F	62	Colon carcinoma	Multiple pulmonary nodules and diffuse interstitial disease	5-Fluorouracil Adriamycin, mitomycin-C CCNU
3	F	67	Breast carcinoma	Multiple skin metastases, anterior chest wall	Cyclophosphamide, methotrexate, 5-fluorouracil, tamoxifen Adriamycin, cyclophosphamide, vincristine 13-*cis*-Retinoic acid
4	F	64	Squamous cell carcinoma of the rectum	Left supraclavicular mass (2 × 2 cm); rectal ulcer with multiple areas of nodularity	Mitomycin-C, vincristine, bleomycin Retinyl palmitate
5	M	63	Gastric carcinoma	Multiple 2 mm to 2 cm skin nodules, face and arms; alkaline phosphatase 608 units; left upper lobe pulmonary nodules	5-Fluorouracil, adriamycin, mitomycin-C 13-*cis*-Retinoic acid
6	M	68	Liposarcoma	Retroperitoneal mass (7.2 × 7.5 cm)	Adriamycin (intra-arterial) Vindesine
7	M	65	Renal cell carcinoma	Right hilar mass (9.5 × 6.5 cm); abdominal mass (17 × 22 cm)	Adriamycin, cyclophosphamide, vincristine, bleomycin, tamoxifen MGBG
8	M	56	Lung (adenosquamous) carcinoma	Multiple pulmonary nodules (0.5 × 1.0 cm); skin nodules (0.5 × 0.5 cm)	5-Fluorouracil, vincristine, mitomycin-C 5-Fluorouracil, vindesine, mitomycin-C mAMSA
9	M	66	Hypopharyngeal squamous cell carcinoma	Bilateral neck masses (8 × 4 cm)	Methotrexate, bleomycin, *cis*-Platinum

Treatment Plan

Mitoxantrone was formulated and supplied for clinical use by the American Cyanamid Company at a drug concentration of 0.5 mg per ml solution (calculated as the free base). Mitoxantrone was infused over 30 min in 100 ml 5% dextrose in water. The starting dose of 4 mg/m^2 once weekly was determined by taking one-third of the maximally tolerated monthly human dose of 12 mg/m^2 [6].

Study Parameters

During treatment, the patients had weekly complete blood counts with differential and platelet counts, SMA-20 chemistry panels, urinalyses and electrocardiograms. Other laboratory and radiologic examinations for evaluation of tumor size were performed at 1- to 2-week intervals.

Termination of the Study

Individual patients were taken off study if objective tumor progression or clinical deterioration occurred following two to four doses of mitoxantrone. The phase I study was terminated when the maximally tolerated dose was established.

Table 2. Mitoxantrone doses, toxicities, and response

Patient	Mitoxantrone dose (mg/m^2)	Total dose (mg)	Number of doses	Nadir WBC ($\times 10^3$/mm^3)	Week of nadir WBC	Response	Comments
1	4	6.4	3	2.8	4	No response	Prior pelvic irradiation
2	4	6.8	2	2.6	3	Increasing disease	EKG changes of ischemia; 2° hypoxia from pulmonary metastases
3	4	6.4	4	2.7	5	Increasing disease	Blue skin discoloration at site of IV injection, left hand, without resultant inflammation
4	4	6.4	6	1.8	3	Partial response	Prior pelvic irradiation > 50% regression left supraclavicular mass and rectal ulcer for 6 weeks
5	4	8.0	4	5.8	No leukopenia	Mixed response	Flattening of skin lesions and alkaline phosphatase down to 234 units; Hgb down by 2.1 gm%; 2° gastric bleeding
6	4	6.7	5	7.3	No leukopenia	Increasing disease (seen on CT scan)	Pre-existing arteriosclerotic coronary artery disease – there was no change in cardiac status on mitoxantrone
7	5	7.7	3	1.8	4	Increasing disease	WBC > 3,000/mm^3 by week 6
8	5	10.0	4	1.9	4	No response	WBC > 3,000/mm^3 by week 6
9	5	10.0	4	2.5	4	Partial response	Bilateral neck masses decreased to 4 × 2 cm by 4th week Dead of tracheostomy hemorrhage in partial remission during 5th week WBC 5,100 and platelets 434,000/mm^3 3 days prior to death

Results

Nine patients were entered into this study over a 5-month period. As shown in Table 2, 35 doses of mitoxantrone were administered with four patients receiving four doses, two patients receiving three doses, and one each receiving two, five, and six doses.

Toxicity

Leukopenia (WBC $< 3000/mm^3$) was the dose-limiting toxic effect of mitoxantrone therapy (Table 2). Mild (WBC $< 2000-2999/mm^3$) to moderate (WBC $< 1000-1999/mm^3$) leukopenia occurred after a mean of 2.75 weekly doses (range, 2–4 doses) in four of the six patients who received the 4 mg/m^2 doses. These four leukopenic patients had previously received pelvic irradiation and/or extensive multiple-agent chemotherapy. All three patients on 5 mg/m^2 of mitoxantrone became leukopenic after three weekly doses. No patient had neutropenia (i.e., neutrophil count $< 500/mm^3$), and leukopenia reversed within 7–14 days after cessation of therapy in all cases. The platelet count remained above $150,000/mm^3$ throughout the period of mitoxantrone treatment in all nine patients.

Only one patient (No. 5, Table 2) had mild nausea and vomiting, which occurred for up to 12 h after each weekly mitoxantrone dose. This patient had gastric cancer and far-advanced intra-abdominal carcinomatosis, which may have contributed to a decreased threshold for emesis. Drug extravasation did occur in one patient but resulted in only a reversible bluish skin discoloration. No patient experienced alopecia or mucositis, and none showed evidence of any cardiac, renal, hepatic, pulmonary or neurologic abnormality attributable to mitoxantrone therapy.

Antitumor Activity

Mitoxantrone induced two partial remissions (i.e., 50% regression of the sums of the products of all measurable tumor masses), and one mixed response (i.e., objective regression of one set of tumor masses and progression of others) (Table 2). Patient 9 had a greater than 50% regression of large (i.e., 8×4 cm) bilateral neck metastases from a hypopharyngeal carcinoma following the third dose of mitoxantrone at 5 mg/m^2. Unfortunately he died of a massive hemorrhage from his tracheostomy 1 week after the fourth mitoxantrone dose. Three days prior to death his WBC was 5,100 and platelet count was $434,000/mm^3$. Patient 4 had a 60% regression in her left supraclavicular metastasis and a 50% regression in the primary squamous cell carcinoma in her rectum for a period of 6 weeks. Finally, patient 5 had a greater than 60% decrease in serum alkaline phosphatase (i.e., 608 to 234 units) and flattening of multiple facial and upper extremity skin metastases from his gastric cancer while on mitoxantrone therapy. Unfortunately, his general condition deteriorated during that period, perhaps owing to progression of intra-abdominal metastases.

Discussion

mitoxantrone, an anthracenedione derivative, is a member of a new class of antitumor agents [1–5]. It proved to be very well-tolerated therapy in this phase I trial. Dose-limiting leukopenia occurred after two to four weekly doses of 4–5 mg/m^2 in seven of nine patients, but no other important local or systemic toxicities were observed. Although this study was intended primarily to determine the maximal safe, weekly dose, therapeutic effects were observed. Two partial responses and one mixed response occured in nine patients.

For phase II studies the starting dose of mitoxantrone, when used on a weekly schedule, should be 5 mg/m^2 in patients who are known to have adequate bone marrow reserve (i.e., no history of extensive abdominal or pelvic irradiation or severe hematologic toxicity from prior chemotherapy). A dose of 4 mg/m^2 per week should be used in patients who have been shown to have inadequate bone marrow reserve. Patients should tolerate the 4–5 mg/m^2 weekly dosing schedule for 3–4 weeks before developing mild to moderate leukopenia. Thereafter, therapy should be continued in responding patients at 1- to 2-week intervals as tolerated.

There was no evidence of drug-related cardiotoxicity in this limited phase I trial. The ultrastructural results of studies on rat and dog hearts as well as the preliminary results of the phase I trial of Von Hoff et al. [6] suggest that cardiotoxicity should not be a dose-limiting problem of mitoxantrone therapy. The documentation of mitoxantrone's apparent lack of adverse cardiac effects will require extended phase II trials.

Acknowledgements. We wish to thank Drs. Sydney Salmon, Bruce Dana, and Heather Allen for contributing patients to this study.

This work was supported by a grant from the Department of Clinical Pharmacology, Medical Research Division, The American Cyanamid Co., Pearl River, NY.

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Received April 14/Accepted June 5, 1980