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# Chemotherapy in Metastatic Melanoma: Phase II Studies of Amsacrine, Mitoxantrone and Bisantrene

ALAN S. COATES,*†‡ J. BISHOP,§ G. J. MANN*† AND DEREK RAGHAVAN†

*Ludwig Institute for Cancer Research (Sydney Branch), University of Sydney, Sydney, NSW 2006, Australia, †Department of Clinical Oncology, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia, ‡The Melanoma Unit, Royal Prince Alfred Hospital, Camperdown NSW 2050, Australia and §The Cancer Institute, 481 Little Lonsdale St., Melbourne, VIC 3000, Australia

**Abstract**—*In a phase II study 20 patients with measurable metastatic melanoma were treated with amsacrine 120 mg/m² every 3 weeks. No objective responses were observed. In a separate study 29 patients received mitoxantrone 12–14 mg/m² every 3–4 weeks. One objective partial response was seen. The drug was well tolerated. Seventeen patients were treated with bisantrene 135–200 mg/m² weekly. No objective responses were observed. Phlebitis was the major non-hematologic toxicity of bisantrene. These agents are not recommended for treatment of malignant melanoma.*

## INTRODUCTION

BECAUSE of the resistance of melanoma to standard agents [1], we have performed a series of phase II studies in this disease. Amsacrine (4′-(9-acridinylamino) methanesulfon-*m*-anisinide, AMSA, NSC-249992) is an acridine derivative described by the late Bruce Cain. The anthracenedione drugs mitoxantrone (1,4-dihydroxy-5,8-bis[(2(2-hydroxyethyl)amino ethyl)amino]-9,10-anthracendione dihydrochloride, NSC-310739) and bisantrene (9,10-anthracene dicarboxaldehyde [bis(4,5-dihydro-1H-imidazol-2-yl)hydrozone] dihydrochloride, NSC-337766) are a new class of drugs chemically related to the anthracyclines. We describe our experience using these agents in melanoma.

## MATERIALS AND METHODS

Patients eligible for study had measurable or evaluable recurrent or metastatic melanoma. Prior chemotherapy must not have been given within 3 weeks before study entry. ECOG performance status of 0–3, WBC $> 3.0 \times 10^9/l$, platelet count $> 125 \times 10^9/l$, serum bilirubin and creatinine $< 1.25$ times normal were required. Pregnant or lactating patients, and those with unstable cardiac rhythm, cardiac failure or significant coronary artery disease were excluded. All patients gave informed consent in accordance with the requirements of Institutional Ethics Review Committees. Details of prior therapy, performance status and sites of evaluable disease are summarized in Table 1. Two-thirds of entered patients had received 0–1 prior chemotherapy regimens. Patients were defined as 'good risk' if they were aged less than 65 yr with neither known bone marrow infiltration nor prior therapy with nitrosoureas or mitomycin, had tolerated any previous chemotherapy well and had not received radiation therapy to more than 50% of bone marrow. All others were regarded as 'bad risk' for dosage purposes.

Amsacrine was supplied by Parke Davis Pty Ltd as ampoules containing 75 mg of amsacrine in anhydrous *N*–*N*–dimethylacetamide. Prior to use each ampoule was mixed with 13.5 ml lactic acid, then the calculated dose was further diluted in 500 ml of 5% dextrose. Mitoxantrone was supplied by Cyanamid Australia Pty Ltd in vials containing sterile solution of 20 mg mitoxantrone in 10 ml. The calculated dose was diluted to 100 ml in 5% dextrose and administered as a 30-min i.v. infusion. Bisantrene was supplied by Cyanamid Australia Pty Ltd as lyophilized powder equivalent to 250 mg of bisantrene-free base without preservative, and was reconstituted with 5.0 ml of sterile water, then administered in 1 l of 5% dextrose within 2 hr. Solutions were protected from light.

Amsacrine was administered every 3 weeks in a dosage of 120 mg/m² for good risk patients or 90 mg/m² for poor risk patients. Mitoxantrone was administered every 3 weeks. For good-risk patients the dose was 14 mg/m² and for poor risk patients 12 mg/m². Bisantrene dosage followed phase I results [2]. For good risk patients the dose was 200 mg/m² weekly; for bad risk patients 135 mg/m². After three doses of bisantrene, patients were observed for at least 2 weeks or until toxicity resolved. Dosage modifications of all three drugs

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*Table 1. Patient characteristics*

| | Amsacrine | Mitoxantrone | Bisantrene |
|---|---|---|---|
| Number entered (M:F) | 29 (21:8) | 29 (22:7) | 17 (12:5) |
| ECOG Performance status | | | |
| 0 | 8 | 17 | 7 |
| 1 | 11 | 9 | 5 |
| 2 | 9 | 3 | 2 |
| 3 | 0 | 0 | 3 |
| No. of prior chemotherapy regimens | | | |
| 0 | 4 | 9 | 6 |
| 1 | 15 | 9 | 8 |
| 2 | 7 | 8 | 3 |
| 3 | 2 | 2 | 0 |
| 4 | 1 | 1 | 0 |
| No. with prior radiotherapy | 4 | 8 | 7 |
| No. of patients with evaluable disease at site: | | | |
| Lung | 12 | 19 | 12 |
| Node | 8 | 14 | 3 |
| Skin/soft tissue | 21 | 14 | 11 |
| Abdomen | 3 | 2 | 2 |
| Breast | 0 | 1 | 2 |
| Liver | 3 | 1 | 3 |
| Bone | 1 | 1 | 2 |
| No. of patients with disease: | | | |
| Confined to skin, nodes and soft tissue | 10 | 7 | 2 |
| In viscera or bone | 19 | 22 | 15 |

were defined for hepatic dysfunction and hematologic toxicity. After initial experience of superficial thrombophlebitis at the injection site in patients receiving bisantrene, several patients received an infusion of 50 ml of 20% fat emulsion ('Intralipid', Tuta Laboratories (Australia) Pty Ltd) before and after bisantrene infusion, but this proved ineffective in preventing phlebitis. Three patients received bisantrene by central venous catheter: in one the catheter was removed because of fever. In most cases a central catheter was not acceptable to patients and clinicians for administration of an investigational agent. Standard definitions of response categories and toxicity [3] were used. The exact one-sided binomial upper 95% confidence limit of response rate in the various groups were calculated.

## RESULTS

*Amsacrine*

No objective responses were observed among the 29 patients. When all 29 patients were considered, the response rate was estimated as less than 10%, while the 20 patients receiving at least two cycles yielded an estimate of less than 14%. Overall, the median time to disease progression was 5 weeks (range 1–16 weeks) and the median survival 14 weeks (range 1–100 weeks) from the initiation of treatment. Myelosuppression was the major adverse effect (Table 2), and led to one drug-related death.

*Mitoxantrone*

One objective partial response lasting 6 months was seen in a patient with metastatic disease in left hilar node and lung. After six cycles treatment was discontinued, and reintroduced at the time of disease progression, when stable disease status lasting 23 weeks was achieved. This patient received a total of 152 mg/m$^2$ of mitozantrone. The one response among 29 patients indicated a response rate of less than 16%. Overall, the median time to disease progression was 5 weeks (range 3–47 weeks) and the median survival from the time of starting mitoxantrone was 21 weeks (range

*Table 2. Toxicity – WHO grades* [3]

| | Amsacrine | Mitoxantrone | Bisantrene |
|---|---|---|---|
| Cycles administered | 60 | 58 | 39 |
| WBC | | | |
| 0 | 19 | 15 | 12 |
| 1 | 10 | 14 | 9 |
| 2 | 13 | 13 | 4 |
| 3 | 7 | 11 | 1 |
| 4 | 2 | 1 | 0 |
| ? | 9 | 4 | 13 |
| Platelets | | | |
| 0 | 49 | 47 | 25 |
| 1 | 2 | 0 | 1 |
| 2 | 0 | 1 | 0 |
| 3 | 0 | 1 | 0 |
| ? | 9 | 9 | 13 |
| Nausea and vomiting | | | |
| 0 | 38 | 31 | 11 |
| 1 | 10 | 21 | 13 |
| 2 | 6 | 2 | 5 |
| 3 | 0 | 1 | 0 |
| ? | 6 | 3 | 10 |
| Diarrhea | | | |
| 0 | 53 | 54 | 30 |
| 1 | 1 | 3 | 0 |
| ? | 6 | 2 | 9 |

? = grade not recorded.

3–134+ weeks). Moderate leukopenia was the major hematologic toxicity, and other side-effects were rare and mild (Table 2). There was no clinical or autopsy evidence of cardiac toxicity in patients who received 152mg/m$^2$, and cardiac toxicity was not encountered in the other patients treated with mitoxantrone. There were no drug-related deaths.

*Bisantrene*

No objective tumor responses were observed. Because of thrombophlebitis, only ten patients treated with bisantrene received more than a single injection, fewer than the number usually accumulated in a phase II trial [4], but sufficient to exclude a response rate exceeding 26%. When all 17 patients were considered, the success rate for the policy of commencing bisantrene was estimated as less than 17%. The median time to disease progression was 5 weeks (range 2–15 weeks). Median survival from the start of bisantrene treatment was 18 weeks (range 2–63 weeks). Thrombophlebitis occurred at the infusion site in most infusions given into a peripheral vein, including those accompanied by intravenous fat emulsion. Hematologic toxicity was not assessed after 13 of 39 doses because of difficulties in venous access and patient compliance, but when measured was generally mild (Table 2), with only one patient showing grade 3 leucopenia. Other toxicities were not a problem. There were no drug-related deaths.

## CONCLUSION

The lack of activity of amsacrine, mitoxantrone and bisantrene is in accordance with previous reports [5–7]. There remains a need for effective new agents for the treatment of metastatic melanoma.

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