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Phase II Trial of Amsacrine (*m*-AMSA) in Advanced Ovarian Carcinoma*†

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Abstract—*A phase II study of 4'-(9-acridinylamino)methanesulfon-m-anisidide (amsacrine, m-AMSA) was carried out in previously treated patients with advanced ovarian carcinoma. The dose of amsacrine was 90 mg/m² every 3 weeks in 34 patients having received prior extensive chemotherapy and/or radiotherapy, and 120 mg/m² in 5 patients who had previously only received moderate amounts of chemotherapy. Among patients evaluable for response the median number of courses was 3 (range 2–17). Two patients (5%) experienced complete response for 15+ months. Leucopenia was the most frequent toxic effect. WBC nadir was 2700/mm³ (range 1000–7300). Other toxic effects were of lesser significance and included thrombocytopenia, anemia, nausea and vomiting. It is concluded that amsacrine has only marginal activity in patients with previously treated ovarian carcinoma.*

INTRODUCTION

AMSACRINE (*m*-AMSA, NCS 249992, 4'-(9-acridinylamino)methanesulfon-*m*-anisidide) is an acridine derivative synthesized by Cain and Atwell [1]. It is believed to act by intercalation, with a suggestion of base specificity for adenine–thymine pairs [1], and antitumor activity has been shown against a wide spectrum of animal leukemias and solid tumors [1].

Phase I studies have been performed with a variety of schedules [2–6]. In trials with solid tumors, the dose-limiting factor of amsacrine was myelosuppression, generally without any other major effect. Overall, the drug was well tolerated, with mild predictable and reversible toxicity.

A large number of phase II studies have been performed [7–15] and some activity has been reported in acute leukemia, breast cancer, lymphoma and melanoma. In this article we report the results of a phase II evaluation of amsacrine in patients with advanced ovarian carcinoma.

MATERIALS AND METHODS

Patients included in the study had histologically proven serous, mucinous, endometroid or undifferentiated ovarian carcinoma FIGO stage III and IV not amenable to conventional therapy. Subtyping and grading were not performed. The disease had to be measurable for inclusion of the patient in the trial. Pleural effusion, ascites, osseous and CNS metastases were not acceptable as measurable lesions. Lesions measured by ultrasound or CT scans only were considered evaluable provided that their malignant nature was pathologically demonstrated.

An eligible patient should have an expected survival of at least 2 months and no radiotherapy or chemotherapy for at least 4 weeks prior to entry in the study. This time interval was 6 weeks for patients who had received extensive radiotherapy or treatment with nitrosoureas. WBC $\geq 4000/\mu l$, platelets $\geq 100{,}000/\mu l$, creatinine < 1.5 mg% ($120\ \mu mol/l$), and bilirubine < 2.5 mg% ($40\ \mu mol/l$) were mandatory.

Initial work-up included physical and pelvic examination. Blood counts, liver function test and serum creatinine evaluations were repeated weekly in the first course and every 3 weeks thereafter. Response to therapy was assessed after 2 courses.

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In most patients the starting dose of amsacrine was 90 mg/m^2, repeated every 3 weeks. Dosage was increased to 120 mg/m^2 in patients without extensive prior chemotherapy and/or radiotherapy. Patients had to be treated for a minimum of 2 courses (42 days) to be evaluable. Amsacrine was postponed by a week if myelosuppression (WBC $< 3000/\mu l$, platelets $< 100{,}000/\mu l$) persisted at scheduled retreatment. Doses were modified according to myelosuppression in previous courses as follows: if the nadir values of WBC and platelets between two courses were $< 1500/\mu l$ and/or $< 50{,}000/\mu l$, the next dose of amsacrine was reduced to 2/3. If WBC and platelets were not below $4000/\mu l$ and 100,000 $\mu l/l$ respectively after 2 courses, the next dose of amsacrine was increased by 1/3.

Amsacrine was supplied by the Warner-Lambert Company, Morris Plains, NJ, U.S.A. in 2 ml ampules containing 1.5 ml of a 50 mg/ml solution of amsacrine in anhydrous N,N-dimethylacetamide. This mixture was dissolved in 13.5 ml lactic acid prior to treatment and the solution was infused in 500 ml isotonic (5%) glucose for one hour.

Definitions for response were identical to the WHO criteria [16]. with the exception that response duration was always calculated to start when responses were observed. Patients with objective response or stable disease (NC) were treated until progression. Informed consent from the patient was necessary before starting the treatment with amsacrine.

RESULTS

From August 1979 to April 1980, 50 patients entered the study. Of these, 49 patients were eligible and 39 were evaluable. Ten patients received one course of chemotherapy and were excluded from the analysis. They were excluded because of death within 7–20 days from initiation of therapy (4 patients), disease progression with worsened condition (5 patients) and treatment refusal (1 patient).

Among fully evaluable patients, median age was 55 years (range 26–70) and median Karnofsky index was 80 (range 50–100) (Table 1). Median time from histologic diagnosis to start of protocol treatment was 13 months (range 1–72). Prior treatment included chemotherapy alone in 32 patients and chemotherapy + radiotherapy in 7 patients. All patients had already received one alkylating agent and 21 (54%) had received adriamycin. Overall 64% had responded to previous chemotherapy.

Indicator lesions included pelvic or other intra-abdominal tumor masses in 82%, cutaneous metastases in 11%, lungs in 11% and peripheral lymph nodes in 8% of the patients. Among the 39 patients evaluable for response, the medium number of courses of amsacrine was 3 (range 2–17).

In this trial 2 of the 39 patients achieved response with amsacrine, for an overall response rate of 5% (95% confidence limits 1–15%). One patient with histologically documented abdominal disease previously treated with an alkylating agent is in complete remission. This complete remission was substantiated by a second-look operation performed after 16 courses of amsacrine. Remission was unmaintained thereafter and is still ongoing for 15+ months. Another patient previously treated with adriamycin, cisplatin and hexamethylmelamine had complete disappearance of liver metastases on CT scan and a complete remission of a pelvic mass, both of 15+ months duration. Among the 37 non-responders, 9 had NC in a median of 5 months (range 2–12).

Table 1. Patient characteristics

No. of patients fully evaluable	39
Median age in years (range)	55 (26–70)
Median Karnofsky index (range)	80 (50–100)
Site of indicator lesions (1 or more)	
pelvis + abdomen	82%
skin	11%
lungs	11%
peripheral lymphnodes	8%
Prior chemotherapy	
alkylating agents	100%
adriamycin	54%
others [cisplatin, fluorouracil, hexamethylmelamine, methotrexate and etoposide (VP-16-213)]	72%
Response to previous chemotherapy	64%
Prior radiotherapy	23%

Toxicity

The median lowest WBC during the whole treatment was 2700/μl, with a range from 1000 to 7300 respectively. Fifty-four per cent of the evaluable patients had WBCs below 3000/μl in at least one course. In the first course of amsacrine, WBC median and range after 0, 1, 2 and 3 weeks were 5000 (4000–12,100), 3400 (1400–5900), 2900 (1700–7500) and 4300 (2100-9600) in 30 patients with weekly cell counts.

Thrombocytopenia occurred less frequently and only 22% of patients had platelets below 100,000/μl in at least one course. The median lowest platelet count was 215,000/μl, with a range of 19,000–424,000. No significant anemia was noted. No life-threatening infection or signs of clinical bleeding was observed.

Non-hematological side effects of amsacrine were modest. Fifty-eight per cent of the patients experienced mild to moderate nausea and vomiting in at least one course. No signs of liver and kidney function abnormalities were observed. No patients developed cardiac arrhythmias or neurologic manifestations.

DISCUSSION

Previous experience with amsacrine in ovarian carcinoma is limited to patients treated in phase I studies. One out of seven reported patients with this disease achieved a minor response in these studies [5, 6]. Response rate was disappointingly low in our trial. Patients had relatively good performance status, but all had been previously treated with an alkylating agent and 80% also had other drugs, including adriamycin (54%), cisplatin, fluorouracil, hexamethylmelamine, methotrexate and etoposide (VP-16-213). The extent of prior therapy might account, at least in part, for the low response rate seen with amsacrine [17].

Of the two patients responding in this study one had previously received adriamycin. Data regarding cross-resistance between amsacrine and adriamycin are inconclusive. Cross-resistance has been reported in the P388 mouse leukemia [18], but responses to amsacrine have been observed in apparently adriamycin-resistant breast cancer and acute leukemia [11].

The low response rate in the present study could also be ascribed to suboptimal dosage of amsacrine. Dose levels chosen for this trial were based on phase I data reported by Von Hoff *et al.* [5]. Only modest hematologic toxicity was observed with these dose levels in other studies [8, 12, 14, 15]. Higher drug doses could have conceivably resulted in an increased response rate, as suggested by the encouraging results obtained in acute leukemia with high-dose regimens [11].

We conclude that amsacrine as second- or third-line chemotherapy at the dose and schedule used in this group of patients has only minimal antitumor effect as a single agent in the treatment of advanced ovarian carcinoma.

REFERENCES

1. WEISS RB, LLOYD MC, MACDONALD JS. *m*-AMSA: An exciting new drug in the National Cancer Institute Drug Development Program. *Cancer Clin Trials* 1980; **3**: 203–209.
2. LEGHA SS, GUTTERMAN JU, HALL SW *et al.* Phase I clinical investigation of 4′-(9-acridinylamino)-methanesulfon-*m*-aniside (NSC 249992), a new acridine derivative. *Cancer Res* 1978; **38**: 3712–3716.
3. RIVERA G, EVANS WE, DAHL GV, YEE GC, PRATT CB. Phase I clinical and pharmacokinetic study of 4′-(9-acridinylamino)-methanesulfon-*m*-aniside in children with cancer. *Cancer Res* 1980; **40**: 4250–4253.
4. VAN ECHO DA, CHIUTEN DF, GORMLEY PE, LICHTERFIELD LJ, SCOLTOCK M, WIERNIK PH. Phase I clinical and pharmacological study of 4′-(9-acridinylamino-methanesulfon-*m*-aniside using an intermittent biweekly schedule. *Cancer Res* 1979; **39**: 3881–3884.
5. VON HOFF DD, HOWSER D, GORMLEY P *et al.* Phase I study of methanesulfonamide, *N*-(4-(9-acridinylamino)-3-methoxyphenyl)-(*m*-AMSA) using a single-dose schedule. *Cancer Treat Rep* 1978; **62**: 1421–1426.
6. WOODCOCK TM, SCHNEIDER RJ, YOUNG CW. Phase I evaluation of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (AMSA) by a weekly i.v. dose schedule. *Cancer Treat Rep* 1980; **64**: 53–55.
7. CABANILLAS F, LEGHA S, BODEY GP. Phase II study of AMSA (acridinylamino-methanesulfon-*m*-aniside) in lymphoproliferative disorders. *Proc Am Assoc Cancer Res* 1980; **21**: 156.
8. CASPER ES, GRALLA RJ, KELSEN DP, NATALE RB, SORDILLE P, HOUGHTON A. Phase II evaluation of 4′-(9-acridinylamino)-methanesulfon-*m*-aniside (AMSA) in patients with non-small cell lung cancer. *Cancer Treat Rep* 1980; **64**: 345–347.
9. HALL SW, BENJAMIN RS, LEE SS, GUTTERMAN JU, BURGESS MA, BODEY GP.

AMSA: A new acridine derivative with activity against metastatic melanoma. *Proc Am Assoc Cancer Res* 1979; **20**: 372.

10. LEGHA SS, BLUMENSCHEIN GR, BUZDAR AU, HORTOBAGYI GN, BODEY GP. Phase II study of 4'-(9-acridinylamino)methanesulfon-*m*-aniside (AMSA) in metastatic breast cancer. *Cancer Treat Rep* 1979; **63**: 1961–1964.
11. LEGHA SS, KEATING MJ, ZANDER AR, MCCREDIE KB, BODEY GP, FREIREICH EJ. 4'-(9-acridinylamino)methanesulfon-*m*-anisidide (AMSA): A new drug effective in the treatment of adult acute leukemia. *Ann Intern Med* 1980; **93**: 17–21.
12. LEICHMAN L, BUROKER TR, O'BRYAN RM, BAKER LH. Phase II trial of AMSA in disseminated adenocarcinoma of colon and rectum. *Proc Am Assoc Cancer Res* 1980; **21**: 355.
13. MURPHY WK, VALDIVIESO M, LEGHA S, BODEY GP. A Phase II study of 4'-9-acridinylamino-methane-sulfon-*m*-anisidide (AMSA) in patients with metastatic lung cancer. *Proc Am Assoc Cancer Res* 1980; **21**: 456.
14. SAMSON MK, FRAILE RJ, BAKER LH, TALLEY RW. A phase II study of AMSA in lung cancer. *Proc Am Assoc Cancer Res* 1980; **21**: 357.
15. SCHNEIDER RJ, WOODCOCK TM, YAGODA A, Phase II trial of 4'-(9-acridinylamino)methanesulfon-*m*-aniside (AMSA) in patients with metastatic hypernephroma. *Cancer Treat Rep* 1980; **64**: 183–185.
16. WHO Handbook for Reporting Results of Cancer Treatment. World Health Organization, Geneva, 1979.
17. HUBBARD SM, BARKES P, YOUNG RC. Adriamycin therapy for advanced ovarian carcinoma recurrent after chemotherapy. *Cancer Treat Rep* 1978; **62**: 1375–1377.
18. JOHNSON RK, CHITNIS MP, EMBREY WM, GREGORY EB. *In vivo* characteristics of resistance and cross-resistance of an adriamycin-resistant subline of P388 leukemia. *Cancer Treat Rep* 1978; **62**: 1535–1547.