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Phase II Study of Amsacrine in Solid Tumors: a Report of the EORTC Early Clinical Trial-Group*

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Abstract—*A total of* 239 *patients with advanced solid tumors were treated in this phase II trial. Amsacrine was administered as a single i.v. dose of* 120 mg/m^2 *repeated at* 21*-day intervals. The initial dose was reduced to* 90 mg/m^2 *in the case of extensive prior therapy. Some antitumor activity was detected in head and neck cancer but the drug appears to lack significant efficacy in epidermoid lung cancer as well as in carcinoma of the breast, melanoma, renal cell cancer, colorectal cancer and non-seminomatous testicular cancer. Leukopenia was the major toxic effect encountered in this trial and was similar at* 90 *and* 120 mg/m^2.

INTRODUCTION

AMSACRINE or 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (AMSA; NSC-249992) is one of many acridine derivatives synthetized by Cain and Atwell [1]. The drug was selected for clinical trials on the basis of its wide spectrum of activity against experimental tumors and its high therapeutic index against B16 melanoma [2]. AMSA is an intercalating agent but mechanisms other than DNA intercalation might account for its antitumor activity [3–5]. In dogs and monkeys, the most frequently observed toxic effects were related to the liver, gastrointestinal, lymphatic and hematopoietic systems [6]. AMSA is metabolized in the liver and excreted in the bile [7]. Its plasma clearance is reduced in the presence of liver impairment [8].

Several phase I trials showed that the dose-limiting factor for AMSA was leukopenia. Recommended single doses for phase II studies in solid tumors were 90–120 mg/m^2 repeated at 3 to 4-week intervals [9–11]. Phase I experience suggested a broad range of antitumor activity in solid tumors [9–12] and prompted rapid activation of this and a large number of other phase II trials with this compound. Results generated with AMSA in ovarian cancer by the EORTC Early Clinical Trial-Group (ECTG) have been published elsewhere [13].

MATERIALS AND METHODS

Between September 1979 and December 1980, 239 patients with histologically proven solid tumors were entered in a broad phase II study of AMSA. A two-stage plan was adopted for defining the number of patients required in the commonest disease categories to keep the probability of rejecting a drug active in 20% or more of the patients below 0.05. In the absence of complete or partial response, the trial could be discontinued after the first 14 patients; otherwise, additional patients had to be added to a maximum of 25 [14]. These rules applied to squamous cell carcinomas of the lung and the head and neck, and carcinomas of the breast, colon and kidney. Small numbers of patients with other diagnoses were entered since anecdotal information about tumor regression in these diseases could have been of

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interest in orienting the choice of subsequent trials.

Eligibility criteria included age ≤75 yr, performance status (Karnofsky) ≥50, documented progression of disease, no prior chemotherapy within 3 weeks, no prior radiation therapy within 6 weeks, recovery from toxicity induced by prior treatment, white blood cell counts (WBC) ≥4000/mm^3, platelet counts ≥150,000/mm^3, serum creatinine level <1.5 mg/dl and serum bilirubin level <2.0 mg/dl. Patients with second primary tumors, active uncontrolled infection, CNS metastases, congestive heart failure, cardiac arrhythmias, bilateral bundle branch block or history of myocardial infarction were excluded.

All patients had measurable and/or evaluable lesions for response evaluation. Pleural effusions, ascites and bone metastases were not accepted as evaluable lesions. Biochemical markers (α-fetoprotein and β-HCG) were accepted as criteria for evaluation in testicular tumors. Informed consent was obtained according to individual regulations in each participating institutions.

AMSA was supplied by the Warner Lambert Corporation, Morris Plains, NJ as two sterile solutions to be combined prior to administration: AMSA in anhydrous *N,N*-dimethyl-acetamide and 0.0353 M L-lactic acid. The drug was given as a single i.v. dose of 120 mg/m^2 every 21 days. The starting dose was reduced to 90 mg/m^2 in patients with extensive prior chemo- and/or radiotherapy. In the absence of hematologic toxicity in the two first courses, the dose was increased to the next level, 120 or 150 mg/m^2. The initial dose was reduced by 33% if the WBC nadir fell <1500/mm^3 and/or platelet nadir to <50,000/mm^3 during the previous course. Treatment was delayed by one week if the WBC was <3000/mm^3 and platelets <100,000/mm^3 at scheduled retreatment.

A minimum of two cycles (6 weeks) of treatment were required for an adequate trial except for patients taken off study after one cycle because of rapid progression of disease or life-threatening toxicity. These cases were considered as treatment failures. Response to therapy was evaluated by the end of 6 weeks. Final evaluation of objective responses was made at ECTG meetings upon presentation of supportive data, including X-rays and photographs.

Reponses were defined as follows: complete response (CR): disappearance of all known disease, determined by two observations not less than 4 weeks apart; partial response (PR): 50% or more decrease of the measurements of all indicator lesions based on two observations not less than 4 weeks apart. In addition, there could be no new lesions or progression of any lesion; no change (NC): less than 50% decrease in total tumor size, unchanged measurements or less than 25% increase in one or more measurable lesions; progression of disease (PD): a 25% or more increase in the size of one or more measurable lesions, or appearance of new lesions; early death (ED): death within 3 weeks without severe toxicity.

RESULTS

Of the 239 patients entered in the study, 8 were not eligible and 33 were considered to have had an inadequate trial because of early death (20 patients), treatment refusal (7 patients), major protocol violation (4 patients) and loss to follow-up (2 patients). The proportion of non-evaluable patients was 29% (18/63) among those with a Karnofsky score of 40–60 and 9% (15/168) among those with a score of 70–100.

The characteristics of evaluable patients are detailed in Table 1 for the tumor types with the

Table 1. Patient characteristics

Tumor site	No. of evaluable patients	Median age (range)	Median PS* (range)	Prior therapy RT	Prior therapy CT	Initial AMSA dose (mg/m^2) 90	Initial AMSA dose (mg/m^2) 120
Head and neck	23	63 (44–77)	80 (70–100)	22	16	6	17
Lung (epidermoid)	39	66 (39–77)	80 (60–100)	10	13	10	29
Breast	29	60 (35–77)	70 (40–90)	24	29	20	9
Melanoma	26	58 (36–74)	70 (40–100)	10	17	6	20
Kidney	20	60 (37–73)	70 (50–100)	5	3	2	18
Colorectum	17	61 (43–75)	80 (50–90)	3	8	5	12
Testis	13	33 (24–52)	60 (50–100)	9	13	9	4

*Karnofsky score.

largest accrual. A substantial number of patients with squamous cell carcinoma of the lung and renal cell cancer had received no prior chemotherapy. Among the 39 cases with the former diagnosis, 21 had disease limited to one hemithorax. In most disease categories the majority of patients received AMSA at the initial dose of 120 mg/m^2. Those with breast and testicular cancer had been heavily pretreated and usually received a dose of 90 mg/m^2. Twenty of the breast cancer patients and all those with non-seminomatous testicular cancer had been previously treated with doxorubicin.

Most of the 23 evaluable patients with squamous cell head and neck tumors had received extensive prior radiation and chemotherapy but none had received prior anthracycline treatment. Two patients with this disease achieved partial response. No antitumor activity of AMSA was detected in any of the other tumor types evaluated in this report.

Hematologic toxicity was analysed in 201 patients (Table 3). Based on weekly blood counts, WBC and platelet nadirs were similar for patients treated with 90 and 120 mg/m^2, with full recovery by day 21–28. Leukopenia appeared as the dose-limiting toxicity and was more pronounced than thrombocytopenia.

The major non-hematologic toxic effect was mild to moderate gastrointestinal intolerance with nausea, vomiting and anorexia. Peripheral neuropathy was observed in 2 patients. None of the patients experienced acute ventricular fibrillation or congestive heart failure.

CONCLUSIONS

In this large-scale phase II trial, AMSA showed no significant antitumor activity in solid tumors, but a valid evaluation of drug efficacy was largely limited by heavy pretreatment, including doxorubicin, extent of disease and low dose administration. These unfavorable features also characterize most of the phase II evaluations conducted by others with AMSA in a similar range of tumor types.

In our experience, responses were seen only in squamous cell carcinomas of the head and neck. This observation coupled with encouraging findings at Wayne State University [15] might warrant additional investigation of AMSA in this disease, despite negative data reported by others [16].

In lung cancer, occasional responses have been achieved in the non-small cell types [17–19], whereas extensively pretreated small cell tumors appear to be resistant to the drug [17, 20, 21]. This study failed to detect antitumor activity in a large number of patients with squamous cell carcinoma of the lung treated with AMSA as first-line chemotherapy. Our disappointing findings in the smaller number of patients with other cell types of lung cancer are consistent with results in larger series. The promising therapeutic effect initially obtained in far-advanced breast cancer [22] could

Table 2. Therapeutic activity

Tumor type	Entered	No. of patients Evaluable	Partial response	No change	Progression
Head and neck	25	23	2	2	19
Lung (epidermoid)	45	39	–	9	30
Breast	33	29	–	4	25
Melanoma	30	26	–	5	21
Renal	21	20	–	5	15
Colorectal	25	17	–	4	13
Testicular	13	13	–	1	12
Lung (adenocarcinoma)	19	12	–	5	7
Miscellaneous	28*	19	–	9	10

*Small cell (6) and large cell lung (5), cervix (5), pancreas (4), soft tissue sarcoma (3), hepatoma (2), thyroid (1), penis (1) and head and neck muco-epidermoid (1).

Table 3. Hematologic toxicity

Dosage (mg/m^2)	Prior chemotherapy	No. of cases	WBC nadir (×10^3/mm^3) Median	(Range)	Platelet nadir (×10^3/mm^3) Median	(Range)
90	no	10	2.5	(1.5–5.2)	206	(90–330)
90	yes	85	3	(0.1–7.3)	190	(11–450)
120	no	58	2.9	(0.5–11)	189	(85–447)
120	yes	48	3	(0.6–6.4)	204	(43–402)
All patients		201	2.9	(0.1–11)	198	(11–450)

not be confirmed in this and a number of other trials [23–27]. The same conclusion applies to melanoma [28], despite the incorporation of good-risk patients in the phase II evaluations [29–31]. AMSA has been extensively tested as first-line chemotherapy in renal cell cancer [32, 33] and in colorectal cancer [34–36]; its lack of efficacy in these tumor types is also substantiated by our data.

These negative results obtained at a dose consistent with outpatient administration contrast with the therapeutic activity shown by AMSA against lymphomas and acute leukemias. However, responses in these diseases were obtained at much higher dose levels which produced severe marrow depression. Whether some types of solid tumors would respond to similar treatments is still unknown.

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