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A Phase II Trial of m-AMSA in Head and Neck Cancer

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Summary. *Twenty patients with advanced epidermoid carcinoma from primary sites in the head and neck region received adequate trials of therapy with m-AMSA, at starting doses of 90 or 120 mg/m^2. Despite the good median performance status of the group (median 80) and the fact that 50% of the patients had received no prior chemotherapy, only one minor response was achieved. AMSA appears to have no useful activity in this dose and schedule in patients with epidermoid head and neck cancer.*

4′-(9-Acridinylamino)methanesulfon-m-anisidide (AMSA) is an acridine derivative which may function by intercalation and external binding to DNA [2]. In phase I trials, the principal dose-limiting toxicity was myelosuppression; significant nausea and vomiting were uncommon [4, 7, 8]. In phase II studies objective responses have been observed in soft-part sarcomas, acute leukemia, lymphoproliferative disorders, breast cancer, and melanoma [1, 3, 5, 6]. This study evaluated the activity of AMSA in advanced epidermoid carcinoma of the head and neck.

Twenty-three patients with histologically proven epidermoid carcinoma of the head and neck were treated. All patients had a complete history and physical examination, 12-channel screening profile, complete blood count and platelet count, chest X-ray, and scintiscans when indicated. All patients had an expected survival of at least 2 months, adequate renal function (creatinine ≤ 2 mg/dl), and no evidence of obstructive liver disease (bilirubin ≤ 1.5 mg%).

AMSA was started at a dose of 120 mg/m^2 for patients with performance status ≥ 70 (Karnofsky scale) and adequate bone marrow reserve; patients with performance status of 50–60 or compromised marrow function from extensive prior radiation therapy and/or chemotherapy started at a dose of 90 mg/m^2. AMSA was administered by IV infusion over 30 min every 3 weeks. The dose was escalated by 30 mg/m^2 for WBC nadirs of $\leq 3{,}000/\text{mm}^3$ and reduced by 30 mg/m^2 for WBC nadirs of $\leq 1{,}000/\text{mm}^3$.

A trial was considered adequate when disease progression occurred at a dose that produced marrow toxicity. Response criteria were defined as: *partial response* (PR), $\geq 50\%$ reduction in the sum of the products of the two greatest perpendicular diameters of all measurable lesions for at least 1 month; *minor response* (MR), objective tumor regression less than that required for a PR; *progression* (P), increase in the size of any measurable disease parameter or the appearance of new disease.

Twenty of 23 patients were evaluable; two patients were lost to follow-up and one died of disease shortly after the first dose. Patient characteristics are detailed in Table 1. Median initial performance status was 80. Ninety percent of patients had received prior radiation therapy, 75% prior surgery, and 50% prior chemotherapy. Disease recurred at primary or neck sites in 60% of patients and at distant sites in 40%.

As indicated in Table 2, most patients had at least two courses of AMSA. The chief dose-limiting toxicity was leukopenia. Eighty-five percent of patients achieved WBC nadirs of $\leq 3{,}000/\text{mm}^3$. No clinically significant thrombocytopenia occurred. Other side-effects, occurring in 30% of patients, were mild nausea, vomiting, and stomatitis of brief duration.

One patient with a carcinoma of the tongue achieved a minor response lasting for 2 months. There was one mixed response in a patient with recurrent disease of the maxillary antrum; a partial regression occurred at the primary site, but lung

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Table 1. Patient characteristics

Median age in years (range)	61 (26–73)
Sex	
Male	14
Female	6
Median performance status (range)	80 (50–100)
Prior treatment	
Total	20
Surgery only	0
RT only	2
Surgery + RT	8
Surgery + chemotherapy	2
RT + chemotherapy	3
Surgery + RT + chemotherapy	5
No prior chemotherapy	10
Primary site	
Nasopharynx	6
Pyriform sinus	2
Oral cavity	5
Oropharynx	3
Larynx	2
Maxillary antrum	1
Scalp	1
Sites of measurable disease	
Primary	5
Neck	8
Lung	7
Bone	2
Skin	2

Table 2. Dosage and toxicity of AMSA

	No. of patients
Initial dose (mg/m^2)	
90	6
120	14
Courses of AMSA	
1	4
2	9
3	2
4	4
Toxicity	
Hematologic (cells/mm^3)	
WBC nadir	
3,000–3,999	2
2,000–2,999	7
< 2,000	8
Platelet nadir	
< 150,000	0
Nausea	3
Vomiting	2
Stomatitis	2
Response	
PR	0
MR	1
P	19

metastases developed simultaneously. Both these patients had received extensive prior treatment with radiation and chemotherapy. No major therapeutic responses were observed.

Discussion

In this phase II trial of AMSA for advanced epidermoid carcinoma of the head and neck no clinically useful responses were observed. Although all patients had some form of prior treatment, 50% had not had chemotherapy and 70% had a performance status and bone marrow reserve that allowed them to tolerate the 120 mg/m^2 dose of AMSA. All patients were pushed to dose-limiting toxicity except for three, who demonstrated rapid progression of disease after the first dose. We conclude that AMSA in the present dose and schedule is not a useful agent for the treatment of epidermoid carcinoma of the head and neck.

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