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Southwest Oncology Group Study of mitoxantrone for treatment of patients with advanced adenoid cystic carcinoma of the head and neck

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Summary

Eighteen patients are evaluable for response in a Phase II trial of Mitoxantrone for advanced adenoid cystic carcinoma of the head and neck. One patient had a complete response; there were no partial responses. Twelve patients had stable disease for 3 or more months. There was no significant anti-tumor activity of Mitoxantrone in the group of patients with adenoid cystic carcinoma, all of whom were previously heavily treated with surgery, chemotherapy and/or radiation therapy.

Introduction and methods

Adenoid cystic carcinoma has been reported to respond to both Adriamycin and Mitoxantrone [1–3]. This Phase II study was designed to further evaluate the therapeutic efficacy of the anthracene derivative Mitoxantrone (dihydroxyanthracenedione) in patients with adenoid cystic carcinoma of the head and neck who failed conventional therapy. All patients had histologically confirmed adenoid cystic carcinoma of the head and neck, most had received prior radiation and chemotherapy (See Table 1). Eligibility criteria included: a lesion measurable in two dimensions, an anticipated survival of at least 3 months, a performance status ≤ 2 according to Southwest Oncology Group criteria, WBC $\geq 3{,}500/mm^3$, platelet count of $\geq 125{,}000/mm^3$, serum creatinine ≤ 2.0 mg%, serum bilirubin ≤ 2.0 mg%, previous adriamycin dose of ≤ 400 mg, and recovery from toxicity of previous therapy.

Mitoxantrone was administered intravenously at an initial dose of 12 mg/m^2 as an infusion over 30 minutes in 100 cc of D5W. The dose was repeated every three weeks. This dose schedule was determined as being safe based on an initial Phase I trial [4]. Doses were to be escalated or de-escalated by 2 mg/m^2 increments based on nadir white blood cell counts. Therapy was continued until there was evidence of disease progression or until there was unacceptable toxicity.

Results

Table 1 details the patient characteristics. Twenty patients were registered for the study, one was ineligible because the histologic diagnosis was changed after a repeat biopsy and another because he had received > 400 mg adriamycin, so did not receive the drug. All the remaining patients were evaluable for both response and toxicity. Five patients had disease at the primary site, 11 had metastases to the lung, and two had disease at both the primary site and distant metastases. Twelve of the patients had previous chemotherapy ranging between 1–6 drugs, usually given singly or in two drug combinations. Three of the evaluable patients

Table 1. Characteristics of patients studied

Characteristic	No. of patients
Total No. of patients entered	20
Patients evaluable for response	18
Median age (range 31–72)	53
Sex	
Male	12
Female	6
SWOG Performance status	
0	11
1	5
2	2
Prior radiation therapy	16
Prior chemotherapy	
None	6
1–3 drugs	8
4–6 drugs	4
Median number of cycles of Mitoxantrone (range 2–23)	9
Response	
Complete	1
Partial	0
Stable > 3 months	12
Increasing disease	5

had previous adriamycin, one of whom developed cardiac toxicity (see below). Sixteen patients had previous surgery for local and regional disease (1–21 procedures), and 16 had previous radiation therapy.

The regimen was generally well tolerated by this group of high performance status patients (Table 1). The number of courses ranged from 2 to 23; the median was 9. Six patients required dose de-escalation because of toxicity, six tolerated dose escalation. The most frequent toxicity was leukopenia. The mean recorded nadir granulocyte count was 2200/mm^3 (range 800–5100/mm^3). Thrombocytopenia was not a problem, the mean recorded platelet count nadir was 167,000/mm^3 (range 60,000–375,000). Cardiac toxicity, measured by decreased ejection fraction, occurred in two patients; in one it was life threatening and caused the drug to be discontinued at a total dose of 186 mg. This patient had previously received 380 mg of adriamycin, just 20 mg below the limit for eligibility in the study. He died three months later of progressive disease without apparent lasting cardiac compromise. The other patient with mild cardiac toxicity only required de-escalation of dose (total dose 216 mg). Mild nausea and vomiting was common.

One patient had a complete response. This patient had pulmonary metastases and had no prior chemotherapy except interferon. He developed a partial response after two courses and had a complete response by the 10th course. He was still without evidence of disease 19 months later when therapy was discontnued after the 23rd course. There were no partial responses. Five patients had increasing disease in less than three months from the initiation of therapy. The remaining 12 patients had stable disease for a median of 6 months (range 5–18 months). Eight of these patients had therapy discontinued for increasing disease and the other four for toxicity. The median survival time was 19 months with 7 patients still alive at the time of analysis.

Discussion

Many patients had extended courses of therapy because of the slowly progressive nature of this disease and required long treatment for adequate evaluation. Toxicity was low except in one patient who had received a previous high dose of Adriamycin and developed cardiac toxicity.

Only one complete response and no partial responses were seen. The estimate of the overall response rate is 0.06, with an exact 95% confidence interval of 0.001 to 0.27. Despite previous reports of responses to Mitoxantrone in adenoid cystic carcinoma, this study failed to show significant activity of Mitoxantrone in this group of heavily pretreated patients, even with extended treatment courses.

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