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Phase II Trial of Diaziquone (AZQ) in Advanced Malignant Melanoma*

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Abstract—*Forty-two evaluable patients with malignant melanoma received AZQ* 27 mg/m² *i.v. every* 4 weeks. *In* 5 *patients with poor marrow reserve this dose was reduced to* 20 mg/m². *Doses were rapidly escalated when no significant myelosuppression was encountered in previous courses. Twenty-five patients had received no prior chemotherapy. A single partial response was obtained for* 3 months. *Inconsistent myelosuppression was the main toxic effect in this trial. The median WBC and platelet nadirs were* 3200/mm³ (900–19,500) *and* 105,000/mm³ (33,000–530,000) *respectively. In* 2 *patients leukopenia was complicated by a transient episode of infection. One-third of the patients did not experience significant myelosuppression. Non-hematologic adverse reactions were generally mild to moderate and consisted of nausea and vomiting in* 26 *patients and alopecia in* 1. *It is concluded that at this dose schedule AZQ is ineffective against malignant melanoma.*

INTRODUCTION

AZIRIDINYLBENZOQUINONES appear to be compounds with potential value for the treatment of malignancies in the central nervous system [1, 2]. These drugs possess physicochemical properties which enable them to penetrate the central nervous system, i.e. they are small lipophilic molecules without ionic charge. AZQ [1,4-cyclohexadiene1,4-dicarbamic acid,2,5-bis(1-aziridinyl)-3,6-dioxodiethyl ester] (NSC-182986) was found to be the most promising compound for clinical trials among 31 aziridinylbenzoquinones [3].

AZQ is active against L1210 leukemia, P388 leukemia, B16 melanoma, colon 26, CD8F1 mammary tumor, human mammary tumor xenograft MX1 and human colon tumor xenograft CX-2 [4]. It is of particular interest that AZQ is also active against intracerebrally implanted tumors, including the L1210 leukemia and ependymoblastoma. There is no apparent schedule dependency with respect to the activity of AZQ against L1210 [4] and its toxicity in large animals [5]. The mechanism of action of AZQ is not yet fully understood. It appears to cross-link DNA [6] and to produce free radicals [7]. Pharmacokinetic studies showed that the drug entered the cerebrospinal fluid in animals [8] and in humans [9–11].

Phase II results have been promising in malignant gliomas [12, 13] and have been less

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favorable in colon cancer [14], renal cell cancer [15], bladder cancer [15], prostatic cancer [15], breast cancer [16], small cell [17] and non-small cell lung cancer [18]. Our study was prompted by encouraging findings in a phase I trial that suggested activity in melanoma patients with brain metastases [19]. The dose schedule utilized in this investigation was based on recommendations by Kovach [20].

MATERIALS AND METHODS

All patients had histologically confirmed progressive malignant melanoma with previously non-irradiated measurable lesions. None of the patients had disease amenable to curative surgery. Eligibility criteria included performance status (WHO) <3, life expectancy ≥ 3 months, age ≤ 75 yr, white blood cell counts (WBC) $\geq 4000/mm^3$, platelet counts $\geq 100{,}000/mm^3$, serum bilirubin level ≤ 2.0 mg/dl and serum creatinine level ≤ 1.5 mg/dl. Initial work-up consisted of history and physical examinations, complete blood cell counts, routine chemistry profile, chest X-rays, liver echography or CT-scan, brain CT-scan and bone survey. Blood cell counts were repeated weekly. Other tests were repeated as indicated.

AZQ was given as a 1-hr i.v. infusion in 100 ml of normal saline at a dose of 27 mg/m^2 repeated every 4 weeks. In 5 patients with poor marrow reserve because of extensive prior chemotherapy or radiotherapy this dose was reduced to 20 mg/m^2. Drug administration was postponed by one week if there was no full hematologic recovery at scheduled retreatment. Dosage adjustments were planned for each course according to the WBC and platelet nadirs in the previous course. The dose was increased by 50% with WBC $\geq 4000/mm^3$ and platelets $\geq 150{,}000/mm^3$, and increased by 25% with WBC between 3000 and $3999/mm^3$ or platelets between 100,000 and $149{,}000/mm^3$. The dose was reduced by 25% with WBC $<2000/mm^3$ or platelets $<75{,}000/mm^3$.

AZQ was supplied by the Investigational Drug Branch, Cancer Therapy Evaluation Program, National Cancer Institute as a tripack containing a 10-ml amber vial with 10 mg sterile AZQ in dry form, a 1-ml ampoule of sterile *N,N*-dimethylacetamide and a vial with 9.5 ml of sterile 0.01-M phosphate buffer, pH 6.5. Prior to use the drug was dissolved in *N,N*-dimethylacetamide and diluted further in the phosphate buffer.

A minimum of two courses were necessary for treatment assessment unless there was clear disease progression after one course. The criteria of response were as follows: complete response: disappearance of all known disease, determined by 2 observations not less than 4 weeks apart; partial response: decrease by at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions, determined by two observations not less than 4 weeks apart; no change: $<50\%$ decrease in total tumor or $<25\%$ increase in the size of one or more measurable or evaluable lesions; progressive disease: a 25% or more increase in the size of at least one indicator lesion or the appearance of a new lesion.

RESULTS

Of 48 eligible patients 6 received only one course of therapy with no documented progression: 2 had early death, 2 were lost to follow-up and 2 went off-study because of questionably drug-related cardiac complications or rapid alteration of the general condition respectively. Among 42 evaluable patients 25 had had no previous exposure to chemotherapy, 9 (7 with no prior chemotherapy) had only soft tissue disease and all had at least soft tissue and/or lung indicator lesions (Table 1). Eight patients (6 with no prior chemotherapy) received 1 course, 25 patients received 2 courses, 3 patients received 3 courses and 6 patients received 4–6 courses. Of the 17 patients with prior chemotherapy 5 were started at 20 mg/m^2. Among the 34 patients who received 2 or more courses 20 had their dose escalated and 3 had their dose reduced. Fourteen patients were treated with a dose of 40 mg/m^2 or higher, and 2 of these received up to 90 mg/m^2.

A partial response for 3 months from initiation of therapy was obtained in a 35-yr-old woman with soft tissue disease that had not been previously treated with chemotherapy. Three patients with no prior chemotherapy had stable disease after 2, 2 and 6 months respectively. Two of these patients went off-study after 2 courses because of severe toxicity. The remaining 38

Table 1. Patient characteristics

Number of evaluable patients	42
Men/women	17/25
Median age in years (range)	54 (24–74)
Median WHO performance score (range)	1 (0 – 2)
Prior chemotherapy	11
Prior radiotherapy	4
Prior chemo- and radiotherapy	6
Soft tissue/visceral ± soft tissue disease	9/33
Indicator lesions	
Soft tissue	20
Lung	7
Soft tissue and lung	10
Soft tissue a/o lung and others	5
Median number of courses (range)	2 (1 – 6)

patients had progressive disease under AZQ therapy.

Myelosuppression was the main toxic effect. In 38 patients evaluable for hematologic toxicity, the median WBC and platelet nadirs were 3200/mm^3 (900–19,500) and 105,000/mm^3 (33,000–530,000) respectively. Among the 17 patients with no prior chemotherapy who received 2 or more courses the corresponding figures were 2400/mm^3 (900–6800) and 87,000/mm^3 (41,000–299,000). Of all 25 patients with no prior chemotherapy 8 had no myelosuppression as defined by WBC <4000/mm^3 or platelets $<100{,}000$/mm^3. One patient who had previously received PALA and a combination of cisplatin plus vindesine had normal weekly blood cell counts after a dose of 90 mg/m^2.

Overall, non-hematologic toxic effects were minimal in this trial. Of 42 patients 26 experienced nausea and vomiting, which were severe in 4. Severe gastrointestinal distress occurred in 1 patient with no prior chemotherapy who had no documented myelosuppression and who refused further therapy after 2 courses of AZQ. There were 2 episodes of reversible leukopenia-related infection. Minor loss of hair was seen in 1 patient.

A 65-yr-old man was excluded from this analysis. He had metastatic melanoma in the paraaortic region and occasional ventricular ectopic beats prior to entry into the trial. He was hospitalized on day 11 of his first course for a 20-min episode of sudden loss of consciousness. Upon admission he had non-specific EKG changes and subsequently developed cardiac arrhythmia with coupled ectopic beats. This patient recovered within 48 hr but was not retreated with AZQ. The relationship between drug administration and these complications remains unclear.

DISCUSSION

AZQ was evaluated in 42 patients. Twenty-five had no prior chemotherapy. In this favorable group 7 patients had only soft tissue disease. Nineteen previously untreated patients received 2 or more courses of therapy. Only 1 patient achieved a partial response, indicating that at the dose schedule selected AZQ is not effective in the therapy of advanced malignant melanoma.

Toxic effects consisted of myelosuppression with leukopenia and thrombocytopenia. Despite aggressive dose escalations, nearly one-third of the patients did not show hematologic toxicity. Our data are inconclusive with respect to the occurrence of increasingly severe hematologic toxicity with repeated courses of drug among patients having myelosuppression. The extreme differences in the sensitivity of humans to bone marrow suppression by AZQ are of interest but complicate defining an optimal starting dose for AZQ in the therapy of patients with advanced cancer.

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