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A phase II trial of diaziquone in patients with head and neck cancer*

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Summary. Diaziquone (AZQ) is a lipophilic alkylating agent which crosses the blood-brain barrier and has marked antitumor activity in a broad spectrum of murine tumor systems. Myelosuppression has been the dose-limiting toxicity in phase I trials. In this study 36 patients with head and neck cancer received diaziquone. Thirty-one of these patients (28 male, 3 female) were evaluable for efficacy. The initial starting dose was 7 mg/m^2/day × 5 days i. v. repeated every 28 days. Because of the severe myelosuppression encountered in the first four patients, the starting dose was decreased by 20% to 5.5 mg/m^2/day × 5 days repeated every 28 days. The majority of patients were considered to be good-risk patients as evidenced by performance status (80% 0–1 Zubrod) and prior therapy. Even with this dosage reduction, myelosuppression (especially thrombocytopenia) was again the dose-limiting toxicity with 25% of patients experiencing granulocyte and platelet nadirs below 1000/mm^3 and 50000/mm^3 respectively. Thirty-five percent of patients required a subsequent dosage reduction of 20% prior to receiving a second course of therapy. There was one complete (CR), four partial (PR) and three minor (MR) responses. All but the CR were of relatively short duration (mean of 30 days). The patient with a CR has remained disease-free for nearly 3 years. In this group of patients the activity of diaziquone as a single agent at this dose and schedule (CR + PR + MR = 26%; CR + PR = 16%) is less than that of methotrexate, bleomycin, and cis-platinum but is encouraging. Further trials utilizing combinations are warranted.

Introduction

Cancer of the head and neck (including lip, oral cavity, pharynx, and larynx) of the squamous (epidermoid) cell type accounts for 5% of all new cancer cases (37300) in the USA every year [1]. Standard initial treatment has been and still is surgery and/or radiotherapy, either as single modalities for stage I or II disease or as combined therapy for stage III or IV disease. Even though localized head and neck cancer is curable with surgery and radiotherapy, only one-third of patients present with localized disease [10]. Chemotherapy is limited to palliation of recurrent or widely metastatic disease. In this setting, no single drug or combination of agents has been shown to be superior to weekly low-dose methotrexate, where substantial tumor regression occurs in 30%–50% of patients [6]. Unfortunately, the duration of these responses (usually partial) tends to be very short. The current trend is therefore for early multimodality therapy including chemotherapy as an adjuvant or in early stages of the disease. The role of chemotherapy in the patient with advanced disease also continues to be explored via the use of drug combination regimens. Clearly, it is important to continue the search for agents which are active in this disease that may provide more durable responses.

Diaziquone (AZQ) is a rationally designed antitumor agent [5]. It possesses characteristics thought necessary for crossing the blood-brain barrier: high degree of lipid solubility, low degree of ionization at physiologic pH, and relatively low molecular weight [11]. It has shown a broad spectrum of activity against a wide variety of murine tumor systems, including curative activity against intracerebrally implanted L1210 leukemia and ependymoblastoma [5]. Although the exact mechanism of action is not known, the aziridinyl group is an alkylating function and may be responsible in part for the observed antitumor activity [2]. Generation of a free radical and the subsequent production of superoxide may also be involved in the cytotoxic effect of the drug [9]. Following i. v. administration, plasma disappearance was very rapid with a distribution half-life of 2–6 min and an elimination half-life of 25–35 min [3].

Diaziquone rapidly penetrates the central nervous system, reaching peak concentrations of 30%–50% of corresponding plasma levels in approximately 1 h [7]. It would appear that it is extensively metabolized in man, and that very little of the parent compound is excreted unchanged. The dose-limiting toxic effect in phase I trials has been myelosuppression [5]. Thrombocytopenia is often severe. Based on recommended starting doses of 6–8 mg/m^2/day × 5 [4], a phase II trials of diaziquone in patients with head and neck cancer was initiated.

Materials and methods

Patients between the ages of 18 and 80 years (males or nonpregnant females) with histologic evidence of head

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and neck cancer refractory to conventional therapy were eligible. Additional requirements were: (a) expected survival >4 weeks; (b) Zubrod performance status ≥3 (later upgraded to ≥2); (c) adequate time to recover from prior chemotherapeutic or radiation-induced toxicity; (d) absolute granulocyte count >1500/mm^3 and platelet count >100000/mm^3 (later increased to >150000/mm^3); and (e) measurable disease with evidence of progression. Patients were excluded from entry if they had: (a) a history of treatment with any other phase I or II investigational agent; (b) more than one primary malignancy; (c) impaired hepatic function (bilirubin >1.5 mg/100 ml, SGOT >60 units/ml) or renal function (creatinine >2 mg/100 ml); or (d) conditions which would require the use of concurrent systemic, intracavitary, or intrathecal chemotherapy or radiotherapy. Patients were informed of the investigational nature of the study and gave written informed consent.

Diaziquone (supplied by Warner-Lambert/Parke-Davis) was initially administered intravenously over 5–10 min at a dose of 7 mg/m^2/day × 5 days every 4 weeks. After the first four patients, the starting dose was reduced to 5.5 mg/m^2/day. For subsequent courses the dose was escalated by 20% in patients not achieving a granulocyte count nadir between 1000 and 1500/mm^3 providing that the platelet count nadir was >75000/mm^3. The dose was decreased by 20% in patients with granulocyte count nadirs <1000/mm^3 or platelet count nadirs <75000/mm^3. Subsequent courses were delayed by weekly increments until full hematologic recovery, defined as granulocytes >1500/mm^3 and platelets >100000/mm^3, had occurred.

During therapy, patients were evaluated on the basis of history, physical examination, performance status, chest X-ray, ECG, glucose, BUN, total protein, albumin, calcium, SGOT, LDH, alkaline phosphatase, uric acid, bilirubin, serum creatinine, serum electrolytes, urinalysis, and tumor measurements. Appropriate X-rays or scans were obtained. Complete blood counts and platelet counts were done weekly. Response criteria were as follows: complete response (CR): the disappearance of all measurable tumors; partial response (PR): a >50% decrease in the sum of the products of the perpendicular diameters of measurable tumors; minor response (MR): a 25%–50% decrease in the sum of the products of the perpendicular diameters of measurable tumors; no response (NR): failure to meet the above criteria or development of new tumors. The duration of response was calculated from the onset of response to the documentation of progression.

Statistical considerations. This stepwise study design was developed for phase II trials of new antineoplastic agents and attempts to ensure that a drug with at least 20% antitumor activity rate will not be missed more than 5% of the time [8].

Results

Thirty-six patients with squamous cell carcinoma of the head and neck were entered into this phase II trial of diaziquone. Five patients died of their disease prior to completing the first course of therapy and so were considered nonevaluable for lack of an adequate trial. Thirty-one patients were evaluable for efficacy (Table 1). Fourteen of these had received prior radiotherapy alone, eight had received radiotherapy and surgery, seven had received prior radiotherapy and surgery and chemotherapy, and two had received prior surgery and chemotherapy.

Table 1. Patient characteristics

Characteristics	Evaluable patients
No. of patients	31
Sex	
Male	28
Female	3
Age (years)	
Median	61
Range	34–78
Zubrod performance status	
0	6
1	19
2	6
3	0
4	0
Prior therapy	
None	0
RT only	14
RT and surgery	8
RT, surgery and chemotherapy	7
Surgery and chemotherapy	2
Response	
CR	1
PR	4
MR	3
NR	23
Response rate	
CR + PR + MR =	8/31 (26%)
CR + PR =	5/31 (16%)

RT, radiotherapy; CR, complete response; PR, partial response; MR, minor response; NR, no response

The first four patients received 7 mg/m^2/day × 5 days. One patient died of asphyxiation on day 6 of the first course of treatment after pulling out his tracheostomy tube and was therefore not evaluable for drug-induced myelosuppression. Two of the other three patients experienced severe bone marrow suppression with mean platelet count or granulocyte count nadirs of 20000/mm^3 (range 6000–33000) and 245/mm^3 (range 190–300), respectively. Because of this, the initial dosage was decreased by 20%, and 32 subsequent patients received 5.5 mg/m^2/day × 5 as initial therapy. Even with the 20% dosage reduction for initial therapy, myelosuppression was still the major toxic effect. Hematologic toxicity induced by diaziquone is illustrated in Table 2.

Eight patients experienced mild to moderate nausea with treatment and five patients had fever and/or infection with their neutropenia. Five patients required platelet transfusions. No evidence of renal, hepatic, neurologic, or allergic toxicity was observed. No patient experienced alopecia with diaziquone therapy. There was one CR, four PR, and three MR. All but the CR were of relatively short duration (mean 30 days). All subsequent failures were marked by local disease progression (Table 3).

Table 2. Hematologic toxicity of diaziquone (evaluable patients)

Characteristics	Dose			
	7 mg/m²/day		5.5 mg/m²/day	
	Course 1	Course 2	Course 1	Course 2
No. of patients	3	1[a]	28	19[b]
Lowest neutrophil count ($\times 10^3$)				
Median	1.1	2.4	2.1	2.0
Range	0.2–2.8	2.4	0.1–11	0.3–9.4
Day (median)	23	14	19	17
% <1.0	66	0	26	20
% <0.5	66	0	16	5
Lowest platelet count ($\times 10^3$)				
Median	66	62	149	111
Range	6–159	62	6–393	21–248
Day (median)	15	14	22	22
% <100	66	100	39	45
% <50	66	0	26	25

[a] This patient required a 20% dosage reduction for course 2

[b] Seven of these 19 patients (37%) required 20% dosage reduction for course 2 (i.e., 4.4 mg/m²/day). Two patients received the same dose as in course 1, and the remaining 10 patients were able to receive a 20% increase

Table 3. Response characteristics

Response	Site	Prior therapy	Dosage (mg/m²)	Course	Onset (day)	Duration (days)
CR	Vallecula epiglottica	RT, SX	5.5	2	54	446+
PR	Larynx	RT, SX, MTX, FU folinate	5.5	2	56	22
PR	Neck, oropharynx	RT	5.5	1	12	64
PR	Neck, hypopharynx	RT, SX	5.5	1	19	1+*
PR	Neck, nasopharynx	RT	5.5	2	51	60
MR	Not stated	Ametantrone, SX	5.5	1	9	23+
MR	Neck, jaw, oral cavity	RT	5.5	1	9	36
MR	Neck	RT, SX	5.5	2	36	1+*

CR, complete response; PR, partial response; MR, minor response; RT, radiation therapy; SX, Surgery; MTX, methotrexate; FU, Fluorouracil; +, response ongoing; *, patient lost to follow-up

Discussion

In the present study we have evaluated the potential efficacy and toxicity of diaziquone as a single agent in patients with head and neck cancer. Following the statistical design of our study we continued to treat patients after observing at least one response in the first 14 patients. Although the response rate (CR+PR+MR) was 8/31 (26%) at the end of the second stage of our three-stage phase II design, we terminated the trial because a response rate of 26% for diaziquone as a single agent puts it at the bottom of the list of single agents with activity in this disease. In addition, if we consider only the CR and PR (which corresponds more closely with the WHO criteria for response) the figure becomes 5/31 (16%). The utility of the MR category was to identify any suggestion of antitumor activity of the compound in the hope that appropriate dosage and schedule adjustments could be made subsequently.

In this study, bone marrow suppression was the dose-limiting toxicity but was quite variable. Some patients experienced no marrow suppression and others had profound marrow toxicity requiring multiple platelet transfusions. This is particularly disturbing because virtually all patients received the same dose. The explanation for this variability may be threefold. First, diaziquone is poorly soluble in an aqueous medium. Dissolution of the drug requires the solvent dimethylacetamide. Total dissolution of the 10-mg dose in a vial requires approximately 10 min at room temperature with constant agitation. Any drug which is not in solution when the buffering solution is added will not dissolve. It is therefore possible to obtain differing concentrations of drug depending upon the method of preparation. Second, in animal toxicity experiments the dose-toxicity curve was very steep, the difference between the LD_{10} and LD_{90} in mice being 4.8 mg/m². Third, diaziquone has a very short half-life. Therefore, anything that interferes with the metabolism of the drug even slightly could lead to markedly increased clinical toxicity. It is likely that all three of these factors play a role in the variability of the toxicity observed clinically.

In this study, diaziquone had definite activity in squamous cell cancer of the head and neck. If we consider all eight responders (CR+PR+MR), the response rate is 26%. The 95% confidence interval for the true response rate is 10%–41%. Therefore, the true response rate is unlikely to exceed 41%. If we consider only complete and

partial responders, then, our response rate is 16% with a 95% confidence interval of 3%–29%. Under this more stringent definition of response, the true response rate is unlikely to exceed 29%. In either case, the activity of diaziquone is not as great as that reported for methotrexate and several other drugs as single agents. Therefore, we cannot recommend that diaziquone be used in this dose and schedule as a single agent for the treatment of patients with head and neck cancer. We do believe further studies of this agent are warranted as a component of combination or multimodality regimens.

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