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Letter to the Editor

Effect of AZQ (1,4-Cyclohexadiene-1,4-diacarbamic acid-2,5-bis(1-aziridinyl)-3,6-dioxodiethylester) in Recurring Supratentorial Malignant Brain Gliomas—a Phase II Study*

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IDENTIFICATION of new agents or drug combinations active in malignant brain gliomas is the major challenge in the treatment of these neoplasms where recent progresses have been modest [1–3]. Diaziquone (AZQ) (1,4-cyclohexadiene-1,4-diacarbamic acid-2,5-bis(1-aziridinyl)-3,6-dioxodiethylester), an alkylating agent which crosses the blood-brain barrier easily [4] and was shown to be active against experimental gliomas [5], has been tested in the present trial.

The 33 studied patients had histologically proven malignant supratentorial glioma; 16 glioblastoma multiforme, 12 astrocytoma grade III–IV, three oligodendroblastoma and two anaplastic ependymoma. Twenty were males and 13 females. The median age was 49 yr (range 23–74 yr) and the mean Karnofsky index was 70 (range 20–90). All patients underwent neurosurgery at least 3 months prior to their entry into the trial and all except three had radiotherapy completed at least 6 weeks before first administration of AZQ. Only three patients previously received chemotherapy; one had 4′-dimethyl-epipodophyllotoxine-D-therylidene-glucoside (VM-26) plus 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), another vincristine (VCR), procarbazine (PCZ) and CCNU and the last one VCR, PCZ, CCNU, adriamycin and 4-demethylepipodophyllotoxine-β-D-ethylidene (glocoside (VP-16-213).

The first dose of AZQ was 8 mg/m²/day ×5 given every 28 days in 100 ml of saline over 1 hr. The subsequent doses were adjusted according to the schedule shown in Table 1.

The total doses and the number of cycles of AZQ actually given are summarized in Table 2.

The results of AZQ treatment are given in Table 3. Two patients had an objective remission defined as a clear-cut improvement of the neurological status persisting 6 weeks or more after a complete discontinuation of corticosteroids. In one patient the neurological improvement which lasted 4 weeks was correlated with tumour regression on CT-scan, whereas in the other case CT-scan remained unchanged throughout the clinical remission which lasted 89 weeks.

In 13 patients the concomitant administration of AZQ and corticosteroids was followed by some clinical improvement or stabilization of the neurological status. However, corticosteroids could be discontinued for no more than a few weeks or not at all. Therefore in these patients the effect of AZQ could not be dissociated from that of dexamethazone and those cases could not be considered as remissions due to chemotherapy only. These 13 patients had a duration of survival significantly longer than that of the 18 cases which did not respond at all to the therapy combining AZQ and dexamethazone. Median survival were respectively 127 and 66 days. Interestingly the two groups did not differ significantly by age or tumour pathology. The survival curves of the two groups are given in Fig. 1.

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Table 1. *Changes in AZQ doses*

Lowest absolute granulocyte count		Lowest platelet count	Next course dose change
>3,000	and	>150,000	increase 50%
2000-3000	and/or	100,000-150,000	increase 25%
1000-2000	and/or	75,000-100,000	no change
<1000	and/or	<75,000	decrease 50%
Morbidity (i.e. infection and/or hemorrhage)			decrease 50%

If platelets were lower than 100,000/mm^3 and WBC lower than 3000/mm^3 chemotherapy was delayed.

Table 2. *Doses of AZQ actually given*

No. of patients	No. of cycles	Total doses of AZQ (mg) Median	Range	Change of AZQ dosage as compared to the previous administration Increased	Decreased	Unchanged
6	1	66.5	50-75	-	-	-
21	2	160	112.5-250	18	1	8
5	3	248	146.3-362.5	1	2	3
1	7	-	730	-	-	1

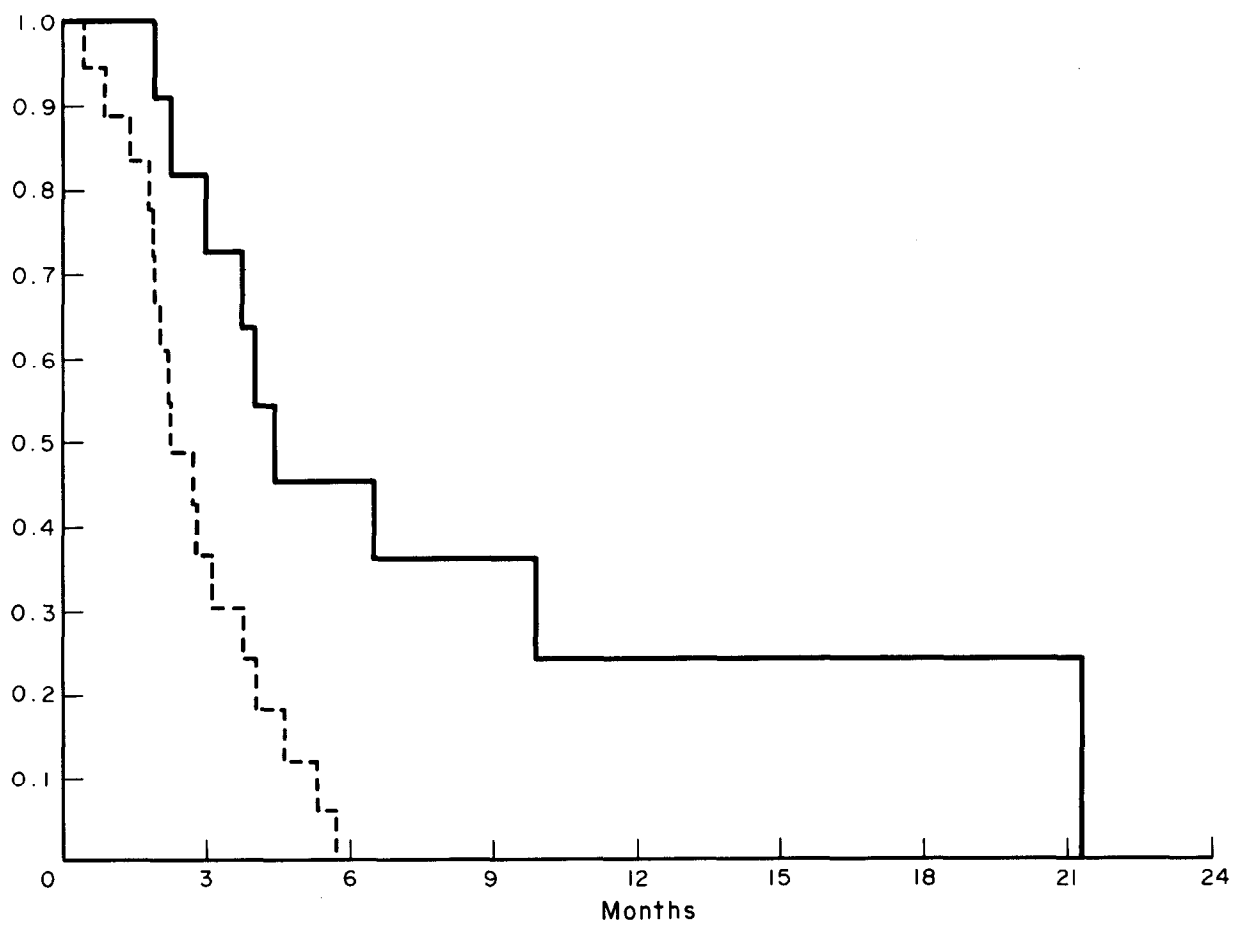

Fig. 1. *Survival curves from start of AZQ treatment: patients who showed some clinical improvement to the administration of AZQ plus corticosteroids ——— ; patients who did not respond - - - - - - .*

Table 3. Results of AZQ treatment

Clinical response	No. of patients	Age (yr)	Karnofsky index	Tumour pathology: Glioblastoma multiforme	Tumour pathology: Astrocytoma III–IV	Tumour pathology: Others	AZQ (mg)	Survival (days)
Objective remission	2	23, 62	80, 70	1	1	-	730, 248	>720, 217
Stabilization	13	52 (median) (range: 32–67)	70 (median) (range: 30–90)	6	3	4	160 (median) (range: 75–260)	127 (median) (range: 29–639)
No response	18	49 (median) (range: 27–74)	60 (median) (range: 20–90)	10	5	3	155 (median) (range: 50–362.5)	66 (median) (range: 14–171)

Table 4. Side-effects

Side-effects	Total	Mild	Moderate	Severe
Hematologic				
WBC		(3.9×10^3-3.10^3)	($2.9.10^3$-1.10^3)	($<1.10^3$)
	14/27*	3	9	2
Platelets		(99.10^3-75.10^3)	(74.10^3-50.10^3)	($<25.10^3$)
	8/26*	2	2	4
Non-hematologic				
Nausea	7/26			
Vomiting	5/26			1 (requiring treatment)
Liver	1/29			1 (hepatitis)
Oral erythema	5/24		5	
Cutaneous erythema	1/14	1		
Fever with drug	2/29	1	1	
Hair loss	4/24	1	3	
Infection	5/24	2	2	1
Death due to chemotherapy	1/33			

*No. of patients where the effect was fully evaluated.

The clinical activity of AZQ in brain tumours has been recently reviewed by Bender *et al.* [6]. The rate of objective responses ranged from 5 to 27%. Our data are in accordance with these results, indicating that AZQ, when used alone, is modestly active in malignant brain gliomas. Although we do not have phase III-type studies comparing the activity of AZQ to nitrosourea derivatives, it seems unlikely that AZQ would yield better results when used alone.

Haematologic toxicity was the most common side-effect, as shown in Table 4. The lowest values were observed mainly during the third week following AZQ administration. The toxicity was reversible in all patients except one, whose death was due to chemotherapy, despite an intensive hematologic rescue. Other toxicities were rare, reversible and unusually mild.

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