Aziridinylbenzoquinone (AZQ) in the treatment of recurrent pediatric brain and other malignant solid tumors

A Pediatric Oncology Group phase II study

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Summary

To assess the response rates and toxicity of AZQ in children with recurrent brain and other malignant solid tumors, a phase II study was implemented by the Pediatric Oncology Group. Eligible patients received AZQ 18 mg/M²/week i.v. for 4 doses followed by a 2 week rest period. Each dose was given over four hours (1/3 over the initial 20 minutes). After the first year, the dosage was reduced to 13 mg/M² due to myelotoxicity resulting in treatment delays. No objective responses were observed in 73 evaluable children with various non-central nervous system tumors. Of the 91 patients with brain tumors, there were 4 CR’s and 2 PR’s in patients with astrocytoma, ependymoma, glioblastoma multiforme, oligodendroglioma, brain stem glioma and intracranial yolk sac tumor (median duration, 10 months; range, 2–20+ months). Three of 4 CR’s were achieved with a dosage of 18 mg/M²/week. An additional 13 children with brain tumors experienced stable or improved disease (duration, 2–36+ months; median 7.5 months). The principal toxicity was myelosuppression which was cumulative but there were also 3 allergic reactions to AZQ. We conclude that for selected brain tumors, the rates of objective response and stable disease plus the duration of responses support further assessment of AZQ in combination with other agents. Furthermore, the 18 mg/M² dosage may provide better responses.

Introduction

Aziridinylbenzoquinone (AZQ) is a synthetic quinone with pharmacologic properties favoring entry into the central nervous system [1,2]. AZQ was synthesized with the hopes of providing an agent with particular activity against central nervous system tumors. Although the mechanism of antitumor effect of AZQ is unknown, members of this class of drugs are known to cross link DNA and to possess structural characteristics typical of alkylating agents [3,4]. Pre-clinical tumor models as well as Phase I and II studies in adults suggest activity against various brain tumors, other malignant solid tumors and leukemia [1,5–10].

With the limited data available from trials of AZQ in children, the Pediatric Oncology Group (POG) designed and implemented a study (POG #8336) to evaluate the efficacy and toxicity of AZQ in brain and other malignant solid tumors.

Materials and methods

Eligibility requirements included: age ≤ 21 years, objective evidence for a recurrent brain or other
solid tumor resistant to standard methods of therapy; no treatment for at least two weeks prior to registration unless progressive disease was well documented while still on previous therapy; a life expectancy of six weeks; and normal marrow (neutrophil count $\geq 1000/\mu$L, platelet count $\geq 100,000/\mu$L), renal (creatinine $\leq 1.2$ mg/dL) and liver (bilirubin $\leq 1.7$ mg/dL, normal SGOT/PT) functions. Allowances regarding blood counts were made for solid tumor patients who had bone marrow involvement. In the patients with brain tumors, lesions were to be measurable by computerized tomography (CT) and centralized neuropathology review of biopsy material from initial or subsequent surgery was required. Informed written consent according to FDA, NCI and institutional guidelines was obtained in all cases prior to registration.

Evaluation criteria

Tumor status was assessed prior to each of the first two courses of AZQ then every other course thereafter.

In patients with brain tumors, physical examination, including detailed neurological assessment, and the dosage of steroids (if any) were monitored closely during therapy. The CT scan was the principal method of assessing patient response. The tumor size was computed as the product of the maximum perpendicular diameters. The following response definitions were used:

- Complete response (CR): complete resolution of tumor.
- Partial response (PR): $\geq 50\%$ reduction of tumor size.
- Minimal response (MR): $<50\%$ reduction of tumor size.
- No response (NR): no appreciable change of tumor size.
- Progressive disease (PD): $>25\%$ increase in tumor size.

Cases of brain tumors in which no or minimal change was noted by CT yet physical exam findings improved were coded as stable disease and continued on therapy until progressive disease or toxicity prevented additional therapy or until one year of treatment had been given.

The response criteria for other malignant solid tumors were:

- CR: complete disappearance of all disease.
- PR: $\geq 50\%$ decrease in the size of all lesions.
- MR: $>25\%$ but $<50\%$ decrease in the size of all lesions.
- NR: $\leq 25\%$ decrease in size of all lesions.
- PD: $>25\%$ increase in the size of one or more lesions or the appearance of new lesions.

Patients were removed from study if 1) progressive disease occurred after one course of therapy, 2) no response was demonstrated after two courses of treatment (except as noted above for brain tumors), 3) evidence of recurrent tumor followed an initial response, or 4) unexpected or unacceptable toxicity occurred.

Drug administration

Initially AZQ was given in a dosage of 18 mg/M$^2$ per week i.v. for four consecutive weeks followed by a two week rest period. Courses were repeated every six weeks.

AZQ was mixed with N,N-Dimethylacetamide and 0.01 M, pH 6.5 phosphate buffer to a concentration of 1 mg/ml. The dose to be administered was further diluted with sufficient volume of either Lactated Ringer's solution or normal saline to a final concentration of 0.2 mg/ml. Based upon the pharmacokinetic studies of Bjornsson et al. [11], one third of the dose was infused over 20 minutes and two thirds over the next 220 minutes. The dose of AZQ was decreased by 25% if patients developed grade 3 myelosuppression, defined as a nadir of the absolute neutrophil count (ANC) of less than 1000/$\mu$L or platelet count less than 75,000/$\mu$L. Repeat courses of therapy were delayed until the absolute neutrophil count was $\geq 1000/\mu$L or platelet count less than 75,000/$\mu$L. Repeat courses of therapy were delayed until the absolute neutrophil count was $\geq 1000/\mu$L or platelet count less than 75,000/$\mu$L and the renal/liver function studies as defined above were observed. Platelet support for brain tumor patients was encouraged for platelet counts less than 50,000/$\mu$L. After the first year of patient accrual (73 patients), the starting dosage of AZQ was reduced to 13 mg/M$^2$ per week because of the inordinate delays within and between courses due to hematopoietic toxicity.