

Phase I Study of Aziridinylbenzoquinone (AZQ, NSC 182986) in Children with Cancer

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ABSTRACT

Aziridinylbenzoquinone is a quinone compound capable of penetrating the central nervous system. It has demonstrated activity against both intracranial and i.p. murine tumors and human tumor xenographs. We have conducted a Phase I trial of aziridinylbenzoquinone in 60 children with advanced cancer who were refractory to conventional therapy. The drug was given by slow i.v. push on a daily schedule for 5 days every 3 to 4 weeks. The dose range explored included 6 dose levels, ranging from 6 to 12 mg/sq m daily for 5 days in patients with solid tumors and leukemia, and in patients with leukemia, 20, 25, and 30 mg/sq m daily for 5 days. Myelosuppression was the dose-limiting side effect. In patients with solid tumor the highest dose studied was 12 mg/sq m, and the median nadir white blood cell and platelet counts were 0.7 x 10³ and 6.0 x 10⁴/μl on Days 17 and 22, respectively. The median recovery day for white blood cells was 39. There may be some evidence of cumulative toxicity with prolonged thrombocytopenia. Other side effects were mild nausea, vomiting, and mucositis. Elevations in liver enzymes and bilirubin were transient and dose dependent, occurring 3 to 4 weeks after drug administration.

Of the 34 children with solid tumors, 33 were evaluable for hematopoietic toxicity. 3 were early deaths, and 31 receiving a total of 55 courses were evaluable for therapeutic response. Partial responses lasting 3 weeks to 6 months were seen in the 4 patients with Hodgkin’s disease, and in a child with a metastatic spinal cord ependymoma. Fifty-two courses were given to 9 patients with acute lymphocytic leukemia and 17 with acute nonlymphoblastic leukemia. Of the 15 patients with acute nonlymphoblastic leukemia treated at doses ≥25 mg/sq m/day for 5 days there was one early death and there were 2 M1 (≤5% blasts with normal cellularity), 3 M2A (6 to 15% blasts), and 2 M2B (16 to 39% blasts) bone marrow responses lasting 1 to 3.5 months.

Aziridinylbenzoquinone demonstrated activity against acute nonlymphoblastic leukemia with maximal tolerated doses of 30 mg/sq m daily for 5 days. Its effect in Hodgkin’s disease is encouraging; however, further study will be required to determine its efficacy in central nervous system cancers. Recommended doses for Phase II studies, using daily schedule for 5 days in children with solid tumors, is 9 mg/sq m, and in children with leukemia, it is 25 mg/sq m.

INTRODUCTION

AZQ³ represents a rationally synthesized drug which has characteristics that help the drug penetrate the central nervous system (9, 14, 18). It has a broad spectrum of activity in murine tumor systems (10, 20). Although the structure of AZQ suggests that it should possess alkylating activity (11), other benzoquinones are known to cross-link DNA. When added to cells in culture, AZQ inhibits DNA synthesis, with little effect on RNA or protein synthesis (2). Toxicity in small and large animals included anorexia, emesis, diarrhea, weight loss, and gastrointestinal bleeding. In addition, there was a myelosuppression and elevated liver function tests (10).

Phase I studies in adult patients using dose schedules of daily for 5 days, weekly, or every 3 to 4 weeks, have reported antitumor effect in patients with brain tumor.

The purpose of this study was to determine the MTD of AZQ in children, to characterize the clinical toxicity, and to document any possible therapeutic effect in children with leukemia and solid tumor.

MATERIALS AND METHODS

Sixty patients were enrolled in this study, 42 males and 18 females. The age range was 7 months to 20 years, with a median age of 11 years (Table 1). All patients had advanced cancer that was no longer responsive to conventional treatment with chemotherapy and/or radiotherapy. Patients had been off all previous therapy for at least 4 weeks and/or recovered from toxic effects of prior treatment. Adequate hepatic, renal, and cardiac functions were required, with a bilirubin of ≤2 mg/dl, blood urea nitrogen of ≤30 mg/dl, creatinine of ≤1.5 mg/dl, and a normal echocardiogram. All patients had a comprehensive history and physical examination documenting subjective and objective evidence of disease prior to entry, with appropriate radiological and radionuclide studies. Base-line laboratory studies included a complete blood count, differential, platelet count, hepatic and renal function tests, electrolytes, and a urinalysis. Follow-up studies for inpatients included daily complete blood and platelet counts, with a screen for hepatic and renal function done weekly. Written informed consent for participation in this study was signed by the patient or his guardian.

Drug Preparation and Administration. AZQ is supplied in 10-mg vials which are stored under refrigeration. The vials are brought to room temperature and the content is dissolved with 0.5 ml of sterile N,N-dimethylacetamide. This is further diluted with 9.5 ml of sterile 0.01 M, phosphate buffer (pH 6.5). The resultant solution contains 1 mg of AZQ per ml. The drug is then administered by slow i.v. push.

RESULTS

Preclinical toxicology studies, using a daily schedule for 5 days demonstrated the low toxic dose in dogs and monkeys to be 1.6 and 1.92 mg/sq m, respectively (10). Phase I studies in adult patients had demonstrated minimal nonhematological side effects with doses of 8 to 10 mg/sq daily for 5 days (5, 19, 26).
Our starting dose was 60% of the MTD in adults, e.g., 6 mg/sq m escalated to 7, 8, 9, 10, and 12 mg/sq m daily for 5 days every 3 to 4 weeks. At doses ≤9 mg/sq m daily for 5 days, AZQ produced only transient nonhematological toxicity, and in 5 patients with leukemia, receiving a total of 10 courses at these lower dose levels, there was no effect on marrow cellularity, except in one course. In addition, Phase I study in adult patients with leukemia reported AZQ was tolerated at 28 mg/sq m daily for 7 days (27). Accordingly, the study was extended in children with leukemia by further dose escalation to levels of 20, 25, and 30 mg/sq m. Doses were not escalated in the same patient. Three patients, one with leukemia and 2 with solid tumors, were evaluated at each initial dose level. Six or more patients were been evaluated at each of 6 dose levels. Myelosuppression was evaluated at each initial dose level. Six or more patients were treated at some dose levels to delineate more fully the nature of the drug-related effect. The toxicity grading used was according to Miller et al. (22), with minor modifications for pediatric patients (Tables 2 and 3).

Table 2 shows the hematopoietic toxicity of AZQ in children with solid tumors and lymphomas. Three to 10 patients have been evaluated at each of 6 dose levels. Myelosuppression was the dose-limiting toxic effect. Leukopenia appeared to be dose related, with median nadirs of WBC of 1.4 × 10^3/µl at ≤8 mg/sq m/day, and 0.7 × 10^3/µl at doses of 9 to 12 mg/sq m/day. White cell count nadirs occurred between Days 17 and 29, with median day to recovery by Day 39. Platelet depression did not follow an obvious dose-response pattern. At ≤8 mg/sq m/day the median platelet nadir was 51 × 10^3/µl, at 9 to 10 mg/sq m/day the median nadir was 25 × 10^3/µl, and in 3 courses at 12 mg/sq m/day, a median of 6.0 × 10^3/µl was seen. The nadirs occurred between Days 18 and 22, with a median recovery by Day 26. A decrease in hemoglobin of 2.0 to 3.8 g/dl was observed on days 17 to 22 and was not dose related. Fifteen of the 19 patients receiving 2 to 4 courses were evaluable for cumulative hematopoietic toxicity. Three patients had prolonged thrombocytopenia, with platelet counts of less than 50 × 10^3/µl persisting for more than 3 months after AZQ administration. Their leukopenia was not prolonged. Two were patients with Hodgkin's disease who had doses of 7 and 9 mg/sq m, and the other patient with spinal cord ependymoma had a dose of 10 mg/sq m. One of these children also had prolonged anemia, with a hemoglobin of 6.2 g/dl at the second course of 10 mg/sq m/day. It is difficult to know whether their prior extensive radiation and chemotherapy and/or disease contributed to this prolonged depression.

Table 3 describes the other side effects seen in patients with solid tumors and leukemia. Hepatic toxicity was monitored by following glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline phosphatase, 5'-nucleotidase, and total bilirubin. Transient increases in serum bilirubin and hepatic enzymes were seen. Of 109 evaluable courses, 27 were associated with significant hepatic dysfunction. In most of these patients, hepatic toxicity occurred in the presence of progressive disease and sepsis, and involved elevations of both bilirubin and hepatic enzymes. In 2 patients there was isolated hyperbilirubinemia, occurring 2 months after AZQ in one patient, and during the 5-day course of treatment in the other. Although acute hemolysis cannot be ruled out, the patient's hemoglobin remained stable and no transfusion was required.

Other nonhematological side effects included mild to moderate hearing loss in 2 patients, and tinnitus in one patient, all of whom...
had received multiple doses of aminoglycosides. Nausea, vomiting, and mucositis were mild, and transient alopecia occurred on 3 occasions. Occasionally, patients developed fever on the day of drug administration.

Patients with leukemia were evaluated for AZQ-induced changes in marrow cellularity and blast percentage, as well as remission duration. Bone marrow aspirates and often bone marrow biopsies with touch preparation were obtained on Days 14 to 21. Changes in marrow cellularity were categorized as follows: aplasia, no evidence of leukemia or hematopoietic activity, and cellular elements were limited to lymphocytes, plasma cells, and histiocytes; hypoplasia, cellularity decreased with marked reduction in the leukemic infiltrate to less than 50% blasts; and minimal or no effect, minor or no reduction in the degree of leukemic infiltration. Bone marrow responses were defined as M1: less than 5% blasts with normal cellularity on bone marrow biopsy, with a platelet count of 75 × 10⁹/µl and neutrophil count of 0.75 × 10⁹/µl within 1 week of bone marrow results. M2 for ALL: 6 to 25% blasts; M3, more than 25% blasts. For ANLL, M2A: 6 to 15% blasts; M2B: 16 to 39% blasts; and M3, more than 39% blasts.

The bone marrow responses in acute leukemia are shown in Tables 4 and 5. No remission was seen in the 9 patients with ALL; one of the 2 patients treated at 30 mg/sq m/day for 5 days did develop an aplastic marrow. Table 5 describes the responses seen in the 17 children with ANLL; at 8 mg/sq m/day for 5 days one child had a significant decrease in blast percentage, with an M2B marrow after 2 courses. A third course, however, failed to produce further response. In the 6 children treated with 25 mg/sq m/day for 5 days, the bone marrow became hypoplastic in 2 patients and aplastic in 3 patients, and one of these had an M2A marrow for 1 month. At 30 mg/sq m/day, of the 9 children treated, the marrow became hypoplastic in 4 patients and aplastic in 5 patients. Two of these had M1 marrows for 1.5 and 2 months, with bone marrow biopsies confirming normal cellularity with all hematopoietic elements present. These 2 patients were continued at 20 mg/sq m as the second course which had no effect.

The dose-limiting toxicity was myelosuppression with leukopenia and thrombocytopenia. Of the 40 patients who received AZQ, 19 had neutrophil counts below 0.5 × 10⁹/µl and 8 had platelet counts below 25 × 10³/µl. Two of the 25 patients who received 30 mg/sq m/day had severe bone marrow suppression with no recovery after 25 days. One of the 2 patients who were evaluated as having the M2B response had a marrow aspirate showing 17% blasts with no effect.

One child with Juvenile Chronic Myelocytic Leukemia in blast crisis with hepatomegaly, who had a WBC of 91.5 × 10⁹/µl and 8% blasts, after AZQ had marked reduction of liver size. Subsequent bone marrow aspirates were M2A (14.5 to 8% blasts) for a period of 3.5 months.

Another child with Juvenile Chronic Myelocytic Leukemia in blastic crisis, with hepatosplenomegaly and marrow aspirate showing 31% blasts, after AZQ had marked decrease in the size of spleen, without a change in liver size. Subsequent bone marrow aspirates showed 15.5% blasts, with erythroid hyperplasia lasting for 1 month.

One of the 2 patients who were evaluated as having the M2B response had a marrow aspirate showing 17% blasts with no leukemia identified on marrow biopsy, and there was a return of normal hematopoietic elements.

Thirty-one children with solid tumors and lymphomas were evaluable for response as detailed in Table 6. One child with spinal cord ependymoma had a partial response for 2.75 months with both clinical and computer-assisted tomography scan improvement; one child with a spindle cell sarcoma had stable disease for 3 months. Marked decrease in bone pain for 1.75 months was observed in a child with embryonal rhabdomyosarcoma. Of the 4 patients with Hodgkin’s disease, 3 had marked decrease in or disappearance of lymph nodes for 0.75 to 2 months. The fourth patient had a minor response with decrease in size of multiple lung nodules. Six children with brain tumors had progressive disease, and one child with a cerebral astrocytoma had stable disease for 3.5 months.

**DISCUSSION**

AZQ was evaluated as a Phase I study to establish the MTD in children with cancers, using 5-day courses of single daily injections. The MTD for children with solid tumor was 10 mg/sq m/day, and for children with leukemia it was 30 mg/sq m/day. Sixteen of the 56 evaluable patients had single courses, while 40 patients received 2 to 4 courses at 2- to 9-week intervals. The dose-limiting toxicity was myelosuppression with leukopenia, thrombocytopenia, and anemia. Questions pertaining to
cumulative hematopoietic toxicity remain to be answered. Three patients had thrombocytopenia for more than 3 months. In general, children tend to develop more severe leukopenia secondary to chemotherapy than is seen in adults. A high incidence of myelosuppression with leukopenia following adjuvant chemotherapy was also seen in previously untreated patients with solid tumors (17, 24). In this study, children with leukemia, in the absence of fever, have not required hospitalization. Platelet transfusions were given to those patients whose platelet counts were below 20 × 10^9/μl. There was no drug-related death. Three patients with solid tumor and one patient with leukemia were classed as early death, due to progressive disease, and were not evaluable for response. These patients were included in the evaluation of toxicity, except in the patient who died too early for hematological evaluation. Elevations in bilirubin and hepatic enzymes were dose-related, occurring in 16% of the children with solid tumors, and in 55% of children with leukemia who received doses of ≥20 mg/sq m/day. These values returned to the normal range, on the average, within 5 weeks. In patients with leukemia, progressive disease and a 45% incidence of sepsis precludes any judgment as to the specific cause of the hepatic abnormalities. Other toxicities were mild and transient.

Encouraging results were seen in children with acute nonlymphoblastic leukemia, all of whom had received extensive prior therapy. Six of the 9 patients receiving doses of 30 mg/sq m/day for 5 days responded, with 2 having M1 marrows for 1.5 and 2 months. Although only 5 patients with ALL were evaluable at comparable dose levels, no responses were seen. Notable among the patients with solid tumors are the 4 patients with Hodgkin's disease. All have received extensive prior chemotherapy, including alkylating agents and nitrosoureas. Three had partial responses with a decrease in adenopathy. This may suggest that other alkylating agents and AZQ may not be completely cross-resistant. One other child with a spinal cord ependymoma had a partial response. The usefulness of the drug, however, was limited for this child by prolonged myelosuppression, which prohibited further therapy.

AZQ is a rationally synthesized compound designed to have both good lipid and water solubility. Good CNS penetration has been documented by Bachur et al. (4), in patients given 16 to 24 mg/sq m of AZQ as a 30-min infusion. They found therapeutic CSF levels for a minimum of 4 hr following the infusion with a CSF: plasma area under the curve ratio of 22 to 42%.

Aroney et al. (3) evaluated 20 patients with recurrent primary tumors and 9 patients with metastatic brain tumors who were given AZQ, 17.5 mg/sq m, as a 30-min infusion on Days 1 and 8 of a 28-day cycle. There were 2 partial responses lasting 38+ and 4 weeks with prolonged thrombocytopenia, necessitating 6-week intervals between courses. Curt et al. (13), using the same schedule, reported responses in 4 of 15 patients with Grade III and IV astrocytoma. The median duration was 2.5+ months. Feun et al. (15) reported a 24% response rate in 16 adults with recurrent gliomas treated with 6 to 8 mg/sq m/day for 5 days. Among our 7 evaluable patients with brain tumor treated with 6 to 12 mg/sq m/day for 5 days, there was one child with cerebral astrocytoma, who had stable disease for 3.5 months. All other patients with brain tumors have had progressive disease.

Kamen (21) described 2 children with ALL treated with AZQ for marrow relapse, who also had a decrease in the number of blasts present in the cerebrospinal fluid. In our experience, however, 2 of 26 patients developed CNS leukemia while on systemic AZQ. Although AZQ used daily for 5 to 7 days in adult patients with acute leukemia (27, 28) produced marrow aplasia and clearing of peripheral blasts, no remissions were reported. A decrease in the number of CSF blasts, in patients receiving i.v. AZQ was also noted. Studies in adult patients using AZQ daily for 5 days on Days 1 and 8 or on Day 1 only every 28 days, have not reported major tumor responses in breast (7), colorectal (6, 25), melanoma (12), head and neck (16), genitourinary (23), and lung (1, 8) cancers. AZQ given by continuous infusion was tolerated, and similar myelosuppression was reported (29).

In this study, AZQ has shown antileukemic effect in acute nonlymphoblastic leukemia, with disappointing poor regeneration of normal marrow elements. More extended study is needed to fully define its role in this disorder. Among possible uses would be cytoreduction prior to bone marrow transplant, or in combination with other agents in the treatment of ANLL. There may also be a role for AZQ in patients with Hodgkin’s disease, refractory to other alkylating agents and the nitrosoureas. Conclusions as to its role in tumors of the CNS await evaluation of additional patients.

REFERENCES


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