Mitoxantrone in Patients with Acute Leukemia in Relapse

Paolo Alberto Paciucci, Takao Ohnuna, Janet Cuttner, Richard T. Silver, and James F. Holland

ABSTRACT

Twenty-six patients with acute leukemia in relapse were treated with mitoxantrone (1,4-dihydroxy-5,8-bis[(2-hydroxyethyl)amino]-9,10-anthracenedione dihydrochloride). The drug was given as a rapid i.v. infusion for 5 days, and doses were escalated from 8 mg/sq m daily for 5 days to 20 mg/sq m daily for 5 days. Five of 12 patients with acute lymphoblastic leukemia were induced into complete remission; one patient was induced into complete remission twice. The marrow response lasted from 3 to 50+ weeks. Among 12 patients with acute myelogenous leukemia, there was one complete and one partial remission, with response duration lasting 8 and 2 weeks. One patient with chronic myelogenous leukemia in blast crisis also had a partial remission lasting 17 weeks. Remissions occurred at doses ranging from 8 to 14 mg/sq m daily for 5 days. All responders had been treated previously with anthracyclines. Drug-induced side effects included dose-limiting oral mucositis, spurious nausea and vomiting, and transient elevations of the hepatic enzymes. Approximately one-third of the patients had septic complications during the myelosuppressive phase following treatment. We believe that mitoxantrone has definite utility in the treatment of acute leukemia in relapse.

INTRODUCTION

Mitoxantrone, [1,4-dihydroxy-5,8-bis{[2-hydroxyethyl]amino}-9,10-anthracenedione dihydrochloride or CL232,315 (NSC 301739), is a synthesized anthraquinone which intercalates into DNA (3,22); its lack of aminosugar was designed to reduce or eliminate the cardiotoxicity seen with the structurally related doxorubicin (1). Mitoxantrone has shown substantial antitumor activity in a variety of experimental murine tumors which include P388 and L1210 leukemias, B16 melanoma, and colon carcinoma 26. Partial cross-resistance was observed in P388/ADR, a subline resistant to doxorubicin (2, 12, 13, 21). The drug was given as a rapid i.v. infusion for 5 days. Remissions in ALL were obtained at dosages between 8 and 14 mg/sq m/day for 5 days. Five of 12 patients with ALL received complete and one partial remission, with response duration lasting 8 and 2 weeks. One patient with acute myelogenous leukemia had a partial remission lasting 17 weeks. Remissions occurred at doses ranging from 8 to 14 mg/sq m daily for 5 days. All responders had been treated previously with anthracyclines. Drug-induced side effects included dose-limiting oral mucositis, spurious nausea and vomiting, and transient elevations of the hepatic enzymes. Approximately one-third of the patients had septic complications during the myelosuppressive phase following treatment. We believe that mitoxantrone has definite utility in the treatment of acute leukemia in relapse.

RESULTS

All of the 26 patients entered in the study were considered evaluable for toxicity and response. Five of 12 patients with ALL (Table 2) achieved a remission status; all but one achieved a CR, since one (ALL Patient 3) could not be categorized as a CR because recorded hemoglobin levels did not reach 12 g/dl. Of these patients, one (ALL Patient 1), who had had 3 prior CRs and who failed to respond to a fourth induction attempt with vincristine, prednisone, and doxorubicin, achieved a fourth CR with mitoxantrone at 8 mg/sq m/day for 5 days; this remission lasted only 3 weeks, but the patient was induced again into CR with a one-step higher dose of mitoxantrone, 10 mg/sq m daily for 5 days. Remissions in ALL were obtained at dosages between

MATERIALS AND METHODS

Mitoxantrone was supplied by the National Cancer Institute, Bethesda, Md., as a 20-mg solution in a 10-ml ampule which also contains 0.2% sodium m-bisulfite (w/v) and 0.8% NaCl solution (w/v); the drug was stored under refrigeration. The initial dose for leukemic patients was 8 mg/sq m/day for 5 days, a schedule selected on the basis of our studies in patients with carcinomas and sarcomas (8). In the absence of dose-limiting toxic side effects, subsequent cohorts of 3 or more patients were treated with progressively higher doses of mitoxantrone: 10; 12; 16; and 20 mg/sq m/day for 5 days. Immediately prior to its use, the drug was diluted in 50 ml of 5% dextrose in water and administered i.v. as a rapid infusion over 5 to 10 min.

ABSTRACT

Twentysix patients with acute leukemia in relapse were treated with mitoxantrone (dihydroxyanthracenedione dihydrochloride). The drug was given as a rapid i.v. infusion for 5 days, and doses were escalated from 8 mg/sq m daily for 5 days to 20 mg/sq m daily for 5 days. Five of 12 patients with acute lymphoblastic leukemia were induced into complete remission; one patient was induced into complete remission twice. The marrow response lasted from 3 to 50+ weeks. Among 12 patients with acute myelogenous leukemia, there was one complete and one partial remission, with response duration lasting 8 and 2 weeks. One patient with chronic myelogenous leukemia in blast crisis also had a partial remission lasting 17 weeks. Remissions occurred at doses ranging from 8 to 14 mg/sq m daily for 5 days. All responders had been treated previously with anthracyclines. Drug-induced side effects included dose-limiting oral mucositis, spurious nausea and vomiting, and transient elevations of the hepatic enzymes. Approximately one-third of the patients had septic complications during the myelosuppressive phase following treatment. We believe that mitoxantrone has definite utility in the treatment of acute leukemia in relapse.

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8 and 14 mg/sq m daily for 5 days. Four of the 5 patients who achieved an M₁ marrow following treatment with mitoxantrone had failed previously to respond to induction regimens containing doxorubicin or daunorubicin; the fifth, who responded to mitoxantrone with a CR of 22 weeks duration, had experienced an unsuccessful first induction with vincristine, prednisone, daunorubicin, and L-asparaginase. Four responders were subsequently treated twice more 8 months later.

All 12 patients with AML had been treated previously with at least one course of an anthracycline in combination with 1,3-D-arabinofuranosylcytosine. Of these, one patient (AML Patient 8) had failed previously to respond to reinduction regimens containing doxorubicin or daunorubicin; the fifth, who responded to mitoxantrone following a first unsuccessful attempt; none of these patients remitted. One patient, who had a clinical improvement following a first course of mitoxantrone and who was thereafter treated with different chemotherapeutic regimens, was subsequently treated twice more 8 months later.

One of the 2 patients with blastic-phase CML achieved an M₂ marrow status with a decrease of marrow blasts from 70 to 9% following treatment with mitoxantrone at 12 mg/sq m/day for 5 days, and one (AML Patient 12) had an M₂ marrow response following a first course at 14 mg/sq m/day for 5 days. All other patients had a temporary decrease of the bone marrow infiltration with blasts and a decrease or disappearance of leukemic cells from the peripheral blood. In order to obtain a response, 5 AML patients were treated with a second course of mitoxantrone following a first unsuccessful attempt; none of these patients remitted. One patient, who had a clinical improvement following a first course of mitoxantrone and who was thereafter treated with different chemotherapeutic regimens, was subsequently treated twice more 8 months later.

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Mitoxantrone in Acute Leukemia

The present study establishes that mitoxantrone is an effective remission-inducing agent in patients with acute leukemia that have been exposed to anthracycline antibiotics. Six instances of marrow remission following 13 courses of treatment in 12 patients with ALL is noteworthy, since all the remitting patients achieved an M0 marrow status after the first course of mitoxantrone administered upon failure to respond to reinduction with anthracycline-containing regimens.

Activity of mitoxantrone has also been observed in AML, with one patient in CR and a second in partial remission. Induction of an M2 marrow in one patient with CML in blast crisis is also encouraging.

All marrow remissions were observed at dosages between 8 and 14 mg/sq m daily for 5 days. At these lower dose ranges, little drug-induced stomatitis was observed. The reason why marrow remissions did not occur at higher dosages is unclear. The number of patients entered at dosages higher than 14 mg/sq m daily for 5 days was too small to assume that remissions would not occur. Decrease in therapeutic benefit with increasing drug dose has, however, been recognized in experimental systems with other anticancer agents (15) and probably in humans.

This dose-escalating study of mitoxantrone in patients with acute leukemia in relapse established that the nonhematological dose-limiting toxicity of the compound is oral mucositis. No therapeutic benefit was seen above 14 mg/sq m/day for 5 days; toxicity became more pronounced up to the maximal level tested, 20 mg/sq m/daily for 5 days, which is probably the maximum dose that could be tolerated. Other toxicities, such as nausea and vomiting, alopecia, and transient hepatic dysfunction, were mild to moderate. The incidence of infectious complications following mitoxantrone appeared comparable to that observed with other regimens in aggressively treated patients with leukemia in relapse. Arrhythmias were not experienced, and 2 transient instances of mild congestive failure were attributable to contemporaneous clinical catastrophes (acute tubular necrosis

Table 3

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<th>Dose (mg/sq m/day for 5 days)</th>
<th>No. of patients</th>
<th>No. of courses</th>
<th>Mucositisa</th>
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<th>Hepaticb</th>
<th>Infectiousc</th>
<th>Hair loss</th>
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</table>

Numbers in parentheses, number of courses of chemotherapy in which Candida mucositis and mitoxantrone-induced mucositis were not distinguishable.

Numbers in parentheses, number of courses of chemotherapy in which hepatic dysfunction was present prior to chemotherapy with mitoxantrone.

Numbers in parentheses, number of courses of chemotherapy in which had mildly abnormal hepatic transaminases prior to treatment with mitoxantrone, the enzyme levels improved to normal range in a median time of 10 days (range, 4 to 26 days) following chemotherapy.

Although the possibility of mitoxantrone-induced cardiotoxicity has been suggested (6), none of our patients developed cardiac injury attributable to mitoxantrone.

DISCUSSION

The present study establishes that mitoxantrone is an effective remission-inducing agent in patients with acute leukemia that have been exposed to anthracycline antibiotics. Six instances of marrow remission following 13 courses of treatment in 12 patients with ALL is noteworthy, since all the remitting patients achieved an M0 marrow status after the first course of mitoxantrone administered upon failure to respond to reinduction with anthracycline-containing regimens.

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from transfusion reaction and hypervolemia from fluid overload).

Although survival of children with ALL has greatly improved over the past 10 years (9, 11), high-risk ALL, e.g., adult ALL and childhood ALL with certain phenotypes (7, 10, 14, 19), continues to represent a therapeutic challenge today. Failure of chemotherapy in this disease may be largely attributable to early development of drug-resistant leukemic cell clones; this contention justifies the search for non-cross-reactive chemotherapeutic agents. The present study confirms the activity of mitoxantrone in acute leukemia that we and others reported recently (4, 17, 20); it suggests that leukemic clones resistant previously to anthracycline-containing antileukemic regimens were still vulnerable to mitoxantrone. This new antitumor agent appears to be dissimilar to those presently in use; its further development in combination regimens in untreated patients, or in those already in remission, will establish its place in the armamentarium for the treatment of leukemia.

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