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Sequential Mitoxantrone, Daunorubicin, and Cytosine Arabinoside for Patients With Newly Diagnosed Acute Myelocytic Leukemia

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Mitoxantrone (M) is a synthetic aminoanthraquinone with anti-leukemic activity in patients with daunorubicin (D) resistant acute leukemia. The Cancer and Leukemia Group B (CALGB) has undertaken a limited access pilot study in which M, 12 mg/m^2, over 30 min, daily for 3 days, and cytosine arabinoside (Ara-C), 100 mg/m^2/day by constant infusion for 7 days were used for the induction of newly diagnosed patients with AML. Responding patients were consolidated with daunorubicin, 45 mg/m^2/day for 3 days, and 7 days of Ara-C. After a second consolidation identical to induction, no further therapy was given. Twenty-nine patients with a median age of 50 years (range 18–72) were entered in the study; 18 were males and 11 females. Twenty-four (83%) patients achieved CR, 1 patient achieved a PR, and 4 died in induction from leukemia-related causes. Two patients died in CR from consolidation-related neutropenic sepsis and two additional patients died in CR. Of 24 patients, 7 remain disease-free at a median follow-up interval of 8 years. The regimen is active and well tolerated. The duration of disease-free survival in responding patients is consistent with that seen in similar regimens using intensification chemotherapy without prolonged maintenance. Am. J. Hematol. 56:214–218, 1997.

Key words: mitoxantrone; cytosine arabinoside, AML

INTRODUCTION

Despite the high initial complete remission rates achieved by induction chemotherapy for acute myelocytic leukemia (AML), the long-term disease-free survival of responding patients has not been substantially improved over the past 20 years, despite different regimens of prolonged maintenance chemotherapy [1,2]. The value of long-term maintenance chemotherapy in improving the prolongation of disease-free survival [3–5], had been challenged by two provocative studies [6,7], which led us to ask the question whether longer relapse-free survival could be achieved by administering intensive post-remission consolidation chemotherapy. In order to avert the insurgence of drug-resistance and to maximize cytotoxic drug effects on leukemic cells after induction chemotherapy, we chose a regimen employing mitoxantrone plus cytarabine for the induction and daunorubicin plus cytarabine for first consolidation, based on our experience of clinical lack of cross-resistance between mitoxantrone and daunorubicin [8,9]. Mitoxantrone was chosen for the initial induction chemotherapy because of the lower toxicity profile we had seen in the treatment of patients older than 60 and in those previously exposed to anthracycline regimens who were primarily refractory to daunorubicin-containing regimens [10].

A total of 29 patients with newly diagnosed acute my-

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elocytic leukemia were studied. After induction, patients were consolidated with a ''seven and three'' regimen of daunorubicin and cytarabine, which was followed by a second consolidation with mitoxantrone and cytarabine. Responding patients were followed for survival and we herein report the toxicity of the regimen and its effects on long-term disease-free survival. Of the twenty-nine patients entered, 23 achieved complete remission (83%) and, of these, 7 (33%) remain disease-free with a median follow-up of 8 years.

PATIENTS AND METHODS

Patients with cytochemically and histologically documented, previously untreated acute myelocytic leukemia were eligible for the study. Patients had to be older than 15 years and could not have a previous or concomitant malignancy other than curatively treated in situ cervical carcinoma or basal cell carcinoma of the skin. Patients could not have other serious medical illnesses, and if presenting with active bacterial, viral, or fungal infections, treatment could not be started until until these were corrected. Required initial laboratory data included BUN and bilirubin less than 1.5 times normal values and serum creatinine less than 1.8 mg/dl. Patients were informed of the investigational nature of the treatment and an informed consent was signed in accordance with institutional and federal guidelines.

Data quality was ensured by careful reviews of all data forms and flow sheets by the CALGB database manager responsible for this study and by the study chairman. Central histologic review of pre-treatment bone marrow and blood smears was required for each patient. Treatment toxicity and therapeutic effects were evaluated and classified according to CALGB criteria [11].

Mitoxantrone was obtained from the National Cancer Institute in 15-ml ampules containing 30 mg of the drug. The dose of the drug was diluted in 50–100 ml of 5% dextrose in water or normal saline. Cytarabine and daunorubicin were commercially available. Induction was the same for all patients and consisted of mitoxantrone 12 mg/m^2/day on days 1 through 3 by a 30-min infusion. Cytarabine was administered in a 7-day continuous infusion at 100 mg/m^2 per day. If the marrow showed >5% leukemic cells on day 18, patients were treated with a second course consisting of 2 days of mitoxantrone and 5 days of Ara-C at the same doses.

Patients who did not achieve complete remission (CR) were given consolidation no. 1 therapy when their bone marrow biopsy showed a cellularity of at least 2, neutrophils were greater than 1,500/μl, and platelets were greater than 100,000/μl. This consisted of daunorubicin, 45 mg/m^2/day (30 mg/m^2 for patients over 60 years old) by intravenous push for 3 consecutive days and an identical course of cytarabine at 100 mg/m^2/day for 7 days.

TABLE I. Patient Characteristics

	N
Males	18
Females	11
Age	
(range)	18–71 years
(median)	50
Age > 60	6
CALGB performance status	
0	14
1	11
2	2
3	2
Peripheral blood	
Hemoglobin (g/dl)	
Median	9.4
Range	3.5–16.4
Platelets/μl	
Median	60,000
Range	10,000–592,000
WBC/ul	
Median	11,000
Range	700–178,000
Extramedullary involvement	
CNS	2
Liver	1
Spleen	4
Lymph nodes	4
Gum hypertrophy	3
Other (ENT)	1

Patients who failed to achieve M1 marrow status following consolidation no. 1 therapy were considered treatment failures and were withdrawn from study.

Patients who achieved CR after 1 or 2 courses of therapy received one last consolidation as soon as marrow cellularity was at least 2 and WBC were greater than 1,500/μl and platelets greater than 100,000/μl. The last consolidation contained cytarabine plus mitoxantrone, if patients had achieved CR after initial induction, or daunorubicin if the response was obtained after consolidation.

RESULTS

Patient Characteristics

Twenty-nine patients were entered on study, and their clinical characteristics at presentation are shown in Table I. There were 18 males and 11 females, aged 18 to 72 (median age 50). Nine patients were younger than 40 years of age, seven were older than 60.

Response

Table II shows the induction results by age and FAB classification. Median time to CR was 35 days (range 18–58). Twenty-four (83%) of the twenty-nine patients achieved a complete remission after the first induction course. Induction rates by age were 89% for patients

TABLE II. Therapeutic Response and Survival

	N	Complete remission	No response	Induction death	Long-term survivors
FAB subtype					
M1	4	3			1
M2	7	6	1	1	
M3	5	4		1	3
M4	7	5		1	
M5	3	2		1	1
M6	2	2			2
Unclassified	1	1			
Age		<40	40–60	>6−	Total
Complete remission		8 (89%)	11 (85%)	5 (71%)	24 (83%)

TABLE III. Treatment-Related Toxicities (Per Patient)

	Grade (CALGB criteria)					
	0 None	1 Mild	2 Moderate	3 Severe	4 Life-threatening	5 Lethal
Mucositis	13	2	5	7	0	0
Nausea/vomiting	9	5	9	4	0	0
Diarrhea	6	4	13	4	0	0
Infection	2	1	4	13	4	3
Hepatic	10	5	4	8	0	0
Renal	20	4	3	0	0	0
Pulmonary	24	1	1	0	1	0
Cardiac	26	0	0	1	0	0

younger than 40, 85% for patients aged 40 to 60, and 71% for patients older than 60 years. Of the remaining 5 patients, 1 failed to achieve M1 marrow and 4 died in induction. Two patients died from central nervous system bleeding on day 3 and 4; one patient died from rupture of a hepatic chloroma after the first day of chemotherapy and one from candida sepsis during marrow hypoplasia.

Toxicities

The maximum toxicity grades, per patient, during the entire treatment are shown in Table III. Two patients were not evaluable for toxicity because of early death. Overall, three patients died from candida sepsis. Of these, two were recovering from consolidation with daunorubicin and cytarabine after having achieved CR. Nonlethal infectious episodes were oropharyngeal candidiasis (5 patients), gram negative rods sepsis (3 patients each with *Escherichia coli* and pseudomonas), dental and peri-rectal abscesses (2 patients each), gram-positive cocci (two patients), aspergillus pneumonia and Candida tropicalis sepsis (1 patient each), non-A, non-B hepatitis (1 patient), and reactivation of oral herpes (1 patient).

Two patients, aged 72 and 61, respectively, died in complete remission from myocardial infarction after 1 and 15 months, respectively, following study entry. All other treatment-related toxicities were mild. Nausea and vomiting after induction were mild and sporadic. Transient hepatic and renal dysfunction were often attributable to multiple antibiotic regimens.

Survival

The overall median survival was 75 weeks. The median time to failure was 38 weeks. For patients achieving complete remission, the median disease-free survival was 38 weeks. Seven patients remain alive and in continuing complete remission after 93–110+ months.

DISCUSSION

Mitoxantrone is a synthetic aminoanthraquinone that has undergone extensive clinical testing and has high antileukemic activity alone [8] or in combination with cytarabine [9,12–15] or etoposide [16,17] in both newly diagnosed and previously treated patients with acute myelocytic leukemia. The drug is well tolerated, with minimal nausea and vomiting. As in previous studies, it caused transient hepatic dysfunction approximately 2 weeks after administration.

Because of its excellent toxicity profile, mitoxantrone has been used at high dose (80 mg/m^2) in combination with cytarabine for the initial induction of AML patients older than 60 [12]. The activity of mitoxantrone we detected in patients who were primarily refractory to anthracyclines [8–10] suggested that the two drugs did not have clinical cross-resistance, and that sequential exposure of chemotherapy-naive leukemic populations to both drugs in combination with cytarabine might decrease the rates of subsequent relapse. One of the aims of the present study was to investigate the feasibility of administering initial induction with mitoxantrone and Ara-C to patients with AML, since the CALGB had already shown that mitoxantrone was equally effective as daunorubicin in inducing complete remission when it was used as initial therapy for newly diagnosed patients with acute lymphocytic leukemia [18].

Two small trials [6,7] had suggested that maintenance therapy did not prolong survival after post-remission intensification therapy, implying that implementation of measures aimed at prolongation of survival should be carried out immediately after achievement of complete remission. In order to determine the feasibility of administering non-cross-resistant induction and intensification therapy, we carried out a trial of mitoxantrone plus cytarabine followed by daunorubicin plus cytarabine in 29 patients with newly diagnosed AML.

Randomized trials of mitoxantrone plus cytarabine vs. daunorubicin plus cytarabine for newly diagnosed patients with AML have shown equivalent results and without a significant difference in the overall survival between the two drugs [15].

The complete remission rate of 83% in our study, despite its small size, confirms the impressive activity of

mitoxantrone as a remission-inducing agent for patients with newly diagnosed AML [15].

Of the 4 fatalities in complete remission, 2 were caused by sepsis following intensification therapy and two, aged 72 and 61, from myocardial infarction. The median time to relapse was 37 weeks. Seven patients (30% of responders) remain in continuing complete remission after a median follow-up greater than 8.5 years. In relation to age, all survivors were younger than 60 years of age at presentation, and the long-term disease-free survival for this cohort is 37%, consistent with the 50-month disease-free survival of 44% reported by the CALGB in a larger study of AML patients younger than 60 who received post-remission intensification with high-dose cytarabine [19].

In conclusion, the administration of sequential mitoxantrone plus cytarabine, followed by daunorubicin plus cytarabine, is highly effective and well tolerated. It is conceivable that the advances in supportive care made since the inception of this study may lessen the infectious complications of intensification chemotherapy in complete remission and allow the achievement of higher cure rates.

Despite its small size, the long-term disease-free survival compares favorably with that of larger trials. The study also suggests that acceptable long-term disase-free survivals may be achieved without maintenance chemotherapy. The issue of post-remission consolidation and maintenance, however, is still not resolved since several large trials have shown either marginal benefit [3,5,20] or no benefit [21,22] for long-term maintenance chemotherapy in AML. This study was conducted by the Cancer and Leukemia Group B and was supported by Public Health Serive grants from the National Cancer Institute, National Institute of Health, The Department of Health and Human Services, and by a grant from the T.J. Martell Foundation.

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