Treatment of Patients with Recurrent and Primary Refractory Acute Myelogenous Leukemia Using Mitoxantrone and Intermediate-Dose Cytarabine

A Pharmacologically Based Regimen

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BACKGROUND. Although chemotherapy can achieve a high rate of disease remission induction in patients with newly diagnosed acute myelogenous leukemia (AML), patients with recurrent or refractory AML generally have a poorer rate of response. This study assessed the utility of mitoxantrone and intermediate-dose cytarabine (Ara-C) in the treatment of patients with recurrent or refractory AML.

METHODS. Forty-seven patients with recurrent or refractory AML were treated with Ara-C, 0.5 gm/m^2, intravenously (i.v.) every 12 hours $\times$ 12 doses on Days 1–6 and mitoxantrone, 5 mg/m^2, i.v. on Days 1–5.

RESULTS. Twenty-nine of the 47 patients (62%) achieved a complete response. The median duration of disease remission was 112 days (range, 29 days–8 years). Of the 25 patients age $\geq$ 60 years, 19 (76%) had a complete disease remission and the median duration of disease remission in this group was 114 days (range, 33–370 days), although all patients subsequently developed a disease recurrence. The chemotherapy generally was well tolerated, with a mean duration of neutropenia of 31 days and a mean duration of thrombocytopenia of 33 days. Three patients died of infectious complications between 23–26 days after the initiation of chemotherapy, 1 patient died of sudden cardiac arrest 13 days after the initiation of chemotherapy, and 1 patient developed cutaneous desquamation. Three patients developed acute cerebellar dysfunction.

CONCLUSIONS. The use of mitoxantrone and Ara-C is effective in the treatment of patients with recurrent and refractory AML. The subgroup of patients age $\geq$ 60 years also had a high rate of disease remission induction with this regimen, and the regimen generally was well tolerated. ***Cancer* 2000;88:2037–41.**
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For patients with recurrent or refractory acute myelogenous leukemia (AML), remission induction is difficult and their overall prognosis is poor. For those patients eligible for bone marrow transplantation, outcome is improved if the patient is in disease remission at the time of transplantation; for those not eligible for transplantation because of age or lack of a donor, adequate re-induction regimens are necessary if the patient is to have any significant survival beyond disease recurrence.

Most patients with AML will be treated initially with combinations of cytarabine (Ara-C) and either daunorubicin or idarubicin. High dose Ara-C often is used either during the induction regimen and/or the consolidation or intensification stages of therapy. The

addition of high dose Ara-C (HiDAC) is highly effective in the treatment of newly diagnosed AML, and this regimen has been reported to provide a complete remission (CR) rate of 89%.[1] Moreover, the inclusion of HiDAC as part of an intensive postremission regimen has been shown to markedly improve overall survival at 4 years for patients age ≤ 60 years.[2] Nonetheless, the majority of patients will develop disease recurrence and will require reinduction therapy.

Ara-C has been known since the 1960s to be an effective agent in inducing disease remission of AML,[3] and it also may play a role in the treatment of leukemic recurrence. Pharmacokinetic investigations have shown previously that maximal intracellular accumulation of Ara-CTP into leukemic blasts can be achieved with intermittent infusion of this agent at a dose of 0.5 g/m^2 over 2 hours.[4] This optimization of Ara-C dosing has translated to some efficacy in the treatment of recurrent or refractory AML. For example, Estey et al. reported that intermediate-dose Ara-C (0.5 g/m^2 every 12 hours) for 9–25 doses in 43 patients with refractory or recurrent AML yielded a CR rate of 23%.[5]

Mitoxantrone, an anthracenedione chemically related to the anthracyclines, produces DNA strand breaks by alkylating G-C base pairs. Mitoxantrone has been reported to exert a synergistic effect with Ara-C in in vitro studies[6] and clinical trials have likewise demonstrated synergism in the treatment of patients with high risk AML. For example, Brito-Babapulle et al.[7] used mitoxantrone, 10–12 mg/m^2 intravenous bolus (IVB), every day for 5 days with Ara-C, 1.0 g/m^2, every 12 hours for 5 days to achieve a 50% CR rate in 42 patients with recurrent, refractory, or newly diagnosed AML. Amadori et al.[8] reported that Ara-C, 1 g/m^2 intravenously (i.v.), every day for 6 days and mitoxantrone, 6 mg/m^2 i.v., every day for 6 days in 47 patients with primary refractory, recurrent, or previously untreated, poor risk AML yielded a CR rate of 66%.

Based on these previous findings, a Phase II study was initiated with intermediate-dose Ara-C and mitoxantrone in patients with recurrent or primary refractory AML. The goal was to maximize the exposure of the leukemic blasts to HiDAC, to minimize toxicity, and to add mitoxantrone with the hope of augmenting drug activity for patients previously treated with daunorubicin.

MATERIALS AND METHODS

Forty-seven of 49 patients with AML who were enrolled between September 1990 and April 1997 were evaluable. Patient characteristics are shown in Table 1. All patients had AML that was refractory to initial therapy (2 patients), in first recurrence (38 patients), or in second recurrence (7 patients). There were 22 women and 25 men. The median age was 60 years (range, 21–79 years); 22 of 47 patients were age < 60 years at the time of enrollment. Patients were considered eligible for the study if they had a performance status of 0–2 (Eastern Cooperative Oncology Group criteria), adequate renal function (creatinine < 2.5 mg/dL), and adequate liver function (aspartate aminotransferase and alkaline phosphatase < 4 times normal, total bilirubin < 2.0). Patients with evidence of congestive heart failure, pregnancy or lactation, or chemotherapy within 3 weeks of study entry were excluded. The majority of patients had been treated previously with daunorubicin and Ara-C with or without HiDAC. Three patients had undergone prior autologous bone marrow transplantation.

Informed consent was obtained before the initiation of therapy. Therapy was comprised of Ara-C, 0.5 g/m^2 i.v., over 90 minutes every 12 hours on Days 1–6

TABLE 1
Patient Characteristics

	Total	Age < 60 yrs	Age ≥ 60 yrs
Total evaluable	47	22	25
Gender			
Male	25	12	13
Female	22	10	12
Disease status at enrollment			
First recurrence	38	16	22
Second recurrence	7	5	2
Primary refractory tumor	2	1	1
Secondary AML	6	4	2
FAB subtype			
M1	5	3	2
M2	9	2	7
M3	5	3	2
M4	9	5	4
M5	3	2	1
Other[a]	16	7	9
Cytogenetic risk[b]			
Favorable	4	1	3
Intermediate	27	11	16
Adverse	11	6	5
Undetermined	5	4	1
Median duration of first CR, mos (range)[c]	9 (2–31)	9 (2–31)	10 (4–28)
Median leukocyte count at enrollment (range) (× 10^9/L)	2.4 (0.11–186)	2.3 (0.11–99)	2.6 (1.0–186)
Patients achieving CR	29	10	19
Median remission duration, mos (range)	3.7 (1–100+)	3.7 (1–100+)	3.8 (1–12)
Median survival, mos (range)	6 (0.5–100+)	3 (1–100+)	9 (0.5–30)

AML: acute myelogenous leukemia; FAB: French–American–British; CR: complete response.
[a] Biphenotypic leukemia (2 patients) or undetermined (14 patients).
[b] Cytogenetic risk determined according to Grimwade et al.[17]
[c] For patients who entered complete response.

(12 doses) and mitoxantrone, 5 mg/m^2 IVB, on Days 1–5. Allopurinol was administered at a dose of 300 mg/day orally to all patients who were not allergic to the drug. All patients received corticosteroid eye drops to prevent conjunctivitis.

The treatment plan was comprised of an initial course of therapy. A bone marrow biopsy was performed at the time of enrollment, on Day 14, and every 7 days thereafter until bone marrow cellularity was $\geq$ 30%. If the treatment was tolerated and the patient achieved a CR (defined as $<$ 5% blasts in the bone marrow with $\geq$ 30% cellularity, granulocyte count $> 1.0 \times 10^9$/L, and a platelet count $> 100 \times 10^9$/L in the peripheral blood), an optional second course of chemotherapy was administered (but not before Day 28); however, only 5 patients were treated with a second course of chemotherapy after documentation of a CR. Moreover, an optional second course of treatment was administered if a CR was not achieved but there was a blast reduction of $>$ 50% with a bone marrow cellularity $\geq$ 30%. Nine patients with evidence of persistent disease were treated with a second course of chemotherapy. Other patients were removed from the study.

Subsequent therapy was individualized according to the patient's remission status, prior drug therapy, age, and performance status. Such treatment ranged from allogeneic bone marrow transplantation for eligible patients with an human leukocyte antigen-compatible donor to hydroxyurea maintenance therapy or no therapy for those patients who did not achieve disease remission.

RESULTS

Twenty-nine of 47 patients (62%) treated achieved a CR. The median duration of remission was 3.7 months (range, 29 days–8 years). Twenty-six of these patients subsequently developed a disease recurrence. Three patients remained alive and free of disease at follow-up times of 8 years, 7 years, and 6.5 years, respectively, after enrollment and remission induction. One of these patients received intensive consolidation with allogeneic bone marrow transplantation. A fourth patient developed disease recurrence 41 days after achieving disease remission and subsequently was reinduced with mitoxantrone/Ara-C off protocol and then with total body irradiation with granulocyte-colony stimulating factor (G-CSF) support; she remained free of apparent disease at the time of last follow-up (1.5 years after disease recurrence). The median overall survival was 6 months.

The CR rate for patients age $<$ 60 years was 45% (10 of 22 patients). The median duration of disease remission for this subgroup was 3.7 months (range, 29 days–8 years). For patients age $\geq$ 60 years, 19 of 25 patients (76%) achieved a CR. The median duration of disease remission in this group was 3.8 months (range, 33–370 days). The difference in CR rates between the two age groups was statistically significant ($P = 0.04$). As noted in Table 1, clinical and cytogenetic characteristics between patients in the younger and older subgroups were similar, and these risk criteria could not account for the difference in CR rates between the two groups.

The chemotherapy generally was well tolerated. However, 3 patients died of infectious complications between 23–26 days after initiation of the first or second chemotherapy cycle. One patient died of sudden cardiac arrest 13 days after the initiation of induction therapy. The mean duration of neutropenia (neutrophil count $< 0.5 \times 10^9$/L) was 31 days (range, 23–51 days), and the mean duration of thrombocytopenia (platelet count $< 20 \times 10^9$/L) was 33 days (range, 16–52 days). One patient developed a palmar rash with blistering and desquamation.

There were three episodes of acute neurotoxicity that were comprised of cerebellar dysfunction. Two patients developed truncal ataxia with persistent gait impairment. The third patient developed simultaneous truncal ataxia and dysarthria; the dysarthria gradually improved but the gait impairment persisted. All three patients with cerebellar toxicity were age $\geq$ 60 years.

DISCUSSION

This Phase II study of the use of mitoxantrone and intermediate-dose Ara-C demonstrates that these agents are effective in the induction of disease remission of recurrent and primary refractory AML. The overall CR rate was found to be 62%, and patients age $>$ 60 years had a CR rate of 76%. It is interesting to note that this regimen was well tolerated by the majority of patients, including patients age $>$ 60 years; such patients are most likely to develop severe toxicity from these agents, particularly neurologic toxicity.

As noted in Table 1, the clinical and cytogenetic characteristics for younger and older patients were relatively similar. The small number of patients in the study, and the small number of patients in each cytogenetic or clinical characteristic group, precludes subset analyses of the effects of these factors on the disease remission rate. It is unlikely that older patients truly fare better than younger patients when treated with this regimen and, although statistically significant, the difference in CR rates between the younger and older patients most likely still is due to chance or other factors we cannot identify. However, our major

conclusion is that this is a well tolerated and effective regimen for older patients as well as younger patients.

The results reported in the current study compare favorably to those reported by Brito-Babapulle et al.,[7] who demonstrated a 50% CR rate for patients with AML treated with Ara-C, 1.0 g/m^2 i.v., every 12 hours for 5 days and mitoxantrone,10–12 mg/m^2 IVB, every day for 5 days. However, the latter series not only contained patients with recurrent (26 patients) or refractory (8 patients) disease, but also some patients with newly diagnosed (8 patients) disease, patients who would be expected to have a higher CR rate. In the study by Brito-Babapulle et al., two patients experienced cerebellar dysfunction (one permanent), and three patients experienced congestive heart failure responsive to diuretic therapy.[7] The median duration of neutropenia was 17 days, and the median duration of thrombocytopenia was 28 days. Similarly, Amadori et al.[8] used Ara-C, 1 g/m^2 i.v., every day for 6 days and mitoxantrone, 6 mg/m i.v., every day for 6 days in 47 patients with primary refractory, recurrent, or previously untreated, poor risk AML to yield a CR rate of 66%. Davis et al.[9] achieved a CR in 14 of 20 patients with recurrent AML treated with mitoxantrone, 12 mg/m^2/day, on Days 1–5 and Ara-C, 100 mg/m^2, twice daily for 7 doses. The results of the current study confirm the efficacy of this regimen in achieving a CR in patients with recurrent or refractory AML.

Our findings also compare favorably with those reported for other chemotherapeutic regimens. de la Serna et al.[10] achieved a CR in 12 of 23 primary refractory AML patients (52%) and 21 of 38 recurrent AML patients (55%) using idarubicin, 12 mg/m^2, every day for 3 days and Ara-C, 1 g/m^2, every 12 hours for 4 days. Visani et al.[11] reported the use of the FLAG regimen (2 courses of fludarabine, 30 mg/m^2/day, on Days 1–5; Ara-C, 2 g/m^2/day, on Days 1–5; and G-CSF) in patients with high risk AML; 75% of refractory AML patients achieved a CR with a median survival of 14 weeks, and 11% of recurrent patients achieved a CR with a median survival of 24 weeks. Huhmann et al.[12] demonstrated a 50% CR (11 of 22 patients) in patients with refractory or recurrent AML treated with fludarabine, 25 mg/m^2/day, on Days 1–5; Ara-C, 2 g/m^2/day, on Days 1–5; and G-CSF. Vignetti et al.[13] have used the MEC regimen (mitoxantrone, 6 mg/m^2, every day on Days 1–6; etoposide, 80 mg/m^2, every day on Days 1–6; and Ara-C, 1 g/m^2, every day on Days 1–6) in patients with primary resistant or recurrent AML to yield a 68% CR rate (34 of 50 patients). This group has reported a disease free survival for these 34 patients of 29% at 69 months.

Significantly, the current study demonstrates a 76% CR rate in patients age $\geq$ 60 years. Remission induction in older patients is notoriously difficult, owing in part to an increased rate of incidence of drug resistance and chromosomal abnormalities in this age group.[14] In the current study the median duration of disease remission for this older age group was $<$ 4 months. Although younger patients often are eligible for consolidation with allogeneic or autologous bone marrow transplantation, such intensive consolidation is contraindicated in older patients because of the increased incidence rate of transplant-related mortality. Nonetheless, the findings of the current study suggest that mitoxantrone and intermediate-dose Ara-C are useful in remission induction for these patients.

Although the treatment regimen reported in the current study generally was well tolerated, three patients died during induction therapy as a result of bone marrow hypoplasia. Considering the age of the patients in the current study, this is a small number. Whether the use of G-CSF or similar cytokines would improve this outcome is controversial. Induction deaths due to prolonged bone marrow hypoplasia have been particularly troublesome in elderly patients. Stone et al.[15] and Dombret et al.[16] have shown that neither granulocyte-macrophage–colony stimulating factor nor G-CSF administration to elderly patients receiving induction therapy for AML reduces the incidence rate of serious infection or improves overall survival.

In summary, mitoxantrone with intermediate-dose Ara-C appears to provide an effective means of achieving induction of CR in a number of patients with primary refractory and recurrent AML, including patients age $>$ 60 years. We speculate that the combined use of these agents also might be effective as part of an induction regimen for previously untreated AML in the elderly.

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