A Single, High Dose of Idarubicin Combined with Cytarabine as Induction Therapy for Adult Patients with Recurrent or Refractory Acute Lymphoblastic Leukemia

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BACKGROUND. The majority of adult patients who are treated for lymphoblastic disease will either develop recurrent disease or will be refractory to their initial therapy. One option for patients with recurrent/refractory disease is to administer a reinduction regimen that employs a dose-intense combination of anthracycline and cytarabine. These salvage regimens are relatively distinct from the traditional vincristine/prednisone-based programs that are used typically as primary induction therapy. The authors studied a regimen that contained high-dose cytarabine and a single high dose of idarubicin as salvage induction therapy for patients with recurrent or refractory lymphoblastic disease.

METHODS. Twenty-nine previously treated adult patients with recurrent or refractory acute lymphoblastic leukemia were treated with a new intensive regimen. Eight patients had primary refractory disease. Twenty-one patients had recurrent disease, and 16 of these patients developed recurrent disease while they were still receiving their primary therapy. The treatment regimen consisted of cytarabine 3.0 g/m^2 by 3-hour infusion daily for 5 days and idarubicin 40 mg/m^2 given as a single dose on Day 3. Filgrastim (granulocyte-colony stimulating factor) 5 μg/kg administered subcutaneously every 12 hours was started on Day 7 and was continued until the absolute neutrophil count was $> 5000/\mu$L. Response was assessed using standard criteria.

RESULTS. There were 11 complete responses (38%; 95% confidence interval, 20–56%). Four patients subsequently underwent allogeneic bone marrow transplantation. Moderate but acceptable toxicity was observed given the severely myelosuppressive nature of the regimen. There was only one treatment-related death (3%). Two patients, both with significant prior exposure to anthracyclines, suffered reductions in left ventricular function to the 20–30% range during episodes of severe systemic infection. After recovery from infection, the ejection fraction in one patient improved to 50%.

CONCLUSIONS. The authors conclude that this regimen has moderate activity and a relatively low incidence of mortality for this high-risk group of patients. This regimen may be most suitable for patients who can undergo potentially curative allogeneic bone marrow transplantation if they achieve a complete response.
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The treatment results for pediatric patients with acute lymphoblastic leukemia (ALL) have been well recognized as one of the success stories of modern combination chemotherapy.[1] Although modeled on

pediatric regimens, treatment programs for adults with ALL have been far less successful.[2] These regimens typically produce a complete response (CR) in 65–90% of adult patients with newly diagnosed leukemia.[3–6] Unfortunately, the majority of patients who achieve a CR will develop recurrent disease and subsequently die of their disease.

There are two widely tested approaches to reinduction therapy for adult patients with recurrent or refractory ALL. One option is to treat the patient with a regimen that mimics the original induction therapy. Combinations of vincristine, prednisone, and an anthracycline intensified with cyclophosphamide and/or L-asparaginase represent traditional induction therapy, and variations on this approach are employed frequently in the salvage setting. By definition, all appropriately treated patients with recurrent or refractory disease already have failed such a regimen. Despite this, patients (particularly those with long first remissions and those who develop recurrent disease after completing maintenance chemotherapy) occasionally can achieve a second CR with a repetition of their initial induction regimen.[7]

Unfortunately, many patients develop recurrent disease within the first 12–24 months of achieving their first remission, at a time when they are still receiving maintenance chemotherapy.[3–6] For these patients (whose leukemia regrows during therapy), the likelihood of achieving a second CR with reinduction therapy similar to their initial regimen is quite low. In addition, for the 10–25% of patients whose disease is primarily refractory to standard induction therapy, simply repeating the same induction treatments offers essentially no hope of obtaining a CR. A second option for these patients is to employ an active salvage regimen that relies on agents that are relatively distinct from traditional induction treatments. The most commonly tested regimens of this type are based on high-dose cytarabine, which, as a single agent, reportedly induces a CR in approximately 30% of patients with recurrent or refractory ALL.[8] In combination with other agents, particularly anthracyclines (or anthracenediones), high-dose, cytarabine-based regimens yield even higher response rates.[9–15]

We previously reported on a Phase I study in which patients with recurrent or refractory ALL received an escalating single dose of idarubicin given on Day 3 with a fixed dose of high-dose cytarabine (3.0 g/m^2 per day for 5 days).[9] Unacceptable toxicity was reached at an idarubicin dose of 50 mg/m^2, with one death from infection and another death from cardiotoxicity in a patient with significant prior anthracycline exposure. There were no instances of Grade 4 nonhematologic toxicity in patients who were treated with an idarubicin dose $\leq$ 40 mg/m^2. The activity of this regimen was promising, because 7 of 12 patients (58%) who received an idarubicin dose $\geq$ 40 mg/m^2 achieved a CR. To further evaluate this regimen as salvage therapy for patients with recurrent or refractory ALL, we conducted a multicenter Phase II trial.

DAY:	1	2	3	4	5	6	7	8	9
CYTARABINE	X	X	X	X	X				
IDARUBICIN			X						
FILGRASTIM							X	X	X*
IT METHOTREXATE		X		X					

FIGURE 1. The treatment plan. The induction regimen consisted of cytarabine 3.0 g/m^2 by 3-hour intravenous (IV) infusion daily for 5 days and a single dose of idarubicin at 40 mg/m^2 by rapid IV infusion given on Day 3. Filgrastim (granulocyte-colony stimulating factor) 5 μg/kg twice daily (every 12 hours) by subcutaneous injection was started on Day 7 and continued until the absolute neutrophil count was $>$ 5000/μL (asterisk). Intrathecal (IT) methotrexate 6 mg/m^2 was administered on Days 2 and 4.

MATERIALS AND METHODS

Trial Design

This study was designed to treat adult patients (age $\geq$ 18 years) with recurrent or refractory acute lymphoblastic disease. All enrolled patients gave written informed consent to be treated on this study. Patients were excluded for significant renal dysfunction (creatinine $>$ 2 mg/dL) or hepatic dysfunction (total bilirubin $>$ 2 mg/dL) or for left ventricular dysfunction (left ventricular ejection fraction [LVEF] $<$ 50%). The induction regimen (Fig. 1) consisted of cytarabine 3.0 g/m^2 by 3-hour intravenous (IV) infusion daily for 5 days and a single dose of idarubicin at 40 mg/m^2 by rapid IV infusion given on Day 3. Intrathecal methotrexate 6 mg/m^2 was administered on Days 2 and 4. If it was indicated clinically, intrathecal therapy could be delayed for thrombocytopenia, coagulopathy, or circulating leukemic blasts. Filgrastim (granulocyte-colony stimulating factor) 5 μg/kg twice daily by subcutaneous injection was started on Day 7 and was continued until the absolute neutrophil count was $>$ 5000/μL.

Evaluation Criteria

The diagnosis of ALL or of lymphoblastic-phase chronic myelogenous leukemia (CML) was made on the basis of bone marrow morphology. For patients with lymphoblastic lymphoma (LBL) without bone

marrow involvement, the diagnosis of lymphoblastic disease was based on lymph node morphology. Pathologic review was performed at the respective institutions. Additional studies, including histochemical stains, flow cytometric immunophenotyping, and cytogenetics, were used in most patients to confirm the diagnosis and to aid in disease subtyping. Bone marrow examination was performed on Day 14 to confirm bone marrow hypoplasia and at 2-week intervals thereafter to assess response.

A CR was defined as the disappearance of all clinical evidence of leukemia for a minimum of 4 weeks. Peripheral blood count recovery requirements included a neutrophil count $> 1000/\mu L$ and a platelet count $> 100{,}000/\mu L$. No circulating blasts could be present. Two bone marrow samples obtained 1 month apart that demonstrated normal, trilineage hematopoiesis and, at most, 5% blasts in qualitatively normal or hypercellular bone marrow were required.

All responses other than a CR were considered treatment failures. Survival was measured from the initiation of protocol treatment. Duration of CR was measured from the first documentation of CR until progression of disease occurred. Patients undergoing allogeneic transplantation were censored for response duration at the time of transplantation, although they continued to be evaluable for survival. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria.[16]

Patient Characteristics

Thirty patients were enrolled on this multicenter protocol (Table 1). One patient was excluded at the time of enrollment (prior to receiving chemotherapy) due to an incorrect diagnosis (acute myelogenous leukemia). Twenty-nine patients (19 male patients and 10 female patients) were evaluable. The median age of the evaluable patients was 36 years (range, 19–70 years). The majority of patients had ALL (23 of 29 patients; 79%). Three patients had LBL (10%), and another three patients had lymphoid blast crisis of CML (10%). Eight patients (28%) had disease that was refractory to their primary therapy. Twenty-one patients (72%) had recurrent disease, and 16 of these experienced disease recurrence when they were still receiving primary therapy. The remaining five patients experienced disease recurrence after completing their initial therapy.

Of 26 patients with ALL or LBL, 22 patients had evaluable metaphases. On cytogenetic analysis, four of these patients were positive for the Philadelphia chromosome. Including the 3 patients with lymphoblastic CML, 7 of 25 patients (28%) for whom cytogenetics could be assessed were positive for the Philadelphia chromosome. In addition, one patient in this study had t(4;11). Overall, 8 of 25 patients (32%) with evaluable cytogenetics exhibited poor-risk karyotypic features.[17–19] Other cytogenetic abnormalities that were seen included three patients with hyperdiploidy and one patient each with del(5q), del(6q), and del(10q).

TABLE 1
Patient Characteristics ($N = 29$ patients)

Characteristic	No. of patients (%)
Male: female ratio	19:10
Median age in yrs (range)	36 (19–70)
ALL	23/29 (79)
LBL	3/29 (10)
CML, lymphoid blast crisis	3/29 (10)
Recurrent disease (off therapy)	5/29 (17)
Recurrent disease (on therapy)	16/29 (55)
Primary refractory disease	8/29 (28)
Philadelphia chromosome positive	7/25 (28)
Hyperdiploid	3/25 (12)
t(4;11)	1/25 (4)
Deletion 6q	1/25(4)
Prior treatment/induction regimens	
Standard (vincristine-based)	25/29 (86)
Mitoxantrone/high-dose cytarabine	3/29 (10)
Other	1/29 (3)

ALL: acute lymphoblastic leukemia; LBL: lymphoblastic lymphoma; CML: chronic myelogenous leukemia.

The vast majority of patients (25 of 29 patients; 86%) had previously received a standard, vincristine or prednisone-based induction therapy. Three patients (10%) had previously received mitoxantrone combined with high-dose cytarabine as prior induction therapy.[20] One patient (3%) with lymphoid blast crisis of CML had received prior therapy with interferon and hydroxyurea.

RESULTS

Response and Outcomes

A CR was achieved in 11 patients (38%; 95% confidence interval, 20–56%). There was little variation in the incidence of CR across various subgroups: Philadelphia chromosome positive, 3 of 7 patients (43%); recurrent disease, 9 of 21 patients (43%); and refractory disease, 2 of 8 patients (25%). Of 16 patients who developed recurrent disease during primary therapy, 7 patients (44%) achieved a CR. The median time to CR for responding patients was 33 days (range, 25–60 days).

Twenty-one patients were enrolled on this study for recurrent lymphoblastic disease. The median duration of first remission in this subgroup was 6.5 months (range, 2.0–40.0 months). Seventeen of these patients (81%) had first a CR duration < 24 months. Of

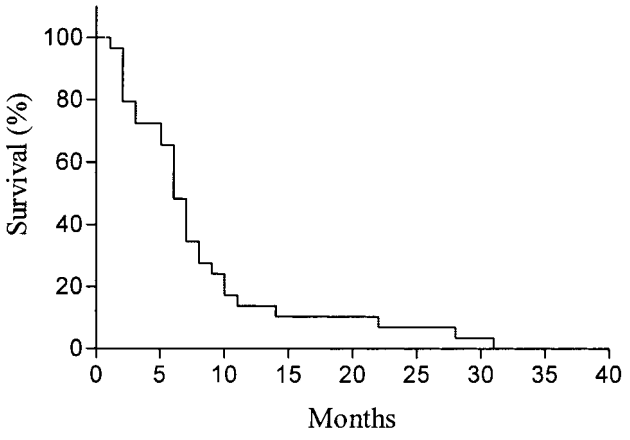

FIGURE 2. Kaplan–Meier survival curve.

these 17 patients with short first remissions, 7 patients (41%) achieved a CR to the study treatment. Two of four patients with first remissions > 24 months achieved a CR. Of the 25 patients who had previously received a standard vincristine-based induction regimen, 10 patients (40%) achieved a CR. None of the three patients previously induced with mitoxantrone/high-dose cytarabine achieved a CR to this salvage regimen. The median duration of CR was 3 months (range, 2–4+ months).

The median survival was 6 months (range, 1–31 months) for all patients and 8 months (range, 3–31 months) for patients who achieved a CR. A survival curve calculated by the method of Kaplan and Meier is shown in Figure 2. Four patients who achieved a CR underwent allogeneic bone marrow transplantation. One of those four patients died of transplantation-related complications, and two of them died of recurrent disease (remission durations of 5 months and 12 months). The final patient who underwent transplantation developed recurrent lymphoblastic disease 11 months after undergoing allogeneic transplantation. He then received a donor leukocyte infusion that resulted in another complete remission of 15 months' duration. He subsequently died of recurrent disease.

Toxicity

All 29 patients who were included in the analysis completed the full course of protocol therapy. Grade 4 hematologic toxicity was universal, as expected. Three episodes of life-threatening infection occurred. One of those three patients died of septic shock and renal failure. Two patients experienced cardiac toxicity with a reduction of the LVEF to 20–30% after study treatment. LVEF was normal (> 50%) in both patients prior to study treatment. Both patients experienced cardiac dysfunction in the setting of severe infections (severe aspergillus pneumonia and *E. faecalis* sepsis). Both patients with cardiac toxicity had significant prior exposure to anthracyclines (daunorubicin 340 mg/m^2 in one patient and daunorubicin 150 mg/m^2 with doxorubicin 96 mg/m^2 in the other patient). In one of these patients, cardiac function improved to 50% after recovery from infection.

Other Grade 3 nonhematologic toxicities seen on this study included fever without infection (6 patients), transient cognitive changes (4 patients), syncope (2 patients), hematemesis (1 patient), and conjunctivitis (1 patient). The median hospital stay was 31 days (range, 8–83 days). For patients who achieved a CR, the median stay was 25 days (range, 16–83 days), and, for nonresponders, it was 32 days (range, 8–68 days).

DISCUSSION

The majority of adult patients with ALL either will develop recurrent disease after primary therapy or will be refractory to the primary therapy they receive. This failure of primary therapy heralds a grave prognosis, and the only realistic chance for long-term survival in this group is allogeneic bone marrow transplantation. Unfortunately, even allogeneic transplantation has limited antileukemic activity in adult patients with ALL, and most investigators believe that, to optimize the likelihood of cure, patients should undergo this procedure with a minimal leukemic burden.[18,21] Therefore, reinduction chemotherapy in an attempt to produce a second CR is recommended for essentially all patients prior to allogeneic transplantation.

The development of salvage regimens for adult patients with ALL has focused on incorporation of alternative agents with known activity in this disease. The majority of recently published regimens focus on high-dose cytarabine combined with various agents. Combinations that include anthracyclines (or anthracenediones) appear to be the most active.[9–13] We previously reported the results of a Phase I study in which escalating doses of idarubicin were given in combination with a fixed, high dose of cytarabine for the treatment of adult patients with refractory or recurrent ALL.[9] The rationale for this regimen was that the active metabolite of idarubicin, idarubicinol, has a very long half-life (> 45 hours). Therefore, giving a single, very high dose of idarubicin would maximize the peak level achieved, thereby enhancing the cytotoxic effect on the leukemic cells, simultaneously achieving active therapeutic levels of anthracycline that would persist for several days. In this way, cell killing may occur for cells that require high peak levels as well as cells that are only susceptible to prolonged exposure to cytotoxic levels of drug. We postulated that this single,

large-dosing strategy would have an improved therapeutic index compared with giving the anthracycline by continuous infusion or in weekly doses, which are schedules that achieve protracted low-level exposure leading to significant mucositis, the dose-limiting toxicity of anthracyclines. The data from the Phase I study indicated that, when combined with high-dose cytarabine in this patient population, the maximum tolerated single dose of idarubicin is 40 mg/m^2. In the current study, we investigated this regimen further as a salvage therapy for adult patients with recurrent or refractory ALL.

The overall CR rate of 38% seen in this study demonstrates that this regimen possesses moderate activity in this patient population. It is interesting to note that this response rate appears lower than the 58% rate seen in the Phase I trial for patients who received an idarubicin dose $\geq$ 40 mg/m^2.[9] The reasons for this may include small patient numbers with overlapping 95% confidence intervals. In addition, in the current study, consolidation therapy was not a part of the treatment protocol, whereas, in the prior (Phase I) study, responding patients received consolidation therapy with intermediate dose methotrexate and mercaptopurine. In the current study, four patients had responses that included a remission bone marrow with normal blood counts followed by a second bone marrow 1 month later that revealed $>$ 5% blasts (range, 6–80% blasts). These patients were characterized as treatment failures. Had this protocol included consolidation treatment (administered prior to performing the second bone marrow), as in the prior study, the second bone marrow may have had $<$ 5% blasts, and the proportion of CRs may have been higher (perhaps 15 CRs; 52%); furthermore, the duration of these CRs may have been longer. The short response durations seen in this study confirm the need for consolidation therapy for patients who achieve a second CR.

There have been few published studies of salvage chemotherapy for adult patients with ALL over the last 10 years. Comparing the results of various Phase II trials is difficult, because differences in the prognostic features of the treated patient groups may have pronounced effects on the outcome of therapy. Given this limitation, however, we note that recent trials typically have reported CRs in $<$ 25% of treated patients. Such reports include a Southwest Oncology Group study in which 23% of patients achieved a CR with a regimen of high-dose cytarabine given with a single high dose of mitoxantrone.[22] Similarly, a low incidence of CR was seen with a vincristine/prednisone-based regimen (combined with methotrexate and pegaspargase). Aguayo et al. reported that this regimen resulted in a CR in only 22% of treated patients.[23] It is noteworthy that the results of Aguayo et al. were markedly different from those of Esterhay et al. (CR rate, 79%), upon which the study by Aguayo et al. was based.[24] It is unlikely that substituting pegaspargase for L-asparaginase is the explanation for these disparate results. Rather, in the 17 years after the publication the regimen of Esterhay et al., adult patients with ALL now typically receive more aggressive initial therapy, making them less likely to respond to salvage regimens at the time they develop recurrent disease. A recently published study by Giona et al. indicated that a high fraction of patients (56%) achieved a CR after receiving therapy with a combination of intermediate dose cytarabine, idarubicin, and prednisone.[25] The patients on that study, however, had a more favorable prognosis, because they were relatively young adults (median age, 28 years; range, 16–55 years) at the time they first developed recurrent disease. A regimen containing hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (the hyper-CVAD regimen) also has been employed as salvage therapy for patients with lymphoblastic disease. In the report by Koller et al.,[26] CRs were observed in 29 of 66 patients (44%). Those authors compared their results with a historic control group that was treated with mitoxantrone (5 mg/m^2 per day for 5 days) and high-dose cytarabine, and they noted a similar CR rate (44% vs. 38% for the historic control group), although that survival may have been superior for patients who were treated with hyper-CVAD.

The toxicities encountered in the current study were moderate but acceptable in this patient population. Two patients (7%) experienced reductions in left ventricular function during their treatment, but both had significant prior exposure to anthracyclines, and both reductions occurred during episodes of severe systemic infection. The heart function in one patient improved to near normal after recovery from infection. In our previously reported Phase I investigation of this regimen, it was found that an idarubicin dose of 50 mg/m^2 caused unacceptable toxicity, with two deaths among four patients who were treated at this dose level. One of those patients who had been heavily pretreated with anthracycline and anthracenedione agents died of cardiotoxicity. Because cardiotoxicity from this regimen has been observed only in a small minority of patients who have had previous anthracycline exposure, it is possible that anthracycline-naïve patients may tolerate higher single doses of idarubicin. Only one patient in the current study died during induction, resulting in a low incidence of treatment-related mortality (3%). This compares favorably with

induction death rates of 5–39% that have been reported for other salvage regimens.[22–29]

Overall, this regimen appears to be acceptably safe and offers moderate activity for adult patients with recurrent or refractory ALL, making this regimen a suitable choice for selected patients. In particular, it is appropriate that patients with recurrent or refractory disease who have suitable allogeneic transplantation options receive reinduction therapy with this regimen followed by allogeneic transplantation. Because the duration of nonmaintained response seen in this study was short (median, 3 months), if this regimen is to be used for patients who do not promptly undergo allogeneic transplantation, we recommend starting consolidation and/or maintenance therapy immediately upon achieving a CR.

Because cardiotoxicity is an occasionally encountered complication of this treatment, particularly in patients who have been pretreated heavily treated with anthracyclines or anthracenediones, we plan to explore future development of this approach with the incorporation of a cytoprotectant, such as dexrazoxane[30] or amifostine,[31] to allow further dose intensification of this regimen.

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