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Low-dose oral etoposide-based induction regimen for children with acute lymphoblastic leukemia in first bone marrow relapse

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We evaluated the clinical response to low-dose etoposide in relapsed acute lymphoblastic leukemia (ALL). Of the 45 patients with ALL in first bone marrow relapse enrolled on the ALL R15 protocol, 44 had received epipodophyllotoxins during frontline therapy. In the first week of remission induction therapy, patients received etoposide (50 mg/m^2 per day) administered orally as a single agent once or twice daily. On Day 8, patients started to receive dexamethasone, vincristine, and L-asparaginase. Etoposide was administered until Day 22. Two courses of consolidation therapy were followed by continuation therapy or hematopoietic stem cell transplantation. After 7 days of single-agent etoposide treatment, peripheral blast cell counts ($P=0.013$) and percentages of bone marrow blasts ($P=0.016$) were significantly reduced. In all, 38 (84.4%) attained second remission. Only time to relapse was significantly associated with outcome ($P=0.025$): the 5-year event-free survival estimates ($\pm$se) were 52.0$\pm$9.6% for those with late relapse and 20.0$\pm$8.0% for those with early relapse. We conclude that low-dose etoposide administered orally has a cytoreductive effect in relapsed ALL.

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Introduction

The prognosis of children with acute lymphoblastic leukemia (ALL) has improved dramatically over the last two decades because of advances in therapy and supportive care.[1,2] Nevertheless, disease in approximately 20–25% of patients relapses or is refractory to frontline therapies.[3] The results of salvage treatments for relapsed ALL, especially for early hematologic relapse, have been disappointing. Although more than 90% of patients with late hematologic relapse achieve second remission and one-half to two-thirds of them become long-term survivors, the treatment outcome of patients with early relapse is dismal: only 75–90% of them achieve a second remission, and the long-term survival rate is less than 20%.[4]

Induction of remission is the first critical step in successful salvage treatment. Conventional induction therapies have consisted of glucocorticoid, vincristine, and anthracycline or asparaginase or both. Postremission strategies have included intensive chemotherapy with or without hematopoietic stem cell transplantation (HSCT).[4] In the Pediatric Oncology Group (POG 8303) study of 297 patients with early hematologic relapse (relapse during frontline therapy or within 6 months after the cessation of therapy), 82% of the patients achieved second remission after 4 weeks of four-drug induction therapy. After 2 additional weeks of induction therapy consisting of teniposide and cytarabine, 87% of patients eventually achieved remission.[5] In ALL-REZ BFM 85, which featured a more intensive regimen composed of prednisone, vincristine, asparaginase, intermediate- or high-dose methotrexate, and high-dose cytarabine, remission occurred in 88% of patients with early hematologic relapse.[6]

Increasing the intensity of contemporary frontline therapy may make salvage therapy less efficacious as leukemic cells are likely to be more resistant to chemotherapy than those treated less intensively in an earlier era.[4] In theory, more effective remission induction could improve salvage rates, as the level of minimal residual disease at the end of induction is strongly correlated with long-term outcome, even that of patients with relapsed ALL.[7,8] Therefore, efforts should be made toward designing novel regimens that induce a better quality of remission.[9]

Epipodophyllotoxins have been an important component of many regimens for relapsed ALL.[4] Prolonged administration of etoposide yields results superior to those achieved by single bolus infusions in preclinical studies[10] and in clinical trials.[11] Previous pediatric studies have shown that etoposide administered orally as a single agent at 50 mg/m^2 daily for 21 days is well tolerated.[12,13] Etoposide was also tolerated when it was given orally for a prolonged period in combination with various anticancer agents.[14,15]

Here, we report the response rates and toxicity associated with a remission induction regimen featuring continual oral administration of low-dose etoposide combined with dexamethasone, vincristine, and L-asparaginase for patients with first hematologic relapse of ALL.

Patients and methods

Patients

The St Jude ALL R15 protocol was approved by the hospital's institutional review board, and informed consent was obtained from each patient, parent, or guardian. Enrollment lasted from 1992 to 1997. Patients with an initial hematologic ALL relapse (isolated or combined with disease at extramedullary sites) or those with T-cell non-Hodgkin's lymphoma with >25% blasts in bone marrow were eligible for this study.

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Treatment

The treatment schedule for remission induction is summarized in Table 1. At the time of entry, patients were randomly assigned to receive etoposide (50 mg/m^2 per day) administered orally as a single daily dose or as two divided doses each day from Day 1 to 22. After etoposide was administered as a single agent in a 7-day window, administration of dexamethasone, vincristine, and L-asparaginase began on Day 8. During induction, etoposide was discontinued if severe mucositis, grade 4 hepatic toxicity, or severe allergic reaction occurred. Triple intrathecal therapy (methotrexate, hydrocortisone, and cytarabine) was given in age-dependent doses as CNS-directed treatment on Days 8 and 22 to patients with no CNS leukemia or weekly to patients with CNS leukemia until blasts were absent from cerebrospinal fluid obtained by two consecutive lumbar punctures. Bone marrow aspiration was performed before the start of induction therapy, on Day 8 to evaluate the effect of etoposide as a single agent, and at the completion of induction therapy.

After induction therapy, patients were given primary consolidation therapy (mitoxantrone 12 mg/m^2 i.v. over 1 h on Days 1–3 and cyclophosphamide 1 g/m^2 i.v. divided in twice daily doses, each of which was administered over 1 h on Days 1–3) and secondary consolidation therapy (methotrexate 5 g/m^2 i.v. over 24 h on Day 1 and cytarabine 1.5 g/m^2 per day i.v. over 48 h on Days 2 and 3). During consolidation, granulocyte colony-stimulating factor (10 μg/kg per day) was given subcutaneously to patients with prolonged severe neutropenia (absolute neutrophil count [ANC] $<$ 500/mm^3 for 10 days) or with life-threatening infection and neutropenia until the ANC was $>$ 2000/mm^3.

Patients who achieved remission and had a 'suitable' donor (related or unrelated) were generally offered allogeneic HSCT. Patients who did not qualify for HSCT received 120 weeks of continuation therapy modeled after that used in the St Jude R11 protocol for relapsed ALL.[16] Four pairs of drugs were given weekly as follows: methotrexate (40 mg/m^2 i.v., Day 1) and mercaptopurine (100 mg/m^2 per day orally, Days 1–7); etoposide (300 mg/m^2 i.v., Day 1) and cyclophosphamide (300 mg/m^2 i.v., Day 1); vincristine (1.5 mg/m^2 i.v., Day 1) and dexamethasone (10 mg/m^2 per day orally Days 1–7); methotrexate (100 mg/m^2 i.v., Day 1) and L-asparaginase (25 000 U/m^2 i.m., Day 1). Reconsolidation therapy consisting of mitoxantrone and cytarabine (the same as secondary consolidation) was given at Weeks 8 and 18, if no irreversible grade 4 nonhematologic toxicity was caused by the same combination administered as primary consolidation therapy. During continuation treatment, triple intrathecal therapy was administered every 8–10 weeks to patients without CNS leukemia or every 4 weeks to those with CNS leukemia.

Craniospinal radiation therapy (24 Gy to the brain and 15 Gy to the spine) was given before the elective cessation of therapy at week 120 for those with CNS disease. For patients who received HSCT, craniospinal irradiation was combined with total body irradiation. Patients with testicular disease received bilateral testicular irradiation (24 Gy) at the beginning of secondary consolidation therapy if they did not undergo HSCT.

Toxicity was graded in accordance with the National Cancer Institute's Common Toxicity Criteria, version 2.0.[17]

Statistical methods

The time interval for overall survival (OS) was defined as the interval from the date of enrollment on the protocol to the date of death attributed to any cause or to the date of last follow-up. The period of event-free survival (EFS) was defined as the minimum time interval from the date of enrollment on the study to the date of last follow-up, relapse, second malignancy, or death due to any cause. Patients who did not achieve remission were considered to have experienced treatment failure at time zero. In the analysis of the cumulative incidence of relapse and second malignancy, any leukemia relapse and second cancer were the events of interest, and death due to any other cause after remission was considered as a competing event. The length of time at risk of relapse or second cancer was calculated as the minimum time interval from the remission date to the date of relapse, second malignancy, date of the competing event, or last follow-up. Data from patients who achieved remission and were still alive with ALL in remission without any event were censored at the time of last follow-up. The Kaplan–Meier method was used to estimate OS and EFS probabilities, and the method of Kalbfleisch and Prentice[18] was used to estimate the cumulative incidence of relapse and second malignancy. Comparison of survival distributions between two randomized arms was performed with the exact log-rank test. The Wilcoxon signed rank test[19] was used to compare cytoreduction (in terms of peripheral blast counts and bone marrow blast percentages) on Day 0 with that on Day 8. The reductions in blast counts of patients who received once daily doses and of those who received twice daily doses of etoposide were compared by using the exact Wilcoxon rank-sum test. Differences in remission rates associated with various prognostic factors were analyzed by using the exact χ^2 test to examine each factor and its association individually. Additionally, the association of these factors with remission rate was examined simultaneously by using multiple logistic regression analysis. The association of the prognostic factors with OS and EFS was examined simultaneously by using the Cox proportional hazards model. The effect of transplantation on the outcome was evaluated with the Cox model in which transplantation status was defined by a time-dependent covariate. All analyses were conducted with SAS release 8.2.

Results

Characteristics of the patients

A total of 45 patients whose ALL was in first hematologic relapse (isolated or combined with extramedullary disease) were treated

Table 1 Remission induction therapy

Drug	*Dose*	*Route of Administration*	*Day of Administration*
Etoposide	50 mg/m^2 once a day or 25 mg/m^2 twice a day	Oral	1–22
L-Asparaginase	10 000 U/m^2	Intramuscular	8, 10, 12, 15, 17, 19, 22, 24, 26
Vincristine	1.5 mg/m^2 (maximum dose, 2 mg)	Intravenous (rapid infusion)	8, 15, 22, 29
Dexamethasone	Total, 8 mg/m^2 daily (three times a day)	Oral	8–35

Table 2 Patients' features at the time of relapse

	All patients (n = 45)	Etoposide arm	
		Once daily (n = 22)	Twice daily (n = 23)
Age (years)			
1–10	19	10	9
⩾10	26	12	14
WBC at relapse			
$<50\times10^9$/l	40	19	21
$\geqslant50\times10^9$/l	5	3	2
Sex			
Female	15	10	5
Male	30	12	18
Frontline therapy			
Total XI	5	1	4
Total XII	18	10	8
Total XIIIA	14	7	7
Total XIIIB	2	1	1
Others	6	3	3
Relapse site			
BM only	30	16	14
BM and CNS	12	6	6
BM and testes	3	0	3
Time to relapse[a]			
Early	20	12	8
Late	25	10	15
Immunophenotype at relapse			
T lineage	7	4	3
B lineage	33	16	17
Unclassifiable	1	1	0
Unknown	4	3	1
Cytogenetic features at relapse			
t(9;22)	5	4	1
t(4;11)	3	3	0
Near-haploid	2	2	0
Pseudodiploid	16	5	11
Normal	2	0	2
Hypodiploid (44–45)	5	4	1
Hyperdiploid (47–50)	2	1	1
Hyperdiploid (51+)	8	2	6
Unknown	2	1	1

BM, bone marrow; CNS, central nervous system.
[a]Early: relapse that occurred during therapy or <6 months from elective cessation of frontline therapy. Late: relapse that occurred ⩾6 months after elective cessation of frontline therapy.

on the R15 protocol (Table 2). In all, 39 patients were previously treated on St Jude Total Therapy studies XI, XII, XIIIA, and XIIIB.[1,20] Six patients including three with an initial diagnosis of non-Hodgkin's lymphoma received frontline therapies other than those used in these Total Therapy protocols.[21,22] All patients but one had received prior treatment with epipodophyllotoxins. The scheduled cumulative doses of epipodophyllotoxins were the following: 5.1 g/m^2 teniposide and 9.0 g/m^2 etoposide in study XI, 14.4 g/m^2 etoposide in study XIIIA, and 10.2 g/m^2 etoposide in study XIIIB. For Total XII, patients were randomly assigned to stratified treatment groups that received teniposide at a cumulative dose of 1.95 g/m^2 or according to target systemic exposure.[23] For the 38 patients for whom data were available about the actual doses administered, the median dose the patients received was 9.0 g/m^2 (range, 1.5–14.4 g/m^2) for etoposide and 1.82 g/m^2 (range, 0.8–6.3 g/m^2) for teniposide.

At the time of relapse, the median age of patients was 12.2 years (range, 1.0–21.1 years); the median white blood cell (WBC) count was 6.4×10^9/l (range, 1×10^9 to 290.4×10^9/l). The median duration of the initial remission was 34.8 months (range, 3.9–105.7 months). In total, 25 patients had late relapse (⩾6 months after elective cessation of the frontline therapy) (Table 2). Of the 20 patients with early relapse (during frontline therapy or <6 months after elective cessation of the frontline therapy), 16 patients experienced relapse while receiving frontline therapies. Seven patients had T-cell ALL; 33, B-lineage ALL; and one, ALL of an unclassifiable immunophenotype. Data for immunophenotypes at the time of relapse were unavailable for four patients. A total of 30 patients had an isolated hematologic relapse, and the other 15 had a combined hematologic and extramedullary relapse (12 in the CNS and three in testes). The median length of follow-up was 1.6 years (range, 0.07–10.6 years) for all patients and 8.2 years (range, 5.3–10.6 years) for patients who remained alive.

Responses to etoposide administered orally as a single agent from Day 0 to Day 7

In total, 22 patients were randomly assigned to receive a daily dose of etoposide; 23 patients were randomly assigned to receive twice daily doses. These two groups showed no significant differences in the time to relapse, immunophenotype, or site of relapse (data not shown). The distribution of cytogenetic features was significantly different between the two groups ($P=0.019$).

We evaluated cytoreduction by analyzing peripheral blast counts on Days 0 and 8 for 24 patients with data available from both days; in addition, we further evaluated cytoreduction by assessing the percentages of bone marrow blasts on Days 0 and 8 in 28 patients with available data from both days. Significant reductions in leukocyte count ($P=0.005$), absolute blast count ($P=0.013$), and percentage of bone marrow blasts ($P=0.016$) were observed after 7 days of etoposide treatment (Table 3). When data for the two etoposide treatment groups were analyzed separately, we observed significant decreases in the leukocyte count and blast count only in patients who received twice daily doses. There was a decrease without statistical significance in the percentage of bone marrow blasts for both treatment groups.

Between the two treatment groups, the decreases in leukocyte count ($P=0.148$) or percentage of blasts in bone marrow ($P=0.982$) did not significantly differ. However, the twice daily treatment group had a greater decrease in peripheral blast counts ($P=0.018$).

Response to remission induction therapy

Of the 45 patients, 38 (84.4%) achieved remission at the end of the 5-week induction period. The 25 patients with late relapse tended to have a higher remission rate (92.0%) than the 20 patients with early relapse (75.0%), although the difference was not significant ($P=0.24$). A multivariate analysis revealed no association between remission induction rate and any of the following factors: time to relapse, site of relapse, immunophenotype, cytogenetic features, and etoposide treatment arm (data not shown).

Table 3 Change in peripheral blood leukocyte counts and percentages of bone marrow blasts in response to oral administration of etoposide as a single agent

	Once daily		*Twice daily*		*Combined arms*	
Time	*Median (range)*	P-*value*	*Median (range)*	P-*value*	*Median (range)*	*P value*
(a) Peripheral blood leukocyte counts ($\times 10^9$/l)						
Day 0	5.3 (2.0∼98.2) (n = 11)		9.1 (1.0∼230.4) (n = 13)		8.8 (1.0∼230.4) (n = 24)	
Day 8	4.2 (0.9∼180.0)	0.123	3.7 (0.6∼43.4)	0.027	3.9 (0.6∼180.0)	0.005
(b) Peripheral blood blast counts ($\times 10^9$/l)						
Day 0	1.1 (0.06∼78.3) (n = 11)		4.0 (0.2∼223.0) (n = 13)		3.0 (0.06∼223.0) (n = 24)	
Day 8	0.4 (0∼169.2)	0.700	0.1 (0∼38.2)	0.011	0.2 (0∼169.2)	0.013
(c) Percentages of bone marrow blasts (%)						
Day 0	86.0 (13.0∼100.0) (n = 15)		82.0 (8.0∼100.0) (n = 13)		83.5 (8.0∼100.0) (n = 28)	
Day 8	60 (16.0∼100.0)	0.115	74.0 (0∼100.0)	0.110	67.5 (0∼100.0)	0.016

Of the seven patients who did not achieve a second remission, three died of sepsis during induction, and four had refractory leukemia despite extended induction therapy. Relapses in these four patients developed during frontline therapy, and the median length of first remission was 13.5 months (range, 4.47–14.5 months). One patient had leukemic blasts with a Philadelphia chromosome, another had leukemic blasts with a t(4;11), one had T-cell ALL, and one had leukemic blasts of an unclassifiable immunophenotype at relapse (a T-lineage immunophenotype was present at diagnosis of the initial disease).

Acute toxicity during induction therapy

During induction, 92.1% of the planned doses of etoposide, 96.8% of the planned doses of L-asparaginase, 96.1% of the planned doses of vincristine, and 97.8% of the planned doses of dexamethasone were administered. In all, 19 patients (seven who received single daily doses of etoposide and 12 who received twice daily doses) were not able to receive the full 22 days of etoposide therapy. The median length of etoposide administration for these 19 patients was 18 Days (range, 13–21 days). The main reason for termination was gastrointestinal toxicity (16 patients). Administration was terminated because of a low-grade fever in one patient and because of unknown reasons for the other two patients.

Two patients did not experience any toxicity during induction, and three patients had only grade 1 or 2 toxicity. The other 40 patients experienced at least one grade 3 or 4 toxicity. The most common toxicity, as expected, was hematologic (32 patients), mostly neutropenia. The median duration of neutropenia (ANC $<500/mm^3$) during induction was 24 days (range, 0–42 days). There were 16 episodes of gastrointestinal toxicity: diarrhea ($n=9$) and mucositis ($n=7$). Of the 20 episodes of infection, eight were presumed to be fungal. Three patients died of *Escherichia coli* sepsis, Klebsiella sepsis, and candidal meningitis between Days 25 and 31. Another patient who developed a fungal infection (*Pseudallescheria boydii*) during induction subsequently died 3 months after remission was achieved.

Treatment after remission induction therapy

Of the 38 patients who achieved remission and the four patients who experienced induction failure, 31 patients proceeded to primary consolidation therapy. Of the 38 patients, 11 did not receive it because of toxicity ($n=4$) or enrollment on HSCT protocols ($n=7$). Therapy in primary consolidation was well tolerated overall, although most patients ($n=20$) had grade 4 hematologic toxicity and three patients had grade 3/4 infections.

Of the 20 patients who received secondary consolidation therapy, four patients had received 18 Gy of cranial irradiation as part of their frontline therapy. The median time from irradiation to secondary consolidation therapy was 4.2 years (range, 2.4–7.5 years). In these patients, there was no grade 3/4 neurotoxicity due to secondary consolidation therapy.

A total of 20 patients (nine patients with early relapse and 11 patients with late relapse) were treated with HSCT. The median time from relapse to transplantation was 4.3 months (range, 2.4–13.1 months). Six patients had matched family donors, two had one antigen-mismatched family donors, two had two antigen-mismatched family donors, eight had matched unrelated donors, and two had one antigen-mismatched unrelated donors. Continuation treatment was carried out on an outpatient basis and was well tolerated overall.

Analysis of EFS and OS estimates

For all patients enrolled on the R15 protocol, the 5-year OS estimate was $40.0\pm7.1\%$ ($\pm$s.e.), and the 5-year EFS estimate was $37.8\pm7.0\%$. Ten patients had a second relapse: eight had an isolated bone marrow relapse, one had an isolated CNS relapse, and one had a combined hematologic and testicular relapse. The median time to relapse was 13.5 months (range, 5.8–156.8 months). One patient on the twice daily etoposide arm developed a second malignancy, that is, acute myeloid leukemia with a t(10;14)(p13;q32), 12 months after the completion of continuation treatment. This patient had received etoposide and teniposide during frontline therapy. The cumulative incidence of relapse and second malignancy at 5 years was $37.8\pm7.4\%$.

In a Cox proportional hazards regression model adjusted for time to relapse, etoposide treatment arm, and site of relapse, only time to relapse was an independent prognostic factor of EFS (hazard ratio, 2.39; 95% confidence interval (CI), 1.11–5.11; $P=0.025$). There was no significant difference in prognosis between the once daily and twice daily etoposide treatment arms ($P=0.908$) or between patients with isolated bone marrow relapse and those with combined relapse ($P=0.606$). Similar results were obtained when the analysis was performed after the

inclusion of the immunophenotype of blasts from 40 patients with available data or the inclusion of immunophenotype and cytogenetic features from 35 patients with available data; the analysis indicated only time to relapse was an independent prognostic factor. The 5-year OS estimate, EFS estimate, and cumulative incidence of relapse and second malignancy were 25.0±8.8, 20.0±8.0, and 55.0±11.6%, respectively, for patients with early relapse. For patients with late relapse, the 5-year OS estimate, EFS estimate, and cumulative incidence of relapse and second malignancy were 52.0±9.6, 52.0±9.6, and 24.0±8.8%, respectively. In a Cox proportional hazards regression model that included the site of relapse, the time to relapse, and HSCT status as time-dependent covariates, HSCT had no significant impact on EFS ($P=0.854$) or OS estimates ($P=0.993$). The 5-year EFS estimate for patients who received HSCT was 45.0±10.6% (95% CI, 24.2–65.8%). The 5-year EFS estimate for those who received only chemotherapy was 32.0±8.8% (95% CI, 14.8–49.2%). Among patients who received chemotherapy alone, the 5-year EFS estimates were 57.1±12.5% (95% CI, 32.6–81.6%) and 0% for those with late relapse and early relapse, respectively ($P=0.0004$).

Discussion

Our study showed that low-dose etoposide, when administered orally for a prolonged period, has a significant antileukemic effect and that its combination with dexamethasone, vincristine, and L-asparaginase can yield a respectable remission induction rate in a group of patients with relapsed ALL after treatment with modern intensive multidrug regimens. In fact, almost all of these patients had previously received substantial cumulative doses of epipodophyllotoxins – etoposide, teniposide, or both.

It should be emphasized the R15 protocol's induction regimen, which did not include anthracyclines, produced a remission rate (84.4%) comparable to that of anthracycline-containing regimens for relapsed ALL.[3–5,24] In the POG 8303 study for patients with early relapse, the CR rate was 82% after four-drug induction therapy consisting of prednisone, vincristine, daunorubicin, and asparaginase.[5] In the CCG 1884 study, the CR rate was 71% for the patients whose disease relapsed within a year after the completion of therapy.[24] Similarly, a CR rate of 75% was achieved in our patients with early relapse, suggesting that prolonged oral administration of low-dose etoposide provided meaningful antileukemic effects and could benefit those who had received a substantial cumulative dose of anthracyclines in their initial therapy.

The superiority of prolonged administration of etoposide over administration by a single bolus infusion has been shown by a randomized clinical trial involving small-cell lung cancer:[25] five infusions of etoposide (single dose, 100 mg/m^2) each day yielded a higher response rate than did a single daily dose (500 mg/m^2), despite the similarity in systemic exposure. It is not completely clear why prolonged administration of low-dose etoposide is more effective than the shorter administration of the same drug at higher doses, although the schedule dependency of etoposide is widely recognized.[11]

The previously published results showed that oral administration of etoposide at a dose of 25 or 50 mg/m^2 yields cytotoxic concentrations in the cerebrospinal fluid, suggesting that this treatment could contribute to control of CNS leukemia.[26] Prolonged administration of low-dose etoposide also has a potential advantage that involves the incidence of recombinogenesis. An *in vitro* study by our group has demonstrated that prolonged exposure of cells to etoposide yields a greater ratio of cytotoxicity to genetic recombination than does brief exposure; therefore, prolonged administration may reduce the risk of etoposide-induced AML.[27]

The twice daily schedule resulted in greater reduction in the number of peripheral blasts than did the once daily schedule, a finding consistent with our pharmacokinetic data, which showed the twice daily regimen resulted in a higher area under concentration–time curve (AUC) on Day 22 (although not on Day 1 or Day 8) than the once daily regimen.[28] Compared with the extent of response as indicated by peripheral leukocyte counts and blast counts, the reduction in the number of bone marrow blasts was relatively small but significant. Perhaps because of the small number of patients studied, the limited use of prolonged administration, and the use of combination chemotherapy, we were not able to demonstrate the clinical benefit of twice daily dosing in terms of the remission induction rate or EFS estimate. It should be noted that cytogenetic features did not influence either the remission rate or survival rate, although the distribution of cytogenetic features differed significantly between the two etoposide arms; therefore, it is unlikely the uneven distribution of cytogenetic characteristics between the two groups affected the outcome.

The major dose-limiting toxicities of the induction regimen were diarrhea and mucositis. Daily administration of the single agent etoposide at a dose of 50 mg/m^2 is generally well tolerated;[12] however, serious infectious complications occurred in our study. Given the facts that etoposide at this dose does not cause significant toxicity and that neither vincristine nor L-asparaginase is very immunosuppressive, the treatment-related death in our study may be attributed to the relatively high dose of dexamethasone.[29] Also, it should be noted that glucocorticoids can increase the clearance rate for etoposide;[20] hence, the tolerable dose of etoposide administered for a prolonged period could be different when it is not combined with concurrent glucocorticoids.

Time to relapse was the only prognostic factor identified in this study. Given the relatively small number of patients studied, it is not surprising that we could not demonstrate the adverse prognostic impact of isolated hematologic relapse or T-cell immunophenotype.[4] Likewise, we could not show any benefit of HSCT. This finding could be due, at least in part, to the use of a variety of transplantation regimens and donors as well as the heterogeneity of our patient cohort.

In summary, prolonged oral administration of low-dose etoposide is an effective regimen for ALL and warrants further testing in patients with relapsed or refractory leukemia, especially those who have received a high cumulative dose of anthracyclines in frontline therapy. It would also be of interest to study whether the MDR-1 status of patients affects the efficacy of etoposide, a substrate of p-glycoprotein.[30]

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