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Comparison of Idarubicin to Daunomycin in a Randomized Multidrug Treatment of Childhood Acute Lymphoblastic Leukemia at First Bone Marrow Relapse: A Report From the Children's Cancer Group

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The outcome of children with acute lymphoblastic leukemia (ALL) and bone marrow relapse has been unsatisfactory largely because of failure to prevent subsequent leukemia relapses.

Ninety-six patients were enrolled and received vincristine, prednisone, L-asparaginase, and an anthracycline as reinduction therapy. Ninety-two patients were randomized to receive either daunomycin (DNR) or idarubicin (IDR). After achievement of second complete remission (CR2), maintenance chemotherapy included the same anthracycline, IDR or DNR, high-dose cytarabine, and escalating-dose methotrexate.

Compared to DNR (45 mg/m^2/week × 3), IDR (12.5 mg/m^2/week × 3) was associated with prolonged myelosuppression and more frequent serious infections. Halfway through the study, the dose of IDR was reduced to 10 mg/m^2. Overall, second remission was achieved in 71% of patients. Reinduction rate was similar for IDR and DNR. Reasons for induction failure differed; none of 15, 1 of 5, and 5 of 7 reinduction failures were due to infection for DNR, IDR (10 mg/m^2), and IDR (12.5 mg/m^2), respectively. Two-year event-free survival (EFS) was better among patients who received IDR (12.5 mg/m^2) (27 ± 18%) compared to DNR (10 ± 8%, $P = 0.05$) and IDR (10 mg/m^2) (6 ± 12%, $P = 0.02$). However, after 3 years of follow-up, late events in the high-dose IDR group result in a similar EFS to the lower-dose IDR and DNR groups.

In conclusion, IDR is an effective agent in childhood ALL. When used weekly at 12.5 mg/m^2 during induction, the EFS outcome during the first 2 years of treatment appears better than lower-dose IDR or DNR (45 mg/m^2), although this difference was not sustained at longer periods of follow-up. Increased hematopoietic toxicity seen at this dose might be reduced through the use of supportive measures, such as hematopoietins and intestinal decontamination.

Key words: idarubicin, daunomycin, childhood acute lymphoblastic leukemia

INTRODUCTION

While several innovations in the treatment of children with newly diagnosed acute lymphoblastic leukemia (ALL) have improved the outlook for disease-free survival (DFS), the treatment of children who experience a relapse remains unsatisfactory. Second complete remissions (CR2) can be achieved in more than 75% of children [1,2], but DFS among children maintained with intensive multidrug therapy is generally reported to be 30% or less [3,4]. Indeed, the improved results of more intensive primary therapies may adversely affect the outcome of retrieval therapies by the adverse selection of patients at higher risk of cumulative toxicity or with leukemia clones more resistant to chemotherapy.

Allogeneic bone marrow transplantation (BMT) has been used as an intensive approach to preserve second or later remissions of childhood ALL. The reported outcome of allogeneic BMT in CR2 of childhood ALL is variable [5–10], but studies which prospectively compare BMT to chemotherapy in this situation are limited [4–11]. The duration of initial remission is a very important determinant of the outcome of retrieval therapy [3,4]. This complicates assessment of the role of allogeneic BMT in relapsed childhood ALL. Thus, the role of BMT in second remission ALL remains controversial [12–15]. Further-

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more, the lack of a histocompatible donor limits the utility of BMT for most potential recipients. Thus, more effective chemotherapeutic modalities are needed in an attempt to improve the outcome for children with relapsed ALL.

Idarubicin (IDR) is a new anthracycline which is superior to daunomycin (DNR) in the treatment of acute myeloid leukemia (AML) [16–18]. The efficacy of IDR in ALL was demonstrated by Tan et al. [19] in phase I studies and confirmed in a subsequent Children's Cancer Group (CCG) trial in which the maximum tolerated dose (MTD) in a four-drug induction regimen with vincristine (VCR), prednisone (P), and L-asparaginase (L-Asp) was found to be 12.5 mg/m^2 [20].

IDR has several attractive features. Preclinical studies suggested that IDR is more potent than DNR [21–23]. An active metabolite, idarubicinol (IDRol), persists in the circulation for a prolonged period and penetrates into the cerebrospinal fluid (CSF) [24]. The drug is absorbed after oral administration and may, in the future, be considered for oral use [25]. Initial animal studies suggested that IDR may be less cardiotoxic than other anthracyclines [26,27], but this has not been proved in early human trials [19].

Because of the demonstrated efficacy and attractive features of IDR, CCG developed a study (CCG-1884) to compare the relative efficacy and toxicity of IDR and DNR in a complex, multiple-drug program of treatment for children with ALL at first bone marrow relapse. This report presents the major clinical observations of that study.

PATIENTS AND METHODS

Patient Population

Patients were eligible for study at the time of first marrow relapse of ALL. Patients must have relapsed while on primary therapy or within 1 year of completing primary therapy. Patients must have been younger than 21 years of age at the time of initial diagnosis and older than 1 year at the time of entry into this study. Patients with a history of isolated extramedullary relapse were excluded, although patients with concurrent extramedullary and bone marrow relapse were eligible (n = 3). Patients who had received more than 300 mg/m^2 of anthracycline during primary treatment were excluded, so that specific issues regarding the relative cardiotoxicity of IDR and DNR could be assessed. Patients with significant functional defects in major organ systems (e.g., cardiovascular, pulmonary, renal, or gastrointestinal) were ineligible. Informed consent was required according to individual institutional policies as approved by the Department of Health and Human Services.

Ninety-six patients were entered on CCG-1884 between May 1990 and April 1992. Four patients were not assigned to treatment by randomization and are not included in this analysis. All 92 remaining patients were eligible and evaluable, with a median follow-up of 37 months for surviving patients. The description of our patient population is presented in Table I. Patients on the treatment regimens were examined for comparability with respect to characteristics of potential prognostic importance. There were no significant differences between patients assigned to the treatment alternatives with respect to white blood cell (WBC) count, age, gender, race, CD10 positivity, intensity of prior treatment, or duration of initial remission (Table I).

Therapeutic Plan

Induction therapy used VCR, P, L-Asp, and an anthracycline, either IDR or DNR (Table II). The selection of anthracycline was done by telephone randomization at the Operations Office of CCG. Anthracycline was administered weekly, for uniformity of dosage schedules. Although most prior studies have used IDR on consecutive days at the onset of induction therapy, there are preclinical data which suggest that intermittent dosing may be more effective [23]. Therapy to the central nervous system (CNS) used intrathecal cytarabine (Ara-C) and hydrocortisone at appropriate doses for age [28]. The schedule of intrathecal chemotherapy was augmented if the patient had CNS leukemia, defined as the presence of >5 cells/μl CSF with blasts present on cytology.

Patients who did not enter remission received alternate therapy. Those patients who achieved CR2 began a course of interim maintenance with VCR, methotrexate (MTX), and L-Asp (Table II) patterned after the protocol of Capizzi [29]. The purpose of this phase of treatment was to provide a period of relatively mild therapy after the intensive induction, during which patients could be assessed for the availability of a suitable marrow donor and arrangements made, if deemed appropriate by the responsible physician, for marrow transplantation. Transplanted patients were followed for disease status and survival only.

Maintenance chemotherapy consisted of repeated cycles of a two-phase program (Table II). The initial phase, modified after Rudnick et al. [30], used the same anthracycline as had been used in induction, at the same dose, followed by two doses of high-dose Ara-C and L-Asp. The second phase, beginning 28 days later, utilized VCR, increasing doses of MTX to maximum tolerance, and L-Asp [29] in 4 cycles, approximately every 10 days. These cycles of maintenance chemotherapy were to be repeated until a patient relapsed or stayed in remission for 2.5 years. Total cumulative lifetime doses of anthracycline were calculated as DNR equivalents, using an isodose conversion factor of 4.5 for IDR (i.e., 10 mg of IDR = 45 mg DNR) [16,17]. When a patient's cumulative dose of anthracycline (DNR equivalent) totaled 550 mg/m^2, anthracycline was discontinued and the first phase of each

TABLE I. Comparability of Randomized Patients*

	IDR	DNR	*P*
WBC at study entry			
<10K	30 (68.2)	34 (70.8)	
10–49K	8 (18.2)	12 (25.0)	0.24
≥50K	6 (13.6)	2 (4.2)	
Age at study entry			
<4 years	9 (20.5)	7 (14.6)	
4–9 years	21 (47.7)	25 (52.1)	0.76
10+ years	14 (31.8)	16 (33.3)	
Gender			
Male	21 (47.7)	25 (52.1)	0.68
Female	23 (52.3)	23 (47.9)	
Race			
White	29 (65.9)	29 (60.4)	0.59
Non-white	15 (34.1)	19 (39.6)	
CD10 immunophenotype[a]			
Negative	6 (17.1)	9 (20.9)	0.67
Positive	29 (82.9)	34 (79.1)	
Intensity of previous treatment			
Non-intensive	4 (9.1)	7 (14.6)	0.42
Intensive	40 (90.9)	41 (85.4)	
Duration of previous initial remission[b]			
<1 year	11 (25.6)	16 (33.3)	
1–3 years	26 (60.5)	25 (52.1)	0.69
>3 years	6 (14.0)	7 (14.6)	

*Numbers in parentheses indicate percentages for each treatment regimen. *P* value is for chi-square test of homogeneity.
[a]CD10 phenotype not available for 14 patients (9 IDR, 5 DNR).
[b]Data *not* available for one IDR-treated patient.

maintenance cycle was altered to use 4 doses of Ara-C (3 g/m^2 over 3 hr, every 12 hr) followed by L-Asp.

CSF Pharmacokinetics

A single CSF sample was obtained from each of 25 patients, 3–5 in each of the following time cohorts: prior to, or 1, 2, 4, 8, or 12 hr following the administration of the second or third dose of IDR during induction. CSF concentrations of IDR and IDRol were determined by high-pressure liquid chromatography, as previously described [24].

Supportive Care Guidelines

It was anticipated that a treatment protocol of this intensity would likely be accompanied by substantial toxicity, particularly hematopoietic suppression. All patients received intravenous immunoglobulin (500 mg/kg/week) during induction, until an absolute neutrophil count of 0.5×10^7/l was achieved. The use of hematopoietic growth factors was prohibited. All patients received prophylaxis against *Pneumocystis carinii* infection with trimethoprim/sulfamethoxazole, 2.5 mg/kg, twice a day, 2 or 3 days/week. Episodes of fever and neutropenia were treated promptly and empirically with parenteral broad spectrum antibiotics according to protocols at participating institutions. All patients had central venous catheters. Cardiac function was monitored closely; a comparison of the relative cardiotoxicity of IDR and DNR will be the subject of a future report.

Statistical Methods

Comparability of the patients randomized to IDR and DNR was examined by the chi-square homogeneity test for several potentially important prognostic factors and presenting features (Table I). Most of the study analyses used life table methods and statistics for describing patient outcome. Life table estimates were calculated by the Kaplan-Meier procedure [31]. The variance of the life table estimate was calculated using Greenwood's formula [31]. The primary endpoints examined were event-free survival (EFS) and survival from randomization, and DFS from end of induction. The last of these three used only those patients successfully achieving second remission with four-drug reinduction therapy. EFS events included induction failure (non-response to therapy or death during induction), leukemic relapse at any site or death during remission, whichever occurred first. DFS events included leukemic relapse at any site or death during remission. All comparisons of the randomized regimens used the "intent to treat" approach of comparing patients according to their originally randomized assignment, irrespective of whether they complied with the treatment approach

TABLE II. Treatment Program

1. Induction therapy		
VCR (1.5 mg/m^2, IV)		Days 0, 7, 14, 21
P (40 mg/m^2, PO)		Days 0–28, then taper
L-Asp (6,000 U/m^2, IM)		Thrice weekly × 9 doses
Plus anthracycline: either		
IDR (10–12.5 mg/m^2, IV)		Days 0, 7, 14
or		
DNR (45 mg/m^2, IV)		Days 0, 7, 14
2. CNS therapy		
No CNS disease	Ara-C and hydrocortisone	Days 0, 14, 28
CNS disease	Ara-C and hydrocortisone	Days 0, 7, 14, 21, 28
3. Interim maintenance		
VCR (1.5 mg/m^2, IV)		Days 1, 10
MTX (100 mg/m^2, IV)		Days 1, 10
L-Asp (15,000 U/m^2, IM)		Days 2, 11
4. Maintenance chemotherapy		
Phase 1—Day 0		
Anthracycline		Hour 0
Ara-C (3 g/m^2, IV)		Hours 0–3, 12–15
L-Asp (6,000 U/m^2, IM)		Hour 18
Phase 2—Day 28 Q 9–11 days × 4		
VCR (1.5 mg/m^2, IV)		
MTX (100 mg/m^2, IV)		
(increasing each dose 50 mg/m^2 to toxicity)[a]		
L-Asp (15,000 U/m^2, IM)		

[a]Diminish MTX dose by 50 mg/m^2 from previous maximum at start of next cycle.

throughout. There was one patient who switched regimens to DNR after being initially assigned to IDR; that patient is included in the IDR group for analysis. When patients went off study due to protocol non-compliance, they were followed for the occurrence of events and that information is used in the analyses up to the time of last patient contact.

Most of the life table comparisons of outcome pattern for randomized regimens, prognostic factor groups, etc., used the log rank statistic over the entire period of patient observation [32–34]. However, some analyses examined life table outcome at specific lengths of follow-up, comparing the differences in the Kaplan-Meier estimates together with their estimated variances. Multivariate regression analyses used the Cox proportional hazards model [35]. Estimates of the relative event rate for a particular event were calculated by the Observed/Expected (O/E) method for log rank analyses and by the regression coefficient method in proportional hazards regression [36,37]. For reporting purposes, the life table estimate is often provided with ±twice its estimated standard deviation, since this gives an approximate 95% confidence interval. The analyses presented reflect outcome as of August 1, 1994.

RESULTS

Forty-eight patients were randomized to receive DNR and 44 patients were randomized to receive IDR. Slightly over halfway into the study, concern was raised regarding prolonged pancytopenia and resulting infectious complications, including fungal septicemia, among the IDR-treated patients. Accordingly, the study was amended to diminish the dose of IDR used in all phases of the study, from 12.5 to 10 mg/m^2. This resulted in 26 patients receiving the 12.5 mg/m^2 dose and 18 patients receiving the 10 mg/m^2 dose of IDR.

The clinical characteristics of patients treated at 10 mg/m^2 IDR were retrospectively compared to those of patients treated with 12.5 mg/m^2 IDR and DNR. The same characteristics shown in Table I were used. No differences were observed between patients treated at the 10 mg/m^2 dose of IDR compared to patients treated with DNR (data not shown). There was only one difference noted in comparing patients treated at the two doses of IDR. The age at diagnosis was higher for patients treated with 12.5 mg/m^2 IDR: there were 2 patients younger than 4 years of age, 14 patients 4–9 years of age, and 10 patients older than 9 years. For patients treated with 10 mg/m^2 IDR, there were 7 patients younger than 4 years of age, 7 patients 4–9 years old, and 4 patients older than 9 years at diagnosis ($P = 0.04$). The potential impact of this difference is not clear. There were no differences in the duration of initial remission comparing the three treatment groups. There were no differences in the clinical characteristics of patients treated with DNR when the children treated in the early portion of the study (while 12.5 mg/m^2 IDR was used) were compared to patients treated later in the study (while 10 mg/m^2 IDR was used) (data not shown).

Induction was successfully achieved in 32 of 44 IDR-treated patients (73%), compared to 33 of 48 DNR-treated patients (69%) (Table III). Among the IDR-treated patients, 19 of 26 children treated at a dose of 12.5 mg/m^2 achieved remission (73%), compared to 13 of 18 patients treated at the 10 mg/m^2 dose (72%). All induction failures among DNR-treated patients were due to persistent leukemia, while half of the induction failures among IDR-treated patients were due to deaths prior to the end of induction therapy. All of these deaths were the result of overwhelming infection (Table IV). There were five deaths during induction among patients treated at the higher dose of IDR, compared to only one death during induction at the lower dose. Two of those patients had residual leukemia identified at the time of death.

Maintenance therapy was tolerated reasonably well. There were only sufficient patients who remained in remission on each arm to allow comparison of the first three cycles of maintenance. These cycles were designed to last approximately 70 days each. For the IDR-treated group, maintenance lasted 80 ± 13 days (mean ± SD) (range: 69–106 days) compared to 76 ± 6 days (range: 66–91 days) for the DNR-treated patients. The major toxicities during maintenance were almost exclusively

TABLE III. Induction Results*

	M1	M2–M3	Death
IDR 12.5 mg/m^2 (n = 26)	19 (73)	2 (8)	5 (19)
IDR 10 mg/m^2 (n = 18)	13 (72)	4 (22)	1 (6)
DNR 45 mg/m^2 (n = 48)	33 (69)	15 (31)	0

*Data expressed as number of patients (%).
M1-normocellular marrow with trilineage maturation and less than 5% blasts.
M2/M3->5% blasts.

TABLE IV. Fatal Infections During Induction

Patient	Day of therapy	Organisms
AA-3	17	*Escherichia coli, Aerococcus viridans*
AA-6	32	*Escherichia coli*
EE-3	31	Not specified
H-8	37	*Staphylococcus mitis,* fungus[a]
R-2	20	*Pseudomonas aeruginosa, Aspergillus*[a]
Z-4	24	*Staphylococcus aureus, Candida albicans*

[a]Not otherwise specified.

hematologic; grade III or IV hematologic toxicity was observed in 63% of patients treated with IDR and 64% of patients treated with DNR. A single allergic reaction of L-Asp was reported. The ability to escalate the dose of MTX during maintenance therapy was highly variable; some patients were unable to tolerate more than 100 mg/m^2, while others were able to receive as much as 500 mg/m^2 on a continuing basis.

EFS at 24 months from randomization was 19 ± 12% for the patients treated with IDR vs. 10 ± 8% for patients treated with DNR (Fig. 1) ($P = 0.13$). However, by 36 months the two groups have nearly identical outcome, and the overall EFS pattern does not approach significance (log rank $P = 0.28$; relative event rate 1.27 times higher for DNR).

Survival from randomization was quite similar for the IDR and DNR groups, with 36-month survival rates of 23 ± 13% and 19 ± 14% (overall log rank $P = 0.88$; relative death rate for IDR:DNR = 0.96).

Effect of IDR Dose

There was no difference in efficacy of achievement of CR2 (Table III). EFS from randomization was improved among patients treated with IDR at 12.5 mg/m^2 compared to patients treated at a dose of 10 mg/m^2 (Fig. 2). EFS curves separated at about 4 months into therapy and favored the higher dose of IDR (log rank $P = 0.07$; relative event rate 1.76 times higher at the 10 mg/m^2 dose than at the 12.5 mg/m^2 dose). One- and 2-year EFS for patients

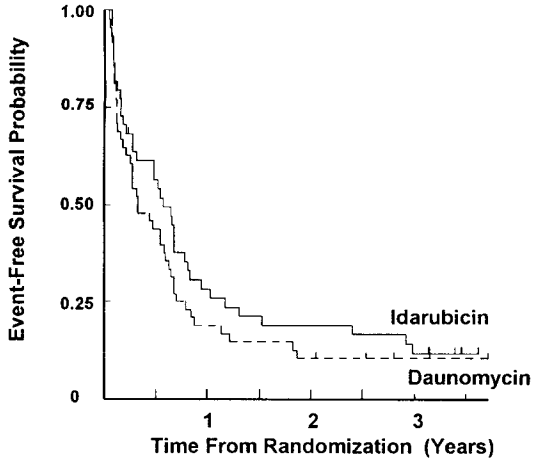

Fig. 1. The probability of EFS for randomization: all patients treated with IDR (n = 44) vs. all patients treated with DNR (n = 48).

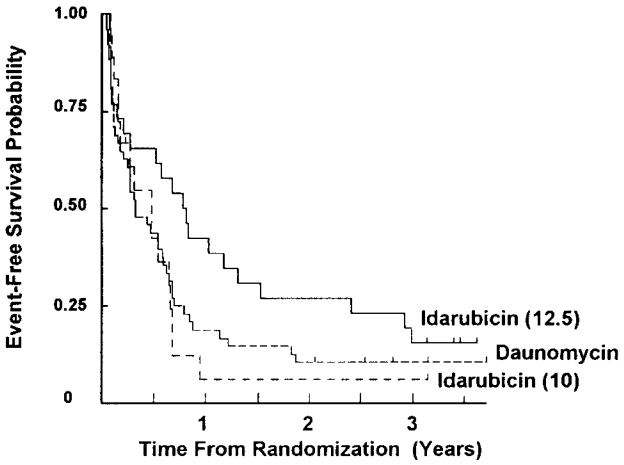

Fig. 2. The probability of EFS for randomization: IDR (12.5 mg/m^2) (n = 26) vs. DNR (n = 48) vs. IDR (10 mg/m^2) (n = 18).

receiving the higher IDR dose were significantly better than for the lower IDR dose (1-year EFS: 42% vs. 6%, $P = 0.0007$; 2-year EFS: 26% vs. 6%, $P = 0.02$), but the difference was no longer significant at 3 years (15% vs. 6%, $P = 0.16$).

There was no difference in EFS of the 28 DNR-treated patients treated early (during the period when the IDR-treated patients received 12.5 mg/m^2) compared to the 20 DNR-treated patients treated late (when IDR-treated patients received 10 mg/m^2) ($P = 0.44$).

The 1- and 2-year EFS for patients treated at the 12.5 mg/m^2 dose of IDR were better than for patients treated with DNR (1-year EFS: 42% vs. 19%, $P = 0.02$; 2-year EFS: 27% vs. 10%, $P = 0.05$), but the 3-year results were similar (15% vs. 10%, $P = 0.28$); overall log rank $P = 0.10$). The 12-month EFS comparison for DNR compared to the lower IDR dose approaches significance

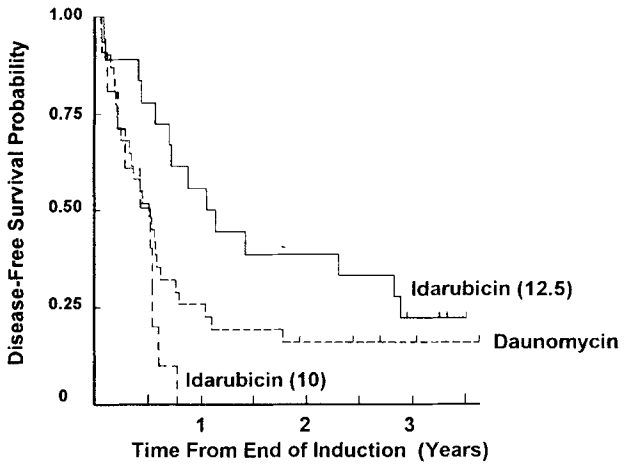

Fig. 3. The probability of DFS from achievement of CR2: IDR (12.5 mg/m^2) (n = 19) vs. DNR (n = 33) vs. IDR (10 mg/m^2) (n = 13).

(P = 0.06), but by 24 months the results do not differ appreciably (P = 0.28; overall log rank P = 0.72).

The effect of IDR dose was clearly seen among the patients achieving CR2. Two years after achieving CR2, the DFS among patients treated at the 12.5 mg/m^2 dose of IDR was superior to that of patients treated at the lower dose of IDR (39% vs. 0%, P = 0.0004; overall log rank P = 0.0005) and close to significant compared to patients treated with DNR (39% vs. 16%, P = 0.04; overall log rank P = 0.07; Fig. 3). However, by 3 years, the DFS rates for the higher dose of IDR and for DNR are similar (22% vs. 16%, P = 0.30).

Five patients died during second remission; two IDR-treated patients and one DNR-treated patient died of complications of BMT. There were 11 relapses and 3 deaths in remission among the patients treated at the 12.5 mg dose of IDR, compared to 10 relapses and no deaths in remission among patients treated at the lower dose of IDR and 24 relapses and 2 deaths in remission among DNR-treated patients. Among IDR-treated patients, there were 17 isolated bone marrow relapses, 2 isolated CNS relapses, and 2 concurrent relapses in the marrow and CNS. There were 24 relapses and 2 deaths in remission among patients treated with DNR. These included 18 marrow relapses, 3 isolated CNS relapses, and 3 simultaneous relapses in the marrow and CNS.

Prognostic Factors

EFS was analyzed to assess potential prognostic factors (Table V). Patients whose initial remission was greater than 3 years had a markedly improved EFS, compared to patients who had experienced shorter first remissions (P = 0.001). There was no difference comparing EFS for patients with very short initial remissions (less than 1 year) to those with remissions of intermediate duration (1–3 years). The 24-month EFS in patients with the longest initial remission duration was 54% compared with 7% and 8% for the short and intermediate remission groups, respectively. Multivariate analyses using the Cox proportional hazards model tended to agree with the results obtained by the previously described methods. These analyses showed that duration of initial remission was an important independent prognostic factor for predicting EFS (P = 0.0001 for an improved outcome in those having initial remissions of 3+ years; relative event rate of 4.93 for those with initial remission of <1 year compared to patients with initial remissions of >3 years). Age at study entry showed a modest prognostic effect in multivariate analysis, with patients between 4 and 9 years of age having a slightly better outcome than those who were younger or older (P = 0.06). WBC at study entry, sex, race, and the presence of CALLA(CD10)-positive immunophenotype were unrelated to EFS in this population of patients.

There was concern that intensity of prior therapy may have selected for unusually refractory disease among our patients. Patients were separated into groups based upon intensity of initial therapy. Standard therapy was defined as minimal therapy with three-drug induction, treatment of occult CNS disease, and maintenance with oral 6-mercaptopurine (6MP) and MTX [38]. Intensive therapy was defined as having more intensive induction (e.g., Berlin-Frankfurt-Munster [BFM] [39] or New York [40]), intensive consolidation (e.g., BFM), or intensive maintenance (e.g., New York). Neither EFS, survival, nor DFS was substantially affected by the intensity of initial therapy (Table V). Patients had events at approximately the same rate, regardless of primary therapy, but seemed to survive longer after a second relapse if primary therapy had not been intense.

CSF Pharmacokinetics

In a previous phase I study of IDR in pediatric patients, CSF samples obtained 24 hr after drug administration were found to contain substantial quantities (≅0.5 ng/ml) of the alcohol metabolite IDRol, but little if any parent drug. In this study, we obtained single samples from patients at various time points in order to construct a time profile of IDR and IDRol appearance and disappearance in CSF. As in the previous study, little IDR was detected, even at early times following IDR administration. IDRol was detected in all but one (8 hr) sample obtained after drug administration. Peak concentrations (mean value = 1.6 ng/ml, n = 5) were observed 4 hr following IDR administration. IDRol concentrations at 12 hr (mean value = 0.56 ng/ml, n = 3) were similar to those previously observed 24 hr after IDR administration (mean value − approximately 0.5 ng/ml, n = 20) [24].

DISCUSSION

Results of treatment for children with relapsed ALL are unsatisfactory. This study was undertaken to compare

TABLE V. Potential Prognostic Factors*

				P
Duration of CR1	<1 year	1–3 years	>3 years	
N	27	51	13	
24-month EFS[a]	7 ± 10%	8 ± 8%	54 ± 26%	0.001
WBC at study entry	<10,000	10,000–50,000	>50,000	
N	64	20	8	
24-month EFS[a]	13 ± 8%	22 ± 19%	13 ± 23%	0.38
Age at study entry	<4 years	4–9 years	>10 years	
N	16	46	30	
24-month EFS[a]	6 ± 12%	18 ± 11%	13 ± 12%	0.14
Gender	Male	Female		
N	46	46		
24-month EFS[a]	13 ± 9%	16 ± 11%		0.25
Race	White	Other		
N	58	34		
24-month EFS[a]	17 ± 9%	9 ± 26%		0.42
CD10 phenotype	Positive	Negative		
N	63	15	14	
24-month EFS	14 ± 33%	7 ± 13%		0.91
Intensity of primary therapy	Standard	Intensive		
N	11	81		
24-month EFS[a]	18 ± 23%	14 ± 7%		0.36
24-month survival[a]	27 ± 23%	21 ± 10%		0.21
24-month DFS[b]	13 ± 23%	22 ± 12%		0.99

*Data expressed as proportion ± 95% confidence interval. *P* values are from overall log rank test.
[a]From randomization (diagnosis of relapse).
[b]From achievement of CR2.

the efficacy of a new anthracycline, IDR, to DNR in a complex multidrug reinduction and maintenance program for children with relapsed ALL. Our first observation was that IDR was extremely toxic, especially with respect to prolonged hematopoietic suppression observed in the weekly induction schedule used in this study. This led to a high frequency of severe infections. The protocol was amended to diminish the dose of IDR for the latter half of the study, a decision that may have been hasty in light of the subsequent outcomes. We postulated that the more severe toxicity with IDR might be related to the pharmacologic characteristics of IDR. The active metabolite of IDR, IDRol, persists in the circulation for prolonged periods of time [24]. This creates prolonged exposure of tissues to this active agent. Most prior studies of IDR used the drug in three daily doses at the beginning of therapy, which shortened the exposure time, and less hematopoietic toxicity was observed [16–19]. When IDR is used in a weekly dosing schedule, hematopoietic suppression is prolonged and infectious complications occur with increased frequency.

In spite of the regimen-related toxicity seen at the higher dose of IDR, the success of remission induction was similar for both dose schedules of IDR (12.5 or 10 mg/m^2) and for DNR. Infectious complications accounted for the majority of deaths with the higher dose of IDR, while persistent leukemia was responsible for the majority of induction failures at the lower dose of IDR and with DNR. This protocol did not recommend intensive supportive care measures to diminish the infectious risk of prolonged neutropenia. Indeed, the use of hematopoietic growth factors was proscribed. A more intensive program of supportive care in patients receiving high-dose weekly IDR might result in diminished mortality from infection. Interventions which might be helpful in this regard include the use of protective environments, the use of antifungal prophylaxis to diminish gastrointestinal colonization, and the use of hematopoietic growth factors such as granulocyte colony stimulating factor (G-CSF).

The induction rate of CR2 in this study was only 71%. This rate is lower than the previous reports of successful reinduction of childhood ALL [1]. The poorer induction rate in this study might reflect an unfavorable population of patients with relapsed ALL because most patients had been treated with more intensive front line therapies. Indeed, we found that fewer than 15% of our patients had received "standard" initial therapy. However, when we compared the outcome of children who had been less intensively treated initially to those more intensively treated, EFS and DFS were not substantially different, although overall survival was slightly better among the less intensively treated children.

The use of high-dose IDR in this complex chemotherapeutic regimen produced superior 1-year and 2-year EFS and DFS compared to DNR and to lower-dose IDR. Since IDR was used in both the induction and maintenance phases of therapy, it is not possible to distinguish whether the use of weekly higher-dose IDR in induction produced

a more stable remission or whether the continued use of IDR during maintenance resulted in the prolongation of DFS. We suspect that the induction treatment with weekly IDR may have provided the crucial difference, because relatively little IDR was used during induction. This observation would be consistent with preclinical data which suggest that an intermittent dosage of IDR might be more effective in the eradication of tumor [23]. Improved efficacy of IDR might also be due to the prolonged circulation of IDRol, the penetration of IDRol into sanctuaries such as the CNS, or to a putative effect of IDR in overcoming multiple-drug resistance [41,42].

The prolongation of DFS is important, even though this effect could not be sustained. Until curative chemotherapies are developed, BMT will probably remain a common approach to the treatment of children with relapsed AML. Since most patients will not have matched related donors, the use of alternative transplants, using autologous marrow or unrelated donors, will be considered. In the former, the potential for decreased contamination of marrow by tumor would be beneficial; in the latter, prolonged DFS would allow for the greater time required to identify, consent, and harvest a suitable donor.

This study also confirms previous findings [24] that IDRol was present in CSF of pediatric patients receiving IDR, even though very little parent drug was detected in those same samples. These findings are of potential importance because IDRol, unlike alcohol metabolites of daunorubicin and doxorubicin, is a potent growth inhibitory agent. For example, Kuffel and coworkers [43] demonstrated that IDRol was from 16 to 122 times more potent than daunorubicinol and doxorubicinol when incubated with human tumor cell lines. IDRol was in fact equipotent with IDR. If, as we believe, IDRol is present in CSF for several days following doses of IDR such as those employed in this study, the CSF exposure may be relevant to the prevention of CNS relapse. In this study, CNS relapse was not a frequent event and the occurrence of CNS did not differ among the two treatment groups.

Attempts to identify potential prognostic factors among our patients were largely unsuccessful. Relapse early in the course of primary treatment of ALL overwhelmed the influence of many of the other factors. Nevertheless, we were able to confirm previous reports of the importance of the timing of relapse [3,4]; patients who relapsed more than 3 years after initial diagnosis responded better to salvage therapy than did patients who relapsed earlier. We were unable to confirm any improved outlook for patients who relapsed between 1 and 3 years; these patients did as poorly as patients who relapsed within 1 year of initial diagnosis.

In summary, the treatment programs available for children with relapsed ALL do not provide good long-term results. While BMT offers an alternative to some children, most patients do not have suitable allogeneic donors. Autologous transplantation is under investigation, but as with chemotherapy, relapse is a substantial problem. Given the need for improved anti-leukemic efficacy, IDR is a promising agent for use in children with ALL. Our data suggest that higher-dose IDR has benefits over DNR; however, use of IDR at higher doses in an intermittent schedule also has serious hematopoietic toxicity. If used in this manner, intensive supportive measures may diminish the risk of infectious morbidity and mortality. Alternatively, IDR might be studied in a schedule that uses three daily doses of drug at the start of induction. There remains substantial concern regarding the potential of IDR to cause late cardiotoxicity. This study was designed to compare the late cardiac toxicities of IDR and DNR and those evaluations are underway. There has not been sufficient follow-up to draw any conclusions. Those studies will be reported in the future.

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REFERENCES

1. Reaman GH, Ladisch S, Echelberger C, Poplack DG: Improved treatment results in the management of single and multiple relapses of acute lymphoblastic leukemia. Cancer 45:3090–3094, 1980.
2. Buchanan GR, Rivera GK, Boyett JM, Chauvenet AR, Crist WM, Vietti TJ: Reinduction therapy in 297 children with acute lymphoblastic leukemia in first bone marrow relapse: A Pediatric Oncology Group Study. Blood 72:1286–1292, 1988.
3. Rivera GK, Buchanan G, Boyett JM, Camitta B, Ochs J, Kalwinsky D, Amylon M, Vietti TJ, Crist WM: Intensive retreatment of childhood acute lymphoblastic leukemia in first bone marrow relapse: A Pediatric Oncology Group Study. N Engl J Med 315:273–278, 1986.
4. Henze G, Fengler R, Hartmann R, Kornhuber B, Janka-Schaub G, Niethammer D, Riehm H: Six-year experience with a comprehensive approach to the treatment of recurrent childhood acute lymphoblastic leukemia (ALL-REZ BFM 85). A relapse study of the BFM Group. Blood 78:1166–1172, 1991.
5. Dopfer R, Henze G, Bender-Gotze C, Ebell W, Ehninger G, Friedrich W, Gadner H, Klingebiel T, Peters C, Riehm H, Suttorp M, Schmid H, Schmitz N, Siegert W, Stollmann-Gibbels B, Hartmann R, Niethammer D: Allogeneic bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission after intensive primary and relapse therapy according to the BFM and CoALL protocols: Results of the German Cooperative Study. Blood 78:2780–2784, 1991.
6. Coccia PF, Strandjord SE, Warkentin PI, Cheung N-KV, Gordon EM, Novak LJ, Shina DC, Herzig RH: High-dose cytosine arabinoside and fractionated total-body irradiation: An improved preparative regimen for bone marrow transplantation of children with acute lymphoblastic leukemia in remission. Blood 71:888–893, 1988.
7. Sanders JE, Thomas ED, Buckner ED, Doney K: Marrow trans-

plantation for children with acute lymphoblastic leukemia in second remission. Blood 70:324–326, 1987.
8. Dinsmore R, Kirkpatrick D, Flomenberg N, Gulati S, Kapoor N, Shank B, Reid A, Groshen S, O'Reilly RJ: Allogeneic bone marrow transplantation for patients with acute lymphoblastic leukemia. Blood 62:381–388, 1983.
9. Woods WG, Nesbit ME, Ramsay NKC, Krivit W, Kim TH, Goldman A, McGlave PB, Kersey JH: Intensive therapy followed by bone marrow transplantation for patients with acute lymphocytic leukemia in second or subsequent remission: Determination of prognostic factors (A report from the University of Minnesota Bone Marrow Transplantation Team). Blood 61:1182–1189, 1983.
10. Thomas ED, Sanders JE, Flournoy N, Johnson FL, Buckner CV, Clift RA, Fefer A, Goodell BW, Storb R, Weiden PL: Marrow transplantation for patients with acute lymphoblastic leukemia: A long-term follow-up. Blood 62:1139–1141, 1983.
11. Johnson FL, Thomas ED, Clark BS, Chard RL, Hartman JR, Storb R: A comparison of marrow transplantation with chemotherapy for children with acute lymphoblastic leukemia in second or subsequent remission. N Engl J Med 305:846–851, 1981.
12. Chessells JM, Rogers DW, Leiper AD, Blacklock H, Plowman PN, Richards S, Levinsky R, Festenstein H: Bone-marrow transplantation has a limited role in prolonging second marrow remission in childhood lymphoblastic leukaemia. Lancet 1:1239–1241, 1986.
13. Pinkel D: Bone marrow transplantation in children. J Pediatr 122:331–341, 1993.
14. Butturini A, Rivera GK, Bortin MM, Gale RP: Which treatment for childhood acute lymphoblastic leukaemia in second remission? Lancet 1:429–432, 1987.
15. Uderzo C, Valsecchi MG, Bacigalupo AM, Meloni G, Messina C, Polchi P, Di Girolamo G, Dini G, Miniero R, Locatelli F, Colella R, Tamaro P, LoCurto M, Di Tullio MT, Masera G: Treatment of childhood acute lymphoblastic leukemia in second remission with allogeneic bone marrow transplantation and chemotherapy: Ten-year experience of the Italian Bone Marrow Transplant Group and the Italian Pediatric Hematology Oncology Association. J Clin Oncol 13:352–358, 1995.
16. Berman E, Heller G, Santorsa J, McKenzie S, Gee T, Kempin S, Gulati S, Andrief M, Kolitz J, Gabrilore J, Reich L, Mayer K, Keefe D, Trainor K, Schluger A, Penenberg D, Raymond V, O'Reilly R, Jhanwar S, Young C, Clarkson B: Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukemia. Blood 77:1666–1674, 1991.
17. Wiernik PH, Banks PLC, Case DC, Zalman AA, Periman PO, Todd MB, Ritch PS, Enck RE, Weittberg AB: Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. Blood 79:313–319, 1992.
18. Vogler WR, Velez-Garcia E, Weiner RS, Flaum MA, Bartolucci AA, Omura GA, Gerber MC, Banks PK: A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: A Southeastern Cancer Study Group Study. J Clin Oncol 10:1103–1111, 1992.
19. Tan CTC, Hancock C, Steinherz P, Bacha DM, Steinherz L, Luks E, Winick N, Meyers P, Mendora A, Dantis E, Neidzwiecki D, Stevens Y-W: Phase I and clinical pharmacological study of 4-demethoxydaunorubicin (idarubicin) in children with advanced cancer. Cancer Res 47:2990–2995, 1987.
20. Feig SA, Krailo MD, Harris RE, Baum E, Holcenberg JS, Kaizer H, Steinherz L, Pendergrass TW, Saunders EF, Warkentin PL, Bleyer WA, Hammond GD: Determination of the maximum tolerated dose of idarubicin when used in a combination chemotherapy program of reinduction of childhood ALL at first marrow relapse and a preliminary assessment of toxicity compared to that of daunorubicin: A report from the Childrens Cancer Study Group. Med Pediatr Oncol 20:124–129, 1992.
21. Arcamone F, Bernardi L, Giardino P, Patelli B, DiMarco A, Casazza AM, Pratesi G, Reggiani P: Synthesis and antitumor activity of 4-demethoxydaunorubicin, 4-demethoxy-7, 9-diepidaunorubicin and their β-anomers. Cancer Treat Rep 60:829–834, 1976.
22. DiMarco A, Casazza A, Soranzo C, Pratesi G: Effect of various substitutions in positions 1,2,3, and 4 of 4-demethoxydaunorubicin and 4-demethoxyadriamycin. Cancer Chemother Pharamcol 1:249–254, 1978.
23. Casazza AM, Pratesi G, Guiliani F, DiMarco A: Antileukemic activity of 4-demethoxydaunorubicin in mice. Tumori 66:549–564, 1980.
24. Reid JM, Pendergrass TW, Krailo M, Hammond GD, Ames MM: Plasma pharmacokinetics and cerebrospinal fluid concentrations of idarubicin and idarubicinol in pediatric leukemia patients. A Childrens Cancer Study Group Report. Cancer Res 50:6525–6528, 1990.
25. Pannuti F, Camaggi CM, Strocchi E, Comparsi R, Angetelli B, Pacciarini MA: Low dose oral administration of 4-demethoxydaunorubicin (idarubicin) in advanced cancer patients. Cancer Chemother Pharmacol 16:295–299, 1986.
26. Bellini O, Tosana MG, Bertazzoli C: Comparison of the cardiotoxicity of anthracyclines in two experimental models in mice. Drugs Exp Clin Res 10:91–95, 1984.
27. Casazza AM, DiMarco A, Bonadonna G, Bonafante V, Bartazzoli C, Bellini O, Pratesi G, Sala L, Ballerini L: Effects of modifications in position 4 of the chromophore or in position 4′ of the aminosugar, on the antitumor activity and toxicity of daunorubicin and doxorubicin. In Crooke ST, Reich SD (eds): "Anthracyclines: Current Status and New Developments." New York: Academic Press, 1980, pp 403–430.
28. Bleyer WA: Clinical pharmacology of intrathecal methotrexate. II. An improved dosage regimen derived from age-related pharmacokinetics. Cancer Treat Rep 61:1419–1425, 1977.
29. Capizzi RL: Improvement in the therapeutic index of methotrexate (MSC-740) by L-asparaginase (MSC-109229). Cancer Chemother Rep 6(3):37–41, 1975.
30. Rudnick SA, Cadman EC, Capizzi RL, Skeel RT, Bertino JR, McIntosh S: High dose cytosine arabinoside (HDARAC) in refractory acute leukemia. Cancer 44:1189–1193, 1979.
31. Kaplan E, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958.
32. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163–170, 1966.
33. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 35:1–39, 1977.
34. Breslow N: Comparison of survival curves. In Buyse M, Staquet M, Sylvester M (eds): "Cancer Clinical Trials: Methods and Practice." Oxford: Oxford University Press, 1988, pp 381–406.
35. Cox DR: Regression models and life tables. J R Stat Soc B 34:187–220, 1972.
36. Breslow N: Analysis of survival data under the proportional hazards model. Int Stat Rev 43:45–58, 1975.
37. Bernstein L, Anderson J, Pike MC: Estimation of the proportional hazard in two-treatment group clinical trials. Biometrics 37:513–519, 1981.
38. Aur RJA, Simone J, Hutsu HO, Walters T, Barella L, Pratt C, Pinkel D: Central nervous system therapy and combination chemotherapy of childhood lymphocytic leukemia. Blood 37:272–281, 1971.
39. Reihm H, Langermann HJ, Gadner H, Odenwald E, Henze G: The Berlin Childhood Acute Lymphoblastic Leukemia Therapy Study, 1970–1976. Am J Pediatr Hematol/Oncol 2:299–306, 1980.
40. Gaynon PS, Steinherz PG, Bleyer WA, Ablin AR, Albo VC, Finklestein JZ, Grossman NJ, Littman PS, Novak LT, Pyesmany AF,

Reaman GH, Sather HN, Hammond GD: Intensive therapy for children with acute lymphoblastic leukaemia and unfavourable presenting features: Early conclusions of study CCG-106 by the Childrens Cancer Study Group. Lancet 2:921–924, 1988.
41. Ross D, Tong Y, Cornblatt B: Idarubicin (IDA) is less vulnerable to transport-mediated multi-drug resistance (MDR) than its metabolite idarubicinol (IDAol) or daunorubicin (DNR). Blood 82(Suppl 1):257a, 1993.
42. Berman E, McBride M: Comparative cellular pharmacology of daunorubicin and idarubicin in human multidrug-resistant leukemia cells. Blood 79:3267–3273, 1992.
43. Kuffel MJ, Reid JM, Ames MM: Anthracyclines and their C-13 alcohol metabolites: Growth inhibition and DNA damage following incubation with human tumor cells in culture. Cancer Chemother Pharmacol 30:51–57, 1992.

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