

CONVENTIONAL COMPARED WITH INDIVIDUALIZED CHEMOTHERAPY FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Background The rate of clearance of antileukemic agents differs by a factor of 3 to 10 among children with acute lymphoblastic leukemia. We hypothesized that the outcome of treatment would be improved if doses were individualized to prevent low systemic exposure to the drugs in patients with fast drug clearance.

Methods We stratified and randomly assigned 182 children with newly diagnosed acute lymphoblastic leukemia to postremission regimens that included high-dose methotrexate and teniposide plus cytarabine. The doses of these drugs were based on body-surface area (in the conventional-therapy group) or the rates of clearance of the three medications in each patient (in the individualized-treatment group). In the individualized-treatment group, doses were increased in patients with rapid clearance and decreased in patients with very slow clearance.

Results Patients who received individualized doses had significantly fewer courses of treatment with systemic exposures below the target range than did patients who received conventional doses ($P < 0.001$ for each medication). Among the patients with B-lineage leukemia, those who received individualized therapy had a significantly better outcome than those given conventional therapy ($P = 0.02$); the mean (\pm SE) rates of continuous complete remission at five years were 76 ± 6 percent and 66 ± 7 percent, respectively. There was no significant difference between treatments for patients with T-lineage leukemia ($P = 0.54$). In a proportional-hazards model, the time-dependent systemic exposure to methotrexate, but not to teniposide or cytarabine, was significantly related to the risk of early relapse in children with B-lineage leukemia.

Conclusions Adjusting the dose of methotrexate to account for the patient's ability to clear the drug can improve the outcome in children with B-lineage acute lymphoblastic leukemia. (N Engl J Med 1998; 338:499-505.)

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CHILDHOOD acute lymphoblastic leukemia is curable in approximately 70 percent of children.^{1,2} Many of the children who are not cured have presenting features that are indistinguishable from those in children who are cured. We reasoned that because systemic clearance of anticancer drugs differs by a factor of 3 to 10 among patients,³ those with rapid drug clearance may benefit less than those with slower clearance if the dose is

determined only according to body-surface area. This hypothesis was based in part on our finding that the outcome was significantly worse among children with acute lymphoblastic leukemia who had low plasma concentrations of methotrexate due to rapid clearance than among those with slower clearance.⁴ On the basis of these data and similar pharmacodynamic data for teniposide⁵ and cytarabine,⁶ we performed a prospective study in which patients with acute lymphoblastic leukemia were randomly assigned to receive doses of these drugs that were based on body-surface area or the clearance of the drugs in each patient.

METHODS

Patients and Treatment

Between October 1988 and November 1991, we registered 188 consecutive patients with newly diagnosed acute lymphoblastic leukemia (age range, 4.3 months to 18.8 years) in Total Therapy Study XII at St. Jude Children's Research Hospital in Memphis, Tennessee. Figure 1 shows the protocol for randomization and treatment. The study was approved by the institutional review board, and informed consent was obtained from the patients' parents or guardians. The diagnostic studies, immunophenotyping, and cytogenetic analyses were performed as described previously.^{7,8}

Remission-induction therapy for all patients consisted of prednisone, vincristine, asparaginase, daunorubicin, teniposide, and cytarabine, given over a four-week period as described previously.⁹ All patients received low-dose trimethoprim-sulfamethoxazole as prophylaxis against *Pneumocystis carinii* pneumonia. All patients received intrathecal treatment with methotrexate, hydrocortisone, and cytarabine in age-adjusted doses on days 2 and 22 of induction therapy and every six weeks through week 59. Only high-risk patients and those with central nervous system leukemia at diagnosis underwent cranial irradiation (18 and 24 Gy, respectively, during weeks 59 to 61).

Patients with complete remissions were stratified according to race (nonwhite vs. white). White patients were further stratified according to the DNA index (ratio of DNA content in leukemic G_0/G_1 cells to that in normal G_0/G_1 cells, <1.16 vs. ≥ 1.16), and white patients with a DNA index of <1.16 were stratified according to age (2 to 10 years vs. other ages) and leukocyte count per cubic millimeter ($<25,000$ vs. $\geq 25,000$). After stratification, the patients were randomly assigned to receive conventional or individualized treatment.

Patients with complete remissions received continuation thera-

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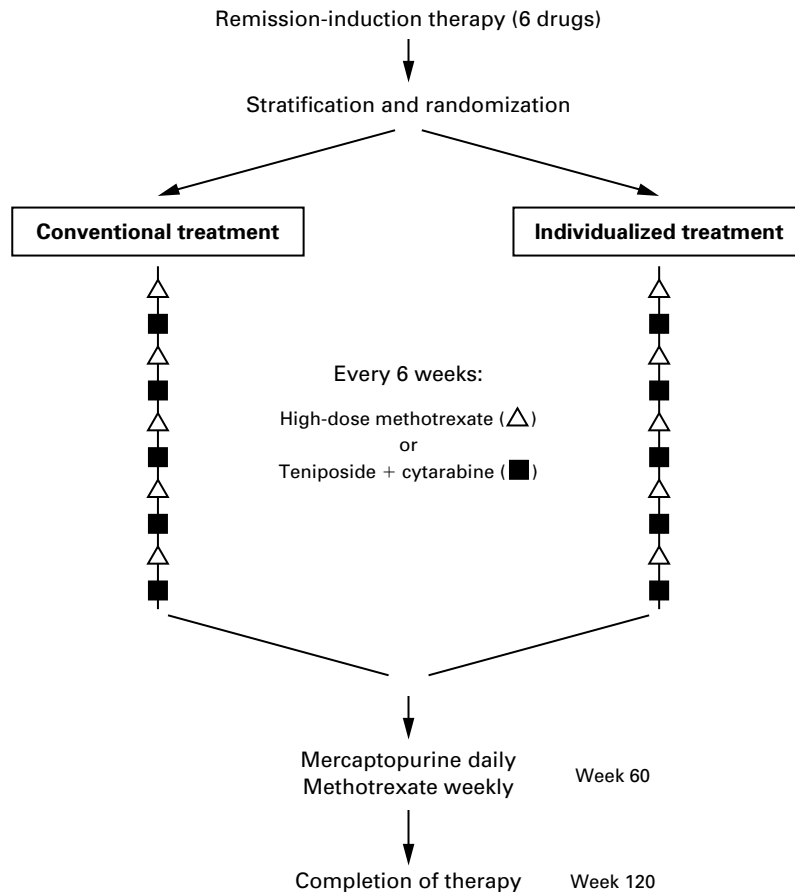


Figure 1. Study Protocol for Patients with Childhood Acute Lymphoblastic Leukemia Treated with Conventional or Individualized Chemotherapy.

After stratification according to leukocyte count, age, race, and DNA index, patients were randomly assigned to receive conventional or individualized treatment. Patients in the conventional-treatment group received standard doses of high-dose methotrexate (1500 mg per square meter of body-surface area), teniposide (200 mg per square meter), and cytarabine (300 mg per square meter). Patients in the individualized-treatment group received doses of these three medications that were based on their rates of drug clearance, with a target range of systemic exposure (the area under the plasma concentration–time curve) corresponding to the 50th to 90th percentile for children receiving conventional doses of the drugs. High-dose methotrexate was given during weeks 1, 13, 25, 37, and 49; the combination of teniposide and cytarabine was given during weeks 7, 19, 31, 43, and 55. From weeks 1 through 60 of continuation therapy, oral mercaptopurine (75 mg per square meter per day) and parenteral methotrexate (40 mg per square meter per week) were given during the five weeks after each course of high-dose methotrexate or teniposide plus cytarabine. From weeks 60 through 120, only mercaptopurine and methotrexate were given.

py for 120 weeks. The regimen consisted of daily oral mercaptopurine (75 mg per square meter of body-surface area) and weekly parenteral methotrexate (40 mg per square meter), interrupted every six weeks during the first year for treatment with either intravenous high-dose methotrexate with leucovorin¹⁰ (given during weeks 1, 13, 25, 37, and 49) or the combination of teniposide and cytarabine (given as simultaneous intravenous infusions during weeks 7, 19, 31, 43, and 55). For patients randomly assigned to receive conventional therapy, fixed doses were given on the basis of the patient's body-surface area (methotrexate, 1500 mg per square meter; teniposide, 200 mg per square meter; and cytarabine, 300 mg per square meter). Plasma samples were obtained from all patients for measurements of methotrexate, teniposide, and cytarabine concentrations. Methotrexate was measured by a

fluorescence polarization immunoassay (TDx, Abbott Laboratories, North Chicago, Ill.) in plasma samples obtained before and 1, 6, 23, and 42 hours after the start of the 24-hour intravenous infusion.¹⁰ After the start of simultaneous, 4-hour infusions of teniposide and cytarabine, teniposide was measured in plasma obtained at 1.5, 3.5, 8, and 24 hours, and cytarabine in samples obtained at 1.5 and 3.5 hours, with the use of assays previously reported.^{11,12}

Dose Adjustments

In the individualized-treatment group, the doses of methotrexate, teniposide, and cytarabine were adjusted according to systemic drug clearance in each patient.¹³ The target range of systemic exposure was defined a priori as the area under the plasma con-

centration-time curve corresponding to the 50th to 90th percentile for children treated with conventional doses of these medications. This range was based on prior pharmacokinetic studies in children.³ The target range was 580 to 950 $\mu\text{M}\cdot\text{hour}$ for methotrexate, 360 to 525 $\mu\text{M}\cdot\text{hour}$ for teniposide, and 22.5 to 60 $\mu\text{M}\cdot\text{hour}$ for cytarabine. Methotrexate clearance was estimated on the basis of the plasma concentrations at one and six hours, with the use of a two-compartment model and a Bayesian algorithm.¹⁰ If the clearance of methotrexate indicated that systemic exposure was outside the target range, the dose rate was adjusted eight hours after the start of the infusion to achieve an exposure within the target range (i.e., 800 $\mu\text{M}\cdot\text{hour}$), but the dose was not decreased to an infusion rate that would produce a steady-state plasma concentration of $<20 \mu\text{M}$ during the infusion. The minimum of 20 μM was selected because it is 25 percent above the value (16 μM) that was associated with an increased risk of relapse in our previous study,⁴ providing a margin of error for dose adjustments. Cytarabine and teniposide clearances were estimated with the use of a one-compartment pharmacokinetic model (for cytarabine) or a two-compartment model (for teniposide) and a Bayesian algorithm.^{13,14} If the clearance of either medication indicated that systemic exposure was outside the target range, the next dose given was calculated to achieve an exposure within the target range (i.e., 450 $\mu\text{M}\cdot\text{hour}$ for teniposide and 42 $\mu\text{M}\cdot\text{hour}$ for cytarabine).

The process described above was repeated for each course with all three medications. As a precaution, the maximal increase in the dose of teniposide or cytarabine was limited to 50 percent of the previous dose, with the escalation in doses continuing from one course to the next, as necessary, until systemic exposure was within the target range. For both treatment groups, if two successive courses of either teniposide plus cytarabine or high-dose methotrexate resulted in a delay of seven or more days before the resumption of treatment (because of an absolute neutrophil count of less than 300 per cubic millimeter, a platelet count of less than 50,000 per cubic millimeter, mucositis of grade 4 according to the National Cancer Institute's classification, grade 4 hepatotoxicity, or grade 3 or 4 infection), subsequent doses were decreased by 25 percent.

Assessment of Outcome and Statistical Analysis

Continuous complete remission was defined as spanning the interval from the date of complete remission to the date of the first treatment failure or the last contact with the patient. Fisher's exact test was used to evaluate correlations between subgroups of patients and base-line clinical characteristics. Distributions of event-free survival and continuous complete remission were estimated according to the method of Kaplan and Meier and compared with the stratified Mantel-Haenszel test. Correlations between continuous complete remission and time-dependent covariates were evaluated with the Cox proportional-hazards model and the Wald test. Longitudinal binary measures, such as the percentage of courses with toxic effects, were analyzed with the SAS version 6.12 macro Glimmix, which uses the Proc Mixed program in the SAS/STAT software. All reported P values are for two-sided tests.

RESULTS

Of the 188 patients enrolled in the study, 182 (97 percent) had complete remissions. Half these patients (91) were randomly assigned to conventional treatment, and the other half to individualized treatment. There were no significant differences in base-line demographic or clinical characteristics between the two groups (Table 1). Likewise, there were no significant differences in the frequency of central nervous system involvement at diagnosis (P=0.48) or in the prevalence of lymphoblasts with rearranged

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	INDIVIDUALIZED TREATMENT	CONVENTIONAL TREATMENT	P VALUE*
Age (no. of patients)			0.50
<1 yr	4	4	
1 to <10 yr	60	67	
≥ 10 yr	27	20	
Race (no. of patients)			1.0
White	82	83	
Black	9	8	
Sex (no. of patients)			0.55
Male	47	52	
Female	44	39	
Leukemia-cell lineage (no. of patients)†			1.0
B	69	74	
T	13	14	
DNA index (no. of patients)‡			0.48
<1.16	67	66	
≥ 1.16	18	23	
Leukocyte count (no. of patients)			0.88
<25,000/mm ³	60	58	
$\geq 25,000/\text{mm}^3$	31	33	
<50,000/mm ³	73	71	0.86
$\geq 50,000/\text{mm}^3$	18	20	
Leukocyte count ($\times 1000/\text{mm}^3$)			
Median	11.5	10.1	
Range	1.2-878	0.9-999	

*The P value for age was determined with the exact Pearson's chi-square test. Fisher's exact test was used for all other comparisons.

†The lineage was not determined in 12 patients.

‡The DNA index was not determined in eight patients.

TEL or MLL genes (P=0.34 and P=1.0, respectively) or t(1;19) or t(9;22) chromosomal translocations (P=0.39 and P=0.68, respectively).

For all patients, the mean rate of clearance was 103 ml per minute per square meter (coefficient of variation, 26.0 percent) for methotrexate, 14.6 ml per minute per square meter (coefficient of variation, 39.6 percent) for teniposide, and 969 ml per minute per square meter (coefficient of variation, 62.3 percent) for cytarabine. The mean rate of clearance did not differ significantly between the group assigned to conventional treatment and the group assigned to individualized treatment: methotrexate, 102 ml per minute per square meter (coefficient of variation, 27 percent) and 104 ml per minute per square meter (coefficient of variation, 26 percent); teniposide, 14.2 ml per minute per square meter (coefficient of variation, 33 percent) and 15.0 ml per minute per square meter (coefficient of variation, 44 percent); and cytarabine, 1010 ml per minute per square meter (coefficient of variation, 68 percent) and 931 ml per minute per square meter (coefficient of variation, 55 percent), respectively. For all the drugs, the median coefficient of variation in clearance was lower in individual patients than between patients: 17 percent versus 26 percent for methotrexate, 17 percent versus 40

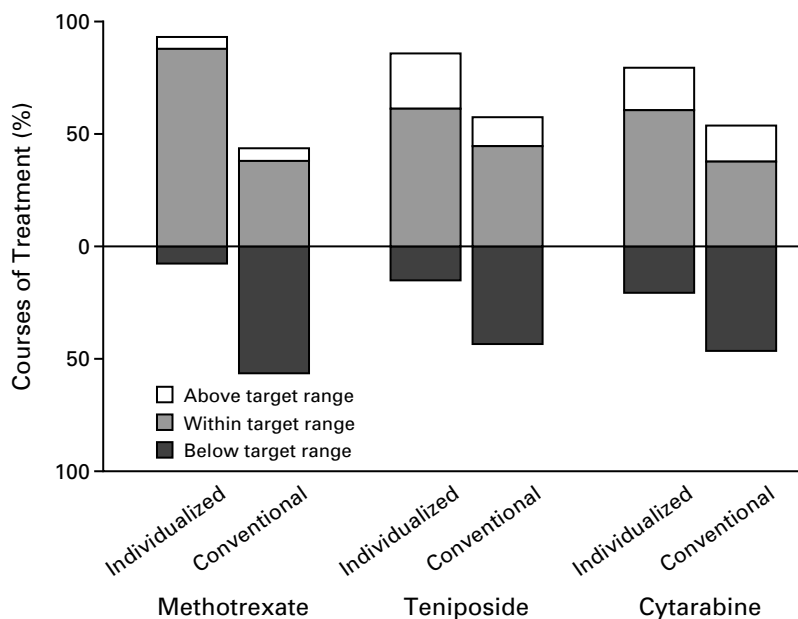


Figure 2. Percentage of Treatment Courses during Which Systemic Exposures Were below, within, or above the Target Range in the 91 Patients Receiving Individualized Doses of Methotrexate, Teniposide, and Cytarabine and the 91 Receiving Conventional Doses.

The percentage of courses during which systemic exposures were below the target range was significantly lower in patients receiving individualized therapy ($P < 0.001$ for all three medications).

percent for teniposide, and 43 percent versus 62 percent for cytarabine.

Systemic Exposure

The proportion of courses of treatment in which systemic exposures were below the target range was significantly lower in the individualized-treatment group than in the conventional-treatment group ($P < 0.001$ for each medication) (Fig. 2). In the individualized-treatment group, systemic exposure was below the target range in 7.7 percent of courses of methotrexate, 14.6 percent of courses of teniposide, and 20.7 percent of courses of cytarabine, in part because the first course of teniposide and cytarabine was not adjusted, and because the maximal increase in the dose of each drug was limited to 50 percent of the previous dose. The respective median doses in the conventional-treatment group and the individualized-treatment group were 1502 mg per square meter (5th to 95th percentile, 1418 to 1580) and 1992 mg per square meter (5th to 95th percentile, 1301 to 3088) for methotrexate, 200 mg per square meter (5th to 95th percentile, 194 to 207) and 245 mg per square meter (5th to 95th percentile, 158 to 424) for teniposide, and 300 mg per square meter (5th to 95th percentile, 290 to 306) and 375 mg per square meter (5th to 95th percentile, 221 to 752) for cytarabine. The five courses of each medi-

cation were given over a median period of 55 weeks in both treatment groups.

Toxicity

There were no differences in the number of severe toxic effects after courses of either high-dose methotrexate or teniposide plus cytarabine in the two treatment groups, with the exception that there were more grade 3 or 4 infections after courses of teniposide plus cytarabine in the individualized-treatment group (7.3 percent, vs. 3.4 percent; $P = 0.02$) (Table 2). There were no deaths from infections related to therapy in either group. The proportions of patients in whom the dose of teniposide plus cytarabine was reduced by 25 percent because of excessive toxicity were identical in the two treatment groups (7.7 percent).

Outcome

Kaplan–Meier estimates of overall and event-free survival at five years for all 188 patients, regardless of randomization, were 83 ± 3 percent and 67 ± 4 percent, respectively (Fig. 3A). The Kaplan–Meier estimate of continuous complete remission at five years was 72 ± 6 percent in the individualized-treatment group and 66 ± 6 percent in the conventional-treatment group (Fig. 3B). Because there was a significant statistical interaction between treatment and leukemia-cell lineage ($P = 0.05$), the comparison of

TABLE 2. TOXIC EFFECTS OF CHEMOTHERAPY IN THE TWO TREATMENT GROUPS.*

VARIABLE	CONVENTIONAL TREATMENT	INDIVIDUALIZED TREATMENT	P VALUE
Chemotherapy missed because of toxicity†			
No. of weeks — median (range)	7 (0–18)	7 (0–28)	
No. of days/100 days at risk — median (range)	10.6 (0–41.7)	10.6 (0–42.4)	0.78
Hospitalizations due to toxicity			
No. — median (range)	2 (0–9)	3 (0–10)	
No./100 days at risk — median (range)	1.7 (0–3.5)	1.7 (0–4.7)	0.79
Grade 3 or 4 mucositis — % of courses			
High-dose methotrexate	1.4	2.3	0.36
Teniposide plus cytarabine	0.5	0.7	0.68
Grade 4 hematologic toxicity — % of courses‡			
High-dose methotrexate	34.5	33.6	0.82
Teniposide plus cytarabine	68.7	71.5	0.46
Grade 3 or 4 infection — % of courses			
High-dose methotrexate	0.7	0.9	0.74
Teniposide plus cytarabine	3.4	7.3	0.02
Grade 3 or 4 hepatotoxicity — % of courses			
High-dose methotrexate	19.3	20.2	0.75
Teniposide plus cytarabine	3.4	4.6	0.35

*Data are based on an analysis of 431 courses of high-dose methotrexate and 425 courses of teniposide plus cytarabine in the individualized-treatment group and 415 courses of high-dose methotrexate and 415 courses of teniposide plus cytarabine in the conventional-treatment group.

†Data are expressed as the numbers of weeks when scheduled chemotherapy could not be given during the first 66 weeks of treatment and the numbers of times per 100 days at risk.

‡Grade 4 hematologic toxicity included leukopenia, neutropenia, thrombocytopenia, and anemia.

outcomes in the two groups was performed separately for patients with B-lineage leukemia (84 percent of the patients) and those with T-lineage leukemia (16 percent of the patients). In the group with B-lineage leukemia, there were 8 hematologic and 2 central nervous system relapses among the 69 patients assigned to individualized treatment, and there were 15 hematologic, 9 central nervous system, and 2 testicular relapses among the 74 patients assigned to conventional treatment. In the group with T-lineage leukemia, three hematologic and three central nervous system relapses occurred among the 13 patients who received individualized treatment, and one hematologic and four central nervous system relapses occurred among the 14 patients who received conventional treatment.

Among the patients with B-lineage leukemia, the individualized-treatment group had a significantly better outcome than the conventional-treatment group ($P=0.02$); the rates of continuous complete remission at five years were 76 ± 6 percent and 66 ± 7 percent, respectively (Fig. 4). The relative risk of a relapse in the conventional-treatment group, as compared

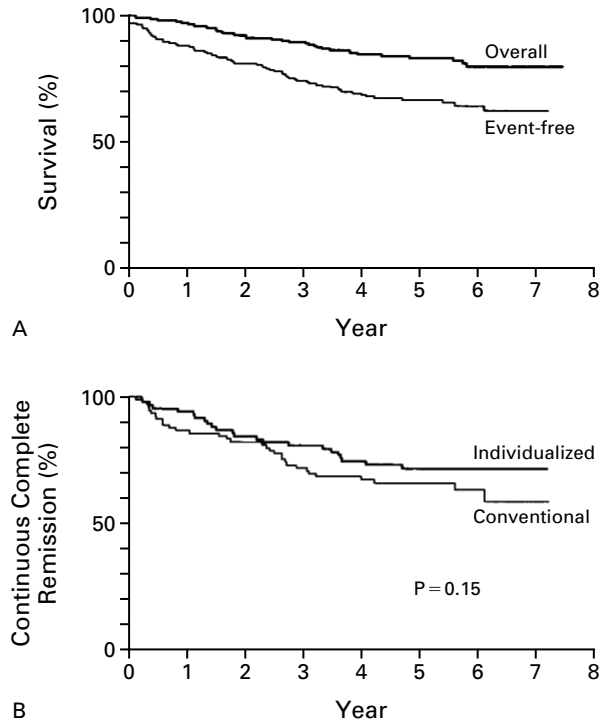


Figure 3. Kaplan–Meier Estimates of Overall and Event-free Survival among All 188 Patients Enrolled in the Study (Panel A), and Kaplan–Meier Estimates of Continuous Complete Remission among the 182 Patients Randomly Assigned to Individualized or Conventional Treatment (Panel B).

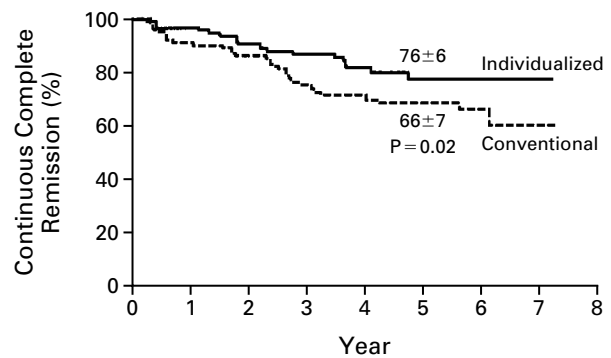


Figure 4. Kaplan–Meier Estimates of Continuous Complete Remission in Patients with B-Lineage Acute Lymphoblastic Leukemia.

The estimated rate of continuous complete remission was significantly higher in the 69 patients receiving individualized treatment than in the 74 receiving conventional treatment. The estimated (\pm SE) rate of continuous complete remission at five years is shown for both groups ($P=0.02$).

with the individualized-treatment group, was 2.0 (95 percent confidence interval, 1.08 to 3.72). In contrast, among the patients with T-lineage leukemia, there was no significant difference in outcome between the patients receiving individualized treatment and those receiving conventional treatment (rates of continuous complete remission at five years, 64 ± 14 percent and 46 ± 14 percent, respectively; $P = 0.54$), although because of the relatively small number of patients with T-lineage leukemia, the study had limited power to detect differences.

Relation of Systemic Exposure to Clinical Outcome

Cox proportional-hazards regression was used to assess the relation between systemic exposure (i.e., the time-dependent average systemic exposure for all courses and the proportion of courses with systemic exposures above the lower limit of the target range) and the duration of continuous complete remission. The probability of failure was assessed for the period during which individualized or conventional therapy was given (i.e., the first 462 days). In patients with B-lineage leukemia, the risk of a relapse during this period was significantly related to both the average systemic exposure to methotrexate ($P = 0.02$) and the proportion of courses with systemic exposures above the target threshold ($580 \mu\text{M}\cdot\text{hour}$, $P = 0.02$). With each decrease of $100 \mu\text{M}\cdot\text{hour}$ in the average systemic exposure to methotrexate, the relative risk increased by a factor of 1.79. In the group of patients with B-lineage leukemia, the risk of an early relapse among patients with no courses involving systemic exposures above the target threshold was 6.5 times the risk among patients with all courses involving exposures above the target threshold. The risk of an early relapse was not related to the average systemic exposure to teniposide or cytarabine ($P = 0.26$ and $P = 0.27$, respectively) or the proportion of courses with systemic exposures above the target threshold ($P = 0.08$ and $P = 0.40$, respectively). In the group with T-lineage leukemia, the risk of an early relapse tended to be associated with the average systemic exposure to cytarabine ($P = 0.07$) but not with systemic exposure to methotrexate ($P = 0.92$) or teniposide ($P = 0.26$).

DISCUSSION

This study demonstrates that in the treatment of childhood B-lineage acute lymphoblastic leukemia, increasing the dose of methotrexate in patients with rapid clearance of the drug significantly improves the outcome without increasing the toxicity. Several previous studies also found a relation between systemic exposure to chemotherapy and anticancer effects,¹⁵ but none of them were prospective, randomized trials designed to determine whether therapeutic interventions based on these relations could result in a better clinical outcome.

Our study indicates that conventional chemotherapy sometimes fails because patients receive inadequate doses of drugs, not because their leukemia is drug-resistant. This finding extends the results of earlier studies documenting inferior results when the intensity of chemotherapy was reduced by giving lower doses of medication.^{16,17} Our results show that lower systemic exposure due to rapid drug clearance can adversely affect the outcome in children with acute lymphoblastic leukemia. The recommended (i.e., conventional) doses of chemotherapeutic drugs are typically within the limits that essentially all patients can tolerate, regardless of the rate at which the medication is metabolized or eliminated in individual patients. For this reason, it is not surprising that such doses may be suboptimal in some patients. That the intensity of early treatment with methotrexate can significantly influence the risk of a relapse in acute lymphoblastic leukemia is consistent with a previous demonstration of a superior outcome in children treated with a single high dose of methotrexate at the time of diagnosis.¹⁸

Why did individualized therapy benefit only the children with B-lineage leukemia? It is possible that the target range of systemic exposure to methotrexate was inadequate in the patients with T-lineage leukemia. Recent studies of methotrexate accumulation in leukemic lymphoblasts have shown that T-lineage blasts accumulate active metabolites (methotrexate polyglutamates) less avidly than do B-lineage blasts but that higher doses can result in greater accumulations.¹⁹⁻²² Improvements in treating T-lineage leukemia have been attributed in part to the use of higher doses of methotrexate (5 g per square meter),²³ which produced concentrations above the target range in our study.

Our findings that individual differences in drug clearance can result in differences in efficacy and that these differences can be overcome in part by individualized therapy are not unprecedented. Other drugs with relatively narrow therapeutic indexes, such as aminoglycoside antibiotics, cyclosporine, and anti-convulsant agents, are commonly administered in individualized doses.

Our findings raise the question whether it is necessary to individualize the doses of antileukemic agents in all children with B-lineage acute lymphoblastic leukemia. We found that individualizing the dose of methotrexate was beneficial, but this approach may not apply to all antileukemic agents; there was no evidence of a benefit in individualizing the doses of teniposide and cytarabine. These results suggest that methotrexate may be the critical drug for dose adjustments in treatment regimens similar to ours. An alternative to individualizing the dose of methotrexate is to select a dose that produces adequate concentrations even in patients with rapid drug clearance (e.g., 2.5 g per square meter in patients

with B-lineage leukemia), although the potential for greater neurotoxicity may limit this strategy. In view of the low variation in drug clearance in individual patients, as compared with the variation between patients, it might be possible to use a single clearance estimate (after the first dose) to adjust the doses for all subsequent treatment courses.

It is possible that with more aggressive treatment of leukemia, optimizing the dose will be less important. However, less intensive protocols are now being evaluated for the treatment of patients who have leukemia with favorable genetic and clinical features, to prevent serious toxic effects.^{24,25} Unfortunately, even with the most sophisticated methods of risk assignment, some of these presumably lower-risk patients have relapses when treated with less intensive regimens.

It remains to be determined whether easily monitored biologic end points (e.g., the leukocyte count) can be used to identify patients who are receiving inadequate doses of antileukemic agents. Nevertheless, in patients receiving combination chemotherapy with agents that have overlapping toxic effects, measurement of drug concentrations in plasma may be the best method for determining whether appropriate doses are being used in individual patients.

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