ORIGINAL REPORT

# Improved Prognosis for Older Adolescents With Acute Lymphoblastic Leukemia

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A B S T R A C T

**Purpose**

The prognosis for older adolescents and young adults with acute lymphoblastic leukemia (ALL) has been historically much worse than that for younger patients. We reviewed the outcome of older adolescents (age 15 to 18 years) treated in four consecutive Total Therapy studies to determine if recent improved treatment extended to this high-risk group.

**Patients and Methods**

Between 1991 and 2007, 963 pediatric patients, including 89 older adolescents, were enrolled on Total Therapy studies XIIIA, XIIIB, XIV, and XV. In the first three studies, treatment selection was based on presenting clinical features and leukemic cell genetics. In study XV, the level of residual disease was used to guide treatment, which featured intensive methotrexate, glucocorticoid, vincristine, and asparaginase, as well as early triple intrathecal therapy for higher-risk ALL.

**Results**

The 89 older adolescents were significantly more likely to have T-cell ALL, the t(4;11)(MLL-AF4), and detectable minimal residual disease during or at the end of remission induction; they were less likely to have the t(12;21)(ETV6-RUNX1) compared with younger patients. In the first three studies, the 44 older adolescents had significantly poorer event-free survival and overall survival than the 403 younger patients. This gap in prognosis was abolished in study XV: event-free survival rates at 5 years were 86.4% ± 5.2% (standard error) for the 45 older adolescents and 87.4% ± 1.7% for the 453 younger patients; overall survival rates were 87.9% ± 5.1% versus 94.1% ± 1.2%, respectively.

**Conclusion**

Most older adolescents with ALL can be cured with risk-adjusted intensive chemotherapy without stem-cell transplantation.

*J Clin Oncol 29:386-391. © 2010 by American Society of Clinical Oncology*

## INTRODUCTION

Contemporary clinical trials for acute lymphoblastic leukemia (ALL) have produced 5-year survival rates of 83% to 94% for children and 27% to 54% for adults.[1-14] Specific treatment outcome data for older adolescents age 15 to 19 years are limited not only because ALL is relatively uncommon in this age group but also because such patients are treated by either adult or pediatric oncologists, depending on referral patterns. Historically, older adolescents have had a much worse prognosis than younger patients, which can be explained, at least in part, by an increased prevalence of high-risk leukemia and a poorer tolerance and adherence to therapy.[15-18] Older adolescents with ALL treated in pediatric clinical trials have consistently fared better than those enrolled on adult trials, perhaps because of the more intensive treatment and the more stringent compliance as a result of parental involvement associated with pediatric trials.[17-20] The poor treatment outcome obtained with adult regimens has led some oncologists to recommend matched-sibling allogeneic transplantation in first remission for older adolescents.[21] In this report, we show that, with effective risk-directed chemotherapy, older adolescents can achieve an excellent treatment outcome, similar to the best results reported to date for younger children with ALL.[1-3,7]

## PATIENTS AND METHODS

### Patients

Four hundred sixty-five patients (including 44 adolescents age 15 to 18 years old) with newly diagnosed childhood ALL were enrolled on the Total Therapy studies

XIIIA, XIIIB, and XIV[9] at St Jude Children's Research Hospital from 1991 to 1999, whereas 498 (including 45 older adolescents) were enrolled on the Total Therapy study XV[3] from 2000 to 2007. All protocols were approved by the institutional review boards, and study XV was registered at ClinicalTrials.gov. Signed informed consent was obtained from the parents or guardians, with assent from the patients as appropriate.

The risk classification system used in studies XIIIA, XIIIB and XIV was based on presenting clinical features and genetic abnormalities of the leukemic cells, as described previously.[9] In study XV, risk classification was based mainly on treatment response.[3] Patients with B-cell precursor disease who were between 1 and 10 years of age and who had leukocyte counts less than $50 \times 10^9$/L, DNA index $\geq$ 1.16, or the t(12;21)(ETV6-RUNX1) were provisionally classified as having low-risk ALL. Patients with the t(9;22)(BCR-ABL1) were considered to have high-risk ALL, whereas the remaining patients, including all those with T-cell ALL, were provisionally classified to have standard-risk (ie, intermediate) ALL. The final risk status was determined by the level of minimal residual disease (MRD), as measured by flow cytometry and/or the polymerase chain reaction.[22] Any patient with $\geq$ 1% bone marrow MRD on day 19 of remission induction, or 0.1% to 0.99% MRD after completion of induction therapy was considered to have standard-risk ALL. The inability to achieve morphologic remission, the presence of MRD $\geq$ 1% after completion of induction therapy, and the persistence of MRD $\geq$ 0.1% beyond week 7 of continuation treatment denoted high-risk ALL and were indications for allogeneic stem-cell transplantation.

### Treatment in Studies XIIIA, XIIIB, and XIV

Details of the treatment regimens of studies XIIIA, XIIIB, and XIV have been reported.[9] In brief, a reinduction phase was first introduced in study XIIIA; double reinductions were administered, and dexamethasone was substituted for prednisone in study XIIIB; methotrexate was given at a higher dose for two courses during consolidation therapy for patients with higher-risk leukemia in study XIV. Antimetabolites and epipodophyllotoxins (for patients with higher-risk ALL) together with glucocorticoid plus vincristine pulses formed the backbone of continuation treatment for all three studies.

### Treatment in Study XV With Remission Induction and Consolidation

After an optional 4-day treatment with methotrexate, remission-induction therapy began with prednisone, vincristine, daunorubicin, and asparaginase (Appendix Table A1, online only). Patients with $\geq$ 1% MRD on day 19 received three additional doses of asparaginase. Subsequent remission-induction therapy included cyclophosphamide, mercaptopurine, and cytarabine. On hematopoietic recovery (between days 43 and 46), consolidation therapy (Appendix Table A2, online only) with high-dose methotrexate, mercaptopurine, and triple intrathecal treatment began, and the dose of methotrexate was based on risk classification.

### Continuation Therapy

During initial continuation therapy (Appendix Table A3, online only), patients with low-risk disease received daily mercaptopurine and weekly methotrexate with pulses of mercaptopurine, dexamethasone, and vincristine. Two reinduction treatments were given between weeks 7 to 9 and weeks 17 to 19. Patients with standard-risk disease received weekly asparaginase and daily mercaptopurine with pulses of doxorubicin plus vincristine plus dexamethasone. They also received two reinduction treatments between weeks 7 to 9 and weeks 17 to 20.

For the remaining part of continuation therapy, patients with low-risk disease received mercaptopurine and methotrexate, with pulses of dexamethasone, vincristine, and mercaptopurine, and patients with standard-risk disease received three rotating drug pairs (mercaptopurine plus methotrexate, cyclophosphamide plus cytarabine, and dexamethasone plus vincristine). Dosages of mercaptopurine and methotrexate were adjusted according to tolerance, thiopurine methyltransferase phenotype, and genotypes.[3] Total scheduled dosages of anthracyclines and cyclophosphamide were limited to 110 mg/m$^2$ and 1 g/m$^2$ for patients with low-risk disease and to 230 mg/m$^2$ and 4.6 g/m$^2$ for patients with standard-risk disease. Continuation treatment lasted 120 weeks for girls and 146 weeks for boys.

### CNS-Directed Therapy

Intrathecal cytarabine was instilled after diagnostic lumbar puncture, and triple intrathecal chemotherapy was given for all subsequent treatments (Appendix Table A1). Depending on the presenting features and the CNS status, patients with low-risk disease received 13 to 18 intrathecal treatments, and patients with standard-risk disease received 16 to 25 intrathecal treatments. According to the protocol design, none of the patients received prophylactic cranial irradiation.

### Allogeneic Hematopoietic Stem-Cell Transplantation

This procedure was an option for patients with high-risk leukemia (whose early treatment was identical to that for patients with standard-risk disease). Reintensification therapy was given to maximize MRD reduction before transplantation.[3]

### Statistical Analysis

The exact $\chi^2$ and Fisher's exact tests were used to compare differences in the distribution of presenting features between the two age groups (ie, 1 to 14 years and 15 to 18 years). Event-free survival and overall survival distributions were estimated by the method of Kaplan and Meier and were compared with the Mantel-Haenszel test; 95% CIs were calculated by the method of Kalbfleisch and Prentice. The cumulative risk of adverse events was calculated by the method of Kalbfleisch and Prentice and was compared with Gray's test. Because the overall treatment results for studies XIIIA, XIIIB, and XIV were similar, patients treated in these three studies were combined for the outcome analyses.

The database frozen on July 9, 2010, was used for the analysis; 80% of survivors in the three earlier studies had been seen within the last 2 years; 92% of survivors in study XV, within the last year. The median follow-up time was 12 years (range, 8.3 to 17.7 years) for survivors treated in the three earlier studies and 5.2 years (range, 1.2 to 9.7 years) for survivors in study XV. All reported $P$ values are two sided and not adjusted for multiple tests.

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## RESULTS

### Clinical and Biologic Features

The presenting characteristics of the 945 patients (excluding 18 infants) separated by age group are listed in Table 1. As expected, the older adolescents were more likely to have standard- or high-risk leukemia, T-cell ALL, and the t(4;11)(MLL-AF4), and they were less likely to have the t(12;21)(ETV6-RUNX1).

### Early Treatment Response

In studies XIIIA, XIIIB, and XIV, older adolescents had higher MRD levels on day 19 of remission induction compared with the younger patients (Table 2). In study XV, older adolescents also had an inferior early treatment response compared with that in younger patients, as indicated by higher levels of MRD on day 19 and at the end of remission induction. Because of initial remission induction failure or MRD level $\geq$ 1% at the end of remission induction, six of the 45 older adolescents in study XV underwent allogeneic transplantation compared with 28 of 453 younger patients ($P = .11$).

### Treatment Outcome

The 44 adolescents enrolled on studies XIIIA, XIIIB, and XIV had a 5-year event-free survival rate of 59.1% (95% CI, 43% to 72%) and a 5-year overall survival rate of 59.1% (95% CI, 43% to 72%), which were strikingly inferior to the 82.6% (95% CI, 78.5% to 86%; $P < .001$) event-free survival and 88.3% (95% CI, 84.7% to 91.1%; $P < .001$) overall survival rates for the 403 younger patients enrolled on the same studies.

**Table 1.** Comparison of Clinical and Biologic Variables According to Age Group

| Variable | Age Group | | P |
| | 1-14 Years (n = 856) | 15-18 Years (n = 89) | |
| --- | --- | --- | --- |
| Risk group | | | |
| Low | 377 | 11 | < .001 |
| Standard/high | 478 | 78 | |
| NCI risk group | | | |
| B-cell precursor ALL | | | |
| Standard | 462 | 0 | < .001 |
| High | 270 | 61 | |
| T-cell ALL | | | |
| Standard | 24 | 0 | .008 |
| High | 100 | 28 | |
| Sex | | | |
| Male | 464 | 65 | < .001 |
| Female | 392 | 24 | |
| Leukocyte count | | | |
| < 10 × 10⁹/L | 385 | 46 | .10 |
| 10 to 49 × 10⁹/L | 255 | 15 | |
| 50 to 99 × 10⁹/L | 103 | 14 | |
| 100 to 300 × 10⁹/L | 76 | 11 | |
| ≥ 300 × 10⁹/L | 37 | 3 | |
| Ethnicity | | | |
| White | 607 | 68 | .61 |
| African American | 142 | 14 | |
| Hispanic | 56 | 4 | |
| Asian or other | 51 | 3 | |
| Immunophenotype | | | |
| B-cell precursor | 732 | 61 | < .001 |
| T-cell | 124 | 28 | |
| CNS status* | | | |
| CNS-1 | 581 | 60 | .91 |
| CNS-2 | 205 | 20 | |
| Traumatic with blasts | 51 | 6 | |
| CNS-3 | 19 | 3 | |
| DNA index† | | | |
| ≥ 1.16 | 205 | 16 | .24 |
| < 1.16 | 651 | 73 | |
| t(9;22)( BCR-ABL1) | | | |
| Present | 21 | 3 | .49 |
| Absent | 835 | 86 | |
| t(1;19)(TCF3-PBX1) | | | |
| Present | 45 | 3 | .61 |
| Absent | 811 | 86 | |
| t(12;21)(ETV6-RUNX1) | | | |
| Present | 181 | 3 | < .001 |
| Absent | 675 | 86 | |
| t(4;11)(MLL-AF4) | | | |
| Present | 5 | 3 | .03 |
| Absent | 851 | 86 | |

Abbreviation: NCI, National Cancer Institute.

*CNS-1, no detectable blast cells in cerebrospinal fluid sample; CNS-2, < 5 leukocytes/$\mu$L with blast cells in an atraumatic sample; CNS-3, ≥ 5 leukocytes/$\mu$L with blast cells in an atraumatic sample or the presence of a cranial nerve palsy; and traumatic lumbar puncture with blasts (≥ 10 erythrocytes/$\mu$L with blasts).

†Ratio of DNA content as measured by flow cytometry in leukemic cells versus normal diploid $G_0$/$G_1$ cells.

**Table 2.** Comparison of MRD Levels During Remission Induction Therapy According to Age Group and Study

| Variable | Age Group | | P |
| | 1-14 Years | 15-18 Years | |
| --- | --- | --- | --- |
| Studies XIIIA, XIIIB, and XIV | | | |
| Minimal residual disease on day 19, % | | | |
| < 0.01 | 72 | 6 | .05 |
| 0.01 to 0.99 | 47 | 3 | |
| 1 to 4.99 | 14 | 2 | |
| ≥ 5 | 13 | 5 | |
| Minimal residual disease on day 46, % | | | |
| < 0.01 | 121 | 11 | .25 |
| 0.01 to 0.99 | 29 | 4 | |
| 1 to 4.99 | 5 | 1 | |
| ≥ 5 | 1 | 1 | |
| Study XV | | | |
| Minimal residual disease on day 19, % | | | |
| < 0.01 | 184 | 14 | .08 |
| 0.01 to 0.99 | 174 | 18 | |
| 1 to 4.99 | 40 | 3 | |
| ≥ 5 | 45 | 10 | |
| Minimal residual disease on day 46, % | | | |
| < 0.01 | 362 | 30 | .02 |
| 0.01 to 0.99 | 66 | 11 | |
| 1 to 4.99 | 14 | 0 | |
| ≥ 5 | 6 | 3 | |

NOTE. Data missing for some patients.

In study XV, the 5-year event-free survival and overall survival estimates (± standard error [SE]) for the entire cohort of 498 patients were 87.2% ± 2.0% (95% CI, 83.7% to 90%) and 93.6% ± 1.1% (95% CI, 91% to 95.5%), respectively. Complete remission was achieved in 44 (97.8%) of the 45 older adolescents and 448 (98.9%) of the 453 younger patients (P = .44). Treatment failures among adolescents consisted of one induction failure, two hematologic relapses (one after transplantation), and three deaths from infection during postremission chemotherapy (one each during consolidation, continuation, and reinduction treatment). Forty adolescents, including the one with induction failure, remain alive in first remission 1 to 9 years from diagnosis (median, 4.3 years).

The 5-year event-free survival probabilities (± SE) for older adolescents versus younger patients in study XV were not significantly different: 86.4% ± 5.2% (95% CI, 72.1% to 93.6%) and 87.4% ± 1.7% (95% CI, 83.7% to 90.3%; P = .61; Fig 1). Although there was no significant difference in the 5-year overall survival between the two groups: 87.9% ± 5.1% (95% CI, 73.1% to 94.9%) and 94.1% ± 1.2% (95% CI, 91.4% to 96% P = .13; Fig 2), older adolescents appeared to have lower survival rate, perhaps because of their relatively high rate of toxic death. When compared with the older adolescents treated in studies XIIIA, XIIIB, and XIV, older adolescents in study XV had markedly superior event-free survival (P = .006; Appendix Fig A1, online only) and overall survival (P = .007; Appendix Fig A2, online only).

The improved prognosis for older adolescents treated in study XV was achieved without undue increases in toxicity. Cumulative rates of seizures, disseminated fungal infections, and allergic reactions
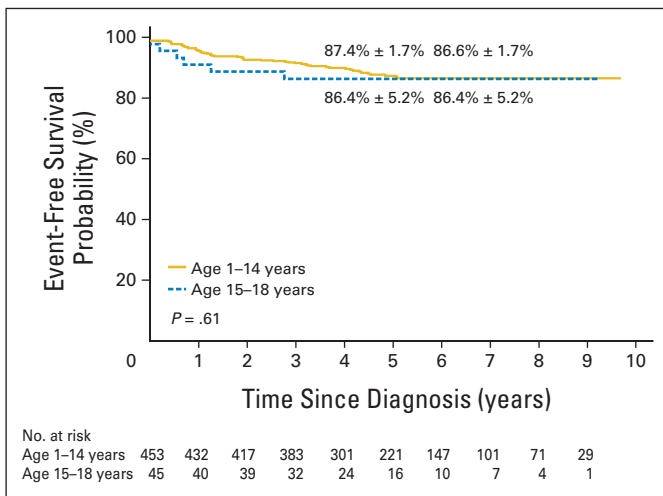
**Fig 1.** Kaplan-Meier estimates of event-free survival in study XV according to two age groups (ages 1 to 14 years and ages 15 to 18 years). Event-free survival rates at 5 and 8 years, respectively, are reported as means ± standard errors.

| Table 3. Summary of Selected Toxicities by Age Group in Study XV | | | | | |
|---|---|---|---|---|---|
| | 3-Year Cumulative Risk by Age Group | | | | |
| | 1-14 Years (n = 453) | | 15-18 Years (n = 45) | | |
| Toxicity | % | SE* | % | SE* | P |
| Seizures, grade 2, 3, or 4 | 4.6 | 1.0 | 4.4 | 3.1 | .89 |
| Severe infection, grade 4 or 5† | 3.9 | 0.9 | 11.7 | 5.0 | .03 |
| Disseminated fungal infection | 5.8 | 1.1 | 0 | 0 | .12 |
| Allergic reactions to asparaginase, grade 2, 3, or 4 | 41.9 | 2.4 | 32.8 | 7.3 | .49 |
| Osteonecrosis, grade 3 or 4‡ | 5.8 | 1.2 | 32.9 | 8.5 | < .001 |
| Thrombosis, grade 2, 3, or 4 | 6.0 | 1.1 | 23.8 | 6.7 | < .001 |
| Hyperglycemia, grade 3 or 4 | 6.6 | 1.2 | 27.7 | 6.9 | < .001 |

Abbreviation: SE, standard error.

*SE data are ± relative risk data.

†Three older adolescents died as a result of toxicity during postremission chemotherapy, whereas four toxic deaths (two during induction and two during reinduction) occurred in younger patients.

‡Eleven older adolescents and 23 younger patients developed grade 3 or 4 osteonecrosis. Six older adolescents underwent core decompression (with subsequent joint resurfacing procedure and arthroplasty in one patient and joint resurfacing procedure in another), and one each had arthroplasty and a joint resurfacing procedure. By contrast, only six patients in the younger age group underwent core decompression (with subsequent arthroplasty in two patients, and joint resurfacing procedure in one), and one had arthroplasty.

to asparaginase were similar between younger patients and older adolescents, but the latter showed higher rates of severe infection, osteonecrosis, thrombosis, and hyperglycemia (Table 3).

## DISCUSSION

The results of this study demonstrate that high cure rate, comparable to the best reported results for younger children, can be achieved for older adolescents with ALL without prophylactic cranial irradiation or routine stem-cell transplantation. The 5-year event-free survival rate of 86.4% observed in the adolescent cohort enrolled on study XV is outstanding and is superior to that of older adolescents treated in three earlier Total Therapy studies (59%) and to those enrolled on adult clinical trials (34% to 41%)[17,19,20]; the rate compares favorably to results achieved in the recent pediatric clinical trials (60% to 78%).[18-20,23,24] In fact, it surpasses those of patients with
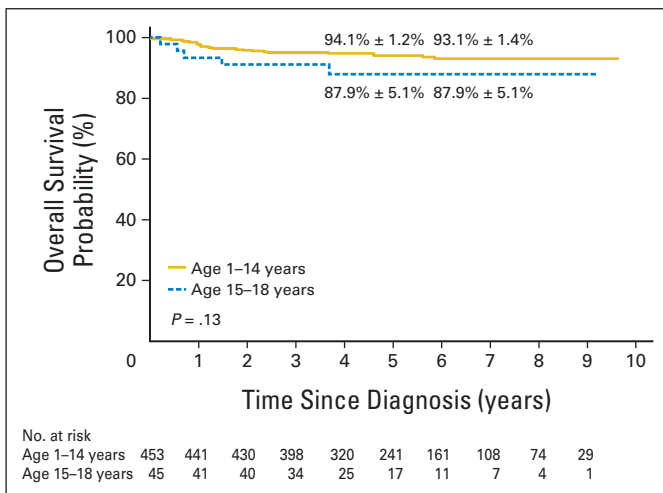


**Fig 2.** Kaplan-Meier estimates of overall survival in study XV according to two age groups (ages 1 to 14 years and ages 15 to 18 years). Survival rates at 5 and 8 years, respectively, are reported as means ± standard errors.

childhood ALL overall treated in other contemporary clinical trials (72.1% to 81.6%).[1,2,4-12] Likewise, the 5-year overall survival rate observed in our study (87.9%) compares favorably with those achieved in both adult (38% to 46%)[17,19,20] and pediatric (67% to 81%)[18-20,23,24] trials and with the rate reported recently by the US Surveillance, Epidemiology, and End Results Program for patients age 15 to 19 years of age treated between 2000 and 2004 (61.1%).[16]

Hematologic relapse developed in only two adolescents treated on study XV: one had early T-cell precursor ALL, and the other severe hypodiploid ALL (DNA index of 0.75), leukemia subtypes associated with an exceptionally poor prognosis.[25,26] It should be stressed that none of the adolescents on study XV developed CNS relapse, despite complete exclusion of prophylactic cranial irradiation from the protocol. Triple intrathecal therapy (ie, methotrexate, hydrocortisone, and cytarabine), which proved more effective than intrathecal methotrexate for CNS control,[27] was used in study XV. Intrathecal treatment was administered immediately after the diagnostic lumbar puncture and was intensified during early remission induction and continuation treatment in those with high-risk features for CNS relapse. Special precautions were taken to decrease the rate of traumatic lumbar punctures and to optimize the administration of intrathecal therapy.[3,28] Absence of cranial irradiation and limited use of anthracyclines, epipodophyllotoxins, and alkylating agents should help to reduce serious late sequelae, especially secondary cancer, and to improve the overall quality of life.

Several factors likely contributed to the improved outcome that we observed. In study XV, we used intensive dexamethasone, vincristine, and asparaginase, as well as early intrathecal therapy, treatment components which have been associated with improved outcome in adolescents and young adults with ALL.[17-20,23,24,26,29] For patients with hypersensitivity reactions to native *Escherichia coli* asparaginase, we substituted *Erwinia* asparaginase at high and frequent doses,

because an inadequate dose of this drug can lead to an inferior outcome.[30] High-dose dexamethasone was used postremission for patients with standard- or high-risk ALL, because leukemia control is positively related to the dose-intensity of corticosteroids.[31] Not surprisingly, the leukemic blast cells from our adolescent patients were significantly more resistant in vitro to dexamethasone and prednisone than those from our younger patients (data not shown). The use of high-dose dexamethasone in study XV might have overcome the relative drug resistance of adolescent ALL.

Treatment intensity in study XV was guided by risk classification that was based on MRD findings, which allowed us to precisely identify patients with a poor early treatment response who might otherwise not have been recognized by conventional morphologic bone marrow examination.[14,22] This strategy was likely beneficial to adolescent patients, who tend to have a higher prevalence of measurable MRD than younger patients. Indeed, there was a trend that a higher proportion of older adolescents than younger patients on study XV underwent transplantation for poor early response, and five of the six older adolescent patients who underwent transplantation remain alive in first remission.

Antimetabolite treatment in study XV was adjusted on the basis of pharmacodynamics of the blast cells and pharmacogenetics of the patients. This is the first St Jude Total Therapy study that included consolidation treatment with four 24-hour infusions (given every other week) of high-dose methotrexate with leucovorin rescue. We targeted doses of high-dose methotrexate individually, a strategy that improved outcome in one of our previous trials.[32] We used higher doses of high-dose methotrexate (ie, steady-state serum concentration of 65 $\mu$mol/L with an average dose of approximately 5 g/m$^2$) in T-cell and t(1;19)(*TCF3-PBX1*) ALL, because these blast cells accumulate methotrexate polyglutamates less avidly than do other cell subtypes[33] and because high-dose methotrexate (5 g/m$^2$ per dose) has improved outcome in T-cell ALL.[34] During continuation treatment, dosages of mercaptopurine and methotrexate were adjusted to the limits of tolerance, but judiciously, to avoid undue interruptions of therapy.[14,35] Because we used a relatively high-dose of mercaptopurine (75 mg/m$^2$ per day), we prospectively identified patients with inherited deficiency of thiopurine-*S*-methyltransferase, and we lowered mercaptopurine dosage accordingly to reduce the risk of acute myelosuppression and the late development of therapy-related acute myeloid leukemia.[36,37] Finally, we routinely monitored levels of thioguanine nucleotides to assess mercaptopurine treatment, and we administered methotrexate intravenously to ensure compliance.

The higher rates of severe infection, osteonecrosis, thrombosis, and hyperglycemia observed in older adolescents could be partly related to a slower clearance of dexamethasone in this age group.[38] More vigilance in supportive care could additionally improve the cure rate of older adolescents, because three deaths from infection occurred in 45 of our patients and accounted for half of the failures in this age group. By contrast, among the 453 younger patients treated in the same protocol, only four suffered from toxic deaths. Recognizing the high risk of osteonecrosis, especially in the older age group,[39] we prospectively performed bilateral hip and knee magnetic resonance imaging examinations after each of the two reinduction treatments in our patients for early detection and therapeutic interventions (eg, dose reduction or discontinuation of dexamethasone) to reduce the severity of the complication. We also gave dexamethasone on an interrupted schedule during reinduction (ie, days 1 to 8 and days 15

through 21) to reduce the risk and severity of this complication. Thus, even though we encountered a high rate of osteonecrosis in our older adolescent patients, only three of them required arthroplasty, and another five had core decompression and/or joint resurfacing procedures. Nachman et al[18] reported no statistical difference in treatment outcome between older adolescent patients with a rapid early response who were randomly assigned to receive either one or two courses of postinduction intensification therapy, a result also reported for younger patients enrolled on the same study.[40] Thus, it will be of interest to test whether dexamethasone treatment can be omitted earlier during postremission treatment without compromising clinical outcome in this age group, or perhaps it can be adjusted individually on the basis of pharmacokinetic parameters to reduce toxicity. In summary, the treatment approach used in Total Therapy study XV abolished the adverse prognostic impact of older age in childhood ALL. We suggest that this strategy be tested in young adults with ALL.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

## AUTHOR CONTRIBUTIONS

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