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ORIGINAL REPORT

Improved Survival for Children and Young Adults With T-Lineage Acute Lymphoblastic Leukemia: Results From the Children's Oncology Group AALL0434 Methotrexate Randomization

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ABSTRACT

Purpose
Early intensification with methotrexate (MTX) is a key component of acute lymphoblastic leukemia (ALL) therapy. Two different approaches to MTX intensification exist but had not been compared in T-cell ALL (T-ALL): the Children's Oncology Group (COG) escalating dose intravenous MTX without leucovorin rescue plus pegaspargase escalating dose, Capizzi-style, intravenous MTX (C-MTX) regimen and the Berlin-Frankfurt-Muenster (BFM) high-dose intravenous MTX (HDMTX) plus leucovorin rescue regimen.

Patients and Methods
COG AALL0434 included a 2 × 2 randomization that compared the COG-augmented BFM (ABFM) regimen with either C-MTX or HDMTX during the 8-week interim maintenance phase. All patients with T-ALL, except for those with low-risk features, received prophylactic (12 Gy) or therapeutic (18 Gy for CNS3) cranial irradiation during either the consolidation (C-MTX; second month of therapy) or delayed intensification (HDMTX; seventh month of therapy) phase.

Results
AALL0434 accrued 1,895 patients from 2007 to 2014. The 5-year event-free survival and overall survival rates for all eligible, evaluable patients with T-ALL were 83.8% (95% CI, 81.2% to 86.4%) and 89.5% (95% CI, 87.4% to 91.7%), respectively. The 1,031 patients with T-ALL but without CNS3 disease or testicular leukemia were randomly assigned to receive ABFM with C-MTX (n = 519) or HDMTX (n = 512). The estimated 5-year disease-free survival ($P = .005$) and overall survival ($P = .04$) rates were 91.5% (95% CI, 88.1% to 94.8%) and 93.7% (95% CI, 90.8% to 96.6%) for C-MTX and 85.3% (95% CI, 81.0%–89.5%) and 89.4% (95% CI, 85.7%–93.2%) for HDMTX. Patients assigned to C-MTX had 32 relapses, six with CNS involvement, whereas those assigned to HDMTX had 59 relapses, 23 with CNS involvement.

Conclusion
AALL0434 established that ABFM with C-MTX was superior to ABFM plus HDMTX for T-ALL in approximately 90% of patients who received CRT, with later timing for those receiving HDMTX.

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ASSOCIATED CONTENT

Appendix
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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common form of cancer in children. Approximately 15% have T-cell ALL (T-ALL), which is more common in older adolescents and African Americans.[1] Historically, T-ALL has had inferior event-free survival (EFS) and overall survival (OS) compared with precursor B-cell ALL (B-ALL).[1-4] Patients with T-ALL often present with high-risk clinical features, including older age, higher WBC count, and extramedullary disease, especially in the CNS. Compared with B-ALL, those with T-ALL frequently display slower kinetics of blast clearance after initiation of therapy.[5-9] Relapse commonly occurs during active therapy, frequently involves the CNS, and has a dismal salvage rate.[1,6,10,11]

Although treatment intensification has improved survival for children with ALL,[12] the best timing and sequence of key therapeutic interventions, such as asparaginase and methotrexate (MTX), which seem to be particularly important for T-ALL, remain unclear.[9,13-16] Two different MTX intensification strategies commonly are used in pediatric ALL trials: high-dose MTX (HDMTX) with leucovorin rescue and Capizzi-style escalating intravenous MTX without leucovorin rescue plus pegaspargase Capizzi-style, intravenous MTX (C-MTX).

We have reported previously that HDMTX is superior to C-MTX for children and adolescents with high-risk B-ALL.[17] Because disease sensitivity to MTX and pegaspargase differ between B-ALL and T-ALL,[5,14,15,18] we designed COG AALL0434, conducted in parallel with AALL0232, to compare C-MTX and HDMTX in T-ALL. AALL0434 was a 2 × 2 pseudofactorial trial with a second randomized question that tested the addition of six 5-day cycles of nelarabine. Because of concerns about high rates of CNS relapse in T-ALL, approximately 90% of patients received presymptomatic cranial radiation therapy (CRT) given during consolidation (month 2 of therapy) in the C-MTX regimen or during delayed intensification (DI; month 7 of therapy) for those who received HDMTX.[19-21] We report the results of the AALL0434 MTX randomization. The results of the nelarabine randomization will be reported separately.

PATIENTS AND METHODS

Patient Characteristics

COG AALL0434 enrolled participants from January 2007 to July 2014. Eligibility included newly diagnosed, untreated (except corticosteroids) patients with T-ALL ages 1 to 31 years. AALL0434 was amended in 2010 to include those with lymphoblastic lymphoma (T-LLy). This report is limited to patients with T-ALL because those with T-LLy did not participate in the MTX randomization study. Enrollment in the COG classification/biology studies AALL03B1 or AALL08B1 was required for study entry. Minimal residual disease (MRD) testing was performed at the University of Washington (B.L.W.) using established methodologies.[22] Before receiving systemic therapy, CSF was obtained for stratification into CNS1 (no blasts in the CSF), CNS2 (CSF WBC $< 5/\mu L$ with blasts), and CNS3 (CSF WBC $\geq 5/\mu L$ with blasts or clinical symptoms of cranial nerve palsies, brain/eye involvement, or hypothalamic syndrome).[17] Adjustments for CSF red cell contamination were determined using the Steinherz/Bleyer algorithm.[23] AALL0434 was approved by the National Cancer Institute, Food and Drug Administration, the pediatric central institutional review board, and institutional review boards at each participating center. Informed consent/assent was obtained from study participants and, when appropriate, their legal guardians, in accordance with the Declaration of Helsinki.

Treatment

AALL0434 used a COG-augmented Berlin-Frankfurt-Muenster (ABFM) regimen to compare the efficacies of HDMTX versus C-MTX with or without nelarabine in a 2 × 2 pseudofactorial design[16,17] (Appendix Fig A1, online only). After receiving a 28-day, prednisone-based, four-drug induction (Appendix Table A1, online only), patients with T-ALL were classified into low-risk (LR), intermediate-risk (IR), and high-risk (HR) groups or as those who experienced induction failure.[16] Patients with LR T-ALL were ages 1 to 9.99 years with an initial WBC $\leq 50{,}000/\mu L$, CNS1 status, and no testicular leukemia (males), rapid early responders (RERs) with an M1 marrow (< 5% blasts) by induction day 15, and < 0.1% day 29 MRD. Slow early responders (SERs) had an M2/M3 marrow at induction day 15 or ≥ 0.1% to 1% day 29 MRD. Patients with HR T-ALL had a day 29 M2 marrow (5% to 25% blasts) or MRD levels ≥ 1%. All other patients were classified as IR (Appendix Table A2, online only). All except the LR patients were assigned to receive CRT (12 Gy for CNS1/CNS2 and 18 Gy for CNS3).

AALL0434 used two consents, one for induction and a second for the postinduction random assignments among arms A (C-MTX/without nelarabine), B (C-MTX/nelarabine), C (HDMTX/without nelarabine), and D (HDMTX/nelarabine). After induction, all patients received an ABFM consolidation phase (with or without nelarabine), with CRT delivered during this phase for those assigned to the C-MTX arm[16] (Appendix Table A2). During the 8-week interim maintenance (IM) phase, patients received either C-MTX with escalating intravenous MTX without leucovorin plus two doses of pegaspargase or HDMTX with leucovorin rescue without pegaspargase.[17] The IM phases also included vincristine (VCR; four with HDMTX, five with C-MTX), intrathecal MTX (two for both), and oral 6-mercaptopurine (6-MP; days 1 to 56 with HDMTX only).

After completion of IM, patients received a single DI) phase, with CRT given during the second half of DI to those assigned to HDMTX. Patients then received maintenance therapy until 2 (females) or 3 (males) years after the start of IM.

The CNS3 patients were nonrandomly assigned to receive HDMTX and 1.8 Gy CRT given during DI. All boys with persistent testicular leukemia after day 29 received 2.4 Gy of testicular radiation during consolidation and were nonrandomly assigned to receive HDMTX. Participants who received corticosteroid pretreatment for > 48 hours before diagnosis were excluded from the LR cohort. Participants with a prior seizure disorder that required anticonvulsant therapy were randomly assigned between the MTX arms but excluded from the nelarabine randomization.[24] Treatment-related adverse events were graded using Common Terminology Criteria for Adverse Events (version 4). Patients with Down syndrome or the Philadelphia chromosome were ineligible. No participants were assigned treatment on the basis of cytogenetics,[25] genomic alterations,[26-31] or the early T-precursor phenotype.[32,33]

Statistical Analysis

EFS was defined as time from study enrollment (first consent) to first event (induction failure, induction death, relapse, second malignant neoplasm, remission death) or date of last contact for those who were event free. Disease-free survival (DFS) was defined as time from postinduction random assignment (second consent) to first event or date of last contact. OS was defined as time from study enrollment or from postinduction random assignment, as appropriate, to death or date of last of contact.

Using a two-sided α of 5%, there was 85.3% power to detect an improvement in 4-year DFS from 82% to 89% between the two randomized MTX regimens, with a total of 980 patients accrued over the life of the study (total expected events, 142), with a minimum follow-up of 3 years. Study accrual duration was driven by the time needed to meet accrual targets for the nelarabine randomization. Interim analyses for efficacy and futility occurred when approximately 20%, 40%, 60%, 80%, and 100% of the expected events were observed. An alpha - t^2 spending function with truncation at 3 standard deviations was used for interim monitoring.

Data current as of March 31, 2017, are included in this report. Survival rates were estimated by using the Kaplan-Meier method with standard errors of Peto et al.[34] Survival rates and hazard ratios are presented with 95% CIs. Because the study was designed for the comparison of the randomized arms (C-MTX *v* HDMTX), no adjustments were made for multiple comparisons among participant subsets. Two-sided log-rank tests were used for comparison of survival curves. Proportions were compared between groups using a χ^2 or Fisher's exact test. Cumulative incidence rates were computed using the cumulative incidence function for

competing risks, and comparisons were made using the *K*-sample test.[35] $P < .05$ was considered significant for all comparisons. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). Graphics were generated with R version 2.13.1 (http://www.r-project.org).

RESULTS

Participants

AALL0434 enrolled 1,895 patients; 47 were ineligible (19 because of timing of therapy initiation, 11 for incorrect disease type, seven for inaccurate disease staging, and 10 for other reasons), four were inevaluable (one for a nonstudy drug shortage and three for lack of baseline MRD testing), and 282 had T-LLy. The remaining 1,562 patients with T-ALL were eligible and evaluable for induction therapy (Fig 1). At the second consent stage, 17 participants with T-ALL were inevaluable for postinduction therapy, and 356 with T-ALL (23%) came off the study almost universally because the physician or patient did not wish to participate in the randomization. The remaining 1,189 eligible, evaluable participants with T-ALL were risk classified at the end of induction as LR (n = 109 [9.2%]), IR (n = 808 [68.0%]), HR (n = 229 [19.2%]), and induction failure (n = 43 [3.6%]; Appendix Table A2). Among the randomly assigned participants, 10.6% were LR, 68.6% were IR, and 20.8% were HR. A total of 519 participants were randomly assigned to receive C-MTX, and 512 to receive HDMTX, with the randomization stratified by risk group.

Patient age ranged from 1 to 30 years, with 52.2% 1 to 9 years of age, 44.9% 10 to 20 years of age, and 2.9% 21 to 30 years of age. Adolescents and young adults ages 15 to 30 years comprised 20.7% of the study population. Seventy-four percent were male and 26% were female. African American enrollment was 13.5%, and Hispanic enrollment was 14.4%. At study entry, 72.8% of participants were classified as CNS1 and 19.7% as CNS2; all participants with CNS3 (7.5%) were nonrandomly assigned to HDMTX (Table 1).

Outcomes of the MTX Randomization

Among the 1,844 eligible and evaluable participants, 40 experienced death as a first event (seven died during induction and 33

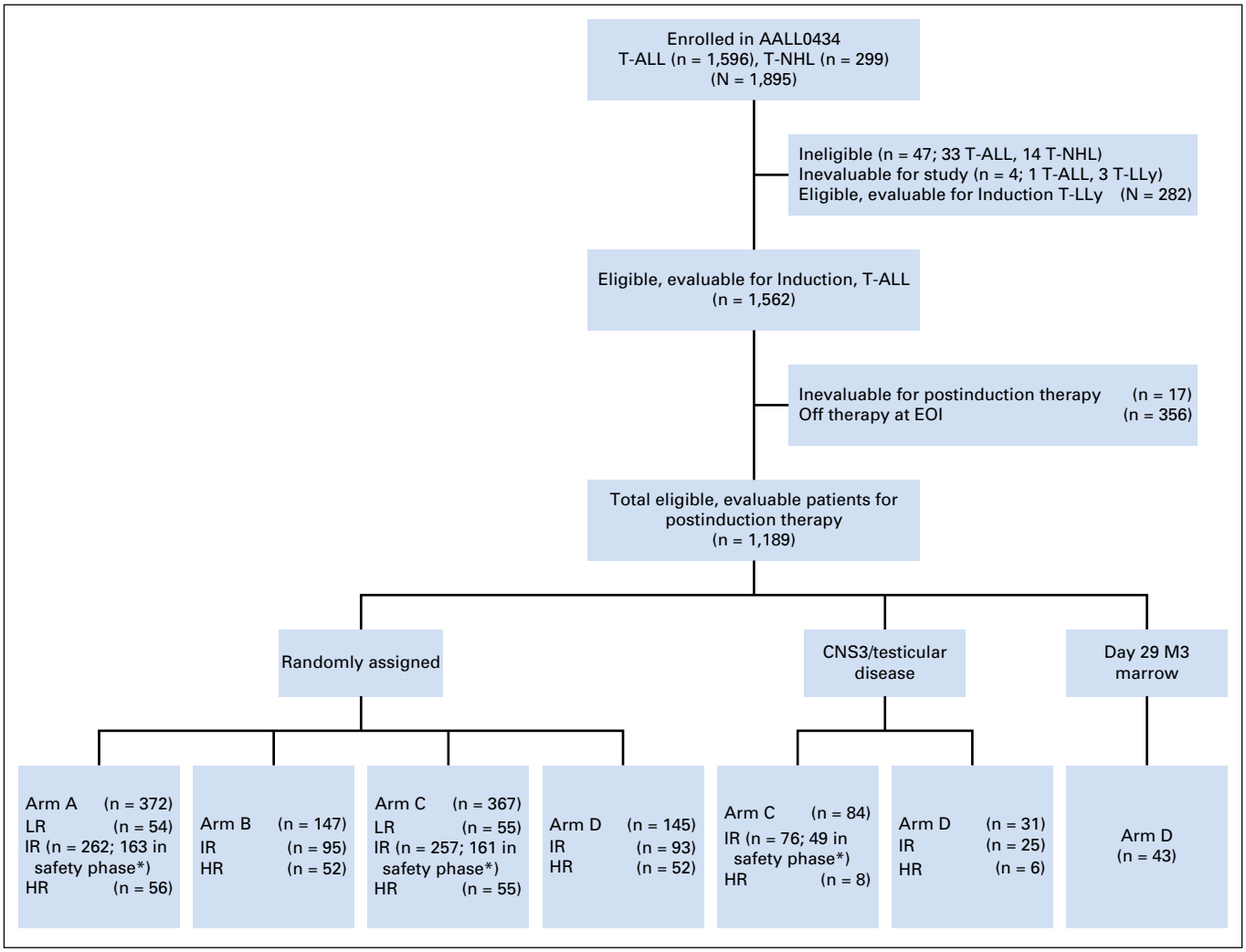

Fig 1. CONSORT diagram for risk-stratified therapy. (*) Includes IR patients not randomly assigned to receive nelarabine during the safety phase (assigned to arms A and C only). EOI, end of induction; HR, high risk; IR, intermediate risk; LR, low risk; T-ALL, T-cell acute lymphoblastic leukemia; T-LLy, T-cell non-Hodgkin lymphoma.

Table 1. Participant Characteristics by Random Assignment

Characteristic	C-MTX, No. (%)	HDMTX, No. (%)
Age, years		
< 10	280 (54.0)	291 (57.0)
≥ 10	239 (46.0)	221 (43.0)
Sex		
Male	396 (76.0)	386 (75.4)
Female	123 (24.0)	126 (24.6)
WBC × 1,000/μL		
< 50	233 (44.9)	215 (42.0)
≥ 50	286 (55.1)	297 (58.0)
CNS		
CNS1	398 (77.3)	411(81.0)
CNS2	117 (22.7)	97 (19.0)
CNS3*	—	—
Race		
American Indian or Alaska native	1 (0.2)	1 (0.2)
Asian	22 (4.2)	29 (5.6)
Native Hawaiian or Other Pacific Islander	4 (0.8)	4 (0.8)
Black or African American	69 (13.3)	65 (12.7)
White	377 (72.6)	352 (68.8)
Unknown	46 (8.9)	61 (11.9)
Ethnicity		
Hispanic or Latino	80 (15.4)	72 (14.1)
Not Hispanic or Latino	423 (81.5)	417 (81.4)
Unknown	16 (3.1)	23 (4.5)
Marrow induction day 29		
M1	507 (98.0)	496 (96.9)
M2	12 (2.0)	16 (3.1)
M3†	—	—
MRD induction day 29		
MRD < 0.01%	299 (57.6)	308 (60.2)
0.01% ≤ MRD < 0.1%	32 (6.2)	33 (6.4)
0.1% ≤ MRD < 1.0%	79 (15.2)	64 (12.5)
1.0% ≤ MRD < 10.0%	87 (16.8)	83 (16.2)
MRD ≥ 10%	21 (4.0)	23 (4.5)
Indeterminate	1 (0.2)	1 (0.2)

Abbreviations: C-MTX, Capizzi-style escalating intravenous methotrexate; HDMTX, high-dose methotrexate; MRD, minimal residual disease.
*CNS3 and testes positive: Participants were nonrandomly assigned to HDMTX.
†M3: Participants for whom induction failed were nonrandomly assigned to arm D.

during remission). The 5-year EFS and OS rates for all eligible, evaluable participants with T-ALL were 83.8% (81.2% to 86.4%) and 89.5% (87.4% to 91.7%), respectively (Fig 2A). For the 1,031 participants with T-ALL who participated in the MTX randomization, the 5-year DFS rate was 88.4% (85.7% to 91.1%), and the OS rate was 91.6% (89.2% to 94.0%). At the time of interim monitoring in April 2015, a predetermined efficacy monitoring boundary was crossed, with estimated 4-year DFS rates of 92.5% (89.0% to 96.0%) for C-MTX and 86.1% (81.4% to 90.8%) for HDMTX (P = .017). Because all participants who were randomly assigned to receive HDMTX had completed IM when the monitoring boundary was met, no alterations were made to therapy. At the time of final analyses, the estimated 5-year DFS (hazard ratio, 0.595; P = .005) and OS (hazard ratio, 0.632; P = .036) rates were 91.5% (88.1% to 94.8%) and 93.7% (90.8% to 96.6%) for C-MTX and 85.3% (81.0% to 89.5%) and 89.4% (85.7% to 93.2%) for HDMTX (Figs 2B and 2C). No significant qualitative interaction was found between the MTX and nelarabine randomizations (P = .41). For participants assigned to receive HDMTX for CNS3 or testicular disease, the 5-year DFS rate was 76.7% (65.1% to 88.4%) and 89.5% (70.5% to 100%), and the OS rate was 85.4% (75.9% to 94.9%) and 89.2% (70.0% to 100%).

Patterns of Treatment Failure

Approximately 90% of AALL0434 participants with T-ALL in the MTX randomization received 12 Gy prophylactic CRT for CNS1 or CNS2 disease. CRT was administered at week 8 (consolidation) in the C-MTX arm versus week 26 (DI) in the HDMTX arm. A total of 122 events (Table 2) occurred in the randomized T-ALL cohort, including 12 second malignant neoplasms (seven in C-MTX; five in HDMTX; P = .58; Tables 2 and 3) and 19 deaths in remission (eight in C-MTX; 11 in HDMTX; P = .47). There were 91 relapses (32 in C-MTX [six that involved the CNS] and 59 in HDMTX [23 that involved the CNS]). The 5-year cumulative incidence rates of isolated marrow relapse (2.2% [0.8% to 3.6%] for C-MTX *v* 5.9% [3.7% to 8.1%] for HDMTX; P = .005) and isolated CNS relapse (0.4% [0% to 1.0%] for C-MTX *v* 3.0% [1.4% to 4.6%] for HDMTX; P = .001) were significantly higher in those assigned to HDMTX who experienced more relapses (Appendix Table A3, online only; Appendix Figs A2A to A2C, online only).

Outcomes Defined by Risk Groups and Early Response

For participants with LR T-ALL, the 5-year DFS rate was 92.6% (83.3% to 100%) for C-MTX versus 96.2% (88.2% to 100%) for HDMTX (P = .27), and the OS rate was 94.4% (86.2% to 100%) versus 98.1% (92.3% to 100%; P = .34; Fig 3). For IR patients, the 5-year DFS rate was 92.5% (88.7% to 96.3%) for C-MTX versus 88.3% (83.7% to 92.9%) for HDMTX (P = .04), and the OS rate was 94.6% (91.2% to 97.9%) versus 91.3% (87.2% to 95.3%; P = .23). For HR patients, the 5-year DFS rate was 87.4% (78.8% to 96.0%) for C-MTX versus 70.0% (57.9% to 82.0%) for HDMTX (P = .01), and the OS rate was 90.5% (82.8% to 98.2%) versus 79.1% (68.3% to 89.9%; P = .02). Similar comparisons were made for all participant RER/SERs (Appendix Figs A3A and A3B, online only). Compared with LR and IR patients, those with HR or who are SERs had relatively greater improvements in DFS and OS with C-MTX therapy.

Toxicities During the IM Phase

No clinically significant differences were found between C-MTX and HDMTX with respect to grade 3 and 4 febrile neutropenia, seizures, and peripheral motor and sensory neuropathies. The C-MTX regimen included two additional doses of pegaspargase during the IM phase, which did not result in significant differences in the occurrence of grade 3 and 4 clotting/coagulation events, pancreatitis (five with C-MTX, none with HDMTX; P = .062), allergic reactions, or anaphylaxis (Appendix Table A4, online only).

DISCUSSION

To our knowledge, COG AALL0434 is the largest trial of T-ALL ever conducted. It showed a 5-year EFS rate of 83.8% and OS rate

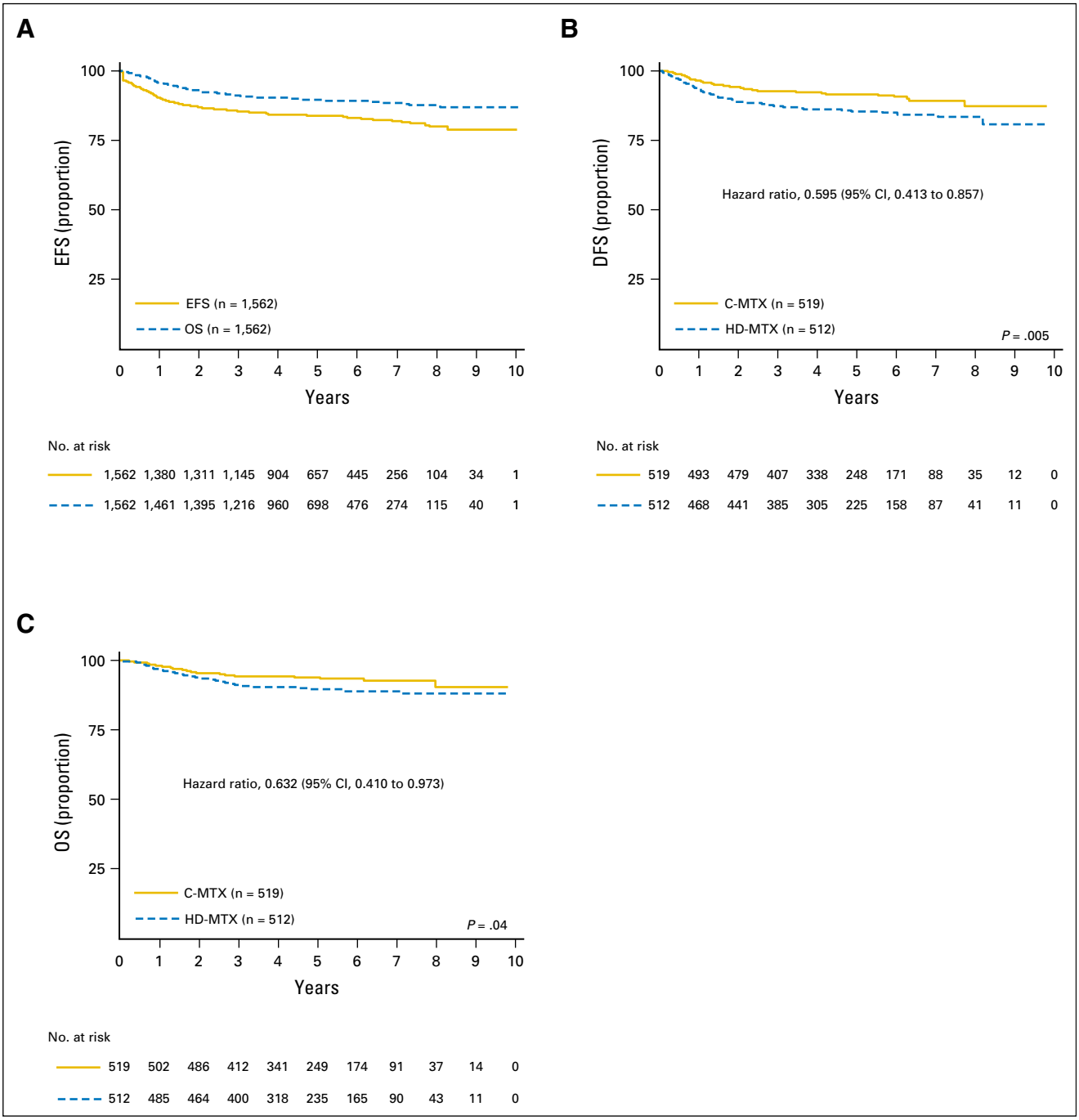

Fig 2. Event-free survival (EFS), disease-free survival (DFS), and overall survival (OS) curves overall and by regimen. (A) EFS and OS curves for all patients with T-cell acute lymphoblastic leukemia; 5-year EFS and OS rates were 83.8% (81.2% to 86.4%) and 89.5% (87.4% to 91.7%), respectively. (B) DFS curves for Capizzi-style escalating intravenous methotrexate (C-MTX) versus high-dose methotrexate (HDMTX) randomly assigned cohorts; 5-year DFS rate was 91.5% (88.1% to 94.8%) for C-MTX and 85.3% (81.0% to 89.5%) for HDMTX. (C) OS curves for C-MTX versus HDMTX randomly assigned cohorts; 5-year OS was 93.7% (90.8% to 96.6%) for C-MTX and 89.4% (85.7% to 93.2%) for HDMTX.

Table 2. DFS Event Summary by Randomized Regimen

DFS Event	Randomized Regimen		
	C-MTX	HDMTX	*P**
None	472	437	
Relapse			
Isolated marrow	11	28	.01
Isolated CNS	2	15	.00
Marrow + CNS	4	8	.24
Marrow + other	4	3	.72
Other	11	5	.14
Second malignant neoplasm	7	5	.58
Remission death	8	11	.47
Total	519	512	

Abbreviations: C-MTX, Capizzi-style escalating intravenous methotrexate; DFS, disease-free survival; HDMTX, high-dose methotrexate.
*χ^2 test.

of 89.5% among eligible, evaluable participants. In comparison, the 5-year OS rate for T-ALL was 80.7% in COG trials conducted from 1995 to 1999 (n = 624) and 81.6% (n = 429) in 2000 to 2005.[1] The AIEOP-BFM-ALL-2000 trial included 464 patients with T-ALL enrolled from 2000 to 2006 who had 5-year EFS and OS rates of 76.3% and 81.2%, respectively.[5] The outcomes (EFS and OS) for T-ALL in AALL0434 were better than those observed in past trials.

Although MTX has long been recognized for its importance in the treatment of ALL, questions about its dose and integration into multiagent therapy have merited continued investigation.[17,36,37] On the basis of improved outcomes with C-MTX in B- and T-ALL study CCG 1961 (1996 to 2002) and with HDMTX in T-ALL study 9404 (1996 to 2001), the COG tested whether C-MTX versus HDMTX differentially affected outcomes for HR B-ALL (AALL0232) and T-ALL (AALL0434) when given during the IM phase.[16,17] In AALL0232, we found that HDMTX was superior to C-MTX in patients with HR B-ALL, with a significantly better 5-year EFS rate (79.6% [76.5% to 82.7%] *v* 75.2% [71.9% to 78.5%]; *P* = .008) and OS rate (88.9% [86.5% to 91.3%] *v* 86.1% [83.4% to 88.8%]; *P* = 0.025) because of reductions in both marrow and CNS relapse.[16] Of note, AALL0434 showed the opposite effect, with the C-MTX regimen being superior to HDMTX with a significantly higher 5-year DFS rate (91.5% [88.1% to 94.8%] *v* 85.3% [81.0% to 89.5%]; *P* = .005) and OS rate (93.7% [90.8% to 96.6%] *v* 89.4% [85.7% to 93.2%]; *P* = .036), also because of reductions in both marrow and CNS relapse. How can these findings be reconciled?

Table 3. Occurrence of Second Malignant Neoplasms Among Randomly Assigned Participants

Disease Subtype	C-MTX (arms A and B)	HDMTX (arms C and D)
Acute myelogenous leukemia	2	1
Myelodysplastic syndrome	1	0
Lymphoproliferative disorder	0	1
Sarcoma, unspecified	1	1
Carcinoma	1	0
LCH/histiocytosis	2	0
Brain tumor	0	1

Abbreviations: C-MTX, Capizzi-style escalating intravenous methotrexate; HDMTX, high-dose methotrexate; LCH, Langerhans cell histiocytosis.

Like AALL0232, AALL0434 was not a strict comparison of two different MTX schedules because the doses of pegaspargase, 6-MP, and VCR and the timing of CRT differed between the two ABFM arms during the 2-month IM phase. Use of ABFM therapy, with additional doses of VCR and no leucovorin rescue with C-MTX showed similar DFS and OS rates for LR (no CRT) and IR (CRT) participants. However, similar to other studies,[5] SERs and participants with HR T-ALL had more relapses but with better OS with C-MTX than with HDMTX, where postinduction therapy had its greatest effect for those who historically experienced relapse more often than lesser-risk participants. The health care costs and time burden associated with C-MTX are substantially less than for HDMTX,[38] which may have affected adherence in some participants.

Leukemic involvement of the CNS is a common problem in T-ALL either at presentation or at relapse.[11] The preceding phase III COG T-ALL trials took different approaches to CRT. In POG 9904, all patients received CRT at week 30.[15] In CCG 1961, only patients with CNS3 status or an SER on the basis of an M3 marrow on induction day 8 received CRT, which was delivered during the first 2 weeks of consolidation therapy.[15,39] Because 35% to 40% of T-ALL relapses in CCG 1961 involved the CNS, AALL0434 was designed to include CRT for all IR and HR patients, who comprised approximately 90% of participants. Because the C-MTX regimen was the same as that used in the ABFM arm of CCG 1961, CRT was delivered during the second month of therapy during consolidation. In contrast, CRT delivered in the HDMTX arm was given during DI in the seventh month, similar to AEIOP-BFM-2000, not only to preserve the timing of CRT administration in POG 9404 but also to reduce the risk of neurotoxicities when CRT is given before HDMTX. In the AALL0434 C-MTX cohort, fewer CNS, marrow, or mixed relapse events were observed. Because T cells traffic between medullary and sanctuary sites, prophylactic CRT may have prevented both local and systemic relapses when given during consolidation.[40,41] The differential timing of CRT between the study arms of AALL0434 possibly affected the observed differences in EFS and OS.

The C-MTX arm included two additional doses of pegaspargase (seven total, two during IM) compared with the HDMTX arm (five total, none during IM). Although pegaspargase does not cross the blood-brain barrier, its asparagine-depleting effects equilibrate across the blood-brain barrier.[42,43] AALL0434 was unique among contemporary frontline COG ALL studies because *Erwinia* asparaginase was commonly available for the approximately 15% of participants who developed grade 3 (or higher) hypersensitivity reactions to pegaspargase.[44,45] Enhanced asparagine depletion with C-MTX also may have prevented relapse events, including those that involve the CNS.

Although the AALL0434 C-MTX regimen was superior to the HDMTX regimen for treating pediatric T-ALL, this finding is in the context of approximately 90% of randomly assigned patients who received CRT. Because CRT is associated with secondary

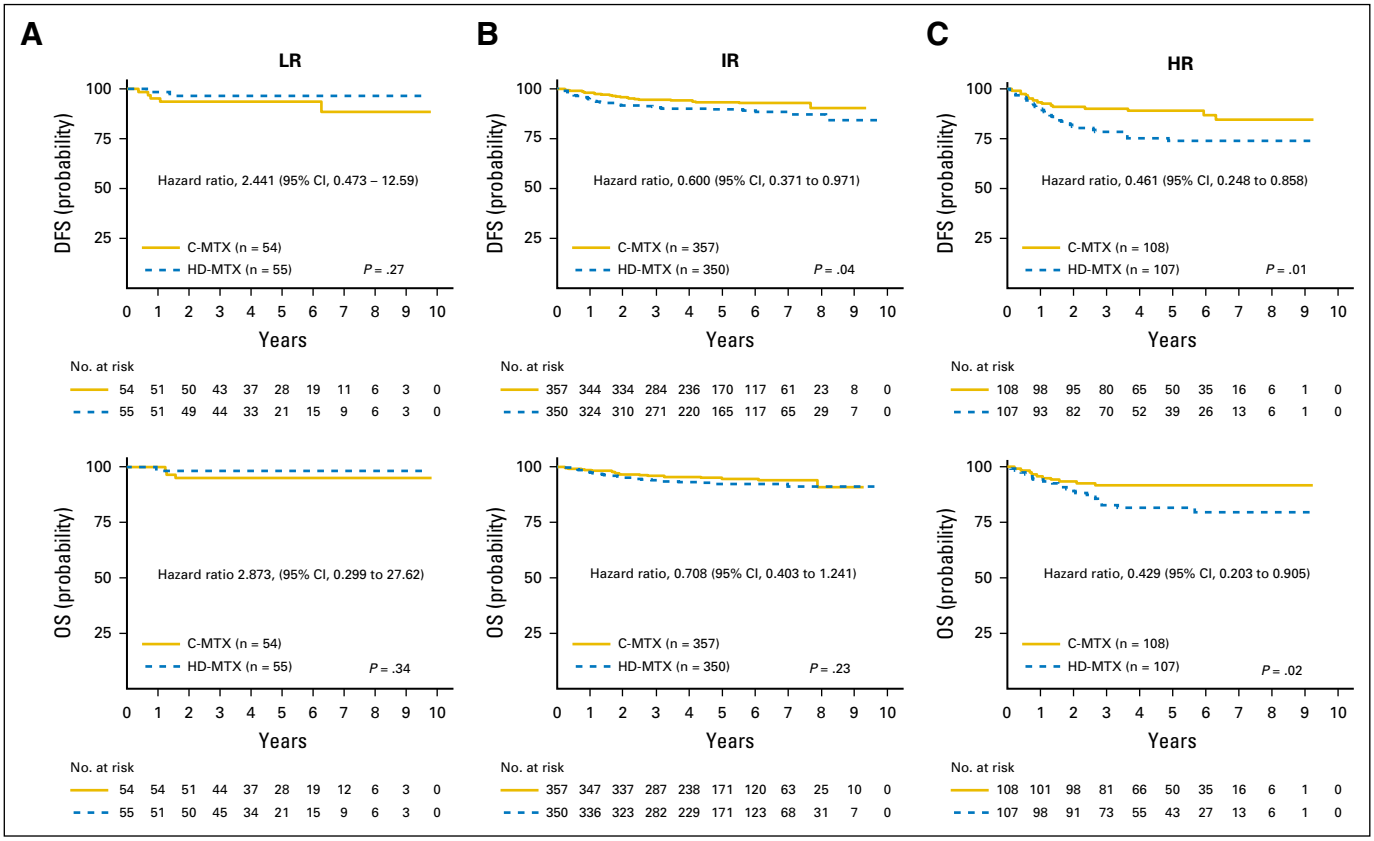

Fig 3. Disease-free survival (DFS) and overall survival (OS) for low-risk (LR), intermediate-risk (IR), and high-risk (HR) groups by regimen. (A) LR T-cell acute lymphoblastic leukemia (T-ALL): 5-year DFS rate was 92.6% (83.3% to 100%) for Capizzi-style escalating intravenous methotrexate (C-MTX) versus 96.2% (88.2% to 100%) for high-dose methotrexate (HDMTX), and the OS rate was 94.4% (86.2% to 100%) for C-MTX versus 98.1% (92.3% to 100%) for HDMTX. (B) IR T-ALL: 5-year DFS rate was 92.5% (88.7% to 96.3%) for C-MTX versus 88.3% (83.7% to 92.9%) for HDMTX, and the OS rate was 94.6% (91.2% to 97.9%) for C-MTX versus 91.3% (87.2% to 95.3%) for HDMTX. (C) HR T-ALL: 5-year DFS rate was 87.4% (78.8% to 96.0%) for C-MTX versus 70.0% (57.9% to 82.0%) for HDMTX, and the OS rate was 90.5% (82.8% to 98.2%) for C-MTX versus 79.1% (68.3% to 89.9%) for HDMTX.

malignancies,[46] cognitive impairment,[47] and other long-term health issues,[48,49] many groups have evaluated alternate strategies for controlling CNS disease.

Either singly or in combination, others either replaced or reduced CRT with dose-intensified pegaspargase,[14,50] HDMTX,[5,51] dexamethasone during induction,[51,52] triple intrathecal therapies,[53,54] and first remission hematopoietic cell transplantation for MRD-defined HR patients.[53] Whether similar differences between C-MTX and HDMTX would be seen if patients did not receive CRT is not known.

Data from previous COG studies have shown that National Cancer Institute risk status, recurring cytogenetic features, and other traditional prognostic factors in B-ALL have limited value in T-ALL,[13-15] but results from the I-BFM-SG MRD[6] and AEIOP-BFM-2000[5] studies have shown that end-induction and end-consolidation MRD levels could portend risk for relapse. Although cytogenetic and phenotypic findings in T-ALL have not been useful for treatment assignment, these and other biomarkers, in combination with MRD, may better risk stratify HR disease, as demonstrated in the FRALLE2000T study.[12,55] The improved survival rates observed for COG AALL0434 may better position us to include biomarkers with MRD to further improve survival in future trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Improved Survival for Children and Young Adults With T-Lineage Acute Lymphoblastic Leukemia: Results From the Children's Oncology Group AALL0434 Methotrexate Randomization

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Appendix

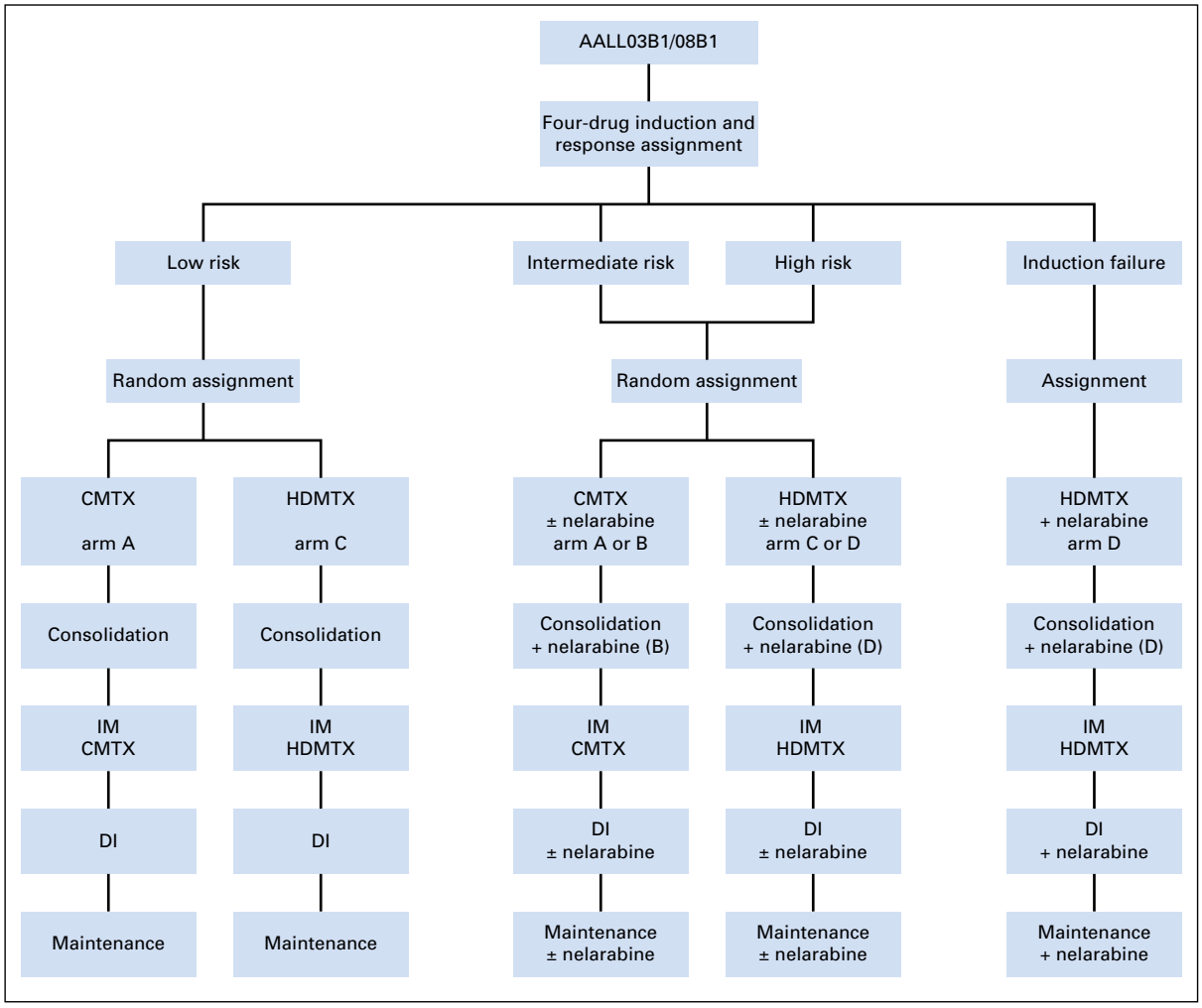

Fig A1. Randomization and assignment strategies. (*) Participants with CNS3 and testicular disease were nonrandomly assigned to high-dose methotrexate (HDMTX). C-MTX, Capizzi-style escalating intravenous methotrexate; DI, delayed intensification.

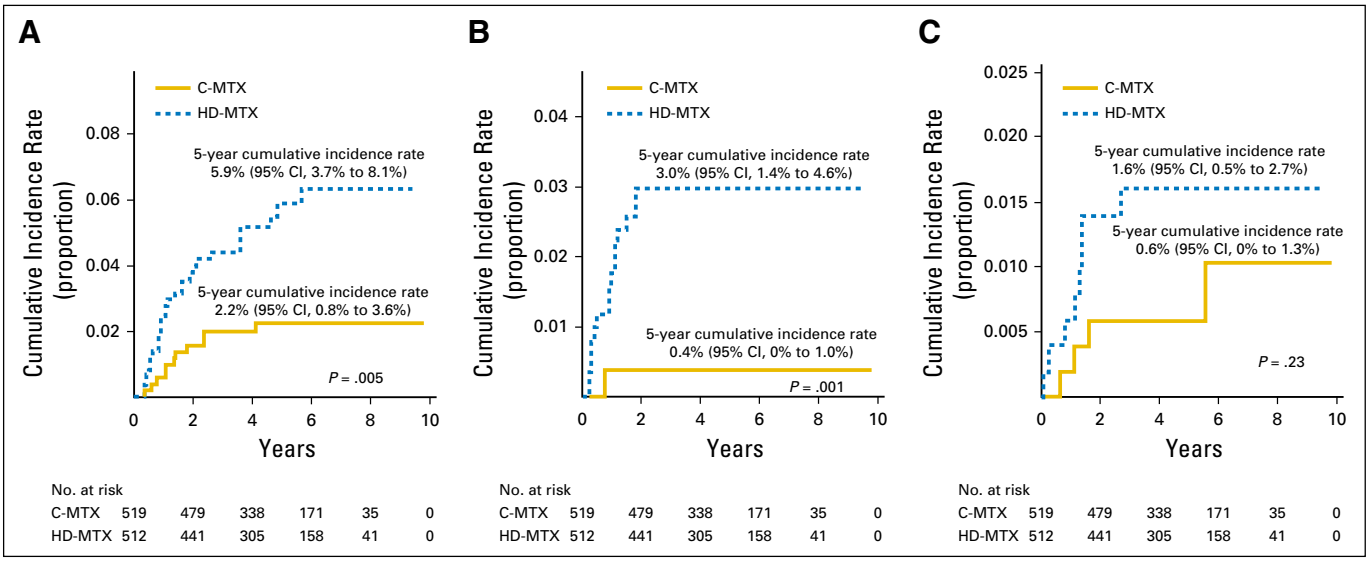

Fig A2. Cumulative incidence rate of relapse by site for Capizzi-style escalating intravenous methotrexate (C-MTX) and high-dose methotrexate (HDMTX) randomly assigned cohorts. (A) Isolated bone marrow relapse. (B) Isolated CNS relapse. (C) Combined bone marrow and CNS relapse.

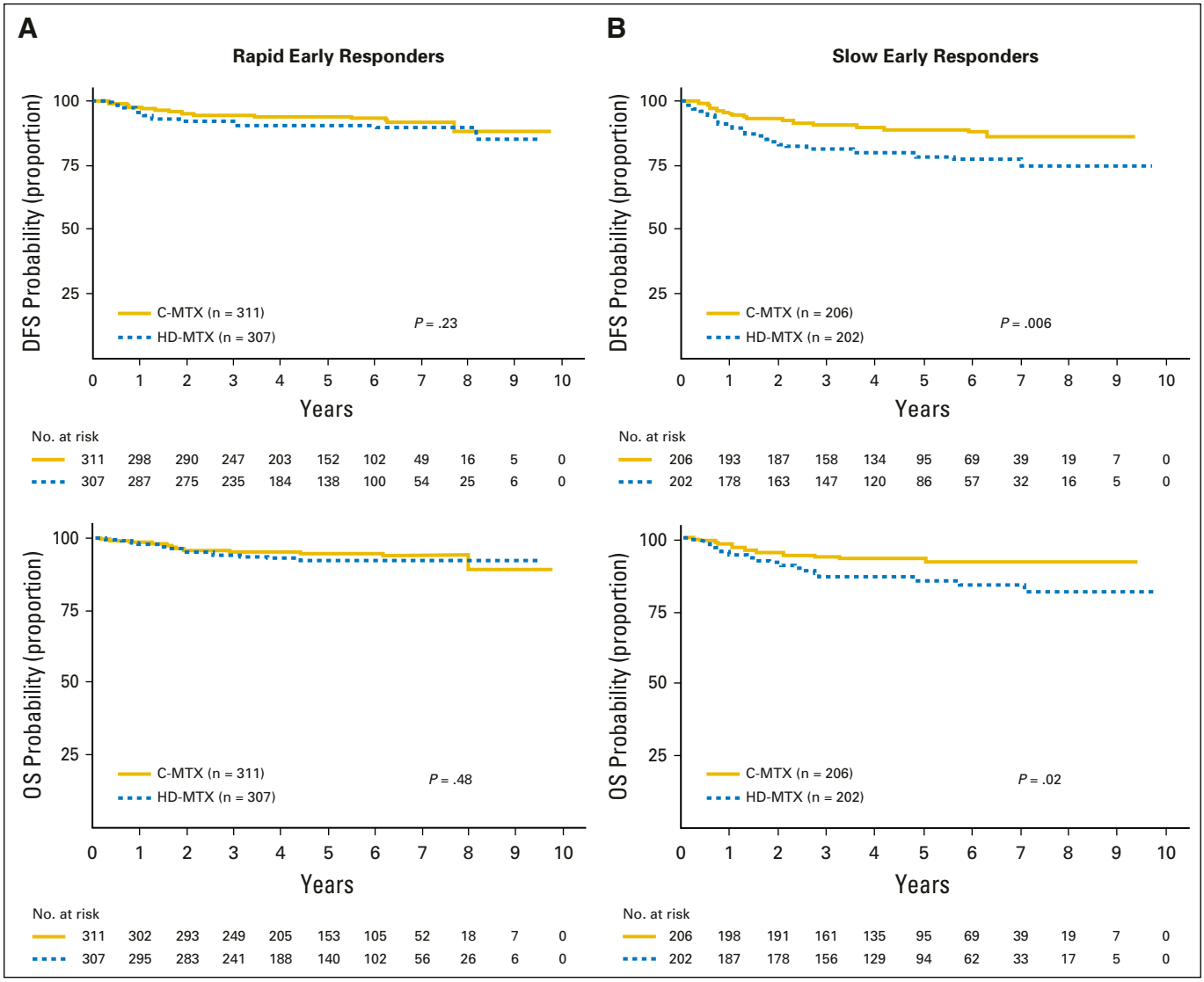

Fig A3. Disease-free survival (DFS) and overall survival (OS) by early response status. (A) Rapid early responders: 5-year DFS was 93.3% (89.4% to 97.1%) for Capizzi-style escalating intravenous methotrexate (C-MTX) versus 90.0% (85.1% to 94.6%) for high-dose methotrexate (HDMTX; hazard ratio, 0.722 [0.421 to 1.238]; $P = .23$), and OS was 94.5% (91.0% to 98.0%) for C-MTX versus 92.1% (87.8% to 96.4%) for HDMTX (hazard ratio, 0.801 [0.429 to 1.493]; $P = .48$). (B) Slow early responders: 5-year DFS was 88.7% (82.7% to 94.7%) for C-MTX versus 78.1% (70.4% to 85.8%) for HDMTX (hazard ratio, 0.501 [0.305 to 0.824]; $P = .001$), and OS was 92.4% (87.3% to 97.5%) for C-MTX versus 85.2% (78.6% to 91.8%) with HDMTX (hazard ratio, 0.506 [0.276 to 0.928]; $P = .03$).

Table A1. Therapy Details

Phase and Regimen	Drug	Dose	Schedule
Induction all arms*	IT cytarabine	Age adjusted†	At diagnostic lumber puncture or day 1
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 22
	Prednisone	30 mg/m^2/dose twice a day	Days 1-28
	Daunorubicin	25 mg/m^2	Days 1, 8, 15, 22
	Pegaspargase	2,500 U/m^2	Day 4, 5, or 6
	IT-MTX	Age adjusted†	Days 8, 29 (CNS3: + days 15, 22)
Consolidation (arms A and C)	Cyclophosphamide	1,000 mg/m^2	Days 1, 29
	Cytarabine	75 mg/m^2	Days 1-4, 8-11, 29-32, 36-39
	Mercaptopurine	60 mg/m^2	Days 1-14, 29-42
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 15, 22, 43, 50
	Pegaspargase	2,500 U/m^2	Days 15, 43
	IT-MTX	Age adjusted†	Days 8, 15, 22,29 (HR); days 1, 8 (CNS3); days 1, 8, 15, 22 (all others)
	CRT‡	12 Gy (18 Gy for CNS3)	Start on day 15 (arm A)
	TRT§	24 Gy (persistent disease only)	Completed before day 15
Consolidation + nelarabine (arms B and D)	Cyclophosphamide	1,000 mg/m^2	Days 8, 50
	Cytarabine	75 mg/m^2	Days 8-11, 15-18, 50-53, 57-60
	Mercaptopurine	60 mg/m^2	Days 8-21, 50-63
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 22, 29, 64, 71
	Pegaspargase	2,500 U/m^2	Days 22, 64
	IT-MTX	Age adjusted†	Days 15, 22, 57, 64 (omit day 22 for CNS3)
	Nelarabine	650 mg/m^2	Days 1-5, 43-47
	CRT‡	12 Gy (18 Gy for CNS3)	Start on day 22 (arm B)
	TRT§	24 Gy (persistent disease only)	Completed before day 15
Interim maintenance C-MTX (arms A and B)	Vincristine	1.5 mg/m^2 (2 mg maximum)	Every 10 days × 5 doses/days 1, 11, 21, 31, 41
	IV-MTX‖	100 mg/m^2	Every 10 days × 5 doses/days 1, 11, 21, 31, 41
	Pegaspargase	2,500 U/m^2	Days 2, 22
	IT-MTX	Age adjusted†	Days 1, 31
Interim maintenance HDMTX (arms C and D)	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 15, 29, 43
	IV-MTX	5,000 mg/m^2	Days 1, 15, 29, 43
	Leucovorin	15 mg/m^2	42, 48, 52 hours post-IV-MTX
	Mercaptopurine (oral)	25 mg/m^2	Days 1-56
	IT-MTX	Age adjusted†	Days 1, 29
Delayed intensification (arms A and C)	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 43, 50
	Pegaspargase	2,500 U/m^2/dose	Day 4 or 5 or 6 and 43
	Dexamethasone	5 mg/m^2/dose twice a day	Days 1-7, 15-21
	Doxorubicin	25 mg/m^2/d	Days 1, 8, 15
	Cytarabine	75 mg/m^2/d	Days 29-32, 36-39
	Cyclophosphamide	1,000 mg/m^2	Day 29
	Thioguanine	60 mg/m^2/d	Days 29-42 (omit for patients receiving CRT)
	IT-MTX	Age adjusted†	Days 1, 29, 36
	CRT‡	12 Gy (18 Gy for CNS3)	Start on day 50 (arm C)
Delayed intensification + nelarabine	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 50
	Pegaspargase	2,500 U/m^2/dose	Day 4 or 5 or 6 and 50
	Dexamethasone	5 mg/m^2/dose twice a day	Days 1-7, 15-21
	Doxorubicin	25 mg/m^2/d	Days 1, 8, 15
	Cytarabine	75 mg/m^2/d	Days 36-39, 43-46
	Cyclophosphamide	1,000 mg/m^2	Day 36
	Thioguanine	60 mg/m^2/d	Days 36-49 (omit for patients receiving CRT)
	IT-MTX	Age adjusted†	Days 1, 36, 43
	Nelarabine	650 mg/m^2	Days 29-33
	CRT‡	12 Gy (18 Gy for CNS3)	Start on day 50 (arm D)
Maintenance¶ (12-week cycles)	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 29, 57
	Prednisone	20 mg/m^2/dose twice a day	Days 1-5, 29-33, 57-61
	Mercaptopurine (oral)	75 mg/m^2/d	Daily/days 1-84
	MTX (oral)	20 mg/m^2/dose	Weekly
	IT-MTX	Age adjusted†	Days 1 (and 29 first four cycles; LR only)
Maintenance + nelarabine¶	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 57
	Prednisone	20 mg/m^2/dose twice a day	Days 1-5, 57-61
	Mercaptopurine (oral)	75 mg/m^2/d	Days 1-28, 36-84
	MTX (oral)	20 mg/m^2/dose	Days 8, 15, 22, 36, 43, 50, 57, 64, 71/weekly—omitted while taking nelarabine
	IT-MTX	Age adjusted†	Day 1
	Nelarabine	650 mg/m^2	Days 29-33 (first three cycles arms B and D)

NOTE. Treatment arms: A (C-MTX), B (C-MTX + nelarabine), C (HDMTX), D (HDMTX + nelarabine).

Abbreviations: C-MTX, Capizzi-style escalating intravenous methotrexate; CRT, cranial radiation therapy; HDMTX, high-dose methotrexate; HR, high risk; IT, intrathecal; IV, intravenous; LR low risk; MTX, methotrexate; TRT, testicular radiation therapy.

*Induction failure (M3 at day 29) begin arm D consolidation as soon as possible. IT therapy is not held during the concomitant administration of CRT.

†IT cytarabine: 1-1.99 years, 30 mg; 2-2.99 years, 50 mg; ≥ 3 years, 70 mg. IT-MTX: 1-1.99 years, 8 mg; 2-2.99 years, 10 mg; 3-8.99 years, 12 mg; ≥ 9 years, 15 mg.

‡CNS1 or 2: 1.5 Gy/d × eight fractions; CNS3 in 1.8 Gy/d × 10 fractions for intermediate risk and HR participants only.

§For biopsy-proven, persistent disease only: 2 Gy/d for 12 fractions.

‖IV-MTX: 100 mg/m^2 (dose escalated by 50 mg/m^2 every 10 days for a total of five doses, adjusted for toxicity).

¶Total duration of treatment from start of interim maintenance: female patients with T-cell acute lymphoblastic leukemia, 2 years; male patients with T-cell acute lymphoblastic leukemia, 3 years.

Table A2. Criteria for and Distribution of Risk Groups

Risk Classification	NCI Risk*	Corticosteroid Pretreatment	CRT	RER *v* SER†	CNS, Testes	Day 29 Marrow Morphology/MRD
LR‡ (9.2%)	Standard	No	No	Yes	Negative	M1 and < 0.1%
IR§ (68.0%)	Any	Allowed	Yes	Any	Any	M1 and 0.1% to < 1.0%
HR (19.2%)	Any	Allowed	Yes	Any	Any	M2 or ≥ 1.0%
Induction failure (3.6%)	Any	Allowed	Yes	Any	Any	M3: > 25% blasts by light microscopy

Abbreviations: HR, high risk; IR, intermediate risk; LR, low risk; MRD, minimal residual disease; NCI, National Cancer Institute; RER, rapid early responder; SER, slow early responder.
*NCI standard risk: 1-10 years, WBC < 50,000 cells/μL; NCI HR: > 10 years, WBC > 50,000 cells/μL.
†Participants were either RER (M1 marrow at or before day 15) or SER (M2 or M3 marrow at day 15).
‡No corticosteroid pre-exposure before start of protocol-specified therapy.
§IR also included age > 10 years, but MRD < 0.1%.

Table A3. Summary of Cumulative Incidence Rates for Relapses for C-MTX Versus HDMTX Randomly Assigned Cohorts

Regimen	Cumulative Incidence, % (95% CI)		
	2 Years	4 Years	6 Years
Isolated marrow relapses			
C-MTX (n = 519)	1.56 (0.48 to 2.64)	1.97 (0.75 to 3.19)	2.24 (0.93 to 3.55)
HDMTX (n = 512)	3.97 (1.16 to 5.68)	5.15 (3.17 to 7.13)	6.33 (3.96 to 8.70)
Isolated CNS relapses			
C-MTX (n = 519)	0.39 (0.00 to 0.94)	0.39 (0.00 to 0.94)	0.39 (0.00 to 0.94)
HDMTX (n = 512)	2.98 (1.49 to 4.47)	2.98 (1.49 to 4.47)	2.98 (1.49 to 4.47)
Combined marrow and CNS relapses			
C-MTX (n = 519)	0.59 (0.00 to 1.26)	0.59 (0.00 to 1.26)	1.03 (0.00 to 2.13)
HDMTX (n = 512)	1.39 (0.37 to 2.41)	1.60 (0.50 to 2.70)	1.60 (0.50 to 2.70)

Abbreviations: C-MTX, Capizzi-style escalating intravenous methotrexate; HDMTX, high-dose methotrexate.

Table A4. IM Toxicities by Treatment Regimen (Grades 3 and 4)

Toxicity During IM	C-MTX, No. %	HDMTX, No. %	*P*
No. who received IM	469	469	
Mucositis (oral)	48 (10.2)	62 (13.2)	.19
Mucositis (any)	6 (1.3)	1 (0.2)	.12
Colitis	1 (0.2)	2 (0.4)	1.00
Esophagitis	2 (0.4)	2 (0.4)	1.00
Gastritis	0 (0.0)	1 (0.2)	1.00
Febrile neutropenia	47 (10.0)	37 (7.9)	.30
Seizure	0 (0.0)	1 (0.2)	1.00
Peripheral motor neuropathy	14 (3.0)	13 (2.8)	1.00
Peripheral sensory neuropathy	8 (1.7)	5 (1.1)	.58
Ischemia cardiovascular	0 (0.0)	0 (0.0)	NA
Allergic reaction	2 (0.4)	1 (0.2)	1.00
Anaphylaxis	4 (0.9)	0 (0.0)	.12
Clotting disorders, thromboses	2 (0.4)	2 (0.4)	1.00
Pancreatitis	5 (1.1)	0 (0.0)	.06

Abbreviations: C-MTX, Capizzi-style escalating intravenous methotrexate; HDMTX, high-dose methotrexate; IM, interim maintenance; NA, not applicable.