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Development of Osteonecrosis and Improved Survival in B-ALL: Results of Children's Oncology Group Trial AALL0232

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Abstract

Osteonecrosis is a significant toxicity of acute lymphoblastic leukemia (ALL) therapy. In retrospective analyses, superior event-free survival was noted among affected adolescents in an earlier trial. We prospectively assessed osteonecrosis incidence, characteristics, and risk factors in patients 1–30 years with newly diagnosed high-risk B-ALL on COG AALL0232. Patients were randomized to induction dexamethasone vs prednisone, and interim maintenance

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AUTHOR CONTRIBUTIONS

All authors participated in protocol development and data collection. LAM, MD, MLL, YD, ZC, and SPH analyzed the data and wrote the draft manuscript. All authors reviewed the paper, provided input on content and interpretation of results, and approved the final version. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTERESTS

LAM has received consulting fees from Novartis and owns stock in Pfizer. MLL has received consulting fees from Medsix Therapeutics. SPH owns stock in Amgen, and has received honoraria from Amgen and Servier, and consulting fees from Novartis. The other authors declare no competing financial interests.

high-dose methotrexate vs escalating-dose Capizzi methotrexate/pegaspargase. Event-free and overall survival were compared between patients with/without imaging-confirmed osteonecrosis. Osteonecrosis developed in 322/2730 eligible, evaluable patients. The 5-year cumulative incidence was 12.2%. Risk was greater in patients ≥10 years (hazard ratio [HR], 7.23; $P<0.0001$), particularly females (HR, 1.37; $P=0.0057$), but lower in those with asparaginase allergy (HR, 0.60; $P=0.0077$). Among rapid early responders ≥10 years, risk was greater with dexamethasone (HR, 1.84; $P=0.0003$) and with prednisone/Capizzi (HR, 1.45; $P=0.044$), even though neither therapy was independently associated with improved survival. Patients with osteonecrosis had higher 5-year event-free (HR, 0.51; $P<0.0001$) and overall survival (HR, 0.42; $P<0.0001$), and this was directly attributable to reduced relapse rates (HR, 0.57; $P=0.0014$). Osteonecrosis in high-risk B-ALL patients is associated with improved survival, suggesting an important role for host factors in mediating both toxicity and enhanced efficacy of specific therapies.

INTRODUCTION

Osteonecrosis is a significant toxicity of contemporary therapies for pediatric acute lymphoblastic leukemia (ALL), affecting 20% of older teens and impacting long-term quality of life for many.[1,2] Acute and chronic morbidity that is dominated by pain and joint dysfunction can be debilitating, often requiring surgery to slow progression, lessen symptoms, and restore mobility.[3–6] The development of osteonecrosis is attributed to corticosteroids, asparaginase, and methotrexate.[3,7–12] Development of osteonecrosis often prompts treatment modifications such as corticosteroid discontinuation, raising concerns about how this might impact treatment efficacy. Limiting the duration of continuous dexamethasone exposure is the only approach shown to reduce osteonecrosis incidence.[3] Since glucocorticoids are essential to treatment, the potential impact of steroid delivery modifications on outcome must be considered and the contributory role of the other agents better delineated.[9,13]

Known clinical risk factors for osteonecrosis include skeletal maturation, age ≥10 years, female sex, hypertriglyceridemia, hypertension, obesity, White race, and genetically determined White ancestry.[3,6,11,14–22] Genetic risk factors associated with host germline polymorphisms of genes encoding proteins involved in bone metabolism, thrombosis, fibrinolysis, lipid and albumin homeostasis, angiogenesis, endothelial cellular migration, and drug effects have been reported.[11,16,23–26]

The Children's Oncology Group (COG) has rigorously studied imaging-confirmed osteonecrosis across sequential high-risk ALL trials since 1993. We demonstrated that augmented post-induction therapy, including additional asparaginase and methotrexate, was associated with more osteonecrosis than standard therapy in older patients, and that osteonecrosis risk was reduced using an alternate-week rather than a 21-day continuous dexamethasone schedule for patients receiving two delayed intensification (DI) courses.[3,17] Surprisingly, the 5-year event-free survival (EFS) on CCG-1961 was better for patients ≥10 years who developed osteonecrosis than those who did not (hazard ratio [HR], 0.32; $P<0.001$).[3] Improved overall survival (OS) was also noted among patients 15–50 years old with osteonecrosis on retrospective analysis of DFCI ALL Consortium trials.[27] However, it

is unknown whether improved outcomes in those with osteonecrosis is primarily related to therapy-specific efficacy, or if underlying host factors predominate.

The COG AALL0232 high-risk B-ALL trial incorporated augmented Berlin-Frankfurt-Münster (BFM)-based therapy derived from CCG-1961 as standard treatment for all patients.[28] Randomized efficacy comparisons included 14 days of dexamethasone (experimental) vs 28 days of prednisone during induction, and high-dose methotrexate (HDMTX; experimental) vs escalating-dose methotrexate with pegaspargase (CMTX) during interim maintenance (IM).[29] Data on osteonecrosis symptoms and imaging findings were captured prospectively during every phase of therapy, enabling systematic analysis of osteonecrosis incidence, risk factors, and the impact of developing osteonecrosis on relapse rates, EFS, and OS in the context of specific treatment variables.

SUBJECTS AND METHODS

Patients and treatment

Patients 1–30 years old with newly diagnosed high-risk B-ALL (age ≥10 years or initial white blood cell count $\geq 50\times10^9$/l) were enrolled on AALL0232 at 210 COG institutions between January 2004 and January 2011. Eligibility criteria, patient characteristics, rapid (RER) and slow early response (SER) definitions, and treatment details were previously reported (Tables S1 and S2).[29] Treatment was further stratified by induction response. Rapid responders received single IM/DI courses, with a randomization between CMTX and HDMTX during the IM phase. Slow responders received two IM/DI courses, with a randomization between CMTX and HDMTX during the first IM phase (IM1), while CMTX was given to all patients during IM2. Treatment duration was 24 months from the start of IM1 for females and 36 months for males.

To limit osteonecrosis, patients ≥13 years received alternate-week dexamethasone (days 1–7, 15–21) during DI, whereas patients <13 years received continuous dexamethasone (days 1–21) when AALL0232 first started. The study was amended twice to address unexpectedly high osteonecrosis rates. After October 2006 all patients ≥10 years received alternate-week dexamethasone during DI. After June 2008 all patients ≥10 years were non-randomly assigned to induction prednisone, and patients of all ages received alternate-week dexamethasone during DI and monthly prednisone pulses (20 mg/m^2/dose twice daily, days 1–5) instead of dexamethasone in maintenance.[29]

AALL0232 was approved by the National Cancer Institute and local institutional review boards. Informed consent was obtained from subjects or parents/guardians per Department of Health and Human Services guidelines. This trial was registered at www.clinicaltrials.gov as # NCT00075725, under the following name: Dexamethasone Compared With Prednisone During Induction Therapy and MTX With or Without Leucovorin During Maintenance Therapy in Treating Patients With Newly Diagnosed High-Risk Acute Lymphoblastic Leukemia.

Randomization and masking

AALL0232 originally used a 2×2 randomized factorial design comparing two induction corticosteroids and two IM1 methotrexate approaches. Randomization was at study entry, using the method of permuted blocks. Down syndrome patients were randomized only for corticosteroid assignment and were ineligible for enrollment after June 2008 due to excess toxicity; they are included here in overall but not randomized cohort analyses. There was no masking. Details on randomized arms and treatments were described earlier.[29]

Osteonecrosis assessment and reporting

Patients were prospectively monitored for clinical signs and symptoms referable to osteonecrosis, including pain, restricted range of motion, gait disturbance, joint collapse, and arthritis. All osteonecrosis sites included in this analysis required confirmation by diagnostic imaging per local practice and interpreted by institutional radiologists. Pre-symptomatic MRI screening was not routinely performed, although scanning sequences for symptomatic hips and/or knees commonly included transverse screening images of all four joints to detect the presence of concurrent asymptomatic sites. Osteonecrosis clinical severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and categorized as absent (grade 0), asymptomatic (grade 1), moderate (grade 2), severe (grade 3), or disabling (grade 4).

Reporting period forms uniformly asked if new osteonecrosis site(s) had been identified during that interval. If yes, detailed reporting via a standardized targeted toxicity form was required, beginning at initial symptom onset and serially thereafter for each subsequent reporting period throughout follow-up, for all known, new, and incidentally identified asymptomatic sites. These forms were reviewed centrally by a single reviewer (LAM) in real time to ensure reporting accuracy, with additional documentation of individual cases when indicated. Required data for each identified site included estimated symptom onset date, clinical severity, imaging diagnosis date, imaging results, and surgical interventions. Reporting ended with progressive leukemia, death, loss to follow-up, or voluntary study removal. Adverse event reporting was required for osteonecrosis grade ≥1 (CTCAE v4.0).

Pre-maintenance therapy was not modified for osteonecrosis. Maintenance steroid pulses were omitted for symptomatic osteonecrosis, and resumed after six-plus months at physician discretion in asymptomatic patients with improved or normalized MRI findings.

Statistical analysis

Event-free survival (EFS) was defined as time from study entry to first event (induction failure, induction death, relapse, second malignant neoplasm, remission death) or date of last follow-up for event-free subjects. Overall survival (OS) was defined as time from study entry to death or date of last follow-up. Disease-free survival (DFS) was defined as time from completion of therapy to first event (relapse, second malignant neoplasm, remission death) or date of last follow-up. Survival rates were estimated using the Kaplan-Meier method with standard errors of Peto.[30,31] Survival curves were compared using the two-sided log-rank test. Cumulative incidence rates (CIR) for relapse were computed using the cumulative incidence function for competing risks (induction death, induction

failure, second malignant neoplasm, or remission death), and comparisons were made using Gray's test.[32] Competing risks (induction death, induction failure, relapse, second malignant neoplasm) were considered in calculating cumulative incidence rates for the first onset of osteonecrosis. EFS, OS, and CIR are presented as percent [95% CI], together with hazard ratios (HR) and p-values. Multivariable Cox regression analysis of EFS/OS included known risk factors for ON. Comparison of proportions between groups used a Chi-square or Fisher's exact test. Multivariable logistic regression analysis was used to examine the effect of age at diagnosis, sex, and body mass index (BMI) at the start of therapy on the incidence of ON (yes/no). Wilcoxon Rank Sum test was used to compare medians between groups. A P-value <0.05 was considered as significant for all comparisons. Data current as of December 31, 2017, are included in this report. All analyses were performed using SAS® software (version 9.4). All graphics were generated using R (http://www.R-project.org, version 3.4.4). Data analysis was conducted by LAM, MD, MLL, ZC, and SPH. All authors had access to the primary clinical trial data.

RESULTS

Patients

A total of 3154 patients were enrolled between January 2004 and January 2011, with 2730 included in this analysis. Reasons for exclusion (n=424) were study ineligibility (n=50), inevaluable for induction (n=23), very-high-risk ALL (n=267) not eligible to continue on trial after induction, and inevaluable post-induction (n=84) (Figure 1). Osteonecrosis was diagnosed in 322/2730 (11.8%) patients. Distributions by age and sex are given in Table S3. The median age at ALL diagnosis was higher in patients with than without osteonecrosis (13.7 years [range, 2.0–30.0] vs 10.0 years [range, 1.0–30.0]; P<0.0001), and lower in females with osteonecrosis than males (12.8 years [range, 3.0–20.0] vs 14.6 years [range, 2.0–30.0]; P<0.0001). Symptom onset occurred during pre-maintenance phases in 60 (18.6%), maintenance in 232 (72.0%), and follow-up in 30 (9.3%). The median time to symptom onset was 455 days (range, 24–1791) from study enrollment, and was earlier in females than males (395 days [range, 24–1693) vs 512 days [range, 57–1791]; P=0.0001]. Clinical risk factors for osteonecrosis are summarized in Table 1.

Osteonecrosis characterization

Osteonecrosis was diagnosed at 907 sites (Table S4), confirmed by MRI in 297 (92.2%) patients and by other imaging in 25 (7.8%). Involvement was multifocal in 234 (73%) patients, with a median of 2 (range, 1–14) joints per patient. Weight-bearing joint(s) were affected in 304 (94%) patients. Maximum reported symptom severity was grade 1 in 23 (7%), grade 2 in 187 (58%), grade 3 in 101 (31%), and grade 4 in 11 (3%) patients. A total of 163 invasive procedures were performed in 71 (22%) patients (Table S4).

Osteonecrosis incidence

The overall cumulative incidence of osteonecrosis was 12.2% (95% CI, 11.0–13.5) at 5 years. Incidence correlated with age (P<0.0001) (Figure S1) and was much higher in patients ≥10 than 1–9 years (17.2% [95% CI, 15.4–19.0] vs 2.6% [95% CI, 1.7–3.8]; HR, 7.23; P<0.0001). Cumulative incidence rates were similar in the age ranges 13–15 years (n=638;

18.4% [95% CI, 15.5 to 21.6]) and ≥16 years (n=529; 18.4% [95% CI, 15.1 to 22.0]; *P*=0.91). In the small cohort ≥21 years old (n=47), the cumulative incidence was 27.4% (95% CI, 15.0 to 41.2). Among patients ≥10 years old at diagnosis the cumulative incidence was higher in females than males (19.7% [95% CI, 17.0–22.6] vs 15.2 % [95% CI, 13.0–17.5]; HR, 1.38; *P*=0.0057), and was uniformly low in patients 1–9 years (females, 2.8% [95% CI, 1.5–4.8] vs males, 2.3% [95% CI, 1.2–4.0]; *P*=0.61). Self-reported race was a significant predictor, with Blacks at a remarkably lower risk than Whites (odds ratio [OR], 0.19; *P*<0.0001) (Table 1). Multivariable logistic regression analysis confirmed age and sex, but not BMI, as risk factors for ON (Table S5).

Based on the October 2006 amendment, we compared osteonecrosis incidence between patients 10–12 years who received alternate-week vs continuous dexamethasone during DI. Alternate-week administration was associated with a 59% reduction in osteonecrosis risk (10.2% [95% CI, 7.4–13.4] [n=405] vs 22.8% [95% CI, 17.5–28.5] [n=228]; HR, 0.41; *P*<0.0001), with no difference in survival. A similar comparison among patients 1–9 years based on the June 2008 amendment confirmed a 74% reduction in osteonecrosis risk with alternate-week administration (0.9% [95% CI, 0.3–2.5] [n=339] vs 3.4% [95% CI, 2.1–5.2] [n=566]; HR, 0.26; *P*=0.021). No increase in incidence was identified among patients who received (n=166) or did not receive (n=2500) extended induction (11.9% vs 12.3%; *P*=0.80), which delivered two additional weeks of glucocorticoid therapy.

Osteonecrosis incidence among rapid responders (n=2111), scheduled to receive single IM and DI phases, was 12.0% (95% CI, 10.6–13.4). Comparisons by glucocorticoid and methotrexate randomization in patients ≥10 years are shown in Figure 2A–B. Incidence was higher in patients treated with dexamethasone than prednisone during induction (HR, 1.84; *P*=0.0003), with no difference by methotrexate randomization. Regimen comparisons by age cohort are shown in Figure 2C–D. The difference seen in older patients was primarily due to higher rates in the dexamethasone regimens, while in younger patients it was attributable to higher rates associated with the CMTX regimens. Noting an apparent difference between methotrexate regimens in both age cohorts following induction prednisone, separate analyses were performed on expanded populations randomized before or after the June 2008 amendment. In patients ≥10 years given prednisone, more osteonecrosis occurred with CMTX than HDMTX (16.1% [95% CI, 12.7–19.7] vs 11.5% [95% CI, 8.7–14.7]; HR, 1.45; *P*=0.044). Findings were similar in patients 1–9 years (4.3% [95% CI, 2.0–7.9] vs 1.1% [95% CI, 0.2–3.8]; HR, 3.86; *P*=0.066). Incidence in patients with vs without asparaginase allergy during therapy was 8.2% (95% CI, 5.7 to 11.3) vs 12.9% (95% CI, 11.5 to 14.3; HR, 0.62; *P*=0.012) in the study population overall, and 11.2% (95% CI, 7.7 to 15.5) vs 18.2% (95% CI, 16.3 to 20.2; HR, 0.60; *P*=0.0076) in patients ≥10 years.

Osteonecrosis incidence among slow responders (n=526), scheduled to receive two IM and DI phases, was 14.2% (95% CI, 11.3–17.4), higher in patients ≥10 than 1–9 years (17.3% [95% CI, 13.7–21.3] vs 4.8% [95% CI, 2.0–9.6]; HR, 3.81; *P*=0.0006), with no difference by sex or regimen. Rates were similar for slow and rapid responders overall (14.2% vs 12.0%; *P*=0.22) and in patients ≥10 years (17.3% [95% CI, 13.7–21.3] vs 17.6% [95% CI, 15.6–19.7]; *P*=0.73). Rates were nominally higher for slow vs rapid responders 1–9 years (4.8% [95% CI, 2.0–9.6] vs 2.2% [95% CI, 1.3–3.4]; HR, 2.25; *P*=0.082), albeit with

small numbers in each group (6/128 vs 16/762). In the overall study population, there was no difference in incidence based on end-induction minimal residual disease (MRD) levels <0.10% or ≥0.10% (12.1% [95% CI, 10.8–13.5] [n=2246] vs 14.0% [10.8–17.5] [n=428]; *P*=0.35).

Survival comparisons

We examined osteonecrosis/survival associations in various patient and treatment cohorts. In the entire analysis population, patients with osteonecrosis had superior EFS (89.8% [95% CI, 86.3–93.2] vs 77.8% [95% CI, 76.0–79.6]; HR, 0.51; *P*<0.0001) and OS (95.8% [95% CI, 93.5–98.1] vs 86.1% [95% CI, 84.6–87.6]; HR, 0.42; *P*<0.0001) at 5 years (Figure 3A–B). Similar differences were seen in patients ≥10 years overall (Figure 3C–D) and by sex (Figure S2). Comparisons in RER and SER cohorts ≥10 years showed statistically significant differences in both, and were of greater magnitude among slow (EFS: HR, 0.40; *P*=0.0002; OS: HR, 0.25; *P*<0.0001) than rapid responders (EFS: HR, 0.51; *P*=0.0016; OS: HR, 0.40; *P*=0.0018) (Figure S3).

Improved survival was directly attributable to reduced relapse rates. The overall cumulative incidence of relapse at 5 years was significantly lower among patients with osteonecrosis than without (8.3% [95% CI, 5.6–11.7] vs 14.8% [95% CI, 13.4–16.3]; HR, 0.57; *P*=0.0014) (Figure 4). Similarly, improvements in EFS and OS observed on both methotrexate regimens correlated with reduced relapse rates (Figure S4). Relapse patterns were compared between patients with (n=33) and without (n=392) osteonecrosis, confirming fewer relapses overall (10.2% vs 16.3%; *P*=0.0051); only isolated central nervous system (CNS) relapse rates differed significantly (n=93; 0.6% vs 3.8%; *P*=0.0027), with no difference in rates observed for either isolated (n=250; 5.4% vs 8.2%; *P*=0.11) or combined (n=49; 1.6% vs 1.7%; *P*=0.64) bone marrow relapse (Figure S5). The median time to relapse was 1059 days (range, 98–3736) overall, and was later in patients with than without osteonecrosis (1305 days [range, 349–2347] vs 1025 days [range, 98–3736]; *P*=0.016). Notably the median time to relapse was approximately 2.3 times longer than the median onset of osteonecrosis symptoms, which occurred at 455 days. There was no difference in DFS from completion of therapy between patients with vs without osteonecrosis (HR, 1.13 [0.78–1.64]; *P*=0.52).

Multivariable Cox regression analysis identified prognostic factors in the entire population (Table 2). Osteonecrosis was highly predictive of both EFS (HR, 0.46 [0.34–0.62]; *P*<0.0001) and OS (HR, 0.36 [0.24–0.55]; *P*<0.0001), as were age, initial white blood cell count, induction response status, and methotrexate assignment. Neither sex nor corticosteroid assignment was prognostic. Symptomatic osteonecrosis (CTCAE grades ≥2) was also highly predictive of both EFS (HR, 0.48 [0.35–0.66]; *P*<0.0001) and OS (HR, 0.41 [0.27–0.62]; *P*<0.0001).

DISCUSSION

In this prospective high-risk B-ALL trial that included detailed prospective and centrally reviewed data on osteonecrosis incidence, sites and severity, patients who developed osteonecrosis exhibited strikingly improved event-free and overall survival, particularly among those ≥10 years old at ALL diagnosis who comprised 93% of the osteonecrosis

patients, an improvement directly attributable to reduced relapse risk. Indeed, this effect was even more profound than the trial's randomized methotrexate intervention itself that was associated with significant improvements in EFS and OS.[29] Moreover, cohort analyses implicate dexamethasone and pegaspargase as principal factors for osteonecrosis risk and improved prognosis among susceptible individuals. Because the overall median time to relapse was approximately 2.5 times longer than the median time to osteonecrosis symptom onset, the favorable outcomes associated with osteonecrosis cannot be attributed to ascertainment bias from undercounting osteonecrosis cases among patients who relapse and are removed from protocol therapy.

We sought to determine if the observed osteonecrosis-related survival benefit simply reflected superior efficacy of therapies most associated with its development, whereby osteonecrosis incidence would be highest in those regimens with best outcomes. Our results show otherwise, arguing against osteonecrosis as a surrogate marker for more effective therapy. We found that osteonecrosis was associated with induction dexamethasone in older rapid responders, and with prednisone-CMTX in rapid responders overall. In contrast, the study's primary efficacy analyses showed no advantage for dexamethasone in older patients, and superiority of HDMTX over CMTX in patients of all ages as confirmed here by multivariate analysis.[29] Secondly, use of alternate-week instead of continuous dexamethasone during delayed intensification for patients ≤12 years old successfully reduced osteonecrosis risk with no impact on survival. Finally, we found no association between osteonecrosis incidence and response to induction therapy, whether by morphologic or MRD criteria. On our study, treatment intensity, efficacy, and osteonecrosis risk were not indelibly linked. Therefore, we believe these observations are best explained by a combination of host factors that simultaneously increase osteonecrosis susceptibility and lymphoblast sensitivity to specific chemotherapeutic agents in some patients.

Adolescent vulnerability to glucocorticoid-induced osteonecrosis is directly related to lower dexamethasone clearance and increased systemic exposure, although preteens are not exempt, and our data indicate that this is particularly true among susceptible individuals.[16] In this study, osteonecrosis risk was effectively reduced in younger patients using alternate-week dexamethasone during DI, as previously reported in older patients.[3] Survival comparisons show that this approach compromised neither therapeutic efficacy nor osteonecrosis-related survival advantage, again pointing toward a complexity of host factors, such as pharmacogenetic variation.[16]

Osteonecrosis was associated with delivery of prednisone-CMTX in rapid responders. In younger patients, longer exposure to induction prednisone may be more toxic to bone than shorter exposures to dexamethasone (28 vs 14 days). In older patients, induction dexamethasone may have masked a CMTX-HDMTX difference that was revealed with less toxic prednisone. Nonetheless, differential pegaspargase exposure during IM phases of therapy, without concurrent glucocorticoid, is a clear contributor to osteonecrosis risk. This is substantiated by the significantly lower incidence of osteonecrosis among patients with clinical asparaginase allergy, a correlate of reduced exposure.[16]

While our findings provide compelling evidence that pegaspargase exposure contributes to the development of osteonecrosis, several recent reports are of interest. The DFCI ALL Consortium identified a higher risk of osteonecrosis among patients 15–50 years old treated on later pegaspargase-based trials versus earlier trials employing native E.coli asparaginase (HR, 5.08; $P<0.001$); 60/367 patients had osteonecrosis, including some who were diagnosed following therapy for relapse.[27] Results from the Nordic Society for Pediatric Hematology Oncology (NOPHO) ALL2008 study showed that osteonecrosis incidence rose proportionately with serum asparaginase enzyme activity elevations, particularly in patients receiving pegaspargase concurrently with dexamethasone.[33] Separate analyses from the same study suggested that intermittent dosing of pegaspargase during post-consolidation phases, in addition to withholding its administration during dexamethasone-based delayed intensification, may be associated with a lower risk of osteonecrosis than continuous dosing (HR, 0.65; $P=0.21$); however, the number of patients with osteonecrosis was small (n=35).[12] Combined toxicity analyses from the Japanese Association of Childhood Leukemia Study group (JACLS) ALL97 and ALL02 studies revealed overall lower osteonecrosis rates than comparable trials despite similar dexamethasone exposure, which they hypothesized could be due to avoiding the concomitant administration of dexamethasone and asparaginase.[20]

Mechanistically, asparaginase may induce osteonecrosis directly via hypercoagulability resulting in intraosseous thrombosis, and indirectly via reduced dexamethasone clearance related to hypoalbuminemia.[7,34] We previously reported an association between osteonecrosis and a glutamate receptor variant in a subset of our study population, suggesting a link with glucocorticoid exposure.[24] In an unrelated study, a distinct glutamate receptor variant associated with asparaginase hypersensitivity was identified.[35] Although enhanced methotrexate-related bone toxicity has been reported in the approximately 20% of ALL patients with low thymidylate synthase expression who are homozygous for the 2R *TS* genotype, the relative contribution of this host polymorphism to our results, and specifically CMTX vs HDMTX dosing schedules, is unknown since all study patients received methotrexate during IM.[8,11] A complex interplay of race and pharmacogenomics likely underlies the observed predilection for osteonecrosis in Whites vs the very low incidence in Blacks, which requires further study.[11,17, 22] Of note, obesity did not emerge as a risk factor for osteonecrosis in multivariable logistic regression analysis including age and sex (Table S5). This contrasts with a report spanning three Nordic ALL protocols (NOPHO ALL-86, 92, and 2000) that differed significantly from our study in methodology, sample size, and range of therapies, making comparisons difficult.[19]

We identified no difference in osteonecrosis among slow responders randomized to CMTX vs HDMTX during IM1 (both cohorts utilized CMTX during IM2). Unlike rapid responders, there was no difference among older slow responders by induction glucocorticoid, although this analysis may have been confounded by post-induction pegaspargase exposure. Slow responders received two and rapid responders one IM/DI, and their overall rates of osteonecrosis were comparable despite differences in drug exposure; this is readily explained by the favorable toxicity profile of alternate-week dexamethasone.[3] Regardless of the rationale, slow responders exhibited a greater osteonecrosis-related disease survival advantage than rapid responders.

Analysis of relapse patterns demonstrated that the survival advantage favoring osteonecrosis was associated with reduced isolated CNS relapse. Dexamethasone is superior to prednisone in potency, cytotoxicity, and CNS penetrance, and its use is associated with a decrease in CNS relapse.[9,36–38] Pegaspargase induces therapeutic CNS asparagine depletion and may potentiate the effect of dexamethasone.[34,39] We hypothesize that host systemic drug sensitivity extends to the CNS and enhances response to CNS-targeted chemotherapy, especially with concurrent administration of dexamethasone and pegaspargase during the induction and delayed intensification phases of therapy.[29]

Our results have important clinical implications. A total of 322 patients developed osteonecrosis in 907 joints, involving weight-bearing site(s) in 94% and requiring a surgical or other invasive procedure in 22%. These findings stress the need for osteonecrosis risk reduction, and in this report, patient and treatment risk factors have been clearly defined. Significantly, we established that osteonecrosis is associated with improved EFS and OS, due in part to reduced CNS events, which may be attributed in part to as-yet undefined host factors. This survival advantage occurred despite glucocorticoid dose modification during maintenance, confirming that the recommended steroid treatment reductions after developing osteonecrosis are safe and appropriate. We emphasize the broader observation that individual patient factors can be independently associated with both increased therapeutic toxicity and increased treatment efficacy, and that this may have relevance in other oncologic and non-oncologic disease settings.

The COG adopted the induction prednisone-HDMTX backbone as standard therapy for patients ≥10 years old in subsequent B-ALL trials, which should reduce overall osteonecrosis risk by more than half without sacrificing outcome, given that otherwise susceptible patients who do not develop osteonecrosis will retain the evident drug sensitivity exposed in our analysis as well as the superior CNS anti-leukemic efficacy of HDMTX.[29] This approach is being evaluated on COG AALL1131 (NCT02883049), combined with MRI screening and host germline molecular analysis.[40] Alternate-week dexamethasone during DI is now standard across COG ALL trials. Our results and those of the ongoing European OPAL (Osteonecrosis in Pediatric Patients with Acute Lymphoblastic Leukemia; NCT01619124) and BONES (British Osteonecrosis Study; NCT02598401) trials will further delineate the natural history of treatment-related osteonecrosis, long-term functional outcomes, and impact on outcome.[2] Such knowledge is requisite in developing interventional studies of preventive therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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at The Children's Hospital of Philadelphia. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing Interests

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DATA AVAILABILITY STATEMENT

The COG Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use. For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests.

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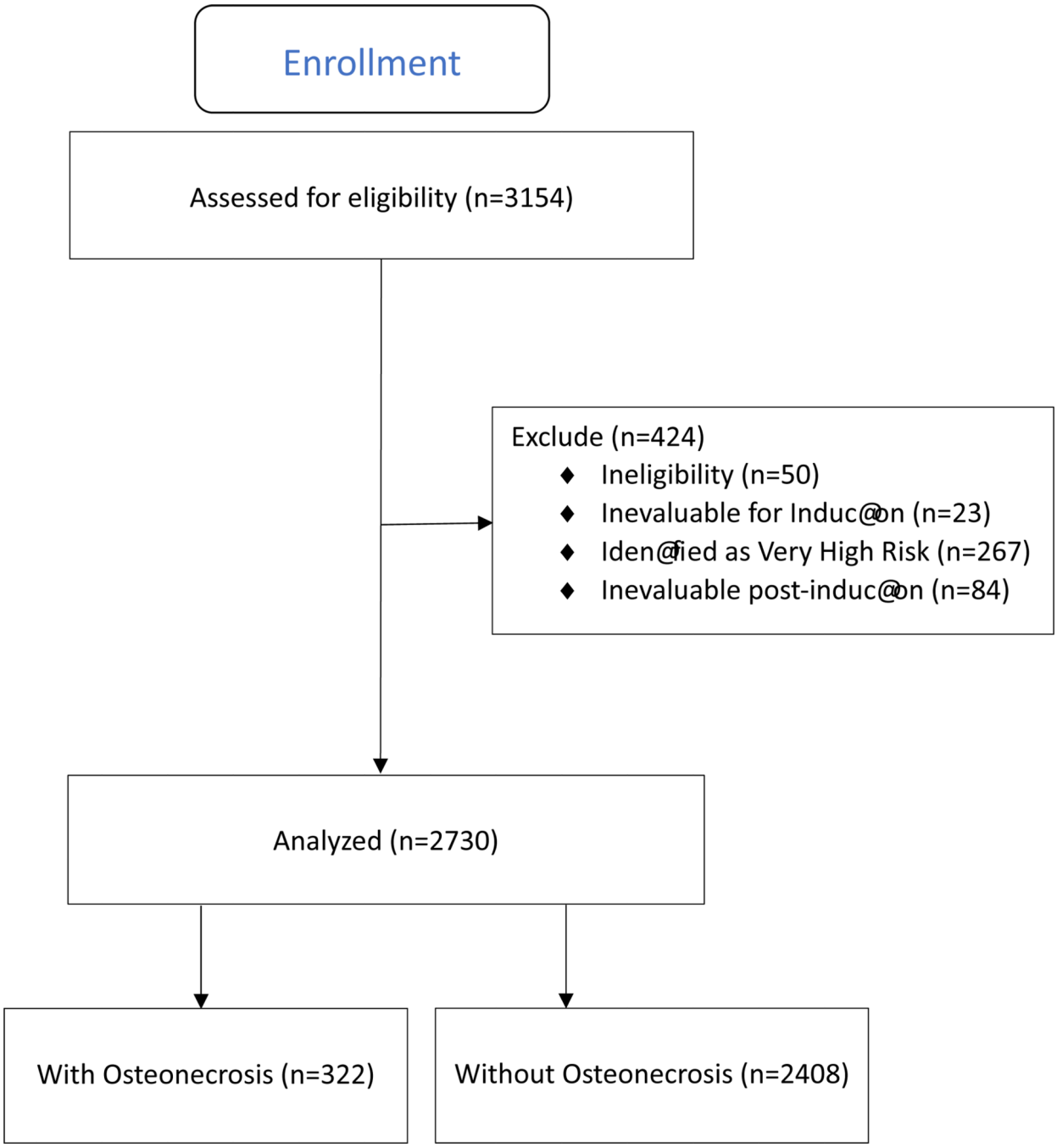
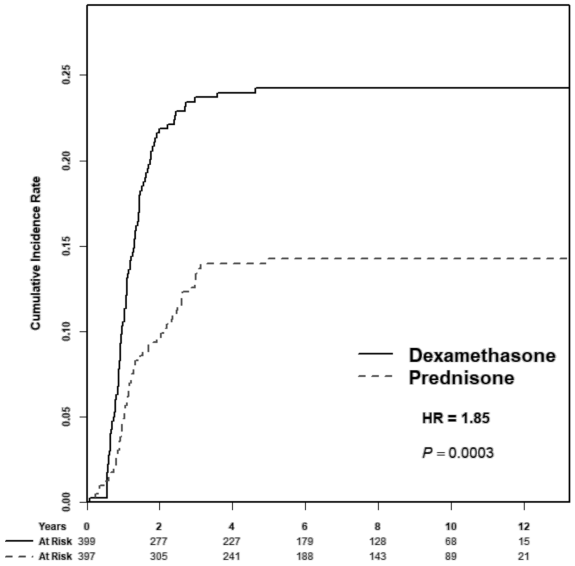


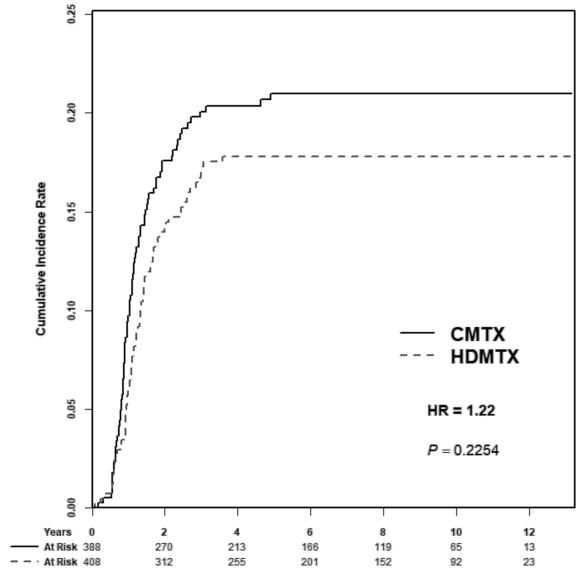
Figure 1. CONSORT diagram

A Glucocorticoid randomization in rapid early response patients age ≥10 years



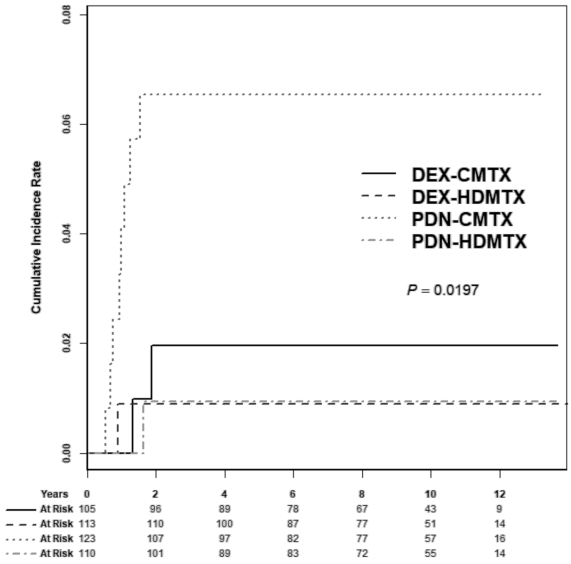
Osteonecrosis cumulative incidence at 5 years		
Dexamethasone	24.3% (20.2%, 28.7%)	(95 / 399)
Prednisone	14.3% (11.0%, 18.0%)	(54 / 397)

B Methotrexate randomization in rapid early response patients age ≥10 years



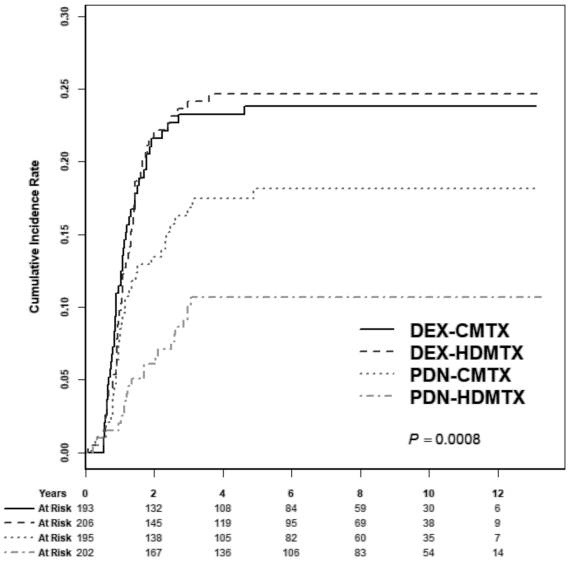
Osteonecrosis cumulative incidence at 5 years		
CMTX	21.0% (17.0%, 25.3%)	(78 / 388)
HDMTX	17.8% (14.2%, 21.7%)	(71 / 408)

C Regimen randomization in rapid early response patients age 1-9 years



Osteonecrosis cumulative incidence at 5 years		
Dexamethasone-CMTX	2.0% (0.4%, 6.3%)	(2 / 105)
Dexamethasone-HDMTX	0.9% (0.1%, 4.4%)	(1 / 113)
Prednisone-CMTX	6.5% (3.1%, 11.9%)	(8 / 123)
Prednisone-HDMTX	0.9% (0.1%, 4.6%)	(1 / 110)

D Regimen randomization in rapid early response patients age ≥10 years

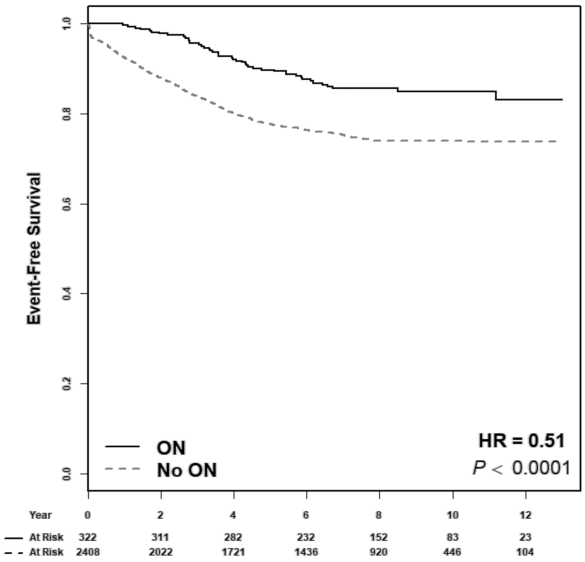


Osteonecrosis cumulative incidence at 5 years		
Dexamethasone-CMTX	23.86% (18.0%, 30.1%)	(45 / 193)
Dexamethasone-HDMTX	24.8% (19.0%, 30.9%)	(50 / 206)
Prednisone-CMTX	18.1% (12.9%, 24.1%)	(33 / 195)
Prednisone-HDMTX	10.7% (6.8%, 15.5%)	(21 / 202)

Figure 2. Cumulative incidence of osteonecrosis by treatment

The cumulative incidence of osteonecrosis at 5 years by glucocorticoid and methotrexate randomization in rapid responders ≥10 years old are shown in Panel A and Panel B, respectively. Findings were similar in the age group ≥13 years (Table S6). Incidence by randomized regimen in rapid responders in age groups 1–9 years and ≥10 years are shown in Panel C and Panel D, respectively. All analyses were limited to patients without Down syndrome who were randomized prior to the June 2008 amendment.

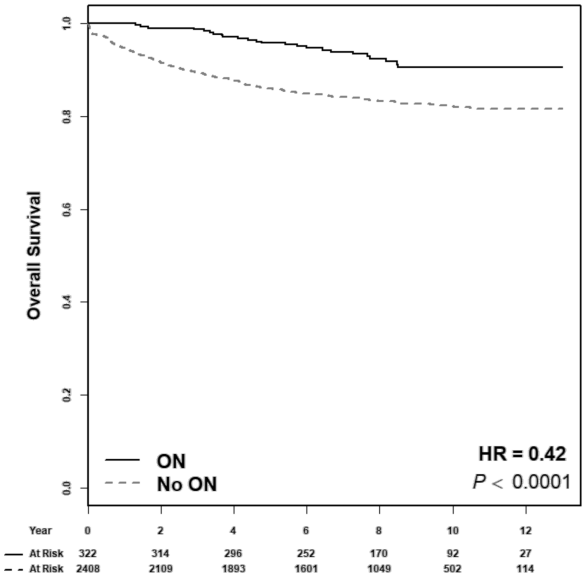
A Event-free survival in analysis cohort patients



Event-free survival at 5 years

Osteonecrosis	**89.8% (86.3%, 93.2%)**	**(45 / 322)**
No osteonecrosis	**77.8% (76.0%, 79.6%)**	**(577 / 2408)**

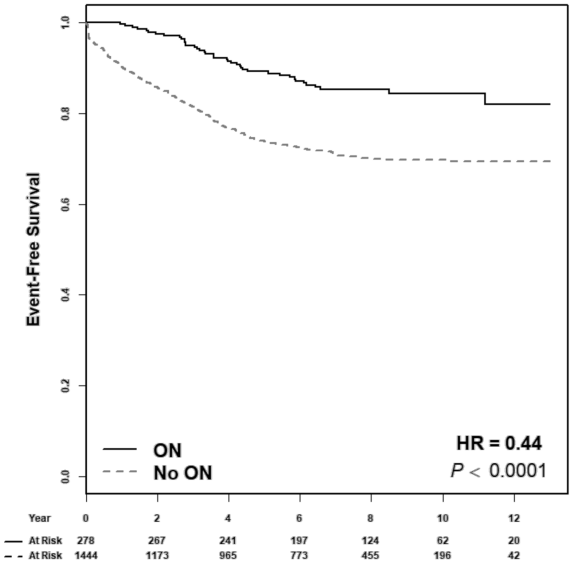
B Overall survival in analysis cohort patients



Overall survival at 5 years

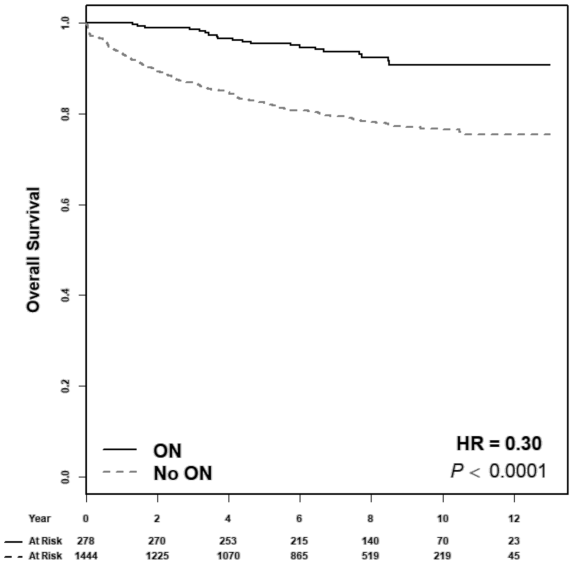
Osteonecrosis	**95.8% (93.5%, 98.1%)**	**(24 / 322)**
No osteonecrosis	**86.1% (84.6%, 87.6%)**	**(381 / 2408)**

C Event-free survival in randomized patients age ≥10 years



Event-free survival at 5 years		
Osteonecrosis	89.2% (85.4%, 93.1%)	(40 / 278)
No osteonecrosis	73.9% (71.4%, 76.4%)	(396 / 1444)

D Overall survival in randomized patients age ≥10 years



Overall survival at 5 years		
Osteonecrosis	95.5% (93.0%, 98.1%)	(20 / 278)
No osteonecrosis	82.5% (80.3%, 84.7%)	(292 / 1444)

Figure 3. Event-free and overall survival by osteonecrosis status

Comparisons of disease outcomes at 5 years in patients with and without osteonecrosis are shown. Panel A and Panel B show event-free and overall survival comparisons, respectively, among all patients in the analysis cohort (n=2730). Panel C and Panel D show comparisons in randomized patients ≥10 years old, excluding patients with Down syndrome. Findings were similar in the age group ≥13 years for each comparison (Table S6).

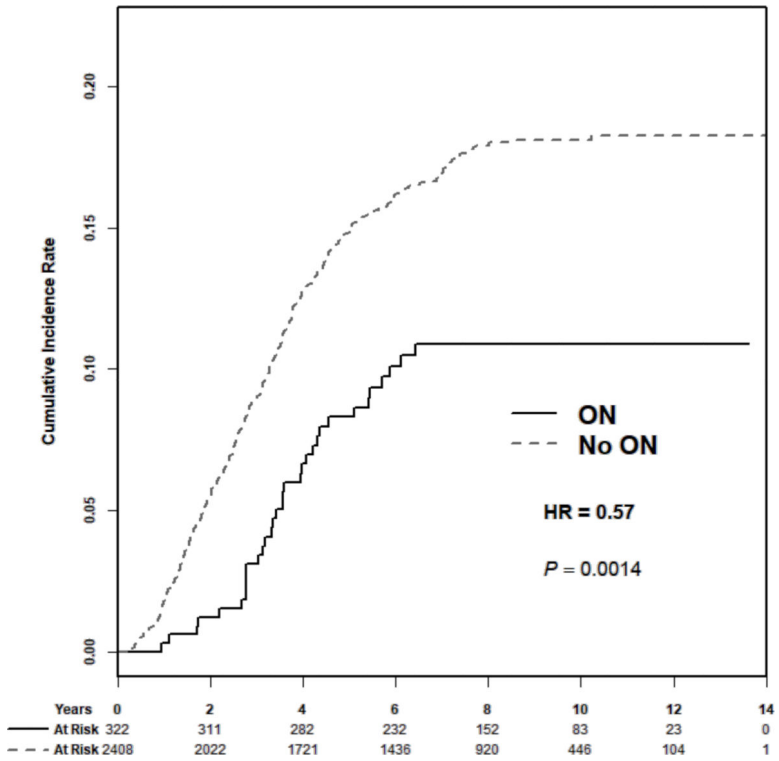


Figure 4. Cumulative incidence of relapse by osteonecrosis status

Shown is the cumulative incidence of relapse comparison at 5 years among all patients with and without osteonecrosis in the analysis cohort (n=2730).

Table 1

Clinical risk factors for osteonecrosis

Risk factor		Osteonecrosis (N=322) # of patients	No osteonecrosis (N=2408) # of patients	Odds ratio (95% CI)	*P* *
Sex	Male	158	1339	0.77 (0.61–0.97)	0.027
	Female	164	1069	–	
Age	1–9 years	23	897	0.13 (0.08–0.20)	<0.0001
	≥10 years	299	1511	–	
Race†	White	264	1793	–	0.0004
	Black/African American	5	182	0.19 (0.08–0.46)	
	Other	16	108	1.01 (0.59–1.73)	
	Unknown	37	325	0.77 (0.54–1.11)	
Asparaginase allergy‡	Present	30	351	0.60 (0.41–0.89)	0.0105
	Absent	292	2057	–	
	Present ≥10 years	28§	231	0.57 (0.38–0.87)	0.0075
	Absent ≥10 years	271¶	1280	–	

*Chi square test

†Patient reported

‡Asparaginase allergic reaction or anaphylaxis (any grade) events were reported during the following phases: induction (n=6), consolidation (n=326), interim maintenance 1 (n=29), delayed intensification 1 (n=17), interim maintenance 2 (n=3), delayed intensification 2 (n=0)

§RER n=23, SER n=5

¶RER n=209, SER n=61, unclassified n=1

Table 2

Multivariable Cox regression analysis for EFS and OS

Parameter	EFS			OS		
	P	HR†	95% CI	*P*	HR†	95% CI
ON: ON vs not ON *	<0.0001	0.46	0.34–0.62	<0.0001	0.36	0.24–0.55
Age (years): ≥10 vs <10 *	<0.0001	2.78	2.19–3.53	<0.0001	4.67	3.39–6.45
Initial WBC (per L): $\geq 50\times10^9$ vs $<50\times10^9$ *	<0.0001	2.20	1.79–2.69	<0.0001	2.20	1.73–2.81
Induction response status: SER vs RER *	<0.0001	2.87	2.42–3.41	<0.0001	3.06	2.47–3.79
Sex: Female vs male *	0.178	0.89	0.75–1.05	0.342	0.90	0.73–1.12
Glucocorticoid: Prednisone vs dexamethasone *	0.619	1.05	0.88–1.25	0.929	1.01	0.81–1.26
Treatment: HDMTX vs CMTX *	0.0012	0.76	0.65–0.90	0.0042	0.74	0.60–0.91

*Reference group

†Hazard ratio