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Prognostic impact of minimal residual disease at end of consolidation in NCI standard risk B-lymphoblastic leukemia: A report from the Children's Oncology Group

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Abstract

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The 5-year disease-free survival (DFS) of NCI high-risk (HR) B-lymphoblastic leukemia (B-ALL) patients with end of induction (EOI) MRD≥0.1% and end of consolidation (EOC) MRD≥0.01% is 39±7%, warranting consideration of hematopoietic stem cell transplant (HSCT). However, the impact of EOC MRD in NCI standard-risk (SR) B-ALL patient using COG regimens is unknown. We found that SR patients with MRD≥0.01% at both EOI and EOC have a 4-year DFS/overall survival of 72.9%±19.0%/91.7±10.8% versus 90.7%±2.9%/95.5±2.0% (P=0.0019/0.25) for those with EOI MRD≥0.01% and EOC MRD<0.01%. These data suggest that routine use of HSCT may not be warranted in EOC MRD≥0.01%SR patients.

Introduction

The most powerful risk predictor in pediatric B-lymphoblastic leukemia (B-ALL) is end induction (EOI) minimal residual disease (MRD)[1–9], which is routinely incorporated into ALL risk stratification schemes[1–6,8–18]. Detectable MRD at later time points is consistently associated with poor outcome[3,6,10,11,15,16,18,19]. NCI high risk (HR) B-ALL patients treated on Children's Oncology Group (COG) AALL0232 with MRD ≥0.1% at EOI and ≥0.01% at end of consolidation (EOC) had a post-consolidation 5-year disease-free survival (DFS) of 39±7% compared to 79±5% for EOI MRD-positive patients with EOC MRD <0.01%[20]. Thus, EOC MRD-positive HR patients warrant consideration of alternative therapies, including allogeneic hematopoietic stem cell transplant (HSCT) or chimeric antigen receptor T-cell therapy (NCT03876769).

Most studies examining EOC MRD have not separately evaluated NCI standard risk (SR) patients. Importantly, the prognostic impact of EOC MRD-positivity in COG SR B-ALL trials has not been previously examined. Extrapolating data from other studies to these patients may not be appropriate because, compared to most other consortia, COG uses less intensive induction therapy for SR patients.

We hypothesized that SR patients with MRD levels ≥0.01% at both EOI and EOC would have inferior DFS compared to EOI MRD-positive who were MRD-negative at EOC, and report here outcome data to address this hypothesis.

METHODS

Patients

The study population included children with SR (age 1–9.99 years and initial white blood cell count <50,000/μL) B-ALL who received induction therapy on COG AALL0932[21] with EOI flow cytometry-determined MRD ≥0.01%. These patients were eligible to enroll and receive post-induction therapy on COG AALL1131[21,22]. Between 08/11/2010 and 03/21/2018, AALL0932 enrolled 9,229 eligible B-ALL subjects; 8,621 non-Down syndrome Philadelphia chromosome-negative subjects had EOI MRD reported (Figure 1). Marrow EOI MRD was ≥0.01% in 1,538(17.8%); because of multiple AALL1131 temporary closures, only 572/1,538 enrolled on AALL1131 for post-induction therapy[21,22] (see Supplemental Methods). EOC MRD was optional on AALL1131 and was reported for 368 EOI MRD-positive SR patients, who form the basis of this report. The median follow-up time from

enrollment to last contact/death/withdrawal for these 368 patients is 1240.5 days. There were no significant differences in patient characteristics between SR EOI MRD-positive subjects who did/did not report EOC MRD (Supplemental Table S1).

MRD

Flow cytometric EOC MRD was determined in the COG central reference labs (University of Washington [BLW] or Johns Hopkins [MJB]) as previously described[20].

Additional Methods described in Supplemental Material.

RESULTS

Among 368 SR patients with EOI MRD≥0.01%, 343 (93.2%) had EOC MRD<0.01%, whereas 25 (6.8%) remained MRD-positive at the 0.01% threshold. Comparing the characteristics of EOI MRD ≥0.01% patients by EOC MRD status, only EOI MRD level (0.01–0.1% versus ≥0.1%) was significantly different on the basis of EOC MRD (P=0.0002) (Supplemental Table S2). Logistic regression analysis showed that higher EOI MRD was strongly associated with likelihood of remaining MRD-positive at EOC, with an odds ratio of 4.2 (95% confidence limits 1.6–11.3, P <0.001) for those with EOI MRD ≥1% versus 0.1–0.99% and an odds ratio of 3.8 (95% confidence limit 1.3–11.1, P <0.001) for patients with EOI MRD 0.1–0.99% versus 0.01–0.099% (Supplemental Table S3). The EOC MRD-positive rates did not differ significantly by cytogenetic subset: 3/25 (12%) with unfavorable cytogenetics (*KMT2A*-rearranged, intrachromosomal amplification of chromosome 21 (iAMP21), or hypodiploidy with <44 chromosomes), 14/222 (6.3%) with favorable cytogenetics (*ETV6/RUNX1* fusion or double trisomies of chromosomes 4 and 10), and 8/121 (6.6%) with neutral cytogenetics (P=0.529) (Supplemental Tables S2, S4).

Post-induction treatment arm on AALL1131 did not impact DFS (P=0.95) for SR patients with EOI MRD ≥0.01%. The EOC MRD-positive rate was not significantly different between the various treatment regimens on the AALL1131 high risk and very high risk sub-studies (Supplemental Table S5)[21,22]. The SR patients with MRD≥0.01% at both EOI and EOC had a significantly worse 4-year DFS compared to EOI MRD-positive patients with EOC MRD <0.01% (72.9±19.0% versus 90.7±2.9%; P=0.0019) (Figure 2A), but 4-year overall survival (OS) was excellent and not significantly different from those with EOC MRD<0.01% (91.7±10.8% versus 95.5±2.0%, P=0.25) (Figure 2B). The 4-year cumulative incidence rate of isolated marrow relapse for EOI MRD-positive patients was 27.1±12.5% for those with EOC MRD ≥0.01% compared to 5.2±1.6% for those with EOC MRD <0.01% (P<0.001) (Figure 2C). Central nervous system (CNS) relapse was rare occurring in 0/25 EOC MRD-positive patients and 6/343 EOC MRD-negative patients, (4 isolated CNS relapse and 2 combined marrow/CNS relapse) (Supplemental Figure S1). Five of the 6 EOC MRD-positive patients who relapsed had EOI MRD ≥0.1%, suggesting those with higher EOI disease burden are at highest risk for relapse (Supplemental Table S6). Given the association between higher EOI MRD and likelihood of having MRD ≥0.01% at EOC, we analyzed the prognostic value of EOC MRD in patients with high (≥0.1%) EOI MRD. Among those with EOI MRD ≥0.1%, the 4-year DFS was 88.8±5.1% for those with EOC MRD <0.01% (N=141) versus 67.7±22.2% for those with EOC MRD ≥0.01% (N=20)

(P=0.0247), demonstrating the prognostic import of EOC MRD even among patients with high EOI MRD (Supplemental Figure S2A).

With recent data suggesting genotype-specific impact of EOI MRD on outcome[23], we attempted to investigate the prognostic impact of EOC MRD on the basis of genetic subtype. For the entire cohort of AALL0932 SR EOI MRD-positive patients, genotype significantly impacted outcome with 5-year DFS of 89.6±10%, 84.3±8, and 70.7±19 for patients with favorable, neutral, and unfavorable cytogenetics, respectively (P=0.0004). For those with EOC MRD ≥0.01%, 4/22 with favorable or neutral cytogenetics relapsed, 2/2 patients with iAMP21 relapsed, and 1 with *KMT2A* rearrangement did not (Supplemental Table S6). While this suggests persistent EOC MRD may be an adverse prognostic factor in SR patients, particularly those with unfavorable cytogenetics, small patient numbers preclude definitive conclusions.

An important limitation of this study is that post-consolidation therapy was not uniform among the EOC MRD-positive patients. Eleven of the 25 EOC MRD-positive patients completed protocol therapy, 2 of those relapsed off therapy, and both remain alive. One patient remains on protocol therapy (maintenance). Thirteen came off protocol therapy for alternative treatment: 8 underwent HSCT in first CR (CR1), one of whom relapsed and died; 4 received alternative therapy without HSCT in CR1, 3 of these relapsed, and one died; and 1 has no follow-up data available (Supplemental Table S6).

DISCUSSION

While rare, EOC MRD-positive SR B-ALL patients present a clinical dilemma given a paucity of existing outcome data. We found that SR B-ALL patients treated on COG protocols who are EOI MRD-positive (≥0.01%) and remain MRD-positive at EOC have significantly inferior DFS but similar OS compared to those who are MRD-negative by EOC. The SR EOI MRD-positive patients who had EOC MRD <0.01% appeared to have superior outcomes to their NCI HR counterparts (4-year DFS 90.7±2.9% on this study vs. 4-year DFS 80.2±4.0% reported previously from COG AALL0232)[20]. Importantly, the outcomes for EOC MRD-positive SR patients (4-year DFS 72.9±19.0%) appear to be better than those of EOC MRD-positive HR B-ALL patients (4-year DFS 55.4±6.8%). Notably, the 4-year OS of 91.7±10.8% for the SR EOC MRD-positive patients treated with a variety of different approaches suggests that many of these patients can be salvaged if they relapse. Prospective analyses of larger, uniformly-treated patient cohorts with a longer duration of follow up are needed to reach definitive conclusions. However, these results suggest that while novel therapeutic approaches warrant testing in patients with EOC MRD-positive SR B-ALL, the routine use of HSCT in first CR may not be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

RER is a consultant for Jazz and Servier. PZ-M is a paid employee of Immunogen. MJBu is a consultant and speaker for Jazz and Amgen and speaker for Servier. SPH has received consulting fees from Novartis, honoraria from Amgen, and owns common stock in Amgen. EAR serves on a DSMB for Celgene and receives research funding (institutional) from Pfizer. MLL is a consultant to MediSix Therapeutics. BLW has received honoraria from Amgen, Seattle Genetics, AbbVie, and Janssen Pharmaceuticals, has research funding (institutional) from Amgen, Seattle Genetics, Pfizer, Juno Therapeutics, BiolineRx, Biosight, and Stemline Therapeutics. MJBo is on the scientific advisory board for Amgen. All other authors have no conflicts of interest to report.

Abbreviations

B-ALL	B lymphoblastic leukemia
ALL	Acute lymphoblastic leukemia
PCR	Polymerase chain reaction
COG	Children's Oncology Group
HSCT	Hematopoietic stem cell transplant
NCI	National Cancer Institute
SR	Standard Risk
HR	High Risk
MRD	Minimal residual disease
EOI	End of induction
EOC	End of consolidation
DFS	Disease-free survival
OS	Overall survival
CNS	Central nervous system
CR	Complete remission

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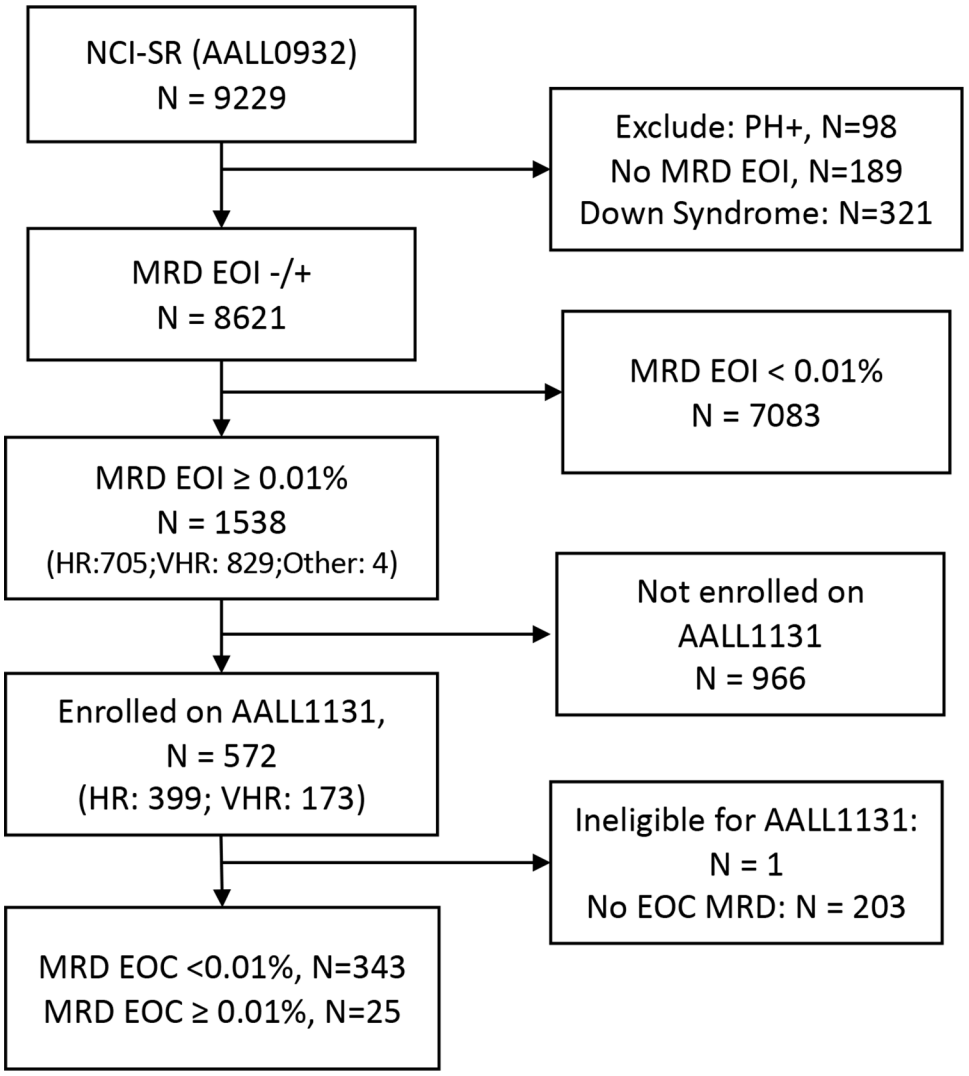

Fig 1:
CONSORT Diagram

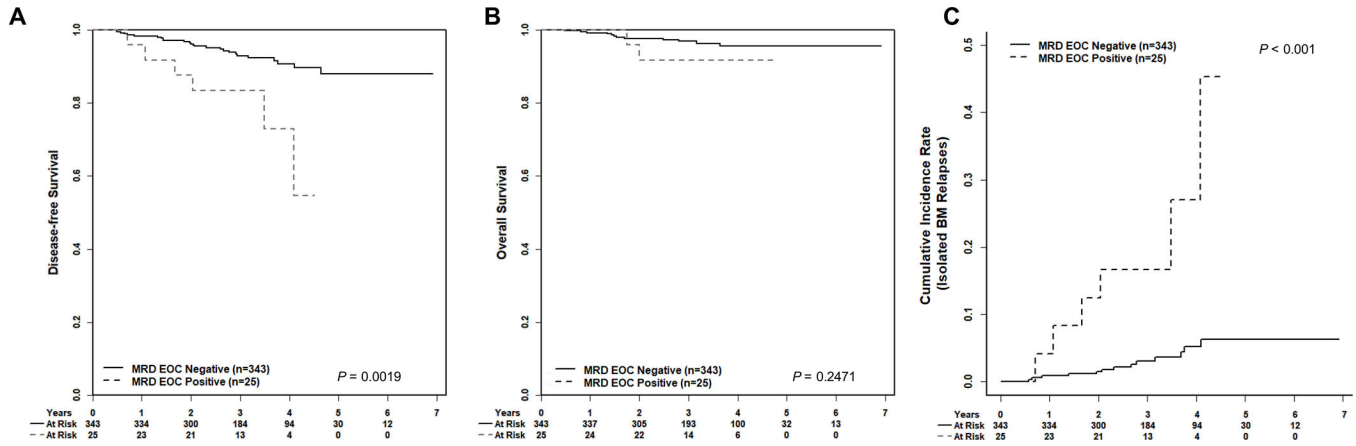

Fig 2: Disease-free survival (DFS); Overall survival (OS); and cumulative incidence of relapse for NCI SR B-ALL EOI MRD-positive patients by MRD at EOC.

A) 4-year DFS ± SE for EOC MRD<0.01% versus EOC MRD ≥0.01%, 90.7± 2.9%, and 72.9 ± 19.0%, respectively. B) 4-year OS for EOC MRD <0.01% versus EOC MRD ≥0.01%, 95.5 ± 2.0% and 91.7 ± 10.8%, respectively. C) 4-year cumulative incidence of isolated bone marrow relapses for EOC MRD <0.01% versus EOC MRD≥0.01%, 27.1 ± 12.5% and 5.2 ±1.6%, respectively.