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618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Minimal Residual Disease-Negative Complete Remission at the End of Induction Is a Prognostic Indicator of Long-Term Survival in Adult Patients with Ph+ Acute Lymphoblastic Leukemia Receiving First-Line Therapy

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Background: Minimal residual disease (MRD) is an established, prognostic indicator for patients with acute lymphoblastic leukemia (ALL), including Philadelphia chromosome-positive (Ph+) ALL. The objective of this study was to evaluate the association between MRD and long-term outcomes (event-free survival [EFS] and overall survival [OS]) in adult patients with Ph+ ALL receiving first-line therapy.
Methods: A systematic literature review (SLR) was performed to identify eligible studies, including interventional and observational studies reporting survival outcomes by MRD status in adults ≥18 years of age with Ph+ ALL receiving first-line therapy. Key outcomes and data elements of interest were EFS, OS, and MRD or MRD-negative complete remission (CR) at end of induction (EOI). Aggregate study-level and individual patient data (IPD) meta-analyses were conducted. The IPD approach included a log-level MRD analysis to evaluate the concordance of deepening levels of molecular response with long-term EFS or OS in patients with CR and an analysis evaluating the utility of MRD-negative CR over CR alone. The analyses were conducted using frequentist and Bayesian approaches with fixed-effects and random-effects models. Kaplan-Meier method with log-rank tests was used for survival analysis. Where applicable, Cox regression method with and without adjustment for prognostic factors were applied.
Results: The SLR identified 19 publications (18 unique studies), 10 (9 unique studies) of which had sufficient MRD and EFS/OS data. Nine studies (n=704) were included in the aggregate study-level analysis; 3 of the 9 studies (Phase II AP24534-11-001 [Jabbour et al. 2015], Phase II GIMEMAINCB 84344-201 [Martinelli et al. 2017], and Phase III GRAAPH-2005 RCT [Chalandon et al. 2015]) had IPD available. MRD was assessed by polymerase chain reaction in all 9 studies. Findings from the aggregate study-level meta-analysis demonstrated a significant long-term survival benefit (EFS and OS) in favor of patients with MRD-negative CR. This significant benefit was generally consistent across analysis types (base-case or sensitivity analyses), analytic models (fixed- or random-effects), and approaches (frequentist or Bayesian). Evidence from the IPD analysis, based on patients with CR, was mostly consistent with the aggregate study-level meta-analysis, supporting MRD-negative CR at the EOI as being predictive of EFS or OS. Log-level MRD analysis showed that patients who are in CR with deeper molecular response (*BCR::ABL1/ABL1* ≤0.01%) at EOI have significantly better long-term EFS and OS compared with patients with other levels of MRD (ie, *BCR::ABL1/ABL1* >0.01%). This significant long-term survival benefit was also demonstrated in patients with MRD-negative CR (*BCR::ABL1/ABL1* ≤0.01%) at EOI compared with patients who were MRD-positive (*BCR::ABL1/ABL1* >0.01%) (**Table 1**) or based on achievement of CR alone (regardless of *BCR::ABL1/ABL1* values).

Results from the IPD analysis standardized for outcome definition, with and without adjustment for prognostic factors (age, gender, white blood cell count at baseline, and stem cell transplant), were consistent with the findings from the log-level MRD analysis. The analysis showed a significant association between MRD-negative/MRD-negative CR status (ie, *BCR::ABL1/ABL1* ≤0.01% threshold) at EOI with improved long-term EFS and OS. The results were significant for EFS in both the adjusted and unadjusted models. The OS results were significant only in the unadjusted model.

Conclusions: These analyses indicate that a deeper molecular response at EOI results in better long-term EFS and OS; MRD-negative CR has a greater prognostic value than CR and is strongly associated with long-term EFS and OS in patients with Ph+ ALL.

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Table 1. EFS and OS for Patients with MRD-Negative CR vs CR (Regardless of MRD Status) at EOI

Survival	MRD-Negative CR	CR (Regardless of MRD Status)
EFS[a]		
Patients, n	82	297
Events, n	37	189
Median, months (95% CI)	77.67 (26.64, NE)	23.89 (17.05, 31.70)
OS[b]		
Patients, n	82	298
Events, n	31	157
Median, months (95% CI)	NE (46.62, NE)	46.49 (34.53, 82.89)

[a]EFS is defined as the time from the last date of week 12 for Study AP24534-11-001 or Study INCB84344-201 or the last date of week 4 for Study GRAAPH-2005 until death due to any cause or relapse.
[b]OS is defined as the time from treatment initiation until death.
CI, confidence interval; CR, complete response; EFS, event-free survival, EOI, end of induction; OS, overall survival.

Figure 1

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