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ORIGINAL REPORT

Minimal Residual Disease–Guided Treatment Deintensification for Children With Acute Lymphoblastic Leukemia: Results From the Malaysia-Singapore Acute Lymphoblastic Leukemia 2003 Study

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose

To improve treatment outcome for childhood acute lymphoblastic leukemia (ALL), we designed the Malaysia-Singapore ALL 2003 study with treatment stratification based on presenting clinical and genetic features and minimal residual disease (MRD) levels measured by polymerase chain reaction targeting a single antigen-receptor gene rearrangement.

Patients and Methods

Five hundred fifty-six patients received risk-adapted therapy with a modified Berlin-Frankfurt-Münster–ALL treatment. High-risk ALL was defined by MRD $\geq 1 \times 10^{-3}$ at week 12 and/or poor prednisolone response, *BCR-ABL1*, *MLL* gene rearrangements, hypodiploid less than 45 chromosomes, or induction failure; standard-risk ALL was defined by MRD $\leq 1 \times 10^{-4}$ at weeks 5 and 12 and no extramedullary involvement or high-risk features. Intermediate-risk ALL included all remaining patients.

Results

Patients who lacked high-risk presenting features (85.7%) received remission induction therapy with dexamethasone, vincristine, and asparaginase, without anthracyclines. Six-year event-free survival (EFS) was 80.6% ± 3.5%; overall survival was 88.4% ± 3.1%. Standard-risk patients (n = 172; 31%) received significantly deintensified subsequent therapy without compromising EFS (93.2% ± 4.1%). High-risk patients (n = 101; 18%) had the worst EFS (51.8% ± 10%); EFS was 83.6% ± 4.9% in intermediate-risk patients (n = 283; 51%).

Conclusion

Our results demonstrate significant progress over previous trials in the region. Three-drug remission-induction therapy combined with MRD-based risk stratification to identify poor responders is an effective strategy for childhood ALL.

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INTRODUCTION

More than 80% of children diagnosed with acute lymphoblastic leukemia (ALL) in developed countries are now long-term survivors.[1-3] This success can be attributed to a combination of factors, including increasingly accurate risk assignment strategies that reduce relapse caused by undertreatment and toxicities caused by overtreatment. However, cure rates for children with ALL treated outside the major US and European multicenter studies have lagged behind, particularly in developing countries.[4]

With contemporary chemotherapy, the prognostic strength of traditional clinical presenting features of ALL is diminishing, whereas established and newly discovered genetic and biologic factors are becoming increasingly more important.[5-7] Early response to therapy is strongly associated with risk of relapse. Initial observations based on morphologic assessment of treatment response[8] have been consolidated by numerous studies performed during the last two decades. Studies of treatment response measured by more sensitive and objective methods that can detect leukemia cells undetectable by morphology (ie, minimal residual disease [MRD]) have provided a rationale for the incorporation of MRD testing in risk assignment strategies.[9-11] In patients with ALL, MRD can be monitored by flow cytometric[12] or molecular methods; among the latter, the clinical usefulness of polymerase chain reaction