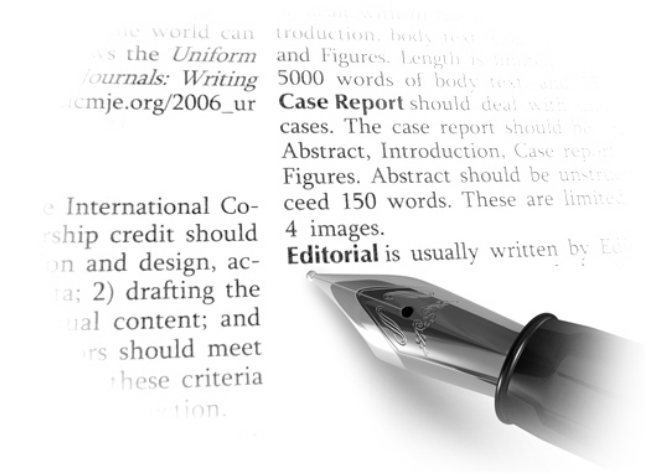

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Editorial

Current treatment for pediatric acute myeloid leukemia

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Pediatric acute myeloid leukemias (AMLs) are a heterogeneous group of diseases that can be classified based on morphology, lineage, and genetics. Recent improvements in the outcomes of pediatric AML reflect the use of intensive chemotherapy and post-remission treatment with additional anthracyclines and high-dose cytarabine or hematopoietic stem cell transplantation (HSCT). Advances in supportive care allowing for the administration of optimally intensive therapy with low morbidity and mortality rates have also contributed to improving the survival rates of patients with pediatric AML. As a result, several groups now achieve complete remission (CR) rates of 80–90%, relapse rates of 30–40%, event-free survival (EFS) rates of 50%, and overall survival (OS) rates of nearly 70% [1]. Along with the improvement of therapeutic strategies, progress in genomic research has revealed numerous somatic, karyotypic, and molecular alterations in pediatric AML. State-of-the-art sequencing technology has identified clinically significant genetic abnormalities that have been since incorporated in clinical practice for risk stratification of adult *de novo* AML [2]. Because pediatric AML has genetic alterations that are distinct from those of adult AML, documentation of pediatric-specific genetic abnormalities is crucial in order to identify new therapeutic targets, as well as for risk stratification [3].

In this issue of *Blood Research*, Song *et al.* [4] reported a retrospective single-institution study evaluating the outcomes of pediatric AML. The 5-year OS and EFS rates improved in the recent cohort (2006–2015) to 70.3% and 56.9%, respectively, compared with the respective 40.0% and 33.3% rates of the earlier cohort (1996–2005). Two remission induction regimens, which include N(4)-behenoyl-1-beta-D-arabinofuranosyl cytosine with idarubicin in the earlier cohort and cytarabine with idarubicin or mitoxantrone in the recent cohort, were utilized, which resulted in similar overall response rates of approximately 85%. In addition, OS and EFS rates did not differ between the two regimens. Currently, remission induction rates have reached 85–90% worldwide [1]. Modified regimens, such as via varying doses or types of anthracyclines, the addition of other agents, and the intensification of cytarabine, have resulted in remission rates similar to those obtained with the standard combination of daunorubicin and cytarabine. Advances in supportive care, along with the various trials of chemotherapy regimens, have also contributed to improved outcomes. Supportive care to reduce the risk of early complications related to the primary disease or to toxicity of chemotherapy and to manage infections, such as bacterial or fungal pathogens, has also steadily improved over the decades.

Risk stratification based on genetic abnormalities is a critical determinant for predicting outcomes of pediatric AML. In the study by Song *et al.*, patients with adverse cytogenetics showed significantly poorer outcomes than those with favorable cytogenetics, including t(8;21) or inv(16). With the progress in sequencing technologies, many genetic abnormalities of prognostic significance have been identified. Mutations of the nucleophosmin 1 gene or biallelic mutations of the CCAAT/enhancer-binding protein-alpha gene are now accepted generally as mutations

conferring favorable prognosis in children [5, 6]. Besides risk stratification at diagnosis, the measurement of minimal residual disease to evaluate the response to therapy is perhaps the best predictor of relapse. Assessments of genetic features at diagnosis and response to therapy have become routine for risk stratification in most current clinical trials.

HSCT is another important treatment modality that has improved the outcomes of AML in children. In the study by Song *et al.* ≥60% of patients received HSCT, which demonstrated the survival benefit of HSCT over chemotherapy alone. Moreover, they also reported that patients who received autologous HSCT showed worse survival than those who received allogeneic HSCT. Therefore, autologous HSCT was abandoned in their recent cohort. Although autologous HSCT has no advantages over chemotherapy, allogeneic HSCT remains a viable option for a significant proportion of patients with pediatric AML. Additionally, while the survival of patients with pediatric AML with favorable risk features is excellent with chemotherapy alone, HSCT continues to be a critical component of treatment for selected patients, particularly those with high-risk or advanced AML. Remarkable improvements have been made in the field of HSCT in children and adolescents over the last decade because of the development of optimal conditioning regimens, more effective graft-versus-host disease (GVHD) prophylaxis, and advancements in post-transplant care. In an experienced transplant center, patients who received HSCT from a matched unrelated donor (URD) showed similar outcomes to those who received HSCT from a human leukocyte antigen (HLA)-matched sibling donor (MSD) [7, 8]. Furthermore, the outcomes of HSCT even with an alternative donor, including transplants using umbilical cord blood or a haploidentical family donor, significantly improved [9, 10]. In Song *et al.*'s study HSCT from MSD showed a favorable outcome of 80%, while that from URD showed a comparable outcome. Although there is no consensus regarding the indication for HSCT upon achieving the first CR, most investigators recommend allogeneic HSCT to patients with high-risk features or a poor response to therapy. Recent advances in HSCT with low transplant-related mortality due to better supportive care, adequate management of infections, effective GVHD prophylaxis, and optimal conditioning, along with an expanded donor pool, justify the application of allogeneic HSCT based on a refined risk group stratification to maximize the outcomes of pediatric AML.

Although the survival in pediatric AML has improved over the last decades, several unresolved issues, including the optimal intensity and combination of chemotherapy, benefits of allogeneic HSCT upon achieving the first CR, and use of risk-directed and response-based therapy, remain. Nationwide collaboration is essential to establish the most effective therapy with the lowest toxicity for pediatric AML. Furthermore, sustained progress in understanding the biology of AML and the concomitant development of new targeted agents for use in combination with conventional chemotherapeutic drugs will further improve the outcomes of pediatric AML.

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