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The Bottom Line

Hematopoietic Cell Transplantation in High-Risk Childhood Acute Myelogenous Leukemia

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In this issue of *Biology of Blood and Marrow Transplantation*, Burke et al. present their findings on the efficacy of allogeneic hematopoietic stem cell transplantation (HCT) in patients with high-risk childhood acute myelogenous leukemia (AML). This limited single-institution study demonstrates that patients with high-risk disease (as defined by cytogenetics/molecular markers) who received allogeneic HCT in first compete remission (CR) have a favorable outcome, similar to those with standard-risk disease.

The role of HCT as consolidation therapy for childhood AML has evolved significantly since Woods et al. first demonstrated that children who received allogeneic HCT from related donors had an improved outcome compared with chemotherapy recipients [1]. This study further demonstrated that pretransplantation chemotherapy can affect posttransplantation survival; patients who received more intensive induction chemotherapy had a significantly lower rate of relapse and more favorable survival after HCT, suggesting that quality of remission (lower residual disease) was an important determinant of post-HCT survival. In this study, although HCT carried higher treatment-related mortality, lower relapse resulted in more favorable outcomes in HCT recipients. This seminal study led to the change in the standard of care in childhood AML in the United States, where patients with newly diagnosed AML with suitably matched related donors were allocated to receive HCT in first CR. Subsequent studies (Children's Cancer Group 2961 and Children's Oncology Group 03P1 pediatric AML trials) allocated all patients with a matched family donor to receive HCT in first CR [2,3]. With the improvements in HLA typing and supportive care, and with broader availability of suitable donors, unrelated HCT has been more broadly used in patients in first CR. Further, re-evaluation of the role of stem cell transplantation in AML in the context of emerging prognostic factors has changed the utility of HCT from a biologic allocation based on donor availability to a more risk-appropriate therapeutic allocation aimed at improving outcome while minimizing risk and toxicity. In this risk-based allocation to HCT, patients with favorable disease would not receive HCT in first CR, whereas those identified to be at high risk of relapse are offered a transplantation in first CR, before an impending relapse. There has been strong rationale to support this approach, where in patients who have favorable survival rates with chemotherapy alone, HCT is reserved for postrelapse management, sparing the majority of patients (>70%) from the short-term and long-term toxicities of allogeneic HCT. Further, as use of HCT from the best available donor in second or subsequent CR remains the standard of care for relapsed AML, for those who are at extremely high risk of relapse after an initial remission, awaiting relapse may eliminate any hope of achieving a second CR, thus justifying HCT when remission is achieved and before almost inevitable relapse. Such a risk-based therapy allocation is an attractive therapeutic model, but its utility is entirely dependent on the availability of clinically informative prognostic markers. Until recently, cytogenetic alterations were the only means of risk identification in AML, where those with core binding factor AML were shown to have a lower risk of relapse, and those with monosomy 7 (-7), or monosomy5/deletion 5q(-5/del5q) were at high risk of failure. However, the majority of children with AML lack clinically informative karyotypes and are not amenable to risk-based therapy allocation based solely on cytogenetic subgroups.

More recently, somatic mutations in several genes (FLT3, NPM, CEBPA) have been shown to correlate with outcome [4-6], where those patients with FLT3 internal tandem duplications (FLT3/ITD) with high allelic ratio have a high rate of failure [4], and those with NPM or CEBPA mutations have a lower risk of relapse and more favorable outcome. Cumulatively, clinically significant cytogenetic alterations or somatic mutations account for nearly 35% of cases of AML in children, leaving more than one-half of children with AML without a prognostic biomarker. Although other clinically significant mutations have been demonstrated in adult AML, such mutations are either not seen in childhood AML (IDH1, DNMT3A mutations) [7,8] or are not independently prognostic (WT1 mutations) [9].

Initial response to chemotherapy has been used to predict outcome in patients with leukemias. In patients with AML without an informative genomic biomarker, response to therapy as defined by multidimensional flow cytometry (MDF) can provide a powerful tool for risk identification. Studies utilizing sensitive second-generation MDF technology have shown that in standard-risk patients, presence of residual disease (RD) after the initial course of chemotherapy was highly associated with eventual relapse [10,11].

Combining the molecular risk factors with the postinduction response assessment by MDF allows risk

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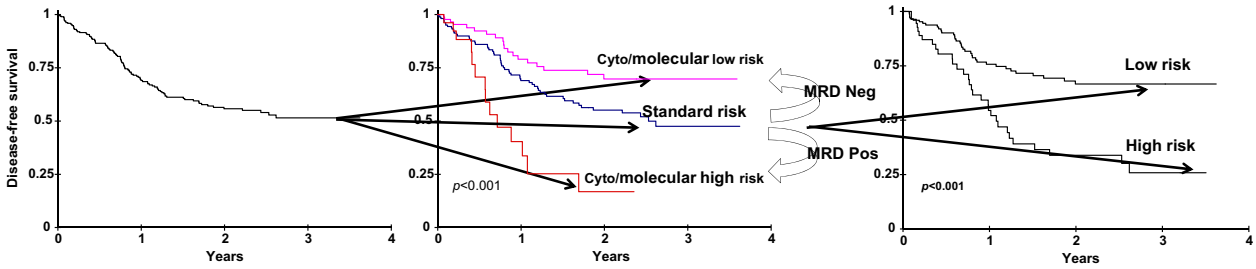

Figure 1. Incorporation of cytogenetic, molecular, and multidimensional flow cytometry data creates a 2-tier risk stratification schema. Informative cytogenetics and mutation data provide a 3-tier risk stratification schema, where approximately 35% of patients have either low-risk (CBF AML, NPMc+ or CEBPA mutations) or high-risk (-7, -5/del5q or FLT3/ITD high AR) disease, and the remaining patients without informative markers are considered to have standard risk. Presence or absence of residual disease after induction chemotherapy can identify patients at high or low risk of relapse in the standard risk patients. Use of cytogenetic, molecular, and multidimensional flow cytometry data can be used to assign risk status to nearly all patients with AML.

assessment in all patients with AML, where those with informative molecular markers are assigned to the appropriate risk class and those without such markers (standard risk) are assigned based on the presence or absence of RD at the end of induction chemotherapy. Such an approach allows appropriate risk-based therapy allocation for nearly all patients by creating a 2-tier risk-allocation system where patients are assigned to either the high-risk (cytogenetic/molecular high risk or standard risk with RD) or low-risk (cytogenetic/molecular low risk or standard risk without RD) arm based on the most comprehensive set of prognostic data available (Figure 1). This 2-tier risk stratification schema was recently incorporated into the ongoing Children's Oncology Group phase III AML trial.

The manuscript presented by Burke et al. highlights the potential benefit of allogeneic stem cell transplantation in high-risk AML using contemporary donor source, conditioning, and supportive care to optimize outcome by minimizing treatment-related mortality and relapse [12]. It is especially notable that more than one-half of high-risk AML patients received double cord transplantation, shown to be associated with lower risk of relapse [13,14], which, if validated, provides additional tools for targeting high-risk AML patients. Some studies have brought into question the efficacy of allogeneic stem cell transplantation for high-risk AML [15]; however, unless a randomized trial to assess the efficacy of HCT in this high-risk population can be devised (unlikely), efforts to harness and optimize the graft-versus-leukemia effect of allogeneic HCT need to continue to improve the survival in this very high risk patient population.

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