Cellular Therapies in Acute Lymphoblastic Leukemia

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- Hematopoietic stem cell transplants
- Chimeric antigen receptor

In general, adult patients diagnosed with acute lymphoblastic leukemia (ALL) have a poor prognosis. Overall, more than 6 of 10 adult patients diagnosed with ALL will ultimately die of the disease.[1] The prognosis is more favorable in the pediatric population, with greater than 8 of 10 patients experiencing long-term survival.[1,2] In most cases, up-front therapy involves long-term, toxic, and complex chemotherapy regimens. However, for adult and pediatric patients, failure to experience response to up-front chemotherapy or disease relapse after remission portends a dismal prognosis.[3–5] These findings suggest that novel approaches to adoptive cell therapies are needed to improve the outcome of patients with ALL. Recent advances in the understanding of tumor biology and immunology, combined with enhanced gene transfer technologies, have increased the interest in the field of adoptive cell therapy among investigators seeking alternative treatment approaches for this disease.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the earliest and most studied form of adoptive cell therapy for leukemia. The original guiding principle of

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allo-HSCT was that it allows for higher-dose chemotherapy with or without additional total body irradiation, ideally resulting in consequent ablation of both tumor and normal bone marrow stem cells, the latter of which is subsequently rescued by the infusion of nonmalignant hematopoietic stem cells from a healthy allogeneic donor. Clinical studies of allo-HSCT illustrate an additional immunologic benefit of this approach, wherein donor T cells may mediate a beneficial graft-versus-leukemia (GvL) effect through donor T cells recognizing antigens present on residual tumor cells. This GvL effect was first described in patients with acute leukemia, including ALL,[6] and is best illustrated by higher relapse rates in patients who have received donor grafts from identical twin siblings and patients treated with T-cell–depleted grafts designed to minimize graft-versus-host disease (GvHD).[7] Consistent with this donor T-cell–mediated GvL effect is the finding that patients who experience acute or chronic GvHD after allo-HSCT are less likely to experience disease relapse compared with those who experience little or no GvHD after treatment.[7] Unfortunately, because this GvL benefit is met with the untoward consequences of GvHD and associated morbidity and mortality, the benefit of allo-HSCT remains debatable.

Human Leukocyte Antigen–Matched Donor Allo-HSCT in ALL as First Remission Therapy

Although a large body of clinical data exists using myeloablative, matched related donor allo-HSCT in patients with ALL, debate remains regarding the use of matched related donor allo-HSCT as a postremission therapy in the setting of adult patients with ALL. Based on the poor overall prognosis of this disease, the contention remains that all patients with a suitable matched related donor should undergo allo-HSCT. However, this contention should take into account the significant treatment-related mortality of 20% to 30% associated with allo-HSCT[8] in addition to quality-of-life considerations. Moreover, patients' age and comorbidities must be carefully considered when determining transplant eligibility to achieve the potential benefit of this modality in terms of overall survival.

Most patients with ALL (>80%), adult and pediatric, will experience disease remission after one or two cycles of induction chemotherapy.[1] Whether patients in first complete remission benefit with matched related donor HSCT versus chemotherapy alone in the adult ALL setting is a critical question with conflicting answers. Adult patients with ALL traditionally have been divided into standard- and high-risk groups based on several clinical and genetic criteria. High-risk patients are variably defined as those older than 35 years, with an elevated white blood cell count at diagnosis, a delayed response (>28 days) after initial induction chemotherapy, and with genetically adverse features, including the presence of the Philadelphia chromosome (Ph^+), t(1;19), and t(4;11). In high-risk transplant-eligible patients, myeloablative matched related donor allo-HSCT is currently the preferred consolidation treatment in the setting of first complete remission,[9] given several large clinical trials and a meta-analysis showing benefit compared with either chemotherapy alone or autologous HSCT.[10–13] However, in contrast to these findings, data from the PETHEMA ALL-93 trial and the international collaborative trial conducted by the Medical Research Council (MRC) and the Eastern Cooperative Oncology Group (ECOG), MRC UKALL XII/ECOG E2993, failed to show a similar advantage for patients with high risk disease, again placing the role of matched related donor HSCT for high-risk patients into question.[14,15]

The high-risk category of patients with ALL harboring Ph+ deserves a separate discussion for several reasons, including (1) poor prognosis predominately secondary to relative chemoinsensitivity,[16] (2) predilection for older patients who may not be able