Hematopoietic Cell Transplantation and Cellular Therapeutics in the Treatment of Childhood Malignancies

Kanwaldeep Mallhi, MD[a], Lawrence G. Lum, MD, DSc[b], Kirk R. Schultz, MD[a,*], Maxim Yankelevich, MD[c]

KEYWORDS

• Hematopoietic cell transplantation • Cellular therapy • Children • Adolescents • Cancer

KEY POINTS

- Hematopoietic cell transplantation continues to be the only established immune therapy for childhood cancer.
- Cellular therapy shows great promise to either replace HCT and act as an adjuvant to standard chemotherapy for childhood cancer.
- Survival after HCT has improved primarily due to new approaches to decrease it's toxicity.
- Better understanding of the immune mechanisms of the graft-versus-leukemia/tumor effect are needed to improve the efficacy of HCT.

INTRODUCTION

Hematopoietic cell transplantation (HCT) represents the most common and effective form of immunotherapy for childhood malignancies. The role of the graft-versus-leukemia (GVL) effect in allogeneic HCT has been well established in childhood malignancies, but is also associated with short-term and long-term morbidity. HCT may be ineffective in some settings at obtaining control of the malignancy, and as such cannot

[a] Department of Pediatrics, BC Children's Hospital, 4480 Oak Street, Vancouver, British Columbia V6H 3V4, Canada; [b] Department of Oncology, Barbara Ann Karmanos Cancer Institute, Wayne State University, 3901 Beaubien, Detroit, MI 48201, USA; [c] Division of Hematology/Oncology, Children's Hospital of Michigan, Wayne State University, 3901 Beaubien, Detroit, MI 48201, USA

* Corresponding author. Division of Hematology/Oncology/Bone Marrow Transplantation, Department of Pediatrics, BC Children's Hospital, University of British Columbia, 4480 Oak Street, Vancouver, British Columbia V6H 3V4, Canada.
E-mail address: kschultz@mail.ubc.ca

Pediatr Clin N Am 62 (2015) 257–273
http://dx.doi.org/10.1016/j.pcl.2014.10.001 **pediatric.theclinics.com**
0031-3955/15/$ – see front matter

be used as a universal cancer immunotherapy. Novel therapies using dendritic cell vaccinations, tumor-infiltrating lymphocytes, and chimeric antigen receptor T cells are being evaluated as potential adjuvants to HCT.

Hematopoietic Cell Transplantation

Allogeneic HCT refers to the transfer of hematopoietic stem cells from one individual to another with the intent to obtain lifelong engraftment of the administered cells. The use of allogeneic HCT as a cellular immune therapy for acute leukemia first became feasible in the early 1960s after the identification and typing of major histocompatibility complexes (human leukocyte antigen [HLA] system). In the 1970s Thomas and colleagues[1] cured several patients with end-stage leukemia by using HLA-identical siblings after ablating the recipient marrow with total-body irradiation combined with cyclophosphamide. It was evident that the occurrence of graft-versus-host disease (GVHD) reduced the incidence of leukemic relapse, suggesting that donor lymphocytes can eradicate tumor cells that survive preparative regimens.[2]

FACTORS THAT AFFECT THE OUTCOME OF HEMATOPOIETIC CELL TRANSPLANTATION

The outcome and efficacy of HCT in malignancies is influenced by several factors, including the underlying disorder, the level of residual tumor, donor source, HLA matching, the degree of graft-versus-leukemia/tumor (GVL/T) effect, and the toxicities associated with the preparative chemotherapy regimens.

Donor Source

Various allogeneic graft sources have the potential to produce a potent antineoplastic GVL/T effect to sustain complete remission of malignant disease. Donor sources for HCT in children include cells from bone marrow (BM), umbilical cord blood (UCB), or mobilized peripheral blood (PBSC) from related or unrelated donors. In addition to the type of the allogeneic graft, secondary non-HLA selection factors such as age of the donor, sex of the donor, total cell count, cytomegalovirus status, and ABO blood groups may contribute to the selection of a donor. However, the most important selection criterion for a donor source is HLA matching. At present, the role of high-resolution matching at HLA-A, HLA-B, and HLA-DRB1 is clearly established. However, the significance of the other loci, including HLA-C, HLA-DQ, HLA-DRB3 and DRB5, and HLA-DPB1, is less clear and is currently under investigation.[3]

HLA-identical sibling donors are considered the preferred stem cell source for allogeneic HCT; they have less transplantation-related mortality, acute GVHD (aGVHD), and chronic GVHD (cGVHD), along with better disease-free and overall survival (OS) than the unrelated donors.[4] Past studies have shown that use of a PBSC source produces a more rapid hematopoietic reconstitution; however, they are associated with a significant increase in cGVHD.[5] Not only is cGVHD significantly higher for patients receiving PBSC in comparison with BM (33% vs 19%, respectively; $P<.001$) but in the pediatric population treatment-related mortality, treatment failure, and overall mortality are also higher in the PBSC group.[6] The use of antithymocyte globulin (ATG) in the preparative regimen lowers the incidence of cGVHD.[7] A distinct advantage of unrelated donor UCB or haploidentical related donors is their rapid availability, and transplantation with cord blood requires less stringent HLA matching than transplant with bone marrow or peripheral stem cells. In general, mismatched cord blood cells are less likely than BM to cause both