Pediatric bone marrow transplantation

K.W. Chan, MD

Bone marrow transplantation (BMT) is used to reconstitute hematopoiesis in patients who have received myeloablative therapy for malignancy, marrow failure, and immunodeficiency syndromes. In the past decade there have been major advances in broadening the scope of application and in improving the margin of safety in BMT. Pediatric patients represent a disproportionately large segment of the patient population undergoing BMT and in general enjoy success from the procedure.

Advances in allogeneic marrow transplantation

BMT using an allogeneic (family or unrelated) donor has been used extensively in children with leukemia or aplastic anemia. Long-term disease-free survival for human leucocyte antigen (HLA) -matched related donor recipients is shown in Table 1.

TABLE 1. LONG-TERM DISEASE-FREE SURVIVAL FOR HLA-MATCHED RELATED DONOR RECIPIENTS

Acute leukemia	First complete remission (CR)	50–65%
Acute leukemia	> First CR	25–35%
Myelodysplastic syndrome		30–60%
Severe aplastic anemia		70–90%

Improved treatment outcome can be attributed to the following factors.

Timely referral

Patients are being referred for BMT at an earlier stage of their disease, i.e., during first or second complete remission (CR). There is a correlation between the risk of leukemia relapse after BMT and the stage of the malignancy at referral.[1] Patients with advanced leukemia also are more likely to perform poorly and are prone to treatment-related morbidity and mortality from BMT.

Hematopoietic recovery

A number of recombinant hematopoietic growth factors were introduced in the past few years that were found to reduce the duration of neutropenia and the incidence of bacterial sepsis before marrow engraftment. The severity of oral mucositis also may be reduced. Early discharge from the hospital was reported in some series. Newer growth factors that may speed up platelet recovery are being investigated.

Opportunistic infections

Opportunistic infections due to immunodeficiency after BMT are common. Acyclovir during the initial period of transplantation has reduced the incidence of herpes simplex virus (HSV) reactivation. High-dose acyclovir has been shown to decrease cytomegalovirus (CMV) reactivation.[2] Ganciclovir, when combined with intravenous gammaglobulin, is effective in eradicating CMV infection.[3] Prophylactic administration of ganciclovir, either routinely or with the first positive surveillance, in the first 3 to 4 months after BMT, has nearly eliminated CMV disease in our patient population. For patients who are CMV seronegative, restricting transfusion only to CMV-negative blood products only is effective to prevent primary CMV infection.

Graft-vs-host disease (GVHD)

Even with fully matched family donors, acute GVHD occurs in 40–70% of BMT cases.[4] The incidence and severity of GVHD is somewhat lower in children, especially those with young donors. Prophylaxis of acute GVHD is more effective than treating established disease. Depletion of mature T lymphocytes from the marrow graft before infusion is effective. A combination of cyclosporin and methotrexate also is commonly used and is more effective than either agent used alone. Cyclosporin inhibits 1L-2 production and 1L-2 receptor expression, thus preventing T-cell activation at its earliest stage. Methotrexate also suppresses donor T-cells but increases the severity of mucositis and delays marrow engraftment. It is now generally given during the first 2 weeks after BMT.

Patient selection

Indications for BMT have become more clearly defined.[1,5] For acute lymphoblastic leukemia (ALL), most BMT are performed during second hematologic remission. Children whose disease relapsed more than 6 to 12 months after completing initial chemotherapy re-

spond well to further chemotherapy and generally are not considered for BMT. BMT should be reserved for those who fail early, i.e., while on treatment or soon after cessation of chemotherapy. Patients with relapsed T-cell leukemia should be considered for BMT. On the other hand, some patients with ALL have features associated with short, leukemia-free survival. These include infants and patients with specific karotypic abnormalities of their leukemic cells, including t (9;22) and 11q23 changes. Children who fail to respond promptly to chemotherapy and who do not enter complete remission as expected are also at high risk of early leukemic relapse. High-dose therapy followed by allogeneic BMT in first CR is being tried for these patients.

For acute nonlymphocytic leukemia, most centers still perform BMT for all patients in first CR, partly because children tolerate the procedure better than adults. Selected groups of patients may not require BMT due to their favorable prognosis, e.g., acute promyelocytic leukemia and patients who enter remission quickly.

Late complications

Chronic GVHD occurs in 20–50% of long-term survivors.[6] Older age, prior acute GVHD, use of donor white cell transfusions, and prior HSV infections are known risk factors. Mononuclear cell infiltrate followed by fibrosis is present in the skin, lips, salivary glands, and liver. Clinical manifestations include the sicca syndrome (dry mouth, reduced tear production, and mucosal abnormalities of the genital and respiratory tract), lichen planus- or scleroderma-like skin reaction, esophageal and intestinal fibrosis with dysphagia and malabsorption, obstructive airway disease, thrombocytopenia, and hepatic dysfunction. Prolonged treatment with steroids and other immune suppressive agents is required.

Other long-term, regimen-related organ dysfunctions include hypothyroidism, gonadal failure, cataracts, dental caries, and leukoencephalopathy. Second malignancies have occurred in 4% of the long-term survivors after BMT. This included B-cell lymphoma, carcinoma of the head and neck and skin, as well as brain tumors.

Use of unrelated marrow donors for BMT

Only one-third of the BMT candidates have a matched family member for marrow donation. Large registries of volunteer donors have been established in the past decade to provide an alternate source of bone marrow. The National Marrow Donor Program (NMDP) in Minneapolis now has more than 1.3 million names and is linked by computers to other international registries in the United Kingdom, Canada, France, Holland, Australia, Israel, and Japan. The increase in size of the donor pool and advances in tissue typing technology have reduced the turnaround time for donor research from an average of 4–6 months to 2–3 months. In 1993, a search for unrelated marrow donor was successful half of the time, and increasing numbers of BMT are being performed using these donors. Unfortunately, the percentage of minority ethnic donors in many registries remains very small, so the chance of identifying donors for this patient population remains remote. Compared with related-donor transplants, these procedures are associated with a higher risk of acute GVHD and graft failure. However, the risk of leukemic relapse seems to have decreased so that the cure rate among leukemic patients with good prognostic features is similar for both types of donors. Overall, children receiving unrelated donor transplants have a more favorable outcome than do adults patients.

Autologous stem cell transplants

Rationale

Many common childhood malignancies are sensitive to chemotherapeutic effects, and cure is common in localized stages after adjuvant chemotherapy. For patients with recurrent disease, the steep dose-response relationship of some chemotherapeutic agents can be exploited utilizing bone marrow or peripheral stem cell rescue to minimize the effect of myelosuppression. Chemotherapeutic agents suitable for this approach should have myelotoxicity as their most important side effect and have insignificant extramedullary complication with increasing dose increments. Most drugs that fulfill these criteria are alkylating agents, including cyclophosphamide, ifosfamide, melphalan, thiotepa, etoposide, BCNU, and carboplatin. A maximum dose escalation of 5- to 30-fold beyond the conventional dose range is possible.

Results

A number of pediatric solid tumors have been treated with high-dose chemotherapy and autologous stem cell transplants.[7,8] These include metastatic neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma. Smaller series involving osteosarcoma, and Wilms' and brain tumors also have been published.

Long-term, disease-free survival after autologous BMT is described in Table 2.

Table 2. Long-term disease-free survival after autologous BMT

	Remission	*Relapsed*
Neuroblastoma	30–40%	10–20%
Ewing's	10–20%	8–23%
Rhabdomyosarcoma	28%	12%

As expected, the best results were obtained when this approach was used as consolidation therapy for disseminated disease before treatment failure was apparent. Patients with recurrent diseases frequently demonstrated response to high-dose therapy but almost all had transient remission, and tumor progression became apparent. Newer approaches, including multiple courses of high-dose therapy and post-transplant immune modulation, are being investigated.

Peripheral blood stem cell (PBSC) transplantation

Hematopoietic stem cells are present in the circulation and have been shown to reconstitute durable marrow function after high-dose therapy. Collection of PBSC is indicated when bone marrow harvest is inappropriate or unsatisfactory, such as tumor infiltration of bone marrow or prior extensive pelvic irradiation. PBSC is collected by an automated computerized cell separator during the recovery phase rebound of chemotherapy-induced hypoplasia or after priming the patient with recombinant hematopoietic growth factors. Normally three to five collections are sufficient, and most children tolerate the procedure well. Recovery of hematologic functions seems to be more rapid after PBSC reinfusion compared with autologous marrow rescue. Part of the transplant procedure can now be carried out on an ambulatory basis. The availability of a large number of hematopoietic progenitors also allows repeated cycles of high-dose therapy to be administered.

Dr. Chan is chief, Pediatric Bone Marrow Transplant Section, Department of Pediatrics, University of Texas M.D. Anderson Cancer Center, Houston, Texas.

1. Horowitz MM, Bortin MM: Results of bone marrow transplants from human leukocyte antigen-identical siblings donor for treatment of childhood leukemias — a report from the International Bone Marrow Transplant Registry. Am J Pediatr Hematol Oncol 15:56–64, 1993.
2. Meyers JD, Reed EC, Shepp DH, Thornquist M, Dandliker PS, Vicary CA, Fluornor N, Kirk LE, Kersey JH, Thomas ED, et al: Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. N Engl J Med 318:70–5, 1988.
3. Goodrich JM, Mori M, Gleaves CA, Du Mond C, Cays M, Ebeling DF, Buhles WC, De Armond B, Meyers JD: Early treatment with ganciclovir to prevent cytomegalovirus disease after allogeneic bone marrow transplantation. N Engl J Med 325:1601–7, 1991.
4. Storb R, Deeg HJ, Pepe M, Applebaum F, Anasetti C, Beatty P, Bensinger W, Berenson R, Buckner CD, Clift R, et al: Methotrexate and cyclosporine versus cyclosporine alone for prophylaxis of graft-versus-host disease in patients given HLA-identical marrow grafts for leukemia: long-term follow-up of a controlled trial. Blood 73:1729–34, 1989.
5. Dopfer R, Henze G, Bender-Görtze C, Ebell W, Ehninger G, Friedrich W, Godner H, Klingebiel T, Peters C, Riehm H, et al: Allogeneic bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission after intensive primary and relapse therapy according to the BFM and CoALL protocols: results of the German Cooperative Study. Blood 78:2780–84, 1991.
6. Sullivan KM, Agura E, Anasetti C, et al: Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol 28:250–59, 1991.
7. Ladenstein R, Hartmann OS, Pinkerton CR: The role of megatherapy with autologous bone marrow rescue in solid tumors of childhood. Ann Oncol 45–58, 1993.
8. Takane Y, Watanabe T, Abe T, et al: Experience with peripheral blood stem cells collection for autografts in children with active cancer. Bone Marrow Transplantation 10:241–48, 1992.

New Diplomates

The American Board of Pediatric Dentistry is pleased to announce the following new Diplomates:

Mathew S. Ausmus – Santa Rita, GU
Jed M. Best – New York, NY
JoAnn C. Boraas – Richfield, MN
Stephen D. Cochran – Jacksonville, FL
Alan B. Dowell – Flagstaff, AZ
Glen F. Ehrenman – Commack, NY
Paul J. Engibous – APO AE
Catharine A. Enright – Atlanta, GA
Sidney R. Gallegos – Federal Way, WA
Marcellious Gladney – Claremore, OK
Curtis Goho – APO AE
Laurie A. Gormley – Las Cruces, NM
Carole L. Havelka – Newton, MA
Stephen M. Heaney – Orland Park, IL
James L. Hutton – Columbia, TN
Ammar A. Idlibi – Bristol, CT
Jenny L. Ison – Louisville, KY
Rhonda M. Kavee – New York, NY
Martha A. Keels – Durham, NC
Ari Kupietzky – Jerusalem, Israel
David F. Laughlin – York, PA
Margaret E. Lochary – Matthews, NC
Vivian F. Lopez – Berkeley, CA
David S. Maddox, II – Gurnee, IL
Robert J. Malek – APO AP
Mauricio Marcushamer – San Antonio, TX
Carol G. McKown – Indianapolis, IN
Stephen C. Mills – Scarborough, ME
Joe S. Olsen – Sioux Falls, SD
Michael G. Page – Brandenberg, KY
Adolfina M. Polk – APO AP
Richard J. Prichard, II – Ft. Benning, GA
Daniel R. Ravel – APO AE
Robert L. Ripley – Marysville, CA
Mark Rogow – APO AE
Deirdre R. Sams – Augusta, GA
Sandra P. Schwann – Calgary, Canada
Bradley R. Smith – Denver, CO
Scott D. Smith – Denver, CO
Mark S. Sorin – Highland Park, IL
Barton D. Swarr – Raleigh, NC
Leslie K. Tanimura – Louisville, KY
John H. Unkel – Morgantown, WV