Pediatric Bone Marrow Transplantation: Current Progress and Future Prospects
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Pediatrics 1983;72;818-822

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drome for which amiodarone therapy was preferred. Fortunately, medically refractory and surgically inaccessible Kent bundles are exceedingly rare, and long-term amiodarone therapy is, therefore, not often necessary.

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REFERENCES
of sustained tachyarrrhythmias in children with the Wolff-
2. Rosenbaum MB, Chiale PA, Halpern MS, et al: Clinical
efficacy of amiodarone as an antiarrhythmic agent. Am J
Cardiol 1976;38:934
treatment of refractory supraventricular and ventricular
4. Leak D, Eydt JN: Control of refractory cardiac arrhythmias
with amiodarone. Arch Intern Med 1979;139:425–428
effects of amiodarone in patients with resistant paroxysmal
tachycardias. Br Heart J 1980;44:91–95
de l'amiodarone intra-veineux chez l'homme. Arch Mal
Coeur 1977;70:219–227
1979;60:1426–1427
8. Sobol SM, Rakita L: Pneumonitis and pulmonary fibrosis
associated with amiodarone treatment: A possible complica-
tion of a new antiarrhythmic drug. Circulation 1982;
65:819–824
9. Harris L, McKenna WJ, Rowland E, et al: Side effects of
long-term amiodarone therapy. Circulation 1983;67:45–51
reactions during amiodarone therapy, abstracted. Circula-
tion 1983;66:II–224
effects of amiodarone therapy, abstracted. Circulation
1983;66:II–224
12. Koren G, Hesslein PS, MacLeod SM: Digoxin—Toxicity
amiodarone (AM) on thyroid function in children, ab-
stracted. Pediatr Res 1983;17:161A
of supraventricular tachycardia in infants and children. Am
J Cardiol 1980;46:781

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Progress and Future Prospects

Allogeneic bone marrow transplantation (BMT) has been applied with increasing frequency and
success to the treatment of children with severe immune deficiency disease,1,2 aplastic anemia,3,4
and the acute leukemias.5–8 Patients with these otherwise rapidly fatal diseases receive an intra-
venous infusion of marrow from a healthy donor. The healthy marrow either “replaces” the deficient mar-
row of children with immune deficiency or aplastic anemia, or “rescues” the marrow of children who
have received ablative antileukemic therapy. The resultant engraftment makes the patient a chimera,
with reconstitution of mature hematopoietic and immunologic cells of donor origin. When successful,
this results in long-term survival with normal marrow function, no recurrence of the original disease,
and a return to normal childhood activity and function with only a few irreversible but major side
effects (such as infertility following total body ir-
radiation).9

This desired result occurs in approximately half
of the patients currently receiving transplantation under optimal circumstances for the above dis-
ases.10 These successes depend on four major fac-
tors.

First, the immune system of the recipient must
not be allowed to reject the donor’s bone marrow.
Potent immunosuppressive pretransplant “condi-
tioning” is required, but is not always effective.
This includes varying combinations of cyclophos-
phamide and busulfan or total body irradiation,
depending on the patient’s disease and immune
status.

Second, the T lymphocytes included with the
donor bone marrow must not be allowed to recog-
nize and destroy host tissues; otherwise the con-
dition recognized as graft versus host disease will
occur. A major factor in preventing graft versus
host disease involves the avoidance of any foreign
major histocompatibility (HLA) antigens which
may serve as targets for donor T-lymphocyte at-
tack.11,12 This is currently accomplished by only
transplanting marrow from an HLA identical sib-

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on their ability to bind soybean agglutinin and sheep RBCs. Initial results with immunodeficient children receiving T-lymphocyte-depleted HLA mismatched marrow prepared by this approach have been encouraging, although graft versus host disease has not been totally avoided. This result has stimulated the development of other approaches designed to thoroughly remove T lymphocytes from marrow using a more convenient treatment to allow T-cell depletion of the larger volumes of marrow needed for BMT of adults and older children with leukemia or aplastic anemia.

A number of monoclonal antibodies specific for human T cells have been identified. Several centers have shown that in vitro pretreatment of bone marrow with anti-T-cell monoclonal antibody alone does not abrogate graft versus host disease; apparently, viable antibody-coated T cells are not entirely removed by the host's reticuloendothelial system and can therefore still cause graft versus host disease. Thus the T cells must be destroyed or removed prior to infusion. The in vitro addition of baby rabbit serum as a complement source to marrow treated with anti-T-cell antibody can efficiently deplete T cells and abrogate T-cell function. This may enable the infusion of HLA-matched or mismatched marrow with little or no resultant graft versus host disease. Preliminary encouraging results with this approach have been reported. We are continuing with this technique, and so far have found far less graft versus host disease than anticipated, both with matched and mismatched donors. Other similar approaches may utilize monoclonal anti-T-cell antibodies bound to potent toxins to deplete conveniently marrow of T cells in vitro. This is a new area of clinical research. As the graft versus host disease problem is avoided by T-cell depletion techniques, new unforeseen problems may arise. The stability of hematopoietic engraftment and the recovery of normal T-cell function following a T-depleted BMT are both concerns that will require more detailed evaluation.

LEUKEMIC RELAPSE

Presently, leukemic patients receive total body irradiation and cyclophosphamide prior to most transplants. The goal is to eliminate all leukemic cells prior to hematopoietic rescue with allogeneic marrow. That leukemia recurs for many patients with acute lymphoblastic leukemia, and a smaller proportion of those with acute myelogenous leukemia, is indicative of survival of leukemic cells resistant to radiation and cyclophosphamide. Many centers are trying to enhance the ablation of these residual leukemia cells by increasing the dose of total body irradiation, while avoiding increased radiation toxicity by fractionating this higher radiation dose. One center has replaced cyclophosphamide (a good immunoablative drug that has only moderate activity against lymphoid leukemias) with the more potent antileukemic agent, cytosine arabinoside. Another ongoing trial is providing patients' "maintenance" chemotherapy posttransplantation. The rationale for further chemotherapy is that the few remaining leukemic cells may be sensitive to maintenance 6-mercaptopurine despite resistance to cyclophosphamide and total body irradiation. Preliminary data with all three of these approaches suggest some benefit.

A retrospective analysis by the Seattle Bone Marrow Transplantation team demonstrated a surprising result. Patients with moderate or severe graft versus host disease following an HLA-matched sibling BMT for acute leukemia have fewer leukemic relapses than patients with mild or no graft versus host disease. As treatment for graft versus host disease has improved, the Seattle team (but not some others) have found that the decreased incidence of leukemic relapses in patients with graft versus host disease is also associated with a better chance for survival. This may potentially be due to the "antileukemic" effect of the immunosuppressive drugs used to treat the active graft versus host disease. In contrast, this may result from an antileukemic immune response triggered in parallel with the graft versus host disease. This graft versus leukemia effect has been directly observed in some patients, and clearly demonstrated in murine bone marrow transplants for leukemia. In fact, the T cells that mediate this murine graft versus leukemia effect can be effective when given alone without need for hematopoietic ablation and subsequent reconstitution of marrow function by BMT. Under appropriate experimental conditions, this form of "adoptive immunotherapy" can eliminate all residual (chemotherapy-resistant) leukemic cells, and supercede the need for a bone marrow transplant. It remains unclear whether these graft versus leukemia responses may be directed against leukemia-specific antigens, or minor locus histocompatibility antigens preferentially expressed on the leukemia cells.

In man, parallel antileukemic immune responses can be triggered and quantitated in vitro. If effective and controllable, this form of intentional T-cell transfer may become included as a routine component of allogeneic bone marrow transplants for patients with leukemia. Conceivably, conventional chemotherapy combined with effective adoptive immunotherapy could replace the need of leukemia patients for BMT.

SUMMARY

Ongoing clinical and laboratory research is being
ling. Any healthy sibling has a 25% chance of being completely identical with the patient for both the maternal and paternal HLA haplotypes. Yet even with perfectly matched sibling donors, clinically significant (moderate or severe) graft versus host disease causes morbidity or mortality in nearly 50% of transplants despite the post-BMT use of immunosuppressive drug regimens designed to prevent graft versus host disease.10

Third, numerous potentially life-threatening complications require vigilant supportive care prior to the acquisition of complete and normal chimeric bone marrow function. Two to 4 weeks are required before the transplanted marrow can begin to support neutrophil production adequate to protect against bacterial infections. Platelet production adequate to stabilize counts and prevent bleeding requires a comparable time. During this 1-month period, an aggressive approach by a multidisciplinary team is required to provide irradiated blood products, treat incipient infections, prevent opportunistic infections, and maintain a stable physiologic environment to allow for recovery of oropharynx, lungs, liver, gastrointestinal tract, skin, muscles, and psyche—all of which are subject to reversible injury by the intense pretransplant conditioning regimens.13 A far longer period (as much as 1 year) is required to regain normal immune function.14 Thus, delayed viral and fungal infections are frequent following myeloid and platelet recovery, and they require diligent prophylaxis, screening, and treatment.

Fourth, the underlying disease can recur. This is unfortunately most common for patients with relapsed acute lymphoblastic leukemia treated by transplantation in second remission.15 Even though these patients receive transplantation while in remission, nearly 50% are at risk for recurrence of acute lymphoblastic leukemia, most often within 12 months following BMT. This leukemia is usually of the same karyotype and histology as the prior leukemia, and suggests that a small cohort of leukemic cells present during remission were resistant to the supralethal chemoradiotherapy conditioning.7

Our transplant team is currently testing newer approaches toward transplanting across HLA barriers, and preventing leukemic relapse.

**TRANSLATION FOR PATIENTS WHO DO NOT HAVE AN HLA IDENTICAL SIBLING**

The HLA system is the most polymorphic genetic region so far identified in the human genome. Given the large number of alleles at each of the five currently typable loci (HLA-A, B, C, D, and DR), there are more than 3 \times 10^8 distinct genotypes possible.16 Because some alleles at one locus are associated with particular alleles at another locus more frequently than anticipated by chance (linkage disequilibrium), the odds are somewhat better than one in 3 \times 10^6 that a randomly selected unrelated individual can be a perfect match for a potential BMT recipient. Advantage can be taken of the fact that some blood banks have files of thousands of potential on-call platelet donors who have been HLA typed for the A and B loci. By computer screening, it is possible to find a handful of donors from such a pool who are closely matched to the A and B alleles for a potential recipient. Provided that these healthy individuals are willing to be considered as potential BMT donors (a major ethical and administrative issue), they can be asked to consider further matching with the potential recipient by HLA DR typing and mixed lymphocyte culture reactivity to quantitate D locus disparity. If these matching tests demonstrate minimal disparity, then some centers have proceeded with BMT. A few such transplants using HLA-similar unrelated donors,17 and more using HLA-similar (but not perfectly matched) relatives,18 have been performed worldwide. The degree of graft versus host disease is clearly greater than with perfectly matched siblings; however, some of these patients are surviving. The posttransplant addition of cyclosporin A, an effective immunosuppressive agent, with no myelosuppressive effect, may potentially ameliorate the magnitude of graft versus host disease observed when HLA matching is not perfect.19 It is, however, noteworthy that a similar matching program to provide HLA A-, B-, and DR-matched cadaver kidneys was unable to reproduce the excellent graft survival results obtained for the recipients of renal allografts from HLA identical siblings.20 This further confirms the distinction between siblings who are identical by descent for the entire HLA region, and unrelated individuals who are identical (or similar) only for typable loci. The HLA identical siblings, unlike the HLA “identical” unrelated donors, share the entire HLA region with one another. The unrelated “matches” in all likelihood differ from one another for alleles at other loci that are important in the allograft reaction, but are not currently being identified by standard HLA typing.21,22

One potential solution is suggested from animal studies. Mice receiving mismatched marrow containing mature immune cells succumb to graft versus host disease. If mature T lymphocytes are removed from the marrow inoculum, the fatal graft versus host reaction is avoided.23 Clinically, the depletion of mature T lymphocytes from the donor marrow infusate should produce the same beneficial result. Initial attempts to “purge” human marrow have involved sequential depletion of T cells based
directed at the many problems and complications associated with clinical bone marrow transplantation. The most important goals are to increase the long-term survival of patients receiving bone marrow transplants, decrease the morbidity associated with the process, and extend this therapeutic modality to patients in need of a transplant, but without an HLA identical sibling. In addition, as these problems are resolved, and the toxicity of BMT is controlled, this form of therapy may become the treatment of choice for a number of inherited and acquired hematologic, immunologic, and metabolic disorders that are chronically progressive but ultimately fatal, yet are not now routinely treated with BMT due to the acute morbidity and mortality associated with this major procedure.

ACKNOWLEDGMENTS

This research was supported, in part, by grants CH-237 of the American Cancer Society and CA-52885 of the National Institutes of Health.

Dr Sondel is a Scholar of the Leukemia Society of America, and a J. L. and G. A. Hartford Foundation Fellow. Drs Trigg, Finlay, and Bozdech are American Cancer Society Junior Faculty Clinical Fellows.

The authors thank Drs J. A. Hank and P. C. Kohler for critical scientific discussions and review, Dr R. Billings for providing CT-2 monoclonal antibody, Grace Baumanns for preparing this manuscript, and the many clinical and research staff members helping to perform successful bone marrow transplantation at the University of Wisconsin Hospital.

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REFERENCES

29. Reinherz EL, Geha R, Rappeport JM, et al: Reconstitution after transplantation with T lymphocyte depleted HLA hap-
Impact of Litigation on Immunization of Children

There have been an increasing number of lawsuits claiming compensation for injuries related to vaccines. Increased litigation can be expected to result in reluctance on the part of some practitioners to use certain vaccines, consideration in changes in recommendations for immunization, and increased cost of vaccines.

The costs of oral polio vaccine (OPV) and diphtheria-tetanus-pertussis (DTP) vaccine have been increased markedly presumably because of litigation. It is estimated that the nearly tenfold increase in DTP vaccine charged by one manufacturer could add approximately $50 million per year to the cost of protecting children against these diseases. Manufacturers have been leaving the vaccine business and now only a few remain. It is conceivable that there may be no producers of vaccines in the future, and the government will have to intervene in order to maintain protection against these diseases. In addition, the fear of litigation may be retarding the development of a new pertussis vaccine.

Paralysis due to polio has decreased from tens of thousands of cases prior to the introduction of the polio vaccine to approximately a dozen cases per annum in recent years. The fact that approximately half of these cases have been associated with administration of OPV has led to a consideration of change in recommendations for immunization. The much more expensive inactivated polio vaccine may be used in addition to OPV or to replace OPV. There is no assurance, however, that administering millions of doses of inactivated polio vaccine will result in fewer lawsuits or less morbidity.

The fear of pertussis immunization in England has led to decreased acceptance of this vaccine, which has resulted in two massive epidemics of pertussis in that country. Thus far, there has been speculation that there has been decreased acceptance of pertussis vaccine in this country, but there is no objective evidence that this is the case. Indeed, there has been no significant increase in the sale of diphtheria-tetanus (DT) vaccine, which suggests that physicians have not shifted from DTP to DT to avoid pertussis vaccine reactions. It may be too early to be certain that there has not been decreased utilization of pertussis vaccine, as epidemics of this disease tend to occur in 3-year cycles.

The obvious solution to the problem of lawsuits is to produce vaccines that are reaction-free. The restriction of funding for medical research and the litigious climate are not conducive to development of new vaccines. Moreover, drug manufacturers appear to be diverting their efforts to produce products that are more likely to yield larger profits, eg, tranquilizers, antibiotics, etc. Even if it were possible to produce vaccines that were free of reactions, this would still not eliminate suits due to tempo-

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