*Chairman's Symposium*

# Bone Marrow Transplantation for Leukaemia – Current Status and Strategies for Improvement[†]

FR Appelbaum,[1]MD

## Introduction

Over the last 35 years, bone marrow transplantation (BMT) has evolved from a highly experimental therapy to a well-established treatment used in the management of tens of thousands of patients annually. The International Bone Marrow Transplant Registry (IBMTR) estimated that approximately 17,000 allogeneic and 30,000 autologous transplants were performed in 2003.[1] Despite its widespread use, marrow transplantation is unavailable to some patients because of the lack of an appropriate source of stem cells, and in many others the treatment fails because of excessive toxicity or an inability to eradicate the disease for which it is being used. The following discussion will briefly review the current status of BMT in the treatment of leukaemia and will discuss some strategies being pursued to improve the technique.

## Current Status of Bone Marrow Transplantation for Leukaemia

### Acute Myeloid Leukaemia (AML)

Allogeneic bone marrow transplantation is the only form of therapy able to cure patients who fail initial induction or re-induction therapy, with 15% to 20% of such patients becoming long-term disease-free survivors in each case.[2] Allogeneic transplantation cures 35% to 40% of patient transplanted in second complete remission, results that are substantially better than can be achieved with chemotherapy.[3] If conducted in first remission, allogeneic transplantation results in cure rates of 45% to 65%. Whether or not these results are superior to that which can be achieved with either autologous transplantation in first remission, or a strategy of an initial trial of chemotherapy followed by transplantation as salvage treatment has been the subject of much discussion and a number of prospective trials. A large prospective trial (AML 8) by the European Organization of Research and Treatment of Cancer (EORTC) reported 4-year disease-free survival (DFS) of 55% with allogeneic transplantation, 48% with autologous transplantation and 30% with chemotherapy.[4] A recent update of a similarly designed North American Intergroup study reported survival at 5 years of 52% with allogeneic transplantation, 42% with autologous transplantation, and 39% with chemotherapy.[5] The EORTC performed a second study (AML 10) with the goal of comparing allogeneic to autologous transplantation for AML in first remission and, as in their first study, found an advantage with allogeneic transplantation (4-year DFS 51.4% versus 41.2%, $P = 0.04$).[6] In contrast the Groupe Ouest Est Leucemies Aigues Myeloblastiques (GOELAM) trial, with a design similar to the EORTC AML 8 trial, saw no advantage to either form of transplantation as compared with chemotherapy.[7] Finally, the Medical Research Council of the United Kingdom compared 3 cycles of intensive consolidation chemotherapy followed by autologous transplantation with consolidation chemotherapy alone and found fewer relapses and improved disease-free survival with the autograft, but no difference in overall survival.[8] None of these studies were perspectively designed to address the comparative utilities of these approaches for specific sub-groups of AML patients, but a recent retrospective study suggested a particular benefit of allogeneic transplantation for patients with high risk disease.[5]

### Acute Lymphocytic Leukaemia (ALL)

As in AML, allogeneic transplantation is the only curative therapy for adults with ALL who fail initial induction or re-induction therapy, curing 10% to 20% of such patients.[2] Five-year survival for adults treated with allogeneic transplantation in second remission averages around 30%, which is much better than expected with chemotherapy. There has been only 1 large prospective study so far published comparing chemotherapy with allogeneic or autologous transplantation for patients in first remission. That study found an advantage for allogeneic transplantation over the other 2 approaches (5-year DFS of 46% versus 31%), with most of the advantage in high-risk patients (DFS 44% versus 11%).[9] Because the outcomes of chemotherapy for ALL are better in children than adults, the indications for transplantation are more limited. Nonetheless, children who relapse on therapy or within 6 months of its completion benefit from allogeneic transplantation. Children with high-risk disease in first remission, particularly those with Ph+ ALL, also appear to do better with transplantation compared to chemotherapy.[10]

### Chronic Myeloid Leukaemia (CML)

Allogeneic or syngeneic transplantation is only known cure for CML with 5-year disease-free survival rates of 15% to 20% for patients transplanted in blast crisis, 20% to 50% for accelerated phase patients, and 50% to 75% for chronic phase patients.[11] For chronic phase patients, the interval from diagnosis to transplantation influences the outcome of the procedure with the best results seen in patients transplanted within one year of diagnosis, and progressively poorer results with increasing delay. Results using unrelated donors now approach those with match siblings, given recent advances in donor selection, graft-versus-host disease (GVHD) prophylaxis and supportive care.[12] Although pilot studies of autologous transplantation for CML show that temporary conversion to Ph negativity is possible, there is no proven role for autologous transplantation in the management of CML.

With the availability of imatinib, the role of allogeneic transplantation in the treatment of CML has become more complex. Because very few patients achieve a molecular complete remission with imatinib and therefore are not cured, many would argue that allogeneic transplantation remains the treatment of choice for younger patients with matched siblings. For older patients and those without matched siblings, an initial trial with imatinib is reasonable to see if a complete cytogenetic response can be obtained. For those who do not obtain a complete cytogenetic response and those who show regrowth of the malignant clone after achieving a response, transplantation should be considered without undue delay.

[1] Fred Hutchinson Cancer Research Center and University of Washington Medical Center, Seattle, Washington, USA

Address of Correspondence: Frederick R. Appelbaum, MD, Director, Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue, N., D5-310 P.O. Box 19024, Seattle, WA 98109-1024, USA

Email: fappelba@fhcrc.org

*Chronic Lymphoid Leukaemia (CLL)*

Because of the indolent nature of CLL and the relatively advanced age of most patients, the experience with bone marrow transplantation as treatment for this disease is relatively limited. Our experience in Seattle using allogeneic transplantation to treat patients who have failed on average 4 different prior therapies showed a 56% 5-year disease-free survival, not too different from the 49% survival reported by the IBMTR and the 54% 3-year disease-free survival reported by the European Bone Marrow Transplant Registry.[13] Experience with autologous transplantation in CLL is very limited.

## Strategies to Improve the Outcome of Transplantation for Leukaemia

*Improved Tumour Ablation*

Although the high-dose preparative regimens commonly used in transplantation, such as busulfan plus cyclophosphamide, or cyclophosphamide plus TBI, are sometimes effective in curing patients, too often patients die from toxicities induced by such regimens or their disease recurs despite the high dose of therapy administered. A number of approaches are being taken to improve this situation.

*Pharmacologic approaches*: One set of studies found considerable variability in the plasma busulfan concentrations seen following administration of a busulfan-cyclophosphamide conditioning regimen. Of particular interest was the observation that the majority of relapses occurred in patients with busulfan plasma concentrations below the median while very high plasma concentrations where associated with excess toxicity.[14] By targeting busulfan levels based on the metabolism of the initial dose, both excessive toxicity and undertreatment with increased relapse rates could be avoided. We have since found similar variability in the metabolism of cyclophosphamide and have reported a tight correlation between high levels of a specific cyclophosphamide metabolite, carboxylethyl phosphoramide mustard, and non-relapse mortality.[15] We are now testing whether adjusting cyclophosphamide dosing based on the metabolism of the initial dose can prevent excess toxicity following marrow transplantation.

*Targeted radiotherapy*: Prior randomised trials comparing different doses of TBI have reported decreased relapse rates with higher doses of TBI, but increased non-relapse mortality nullifying any overall benefit from the more dose-intense regimens.[16] In an effort to capture the benefit of increased dose without increased toxicity, we and others have explored the use of monoclonal antibodies to target locally acting radionuclide to sites of disease, thereby increasing the dose of radiation to tumour, while sparing normal organs. Encouraging results of phase II studies using an anti-CD20 radiolabelled antibody in combination with cyclophosphamide and etoposide as the preparative regimen for patients with B-cell lymphoma have been published, as have data using a preparative regimen of a radiolabelled anti-CD45 antibody combined with busulfan plus cyclophosphamide for patients with AML.[17,18]

*Specific Immunosuppression*

Preparative regimens used in allogeneic transplantation for haematologic malignancies have typically been composed of high doses of relatively non-specific reagents, such as TBI and alkylating agents, in part, because of presumed contributions of such treatment to the eradication of the patients' malignancies and, in part, because of the belief that such high-dose therapy was required to ensure engraftment. It has, however, long been appreciated that much of the anti-leukaemia effect of allogeneic transplantation derives from a graft-versus-tumour (GVT) effect, a view that has been strengthened by the ability of donor lymphocyte infusions to induce remissions in some patients who have relapsed post-transplant. In an effort to capture the benefits of the GVT effect in patients too old or infirm to tolerate high-dose therapy, a number of reduced-intensity preparative regimens have been developed. A very low-dose regimen employing fludarabine 30mg/m$^2$ for 3 days plus 200 cGy TBI with post-transplant mycophenolate mofetil and cyclosporine was developed based on pre-clinical studies. Application of this regimen to a substantial number of patients, including many in their sixth or seventh decade, shows that complete engraftment of match sibling or match unrelated stem cells can be achieved in virtually every case with overall non-relapse mortality rates of less than 10% at 100 days and less than 20% overall.[19] Complete responses have been documented in patients with a variety of hematological malignancies. The most encouraging results to date have been in patients with less tumour burden and those with more indolent malignancies, such as chronic leukaemia, and follicular lymphoma. Combining targeted radiotherapy, with a non-ablative allogeneic transplantation is an attractive approach currently under study.

*Optimising the Stem Cell Source*

*Allele-level typing of unrelated donors*: Only approximately 25% of individuals have HLA-identical siblings to serve as donors, and therefore many patients must rely on unrelated donors. In most studies to date, both GVHD and graft rejection have been more common following matched unrelated transplants than with matched siblings. Part of the explanation is that in the past HLA typing relied on serologic methods that did not identify all HLA subtypes. A recent study using automated direct sequencing of HLA-A, -B, -C, DRB1 and DQB1 found allele level mismatching in 30% of donor-recipient pairs previously thought to be HLA matched.[20] This study also showed that such allele level mismatching resulted in more GVHD and graft-rejection, a finding that argues that more careful selection of unrelated donors should improve transplant outcome.

*Typing for non-HLA polymorphisms*: A number of investigators have hypothesised that polymorphisms in cytokine genes might influence inflammatory and immune responses post transplant. In an analysis of 993 transplants, those recipients with an IL10 promoter genotype AA had a significantly reduced risk of GVHD ($P = 0.02$) and reduced non-relapse mortality compared to other genotypes.[21] This finding suggests that there may be additional polymorphisms affecting outcome that might influence donor selection and patient prognosis.

*Alternative stem cell sources*: Although matched sibling or unrelated donors can be found for approximately 70% of patients, for others, including a disproportionate number of African-Americans and Hispanics, other sources of stem cells are needed. Umbilical cord blood banks provide an alternative for many children, but results of such transplants in adults have been less encouraging due to the low cell content of most cord blood collections. The use of multiple cord blood units for transplantation shows considerable promise for overcoming this limitation.[22] Progress has also been made in the use of haplo-mismatched donors as well.[23] One technique combines a high CD34 cell dose with vigorous T-cell depletion, and a second uses high-dose post-transplant cyclophosphamide to eradicate alloreactive T-cells.

*Harnessing the Power of the Graft-versus-tumour Effect*

As noted earlier, the observation of markedly diminished relapse rates associated with GVHD and the responses seen with donor lymphocyte infusions have generated enormous interest in developing ways of harnessing the GVT effect while avoiding the toxicities of

GVHD. One approach is to transduce donor T-cells with a "suicide" gene, allow GVHD to develop and then rescue patients by triggering the "suicide" gene and thereby eliminating GVHD.[24] Other approaches are centred on identifying antigen targets that distinguish GVT from GVHD. One category of targets is polymorphic minor histo-compatability antigens that are restricted to hematopoietic tissue and differ between donor and host. A number of such antigens have been identified and are being exploited as targets for T-cell adoptive immunotherapy post-transplant.[25] A second category of antigens are those associated with the malignant phenotype such as mutational antigens (e.g. bcr/abl in CML) or overexpressed self antigens (e.g. PR3 in AML).

## Summary

Thirty-five years ago, bone marrow transplantation was first being explored as a last-ditch effort to treat patients with end stage leukaemia. Through the efforts of a large number of laboratory and clinical scientists, the application of transplantation has broadened and outcomes have dramatically improved. The science of transplantation continues to attract a great deal of research, and with this effort we can expect continued progress and patient benefit.

### REFERENCES

1. Appelbaum FR. Hematopoietic stem cell transplantation. In: Dale DC, Federman DD, editors. ACP Medicine, 2004-2005 edition. Vol 1. WebMD®; www.acpmedicine.com. Chapter 99. New York, NY: The American College of Physicians, 2004:1205-15.
2. Biggs JC, Horowitz MM, Gale RP, Ash RC, Atkinson K, Helbig W, et al. Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy. Blood 1992;80:1090-3.
3. Clift RA, Buckner CD, Appelbaum FR, Schoch G, Petersen FB, Bensinger WI, et al. Allogeneic marrow transplantation during untreated first relapse of acute myeloid leukemia. J Clin Oncol 1992;10:1723-9.
4. Zittoun RA, Mandelli F, Willemze R, de Witte T, Labar B, Resegotti L, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. N Engl J Med 1995;332:217-23.
5. Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, Mohamed A, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group study. Blood 2000;96:4075-83.
6. Suciu S, Zittoun R, Mandelli F, de Witte T, Gallo E, Belhabri A, et al. Allogeneic vs autologous stem cell transplantation according to cytogenetic features in AML patients (pts) ≤45 yrs old in first CR: Results of the EORTC-GIMEMA AML-10 trial [abstract]. Blood 2001;98 (Part 1):481a.
7. Harousseau JL, Cahn JY, Pignon B, Witz F, Milpied N, Delain M, et al. Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia. The Groupe Ouest Est Leucemies Aigues Myeloblastiques (GOELAM). Blood 1997;90:2978-86.
8. Burnett AK, Wheatley K, Goldstone AH, Stevens RF, Hann IM, Rees JH, et al. The value of allogeneic bone marrow transplant in patients with acute myeloid leukaemia at differing risk of relapse: results of the UK MRC AML 10 trial. Br J Haematol 2002;118:385-400.
9. Thiebaut A, Vernant JP, Degos L, Huguet FR, Reiffers J, Sebban C, et al. Adult acute lymphocytic leukemia study testing chemotherapy and autologous and allogeneic transplantation. A follow-up report of the French protocol LALA 87 (Review). Hematol Oncol Clin North Am 2000;14:1353-66.
10. Arico M, Valsecchi MG, Camitta B, Schrappe M, Chessells J, Baruchel A, et al. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. N Engl J Med 2000;342:998-1006.
11. Clift RA, Appelbaum FR, Thomas ED. Treatment of chronic myeloid leukemia by marrow transplantation (Review). Blood 1993;82:1954-6.
12. Hansen JA, Gooley TA, Martin PJ, Appelbaum F, Chauncey TR, Clift RA, et al. Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. N Engl J Med 1998;338:962-8.
13. Doney KC, Chauncey T, Appelbaum FR. Allogeneic related donor hematopoietic stem cell transplantation for treatment of chronic lymphocytic leukemia. Bone Marrow Transplant 2002;29:817-23.
14. Slattery JT, Clift RA, Buckner CD, Radich J, Storer B, Bensinger WI, et al. Marrow transplantation for chronic myeloid leukemia: the influence of plasma busulfan levels on the outcome of transplantation. Blood 1997;89:3055-60.
15. McDonald GB, Slattery JT, Bouvier ME, Ren S, Batchelder AL, Kalhorn TF, et al. Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoietic stem cell transplantation. Blood 2003;101:2043-8.
16. Clift RA, Buckner CD, Appelbaum FR, Bearman SI, Petersen FB, Fisher LD, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. Blood 1990;76:1867-71.
17. Press OW, Eary JF, Gooley T, Gopal AK, Liu S, Rajendran JG, et al. A phase I/II trial of iodine-131-tositumomab (anti-CD20), etoposide, cyclophosphamide, and autologous stem cell transplantation for relapsed B-cell lymphomas (Plenary paper). Blood 2000;96:2934-42.
18. Matthews DC, Appelbaum FR. Radioimmunotherapy and hematopoietic cell transplantation. In: Blume KG, Forman SJ, Appelbaum FR, editors. Thomas' Hematopoietic Cell Transplantation. 3rd ed. Chapter 15. Oxford, UK: Blackwell Publishing, 2004:198-208.
19. McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ, Maloney DG, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. Blood 2001;97:3390-400.
20. Petersdorf EW, Gooley TA, Anasetti C, Martin PJ, Smith AG, Mickelson EM, et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and recipient. Blood 1998;92:3515-20.
21. Lin M-T, Storer B, Martin PJ, Tseng L-H, Gooley T, Chen P-J, et al. Relation of an interleukin-10 promoter polymorphism to graft-versus-host disease and survival after hematopoietic-cell transplantation. N Engl J Med 2003;349:2201-10.
22. Barker JN, Weisdorf DJ, Defor TE, Blazar BR, Miller JS, Wagner JE. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. Blood 2003;102:1915-19.
23. Aversa F, Tabilio A, Velardi A, Cunningham I, Terenzi A, Falzetti F, et al. Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. N Engl J Med 1998;339:1186-93.
24. Bonini C, Ferrari G, Verzeletti S, Servida P, Zappone E, Ruggieri L, et al. HSV-TK gene transfer into donor lymphocytes for control of allogeneic graft-versus-leukemia. Science 1997;276:1719-24.
25. Warren EH, Greenberg PD, Riddell SR. Cytotoxic T-lymphocyte-defined human minor histocompatibility antigens with a restricted tissue distribution. Blood 1998;91:2197-207.