The Use of Bone Marrow and Peripheral Blood Stem Cell Transplantation in the Treatment of Cancer

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Introduction
Bone marrow or peripheral blood stem cell transplantation is used in the treatment of cancer for two reasons. First, transplantation permits exploitation of the steep dose-response relationship seen in some tumors by allowing administration of doses of systemic chemotherapy and radiotherapy that without transplantation would cause unacceptably severe or lethal myelosuppression. Second, transplantation of allogeneic marrow confers an antitumor effect, separate from the effects of chemoradiotherapy. The first successful bone marrow transplants in humans were performed in the late 1960s. This year, it is estimated that over 15,000 patients will undergo the procedure worldwide (Fig. 1).

Historical Aspects
The first suggestion that bone marrow transplantation might be possible occurred in 1949 when Jacobson et al.1 made the observation that mice could survive otherwise lethal total body irradiation if the spleen was protected by lead foil. A similar radioprotective effect was seen if bone marrow from one mouse was given intravenously to a radiated recipient of the same strain.2 By the mid-1950s, several laboratories had shown, using cytogenetic markers, that the radioprotective effect of bone marrow transplantation was due to the replacement of the damaged hematopoietic system of the host with healthy cells of donor origin.3 The potential clinical implications of these studies were noted, and in 1959, the first attempts to treat leukemia using high-dose chemoradiotherapy followed by syngeneic marrow transplantation were initiated by Dr. E. Donnell Thomas.4 Initial attempts to apply transplantation outside the setting of identical twins were unsuccessful because of lack of understanding of the human histocompatibility system.

In the late 1950s and early 1960s, human leukocyte antigens (HLA) and their importance in histocompatibility were first recognized. By the mid-1960s, it was demonstrated in an outbred species (the dog) that matching at the major histocompatibility complex allowed for successful allogeneic marrow transplantation.5 The work of Dr. Thomas and fellow investigators led to the first successful allogeneic transplants for leukemia in the late 1960s6 and the gradual acceptance of this therapy during the 1970s.7 Autolo-
gous marrow transplantation was first successfully employed to cure patients with lymphoma in the late 1970s and became widespread in the 1980s. Today, the annual number of autologous transplants surpasses that of allogeneic transplantation. In 1990, a Nobel prize in medicine was awarded to E. Donnell Thomas for his contributions to this field (Table 1).

**Biologic Basis**

Several features of human bone marrow make the transplant procedure feasible. The first is the remarkable regenerative capacity of marrow. In mice it has been demonstrated that the transfer of a single hematopoietic stem cell can result in complete and sustained hematopoietic reconstitution of a lethally irradiated recipient. While human bone marrow has never been put to this test, transplantation of considerably less than 10 percent of a donor’s total body marrow regularly results in complete and sustained replacement of a patient’s entire hematopoietic system. After the transplant, donor marrow cells normally produce all of the patient’s red cells, platelets, granulocytes, and T lymphocytes and B lymphocytes as well as the patient’s pulmonary alveolar macrophages, Kupffer’s cells of the liver, osteoblasts, Langerhans’ cells of the skin, and microglial cells of the brain.

A second feature of marrow which makes transplantation practical is that after intravenous infusion, marrow cells have the capacity to home to the marrow space. The mechanisms by which this happens are not entirely understood, but a remarkably high percentage of primitive hematopoietic cells appear to end up in the marrow, in some murine studies as many as 50 percent. Current studies
suggest that early hematopoietic cells are retained in the marrow because marrow endothelial cells express members of a family of cell adhesion molecules termed “selectins,” which bind to carbohydrate-based ligands on early hematopoietic cells.11

An additional characteristic of marrow stem cells that has made autologous transplantation feasible is their ability to survive cryopreservation with little, if any, damage. Using relatively simple techniques of freezing and thawing, cryopreserved autologous marrow is virtually as effective as fresh marrow in providing protection after otherwise lethal total body irradiation.12

**Cryopreserved autologous marrow is virtually as effective as fresh marrow in providing protection after total body irradiation.**

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**Source of Stem Cells**

**SYNGENEIC TRANSPLANTATION**

An identical twin, when available, is the best possible donor. With syngeneic marrow, there are fewer complications than with autologous marrow transplantation, and unlike autologous marrow, marrow from a healthy identical twin cannot be contaminated with tumor cells. Syngenicity is easily established by DNA typing using restriction fragment length polymorphisms.

**ALLOGENEIC TRANSPLANTATION**

Allogeneic marrow transplantation can be performed using HLA-identical sibling donors, other HLA-matched or HLA-mismatched family members, or HLA-matched unrelated donors. The best results occur with sibling donors who are identical with the patient for HLA class I and class II determinants.

The genes encoding HLA are located on chromosome 6 and are codominantly expressed so that the probability of HLA-identity between any two siblings is 25 percent. Given the average family size in the United States, the chance of having an HLA-matched sibling is about 35 percent. The formula for calculating the chance that a patient has an HLA-identical sibling is 1-(0.75)^n where n equals the number of siblings.

HLA class I antigens (usually referred to as HLA-A and HLA-B) are defined using alloantisera in microcytotoxicity assays. HLA class II antigens are encoded by genes located within the HLA-D region and are termed DP, DQ, and DR. DQ and DR antigens can be identified by alloantisera, but identification of DP requires cellular techniques, such as mixed lymphocyte culture reactions or more current molecular techniques such as sequence-specific oligonucleotide probe hybridization.

While the best results with allogeneic transplantation have been achieved using HLA-identical sibling donors, transplants using family member donors identical with the patient for one haplotype but mismatched for a single locus on the other (A, B, or D) result in nearly equal survival, albeit with a higher incidence of graft-versus-host disease (GVHD).13,14 The results of transplants using family member donors mismatched for two or more loci are considerably worse with more GVHD, more graft rejection, and decreased survival.13,14

Following initial reports that transplantation could be successfully performed using an HLA-matched unrelated donor, there has been a rapid increase in this activity.15,16 Currently, more than 1.3 million normal individuals have volunteered to serve as marrow donors in the United States alone, making the odds of finding an A, B, and D matched unre-
lated donor about 50 percent.17 On average, it takes about four months from the time a search is initiated to identify a donor and initiate a transplant. Analysis of the first several hundred patients transplanted from unrelated donors suggests that GVHD is more common and long-term cure rates are slightly lower than with the use of matched family members.18,19

**AUTOLOGOUS TRANSPLANTATION**

Autologous transplantation involves removing and usually cryopreserving a patient’s own marrow and reinfusing that marrow to reestablish hematopoietic function after the administration of high-dose chemotherapy or chemoradiotherapy. Deciding the type of transplantation to recommend for any individual patient is complex. Autologous transplantation has the advantage of avoiding GVHD and associated complications but has the disadvantage of potentially containing viable tumor cells and lacking a graft-versus-tumor effect.

Because autologous marrow may contain viable tumor cells, numerous strategies have been developed to reduce the number of tumor cells in autologous marrow. Removal of tumor cells (negative selection) using antibodies together with complement, toxins, or immunomagnetic beads is very efficient, removing three to four logs of tumor cells from marrow.20,21 In vitro treatment of marrow with chemotherapy has been studied, as has removal of tumor cells using short-term in vitro culturing of marrow cells.22-24 Techniques involving positive selection of normal hematopoietic stem cells to separate them from tumor cells are also being tested.25

Although gene marking studies have definitively demonstrated that tumor cells in marrow can contribute to relapse,26 it has not been established whether the techniques mentioned above can prevent this outcome. It is also not firmly established how these techniques affect normal marrow function. Several retrospective analyses suggest that purging might be effective in acute myeloid leukemia (AML) and B-cell non-Hodgkin’s lymphoma, but prospective, controlled studies have not been performed.21,27

**PERIPHERAL BLOOD STEM CELL TRANSPLANTATION**

For several decades, it has been recognized that hematopoietic stem cells circulate in the peripheral blood, albeit in very

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**Table 1**

Marrow Transplantation — Historical Aspects

| Year | Event |
|------|-------|
| 1949 | Spleen shielding experiment of Jacobson et al1 |
| 1956 | Cytogenetic proof of marrow engraftment3 |
| 1959 | First human twin transplants for leukemia4 |
| 1962 | Successful engraftment of allogeneic marrow in dogs5 |
| 1968 | First successful allogeneic marrow transplant in human6 |
| 1977 | First successful application of autologous marrow transplantation7 |
| 1990 | Dr. E. Donnell Thomas awarded Nobel Prize |

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low numbers. Initial studies in animal models demonstrated that at least 10 times more mononuclear cells were needed to rescue animals from lethal total body irradiation if collected from peripheral blood as compared with marrow.28,29 Predictably, initial attempts to use peripheral blood stem cells as a source of hematopoietic grafts were complicated by the large number of phereses required (often seven or more) and by slow engraftment.30 Recently, it has been shown that administration of chemotherapy and/or hematopoietic growth factors leads to a marked rise in the number of hematopoietic progenitors in the peripheral blood, measured either as colony-formed units or as CD34+ cells. This has triggered intensive study of the use of peripheral blood stem cells as a substitute for marrow.31-33 The results have been dramatic. In the autologous setting, with one to three leukaphereses after treatment with granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), a sufficient number of cells for engraftment can usually be collected.

Recovery after engraftment using mobilized peripheral blood stem cells is considerably faster than recovery after using marrow.34,35 Similar results have been demonstrated using G-CSF mobilized cells for syngeneic transplantation, and preliminary results suggest the same can be done in the allogeneic setting.36

Concern about the use of peripheral blood cells for autologous transplants centers around the possibility that contamination with tumor cells is greater than with autologous marrow. For allogeneic transplantation, there is the concern that the amount of T-cell contamination is higher than with marrow. However, given the rapid reliable engraftment that has been demonstrated and the fact that the technique avoids a surgical procedure for the donor, it seems likely that mobilized peripheral blood properly manipulated to remove autologous tumor cells or reduce the number of allogeneic T cells will soon replace marrow as the preferred source of stem cells for use after myeloablative therapy in most circumstances.

Preparative Regimens

Following identification of the source of stem cells, the next step in the transplant procedure is the administration of high-dose chemotherapy or radiotherapy or a combination of the two. The goal of the preparative regimen is to eliminate the malignancy and in allogeneic marrow transplantation to sufficiently immunosuppress the patient to allow engraftment. In developing transplant preparative regimens, most investigators have focused on the use of agents that have high activity against the malignancy being treated and also have myelosuppression as their dominant dose-limiting toxicity in the nontransplant setting. Thus, the agents most commonly used are alkylating agents (cyclophosphamide, busulfan, thiotepa, melphalan, carmustine), etoposide, cytarabine, and total body irradiation. The choice of preparative regimen is determined by the particular clinical situation, taking into account the disease under treatment, the age and health of the patient, and the source of marrow.

Marrow Collection and Infusion

Marrow is usually obtained from the donor’s anterior and posterior iliac crests with the donor under spinal or general anesthesia. A total marrow volume of 10
to 15 ml/kg of donor weight is usually obtained with each aspiration site limited to 3 to 5 ml to avoid excessive dilution with peripheral blood. The heparinized marrow is filtered through 0.3-mm and 0.2-mm screens to remove bone spicules and fat. The marrow may require further in vitro treatment to remove unwanted cells, including removing donor red cells to avoid a hematolytic transfusion reaction in the setting of an ABO-incompatible transplant, donor T cells to attempt to avoid GVHD, or tumor cells from autologous marrow as discussed earlier. The risk involved in marrow donation is small. In Seattle, for example, there were six serious but nonfatal complications among 1,220 consecutive donations.37

Peripheral blood stem cells are usually collected using continuous flow apheresis techniques from donors previously treated with hematopoietic growth factor alone or after chemotherapy. In Seattle, attempts are made to collect a minimum of 5 x 10^6 CD34+ cells/kg based on studies demonstrating consistent rapid engraftment when this minimum cell dose is met.38

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Table 2
Estimated Five-Year Disease-Free Survival Following Transplantation

| Disease                  | Stage                      | Allogeneic | Autologous |
|--------------------------|----------------------------|------------|------------|
| Acute myeloid leukemia   | 1st CR                     | 45-65      | 30-50      |
|                          | 2nd CR                     | 20-45      | 20-40      |
| Acute lymphocytic leukemia | 1st CR                  | 40-70      | 30-50      |
|                          | 2nd CR                     | 25-45      | 15-25      |
| Myelodysplastic syndrome | Combined                  | 45         | ND         |
| Chronic myelogenous leukemia | Chronic phase        | 60-75      | 0-5        |
|                          | Accelerated phase         | 30-45      | 0-5        |
|                          | Blast crisis              | 10-20      | 0-5        |
| Non-Hodgkin’s lymphoma   | 1st Relapse, 2nd CR        | 40-60      | 40-60      |
|                          | Advanced                  | 10-25      | 10-25      |
| Hodgkin’s disease        | 1st Relapse, 2nd CR        | 40-60      | 40-60      |
|                          | Advanced                  | 10-25      | 10-25      |
| Multiple myeloma         | Combined                  | 30         | 0-5        |
| Neuroblastoma            | Stage IV                  | 25-50      | 25-50      |
| Breast cancer            | Stage IV                  | ND         | 10-20      |
|                          | Stage II                  |            | 70         |
| Testicular cancer        | Recurrent                 | ND         | 20         |

CR = complete remission; ND = no data.
Marrow and peripheral blood stem cell infusions are usually well tolerated although patients sometime develop fever, cough, or mild shortness of breath. Slowing the infusion usually alleviates these symptoms.

**Engraftment**

The rate of engraftment depends on the source of stem cells, the use of hematopoietic growth factor, and the choice of prophylaxis against GVHD. The most rapid engraftment is seen with peripheral blood stem cells, where recovery to granulocyte counts of 100/mm³ usually occurs by day 10 and 500/mm³ by day 12. If marrow rather than peripheral blood is used, the granulocyte count usually reaches 100/mm³ by day 16 and 500/mm³ by day 22. This rate can be accelerated by four to six days with the use of G-CSF or GM-CSF posttransplant (Fig. 2). The use of methotrexate after allogeneic transplant delays recovery by an average of four days. Platelet recovery generally occurs shortly after granulocyte recovery.

**Complications of Transplantation**

**DIRECT TOXICITIES OF CHEMORADIOTHERAPY**

Following the standard preparative regimen of cyclophosphamide and total body irradiation, nausea, vomiting, and mild skin erythema develop immediately in almost all patients. Occasionally, hemorrhagic cystitis is seen despite bladder irrigation or mesna therapy, and rarely

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Fig. 2. Neutrophil recovery after autologous transplantation for malignant lymphoma. Data on the use of marrow alone or marrow plus granulocyte-macrophage colony-stimulating factor (GM-CSF) from Nemunaitis et al. The curve for recovery with granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSC) from Bensinger et al.
(less than two percent of cases), acute hemorrhagic carditis can develop. Oral mucositis inevitably develops at about five to seven days posttransplant and usually requires narcotic analgesia. Studies at the Fred Hutchinson Cancer Research Center suggest that self-administration of narcotics using a pump provides the greatest patient satisfaction and, surprisingly, uses a lower cumulative dose of narcotics.42 By 10 days posttransplant, most patients have developed complete alopecia and are profoundly granulocytopenic.

Veno-occlusive disease of the liver is a serious complication of high-dose chemoradiotherapy that develops in about 10 percent of patients and is characterized by ascites, tender hepatomegaly, and jaundice occurring any time during the first month posttransplant with a peak incidence at day 16.43 Predisposing factors include pretransplant hepatitis of whatever cause and the use of more intensive conditioning regimens.44 About 30 percent of patients who develop veno-occlusive disease will die with progressive hepatic failure and, terminally, a hepato-renal syndrome. Although there is no proven effective therapy, preliminary studies suggest that treatment with alprostadil or tissue plasminogen activator may reverse the disease.45,46 Randomized trials are in progress.

Most pneumonias occurring post-transplant are infectious in nature, but idiopathic interstitial pneumonia, which is thought to be a direct toxicity of intensive chemoradiotherapy, occurs in five to 10 percent of patients.47 Biopsies reveal some cases to be characterized by diffuse alveolar damage while other have a more clearly interstitial component. Treatment with high-dose steroids is often attempted, but evidence from randomized trials that steroids change the ultimate outcome of this syndrome is lacking.48

Direct complications of chemoradiotherapy seen late after transplantation include decreased growth velocity in children with delay in the development of secondary sex characteristics.49,50 Most postpubertal women will develop ovarian failure, which should be treated, and most men become azospermic.51,52 Cataracts develop in 10 to 20 percent of patients, especially if steroids are required for treatment of chronic GVHD.53 While the above-listed toxicities represent the usual constellation seen after cyclophosphamide and total body irradiation, other preparative regimens may be associated with their own unique problems.

**Graft Failure**

Although complete or sustained engraftment usually occurs following transplantation, in some cases marrow function either does not return or, after temporary engraftment, marrow function is lost. Following autologous transplantation, graft failure may be the consequence of marrow damage suffered prior to collection. For example, in one large randomized study, prior exposure of patients to chemotherapeutic drugs that presumably affect hematopoietic stem cells was highly associated with poor marrow function posttransplant.54 Graft failure after autologous transplantation can also result from marrow damage during ex vivo treatment, during storage, or because of exposure of the patient to myelotoxic agents posttransplant. There is some evidence to suggest that viral infections, for example, with cytomegalovirus (CMV) or human herpesvirus 6, may result in poor marrow function.55,56

Following allogeneic transplantation, graft failure may be the result of graft rejection, which is thought to represent an immunologic reaction against the graft by residual host immune cells.57,58 Immunologically mediated graft rejection is more commonly seen in patients who receive less immunosuppressive conditioning regimens, in recipients of T-cell-depleted marrow, or in recipients of HLA-mismatched marrow.59,60 Recently,
it has been observed that some patients with GVHD after a period of normal engraftment develop graft failure and that it is impossible to grow marrow stromal cells from such patients, suggesting that a graft-versus-stroma effect may be the cause of poor graft function in some.61

The approach to treatment of graft failure depends on the likely cause. The obvious first step in all patients with poor graft function is to remove all potential myelosuppressive agents. A reasonable second step is to attempt a trial of GM-CSF because published studies suggest that 40 to 50 percent of patients respond.62 Further therapy depends on the evidence for immunologic rejection based on identification of persistent host lymphocytes in peripheral blood or marrow of the patient. If persistent host cells are found, the patient should receive further immunosuppression before a second transplant is performed. Regimens now in use are antithymocyte globulin plus cyclophosphamide or high-dose steroids plus an anti-CD3 antibody.53 If no residual host cells are found, sometimes a second marrow infusion without prior immunosuppression can lead to recovery of hematopoiesis.64

The two most commonly used agents to prevent acute GVHD are methotrexate and cyclosporine. and they are equally effective when used individually.68 The combination of the two is more effective in preventing acute GVHD than either alone.69,70 Removal of T cells from the allogeneic marrow is also effective in preventing acute GVHD, but in most circumstances has been associated with an increased incidence of graft rejection and leukemic relapse.71,72 Accordingly, the use of partial T-cell depletion (i.e., complete depletion followed by adding back a fraction of the T cells) and the use of interleukin-2 after engraftment of T-cell-depleted marrow are all under study.73,74 Once acute GVHD develops, it can be treated with steroids, antithymocyte globulin, and monoclonal antibodies against T cells or their receptors.75-78

GVHD that develops or persists after three months posttransplant is termed chronic GVHD and has features in common with collagen vascular diseases, including a malar rash, scleroderma-like changes, sicca syndrome, arthritis, obliterative bronchiolitis, and, in some cases, bile duct degeneration and cholestasis.79 Chronic GVHD develops in 20 to 40 percent of patients and is seen more often in patients with prior acute GVHD and in older patients.80 Prednisone and/or cyclosporine is the usual treatment, and in some cases, azathioprine or thalidomide has been useful.81-83 In most patients, chronic GVHD eventually resolves and
immunosuppressive therapy can be withdrawn, but one to three years of treatment may be required. Patients with chronic GVHD on immunosuppression are susceptible to bacterial infections and should receive prophylactic trimethoprim/sulfamethoxazole and/or penicillin.

INFECTIOUS DISEASES COMPLICATING MARROW TRANSPLANTATION

During the first two to three weeks posttransplant, all patients are severely granulocytopenic. Most develop a fever, and in about one third, a positive blood culture is found. Febrile granulocytopenic patients should be treated with broad-spectrum antibiotics, and in many centers antibiotics are initiated once patients become granulocytopenic to prevent septicemia. The prophylactic administration of fluconazole reduces the incidence of Candida albicans infection.84

Patients who remain febrile despite antibiotic and antifungal prophylaxis represent a difficult challenge, and their management is guided by individual aspects of the patient and the institutional experience. At most centers, the addition of amphotericin B is the usual next step.85

Granulocyte transfusions can be effective in treating specific infections, particularly now that donors can be treated with G-CSF prior to donation, greatly increasing the number of granulocytes that can be collected and transfused.86 There is no established role for prophylactic granulocyte transfusions.87 Laminar air flow isolation can reduce the incidence of infection, but has no impact on survival in patients being transplanted as treatment for malignancy.88 With current supportive care, the risk of death due to an infectious cause during the period of granulocytopenia is less than five percent.

In the past, CMV infection was frequently seen posttransplant. More recently, it has been shown that primary CMV infection can be prevented in CMV-seronegative patients by the sole use of CMV-seronegative blood products.89 In CMV-seropositive patients, treatment with ganciclovir as soon as virus excretion is evident can diminish the incidence of CMV-associated disease and death, but some patients will develop disease simultaneously with or before excretion is noted.90 Ganciclovir prophylaxis beginning at the time of engraftment can prevent the development of CMV disease in most patients, but ganciclovir causes significant marrow suppression in at least 10 percent of patients.91 Therefore, current studies are evaluating alternative strategies to prevent CMV infection such as monitoring peripheral blood posttransplant for the development of CMV antigenemia and only initiating ganciclovir prophylaxis if and when patients turn positive.

Herpes simplex infection, if not prevented, contributes to the severity of early oral mucositis and esophagitis. However, the prophylactic use of acyclovir 250 mg/m² intravenously every eight hours can prevent herpes simplex reactivation in almost all seropositive patients.92 Pneumocystis carinii used to cause pneumonia in five to 10 percent of patients posttransplant, but now can be prevented in virtually all patients by treatment with oral trimethoprim/sulfamethoxazole for one week pretransplant and then resuming treatment two days per week once engraftment occurs. Dapsone may be useful in preventing infection with P carinii in patients allergic to sulfa drugs.

Patients more than three months posttransplant are still at risk for varicella-zoster infections and if they have chronic GVHD for recurrent bacterial infections. Varicella-zoster infection usually presents as localized disease, but it will disseminate in about one third of patients. The case fatality rate of disseminated varicella-zoster infection occurring during the first nine months posttransplant is 33 percent, and thus all patients with varicella-zoster infection occurring
during this early time period should be treated with acyclovir to prevent dissemination. As noted previously, patients with chronic GVHD receiving immuno-suppression should remain on trimethoprim/sulfamethoxazole and/or penicillin to reduce late bacterial infections.

Treatment of Specific Malignancies with Marrow Transplantation

Acute Myeloid Leukemia

Allogeneic marrow transplantation is the only form of therapy able to cure patients with AML who fail induction therapy, curing 15 to 20 percent of such patients. Thus, all patients aged 55 years or younger with newly diagnosed AML should be HLA typed along with their families soon after diagnosis to enable transplantation for those who fail induction. Allogeneic transplantation can cure about 30 percent of patients in second remission and 35 percent of those in untreated first relapse. These results are superior to those achieved without transplantation and therefore represent situations that are clear indications for the procedure.

The best results with allogeneic transplantation are obtained in patients transplanted in first remission, with a cure rate of 40 to 70 percent reported. At least 14 prospective comparisons of marrow transplantation for those with HLAmatched siblings versus chemotherapy for those without have been published. In these series, the cure rate with marrow transplantation has ranged from 40 to 64 percent, while that for chemotherapy has ranged from 19 to 24 percent. However, there have been important advances in both chemotherapy and transplantation since the conduct of most of these studies. Further, it remains untested whether a strategy of transplantation in first remission is superior to the combination of initial chemotherapy followed by transplantation as salvage therapy.

Autologous marrow transplantation for patients with AML in first and second remission in several phase II studies has yielded similar results to those achieved with allogeneic transplantation. In general, relapse rates after autologous transplantation have been substantially higher than for allogeneic transplantation, but the incidence of death from transplant-related complications has been somewhat lower. In the few studies where the two approaches have been compared head-to-head, allogeneic transplantation has shown a small survival advantage. The largest of these studies, presented only in abstract form, assigned 569 patients with AML in first remission to allogeneic transplantation, autologous transplantation, or continued chemotherapy and found disease-free survival at four years to be 54 percent, 49 percent, and 30 percent, respectively.

Acute Lymphocytic Leukemia

As with AML, allogeneic transplantation for patients with acute lymphocytic leukemia (ALL) who fail induction therapy or develop chemotherapy-resistant disease can cure 15 to 20 percent of patients, and thus these settings represent indications for the procedure. The results of transplantation for patients in second remission are better, with cure rates of 30 to 50 percent reported by several groups. However, further intensive chemotherapy also can cure some patients who suffered initial relapse. This is particularly true for children who relapse more than 18 months after initial induction chemotherapy.

A recent study comparing the outcome of allogeneic transplantation in 255 children to that of an equal number of children treated with chemotherapy reported a five-year disease-free survival of 36 percent for transplant patients compared with 16 percent for chemotherapy patients. The relative benefit of transplantation compared with chemotherapy...
was similar for all categories of children. Thus, allogeneic transplantation can be recommended for all patients with ALL in second complete remission with appropriate donors.123

Allogeneic transplantation for ALL in first remission has been reported to result in long-term disease-free survival in 40 to 70 percent of adult patients.125-127 In a retrospective study comparing these results to those achieved with chemotherapy, no clear advantage could be found for either approach.128 In the largest prospective randomized study published to date, involving 572 patients, the three-year disease-free survival was 43 percent for patients receiving an allogeneic transplant, 39 percent for autologous transplantation, and 32 percent for continued chemotherapy.129 There are some categories of patients, such as those with Philadelphia-chromosome-positive ALL, who have a poor prognosis using non-transplant treatments and therefore are particularly likely to benefit from transplantation in first remission.130

Studies comparing allogeneic to autologous transplantation in ALL have consistently shown a substantially higher relapse rate with autologous transplantation but a somewhat higher rate of death from complications of the transplant with the use of allogeneic marrow.131 In balance, most investigators recommend use of allogeneic marrow if an appropriate donor is available.

MYELODYSPLASTIC SYNDROME

Myelodysplastic syndrome (MDS) is generally considered to be incurable except with marrow transplantation. In some patients, MDS has a relatively indolent course and transplantation can be safely withheld until the disease progresses. However, once patients develop significant granulocytopenia (<1,000 cells/mm³) or thrombocytopenia (<40,000 cells/mm³) or the percentage of blasts in the marrow exceeds five percent, the expected survival of patients with MDS if not transplanted is short, and transplantation should be seriously considered.132 If an HLA-matched sibling is available to serve as a donor, the chance of long-term survival with transplantation in this setting is roughly 45 percent.133-135 Although it is now being explored, there is no established role for autologous transplantation in MDS.

CHRONIC MYELOGENOUS LEUKEMIA

Allogeneic and syngeneic marrow transplantation are the only forms of therapy known to cure chronic myelogenous leukemia (CML), with five-year disease-free survival rates of 15 to 20 percent for patients in blast crisis, 40 to 45 percent for accelerated phase patients, and 60 to 70 percent for patients transplanted during chronic phase (Fig. 3).136,137 Time from diagnosis influences the outcome of transplantation during chronic phase, with the best results obtained in patients transplanted within one year of diagnosis and progressively worse results for longer delays.138,139 Prior exposure to busulfan also is an adverse risk factor for transplantation.139 Thus, patients younger than 55 years with HLA-matched siblings should probably be transplanted as soon after diagnosis as possible, and the use of busulfan during chronic phase should be avoided. A small number of patients aged 55 to 65 years with CML have received transplants, and the reported results are not much worse than in younger patients.140

Results of the use of unrelated donor transplants in CML have been accumulating. Although the initial experience was substantially worse than seen with matched sibling transplants, more recent results demonstrate a disease-free survival of 65 percent at three years, at least at some centers.141,142

The use of autologous transplants for CML is increasingly being studied. There are, at present, no data to suggest that with current approaches, this tech-
Hematologic Malignancies

CHRONIC LYMPHOYTIC LEUKEMIA

Use of marrow transplantation in chronic lymphocytic leukemia (CLL) has received only limited attention. Given the indolent nature of the disease and its propensity to occur in older patients, this is not surprising. Among the small number of patients treated using allogeneic transplantation, complete remissions have been achieved in most, and about 50 percent remain disease-free, albeit with a follow-up of only several years so far. Complete remissions have been achieved, some of which appear to be sustained. Much more study will be needed to determine if transplantation significantly improves long-term outcome in this disease.

NON-HODGKIN’S LYMPHOMA

Patients with disseminated intermediate- or high-grade non-Hodgkin’s lymphoma (NHL) who fail conventional therapy are seldom cured without transplantation. High-dose therapy followed by autologous or allogeneic marrow transplantation can cure a substantial proportion of such patients. A number of studies have documented cure rates of 40 to 50 percent for patients transplanted after an initial relapse but while their tumors remain sensitive to chemotherapy. Cure rates decrease substantially once the disease becomes resistant to conventional-
dose treatment.\textsuperscript{146-148} A poor performance status and large tumor bulk are additional adverse risk factors.

As in other diseases, patients transplanted using allogeneic marrow have a lower relapse rate but a higher risk of nonrelapse mortality than patients transplanted using autologous marrow.\textsuperscript{146,149}

For most categories of intermediate- and high-grade NHL, the outcomes of allogeneic and autologous transplantation appear roughly similar, although an advantage for allogeneic transplantation in patients with lymphoblastic lymphoma has been suggested.

Some studies have begun to explore the use of transplantation in first remission. Several encouraging pilot studies have been published.\textsuperscript{150-152} A large, randomized study failed to show an overall benefit for transplantation in first remission but did suggest that patients with significant risk factors for poor outcome with chemotherapy might benefit from early transplantation.\textsuperscript{153}

Marrow transplantation for patients with low-grade NHL has also been intensively studied. Disease-free survival of 40 to 60 percent with a follow-up of three to four years has been reported for patients transplanted after failing front-line therapy.\textsuperscript{21,154} However, late relapses have been seen in some patients, and the ultimate cure rate with this approach is as yet undetermined. Trials of autologous transplantation for low-grade lymphoma in first remission are under way.

**HODGKIN’S DISEASE**

The results of transplantation for Hodgkin’s disease are similar to those for NHL. A substantial proportion of patients who have failed first-line chemotherapy for Hodgkin’s disease can be cured with salvage transplantation.\textsuperscript{155-157} Results are better if transplants are performed when patients have chemotherapy-sensitive disease with minimal bulk and a good performance status. In this setting, cure rates of 40 to 70 percent have been reported.\textsuperscript{158} As with NHL, lower relapse rates but higher nonrelapse mortality are seen with use of allogeneic as opposed to autologous marrow.\textsuperscript{146,157,159}

**MULTIPLE MYELOMA**

Allogeneic marrow transplantation is being increasingly used to treat patients for multiple myeloma. Overall survival rates for allogeneic transplantation in patients who have failed first-line therapy have averaged 35 percent at five years after transplant, and importantly, there appears to be a plateau in disease-free survival, suggesting that some of these patients are cured.\textsuperscript{160,161} Autologous transplantation is also being increasingly studied. There is less evidence that this approach can lead to long-term cure with current techniques. However, if used before patients have truly resistant disease, autologous transplantation can result in a substantial reduction in tumor burden and in many cases to at least temporary complete remissions.\textsuperscript{162-165} In one large randomized study, presented only in abstract form so far, autologous transplantation used shortly after patients had achieved a complete remission led to significantly longer remission durations with a trend toward improved overall survival compared with further conventional chemotherapy.\textsuperscript{166}

**OTHER HEMATOLOGIC MALIGNANCIES**

Long-term survival has been documented following allogeneic marrow transplantation for patients with hairy cell leukemia and various myeloproliferative syndromes, but the number of patients reported in any one disease category is small.

**NEUROBLASTOMA**

High-dose therapy followed by autologous or allogeneic marrow transplantation can apparently cure 15 percent of pa-
patients with recurrent neuroblastoma and up to 40 percent of patients with stage IV disease transplanted while in remission. These results are generally considered to be superior to those obtained with conventional chemotherapy, but randomized trials to substantiate this view are lacking.

**BREAST CANCER**

High-dose therapy followed by autologous marrow transplantation results in a higher rate of complete remission than seen with standard-dose chemotherapy in women with stage IV breast cancer. Studies in a large number of such patients have reported disease-free survival at two to five years of 10 to 30 percent. While these results appear superior to those achieved with standard-dose chemotherapy, longer follow-up will be needed to determine if completely responding patients are cured and whether this percentage is truly higher than seen with conventional-dose chemotherapy. Based on these initial high response rates, high-dose therapy followed by autologous transplantation has been increasingly studied in patients at extremely high risk to recur after conventional-dose adjuvant therapy, such as patients with 10 or more positive nodes. Preliminary results of such an approach appear encouraging and have led to a nationwide controlled trial.

In addition to the important scientific questions raised by the application of autologous transplantation for breast cancer, the number of patients potentially impacted and the relatively high cost of care have made this approach the archetypal in the discussion of who pays for the medical care of patients receiving treatment on clinical trials. How this question is answered will have a profound impact on further clinical research.

**TESTICULAR CANCER**

Although standard-dose chemotherapy for testicular cancer is highly effective, 30 to 40 percent of patients fail conventional regimens. High-dose chemotherapy with autologous marrow support has resulted in a two-year disease-free survival rate of about 20 percent in patients with advanced recurrent disease, a rate that is seemingly better than that achieved with conventional approaches.

Studies of high-dose therapy with stem cell support are currently being conducted for ovarian cancer, small cell lung cancer, glioblastoma multiforme, and soft-tissue sarcoma in addition to the malignancies mentioned above.

**New Approaches in Transplantation**

Numerous new approaches to the clinical application of marrow and peripheral blood stem cell transplantation for the treatment of malignancy are under study. One area of research involves the source and quality of stem cells used for transplantation. Already, the use of mobilized peripheral blood stem cells has improved the safety and diminished the cost of autologous transplantation and may have a similar effect for allogeneic transplantation. Possible sources of allogeneic stem cells have been increased with the expansion of the National Marrow Donor Program and the demonstration...
that stem cells obtained from cord blood offer a viable alternative. Efforts to try to improve the quality of autologous marrow continue through the discovery of more sensitive markers for residual disease and the development of better methods to eliminate contaminating tumor cells, for example, in vitro treatment with immunomagnetic beads, antisense oligonucleotides, and positive selection of hematopoietic stem cells.

A large effort is being made to improve the safety of the transplant procedure. Advances in the prevention and treatment of a number of infectious diseases have already had a major effect, significantly diminishing the impact of *P carinii*, herpes infections, and, most recently, cytomegalovirus disease. Better methods to prevent and treat fungal infections are needed and are under study. Mortality from GVHD after matched-sibling transplants is now distinctly unusual, but GVHD continues to be a major problem limiting the success of mismatched and unrelated transplants. Studies exploring the depletion of subsets of T cells from donor marrow show promise. Recent advances in our understanding of the requirement of T cells to see both their particular antigen plus a costimulatory signal for normal activation have raised the possibility that by blocking the costimulatory signal, anergy or clonal deletion might be achieved. Studies exploring these approaches are ongoing.

Perhaps the most important area of research concerns the development of techniques to more effectively eradicate the underlying malignancy. Most currently used preparative regimens rely on systemic chemotherapy, often with total body irradiation. Clinical studies have demonstrated that higher-dose regimens more effectively eliminate the underlying malignancy but are associated with an increased risk of nonrelapse mortality. Thus, investigators are examining whether monoclonal antibodies or other targeting agents can be used to deliver higher doses of radiotherapy or chemotherapy to sites of malignancy while sparing normal organs. Initial studies demonstrate that this is possible in the treatment of leukemia and lymphoma and have yielded encouraging clinical results.

Other approaches to improve the effectiveness of the transplant regimen in eliminating the underlying malignancy are based on the important observation that relapse of most forms of leukemia and lymphoma is more frequent after syngeneic or T-cell-depleted transplantation than it is after allogeneic transplantation, particularly if patients develop some GVHD. A number of relatively nonspecific attempts to capitalize on this graft-versus-leukemia (GVL) effect are being made, including the use of cyclosporine to try to produce pseudo-GVHD after autologous transplantation and the use of donor buffy coat or interleukin-2 after allogeneic transplantation. Experiments in animal models of the graft-versus-leukemia effect have shown that it is largely a T-cell phenomenon and that the T cells that cause GVHD are not necessarily the same ones responsible for the graft-versus-leukemia effect. Thus, experiments are under way attempting to identify, isolate, and expand T cells with relative specificity for the tumor for use after allogeneic transplantation.

Since its first successful application 25 years ago, the clinical use of marrow and peripheral blood stem cell transplantation has dramatically increased (Fig. 1). While everyone looks forward to a day when antitumor therapies will be less toxic and less expensive than transplantation, current success and the prospects for further improvement argue that, at least for the immediate future, marrow and peripheral blood stem cell transplantation will play a wider role in the treatment of patients with cancer.
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