REVIEW ARTICLE

MEDICAL PROGRESS

Hematopoietic Stem-Cell Transplantation

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Although hematopoietic stem-cell transplantation was originally conceived more than 50 years ago as a treatment for injury from irradiation and, later, for cancer, associated problems needed to be solved before the procedure could be used clinically. Bone marrow, the source of hematopoietic stem cells, is not a solid organ but is rather diffuse and not directly accessible. Furthermore, hematologic cells can initiate immune reactions that may thwart transplantation.

Hematopoietic stem-cell transplantation is used primarily for hematologic and lymphoid cancers but also for many other disorders (Table 1). In this review, I summarize background information about hematopoietic stem-cell transplantation and discuss the role of the procedure in treating malignant and nonmalignant conditions, focusing on recent progress.

EARLY WORK

Studies from the mid-20th century demonstrated that massive total-body irradiation causes fatal damage to the gastrointestinal and central nervous systems. Lower doses lead to delayed death from hemorrhage and infection. In animal models, the transplantation of genetically identical (syngeneic) marrow[1] or the animal's own (autologous) stored marrow[2] averted death. Grafts from histocompatible littermates also permitted survival. The transplantation of marrow that was not genetically identical (allogeneic) to that of the recipient resulted in an immunologic reaction by the donor lymphocytes against the recipient, causing inflammation of the target tissues, termed graft-versus-host disease (GVHD). Treatment with methotrexate suppressed GVHD.[3] As an alternative to total-body irradiation, cyclophosphamide as a preparative regimen also permitted the engraftment of allogeneic marrow.[4]

Thomas was a pioneer in applying the results from early studies in animals to the treatment of leukemia in people. In 1959, he and his colleagues reported that a patient with end-stage leukemia who was treated with total-body irradiation, followed by infusion of her identical twin's marrow, had a three-month remission.[5]

Allogeneic transplantation became feasible in the early 1960s, after the identification and typing of HLA, the major histocompatibility complex. The genes for HLA are closely linked on chromosome 6 and are inherited as haplotypes. Thus, two siblings have about one chance in four of being HLA identical. Transplantation of bone marrow from an HLA-matched child to his immunodeficient sibling was successful because the recipient could not reject the allograft.[6] In the 1970s, Thomas and colleagues cured some patients who had end-stage leukemia by using marrow from their HLA-identical siblings after ablating the host marrow with total-body irradiation combined with cyclophosphamide.[7] Transplantation during the first remission of the leukemia was successful in more than half the patients.[8] The occurrence of GVHD reduced the incidence of leukemic relapse,[9] which sug-

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Table 1. Diseases Commonly Treated with Hematopoietic Stem-Cell Transplantation.

Autologous transplantation*
Cancers
Multiple myeloma
Non-Hodgkin's lymphoma
Hodgkin's disease
Acute myeloid leukemia
Neuroblastoma
Ovarian cancer
Germ-cell tumors
Other diseases
Autoimmune disorders
Amyloidosis
Allogeneic transplantation†
Cancers
Acute myeloid leukemia
Acute lymphoblastic leukemia
Chronic myeloid leukemia
Myelodysplastic syndromes
Myeloproliferative disorders
Non-Hodgkin's lymphoma
Hodgkin's disease
Chronic lymphocytic leukemia
Multiple myeloma
Juvenile chronic myeloid leukemia
Other diseases
Aplastic anemia
Paroxysmal nocturnal hemoglobinuria
Fanconi's anemia
Blackfan–Diamond anemia
Thalassemia major
Sickle cell anemia
Severe combined immunodeficiency
Wiskott–Aldrich syndrome
Inborn errors of metabolism

* More than 30,000 autologous transplantations are performed annually worldwide, two thirds for multiple myeloma or non-Hodgkin's lymphoma.

† More than 15,000 allogeneic transplantations are performed annually worldwide, nearly half for acute leukemias. The vast majority are performed to treat lymphoid and hematologic cancers.

gested that donor lymphocytes can eradicate tumor cells that survive preparative regimens. All of this work was the foundation for the current understanding of hematopoietic stem-cell transplantation.

CURRENT KNOWLEDGE AND THEORY

Mature blood cells are produced continuously by less-differentiated precursors that are in turn descended from more primitive progenitors and, originally, from hematopoietic stem cells. Stem cells, including hematopoietic stem cells, have the unique capacity to produce some daughter cells that retain stem-cell properties; they do not become specialized and thus are self-renewing — a lifetime source of blood cells. In fact, a single stem cell can restore the entire lymphohematopoietic system of a lethally irradiated animal.[10] Just as in the normal hematologic system, the cells that cause leukemia and other cancers consist of hierarchies of cells at various levels of differentiation. Tumors arise from malignant stem cells that usually originate from normal stem cells[11] and retain the mechanism for self-renewal.[12] Most leukemic cells have a limited capacity for proliferation and are continuously replenished by leukemic stem cells. Only 1 in 1 million leukemic blasts appears to be a true stem cell, according to the capacity to propagate and sustain human leukemia in immunologically susceptible mice.[13]

The chemotherapy used to treat cancers acts primarily on proliferating cells. Normal and malignant stem cells, however, are quiescent and therefore insensitive to therapy. Both normal and malignant stem cells repair DNA efficiently, resist apoptosis, and excrete toxic drugs by means of ATP-binding transporters.[14] Thus, although chemotherapy can destroy a tumor almost completely, the stem cells are spared, allowing the cancer to recur. Even in cases of chronic myeloid leukemia that are responsive to imatinib — a molecularly targeted therapy that impairs the transfer mediated by BCR-ABL (a tyrosine kinase) of phosphate to its substrates — studies of bone marrow[15] and sophisticated mathematical modeling techniques[16] have shown the continued presence of leukemic stem cells, which cause relapse. Some malignant stem cells survive even lethal doses of total-body irradiation and chemotherapy given in preparation for hematopoietic stem-cell transplantation. However, such cells may be eliminated by immunologically active donor cells.[17]

Allogeneic grafts initiate immune reactions related to histocompatibility. The severity of the reaction depends on the degree of incompatibility, which is determined by a complex biology in which polymorphic class I and class II HLA cell-surface glycoproteins bind small peptides from degraded proteins. The aggregate of oligopeptides displayed is determined by the binding specificities of a person's HLA molecules. T-cell receptors interact with the surface glycoproteins and the bound peptides. Recipient T cells recognize for-

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eign donor antigens and can reject grafts; donor T cells recognize recipient antigens and can cause GVHD and graft-versus-tumor effects.

The strongest transplant reactions occur when the major histocompatibility antigens (HLA) of the donor and of the recipient are incompatible. The intensity of the reaction increases with the generation of multiple peptides from degraded HLA molecules and in the presence of recognizable determinants on HLA molecules on the cell surface of so-called antigen-presenting cells. In contrast, minor histocompatibility antigens are single peptides derived from polymorphic proteins (which may differ between donor and recipient) that are distinct from the major histocompatibility complex. The minor antigens are presented by a small fraction of HLA molecules and initiate weaker responses than the major antigens do. Minor antigens encoded by genes on the Y chromosome account for the higher incidence of GVHD[18] and lower rate of relapse of underlying disease[19] among male recipients of marrow transplants from female donors than among male recipients of transplants from male donors.

Minor histocompatibility antigens on leukemic cells can provoke a graft-versus-leukemia response[17,19,20] (Fig. 1). Donor T cells reactive to recipient minor histocompatibility antigens inhibit the growth of leukemic colonies and, in one study, prevented the development of acute myeloid leukemia derived from human cells in immunologically susceptible mice.[20] Thus, leukemic stem cells can be eliminated by means of this mechanism. Donor T cells can also target aberrantly expressed proteins (e.g., proteinase 3 in myeloid leukemias) and can inhibit leukemic, but not normal, colony formation.[21] The graft-versus-leukemia effect accounts for reduced rates of relapse both after allogeneic transplantation (as compared with transplantation of marrow from an identical twin) and among patients in whom GVHD develops (as compared with patients in whom it does not).[22] These results explain the effectiveness of infusions of donor lymphocytes in treating leukemia relapse after transplantation.[23]

GVHD is an immune response accentuated, and possibly stimulated, by injury resulting from the preparative regimen used before transplantation.[24] The injury is primarily confined to the gastrointestinal tract, where Peyer's patches have a cen-

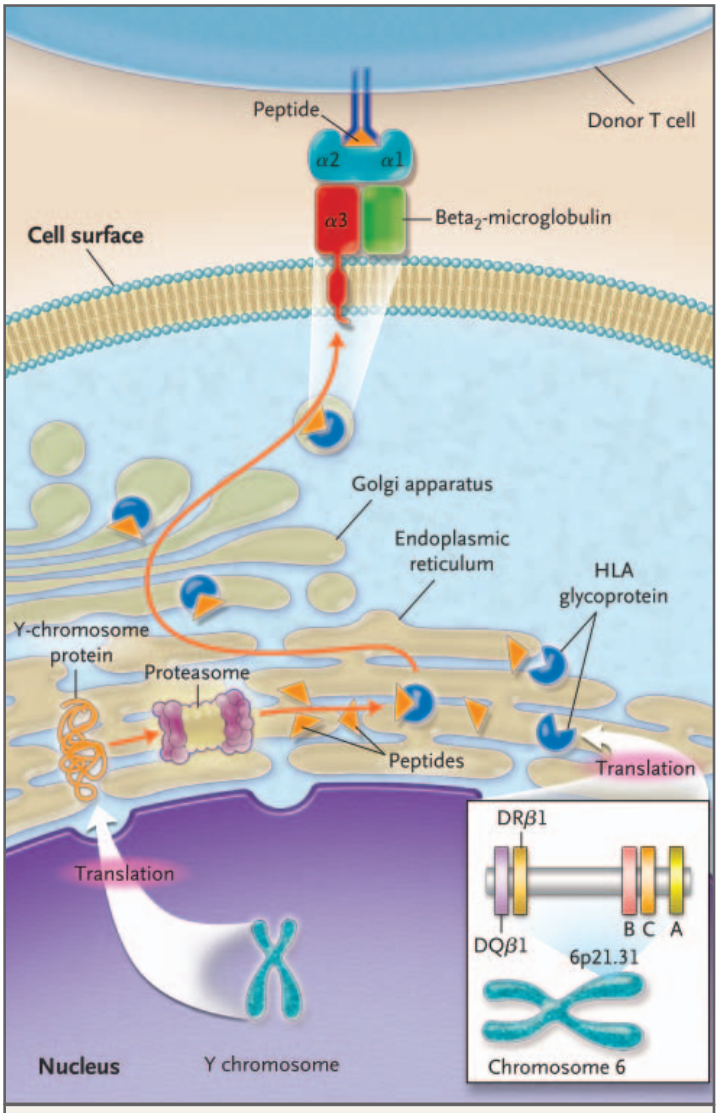

Figure 1. Graft-versus-Leukemia Effect from a Minor Histocompatibility Antigen.

A protein encoded by a Y-chromosome gene of a male graft recipient is degraded within the proteasome. A peptide derived from the polymorphic protein is then transported to the endoplasmic reticulum, where it binds an HLA glycoprotein encoded by one of the HLA-complex genes on chromosome 6 (the HLA loci important in matching are shown). The HLA glycoprotein (here, class I) and bound peptide travel through the Golgi apparatus to the cell surface, where the peptide is recognized as foreign by a T cell from the female donor. The class I gene encodes the α polypeptide chain, which includes the $\alpha 1$ and $\alpha 2$ peptide-binding domains and the $\alpha 3$ immunoglobulin-like domain, the transmembrane region, and the cytoplasmic tail. The beta$_2$-microglobulin is encoded by a gene on chromosome 15 (not shown). Minor histocompatibility antigens selectively expressed on hematopoietic cells cause a graft-versus-leukemia effect but not GVHD; antigens expressed on hematopoietic cells and epithelial cells cause both.

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tral role in attracting donor T cells after the injury, a process that may contribute to the development of GVHD (Fig. 2). Cytokines are critical to GVHD, and their genetic variants influence its development. Indeed, the inactivation of the chemokines or the adhesion molecules that attract donor T cells to Peyer's patches eliminates most deaths from GVHD in mice.[25] By suppressing the release of inflammatory cytokines and the activation of T cells, interleukin-10 promotes tolerance. Homozygosity for a common variant of the interleukin-10 promoter appears to increase the production of interleukin-10 and reduce the incidence of GVHD.[26] The genetic polymorphisms of other cytokines also appear to influence GVHD.[27] In addition, small variations in donor or recipient genes that encode a protein (NOD2/CARD15) critical to the response of macrophages to a bacterial toxin are associated with severe GVHD.[28] Therefore, genotyping may be useful to help estimate the risk of GVHD, identify donors, and develop individualized prevention strategies.

Hematopoietic stem-cell transplantation results in more cures and remissions than alternative treatments but also causes greater morbidity and mortality. Although the mortality rate is less than 2 percent for some autologous transplantations and is less than 10 percent for some allogeneic transplantations, about 40 percent of patients with advanced cancer who undergo allogeneic transplantation die from complications related to transplantation. Reducing the toxicity of the preparative regimen is critical to improving the safety of transplantation.

Figure 2 (facing page). Postulated Mechanism of Acute GVHD.

High-dose preparative regimens damage tissues, particularly in the gut, allowing lipopolysaccharide from bacteria in the bowel to leak into adjacent tissues and the bloodstream. Distinct classes of conserved microbial molecules and necrotic-cell elements (including high-mobility group box 1 protein) activate toll-like receptors on various cells, which leads to release of inflammatory cytokines (including tumor necrosis factor α [TNF-α] and interleukin-1, interleukin-6, and interleukin-12). As part of the innate immune response, neutrophils, macrophages, and eosinophils migrate to the damaged tissue and cause further injury. Dendritic cells, containing antigen captured from damaged intestinal mucosal cells, are activated by toll-like receptors. The cells migrate to lymphoid organs (particularly Peyer's patches), where they mature. The mature dendritic cells, expressing high levels of costimulatory molecules, present peptides to donor T cells. This presentation induces an alloantigenic response involving the proliferation of donor T cells and the secretion of cytokines (interleukin-2 and interferon-γ); such secretion promotes further proliferation of donor T cells and activates cytotoxic T cells and natural killer cells. Natural killer cells produce interferon-γ and TNF-α. The effects of the cytokines (shown at their cells of origin) are widespread: they activate effector cells, particularly macrophages and natural killer cells, which damage tissues. All these responses further increase inflammation and injury. The acquired immune response is controlled and limited by CD4+CD25+ regulatory T cells. The activation of toll-like receptors blocks the suppressive effect of these regulatory cells, which in turn permits activated T cells to enter the circulation, migrate, and damage other organs, particularly the skin and liver.

PREPARATIVE REGIMENS

The object of myeloablative preparation before transplantation is both to eradicate cancer and, in allogeneic transplantation, to induce the immunosuppression that permits engraftment. The preparative regimen can also augment the antitumor immune response by causing a breakdown of tumor cells, which results in a flood of tumor antigens into antigen-presenting cells. This flooding can lead to the proliferation of T cells, which attack the surviving malignant cells.[29]

Total-body irradiation is myeloablative and immunosuppressive, is not associated with cross-resistance to chemotherapy, and reaches sites that are not affected by chemotherapy. The effects of total-body irradiation are independent of the blood supply, and local shielding of organs and boosting of dose are feasible. Fractionating the dose of total-body irradiation reduces toxicity. Fractionated total-body irradiation combined with cyclophosphamide has been the standard preparation since the 1980s. In one study, higher-than-standard doses of total-body irradiation reduced the rate of relapse but did not improve survival, because transplantation-related mortality increased.[30] Selective radiation of leukemias involves the delivery of radiolabeled monoclonal antibodies against antigens on marrow cells.[31] Newer methods of selective radiation promise increased specificity.[32]

The toxicity of total-body irradiation and the scarcity of facilities for the procedure have resulted in the development of radiation-free regimens. In 1983, a regimen of busulfan combined with high doses of cyclophosphamide proved effective in treating acute myeloid leukemia.[33] The

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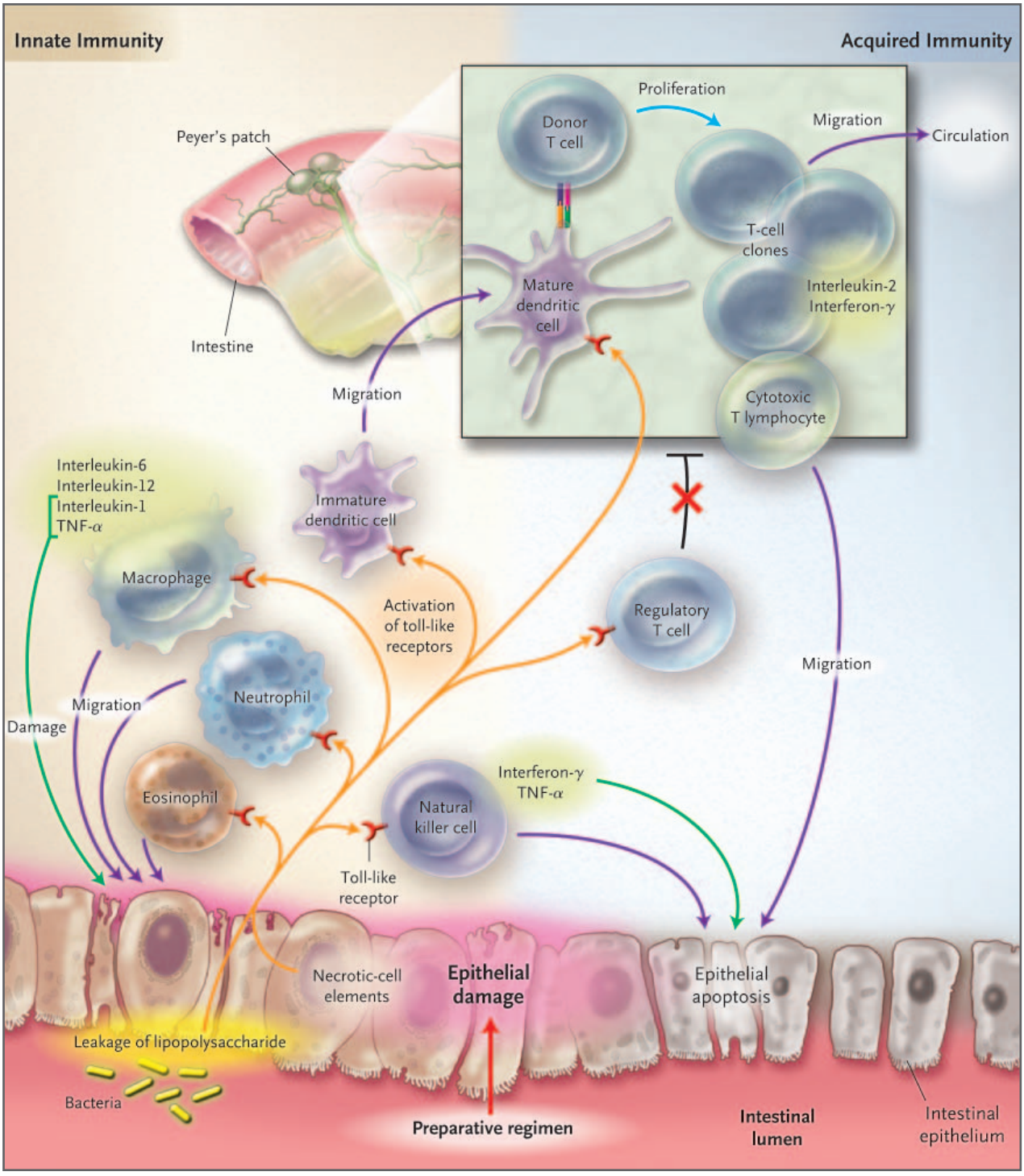

dose of cyclophosphamide was soon lowered to reduce toxicity.[34] With this regimen, acute adverse effects are associated with high plasma levels of busulfan[35] and of metabolites of cyclophosphamide.[36] Toxicity can be reduced by adjusting the busulfan dose according to the plasma levels of the drug[37] or by using intravenous, instead of oral, busulfan.[38]

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A better understanding of graft-versus-tumor biology led to the development of reduced-intensity preparative regimens in the late 1990s. Unlike traditional myeloablative preparations, these regimens are primarily immunosuppressive and depend on the graft to eradicate cancer (Fig. 3). If immunologic elimination of malignant stem cells is the key to successful allotransplantation, then reduced-intensity regimens seem preferable.

Storb and colleagues developed a regimen of low-dose total-body irradiation and immunosuppressive drugs after transplantation to permit engraftment and to prevent GVHD.[39] A high rejection rate was reduced by adding an immunosuppressive agent, fludarabine, before total-body irradiation.[40] With this regimen, neutropenia and thrombocytopenia are mild, toxic effects are minimal, and transplantation is feasible as an outpatient procedure. Within a few months after transplantation, donor lymphocytes can be infused to augment graft-versus-tumor activity. Such reduced-intensity regimens were designed originally for older recipients or for recipients with organ dysfunction. (The toxic effects of myeloablative allotransplantation increase with age, particularly after the age of 50 years, and generally preclude performing the procedure in patients who are older than 65 years.) The safety and effectiveness of these regimens have led to their wider application during the past five years. For patients with advanced hematologic cancer, however, the low mortality rate associated with reduced-intensity preparative regimens may be offset by high relapse rates.[41] Allogeneic transplantation after the receipt of reduced-intensity regimens is most effective in treating slow-growing cancers (e.g., chronic lymphocytic leukemia and low-grade non-Hodgkin's lymphoma). The use of this approach in treating acute leukemia in remission and myelodysplasia is under study.

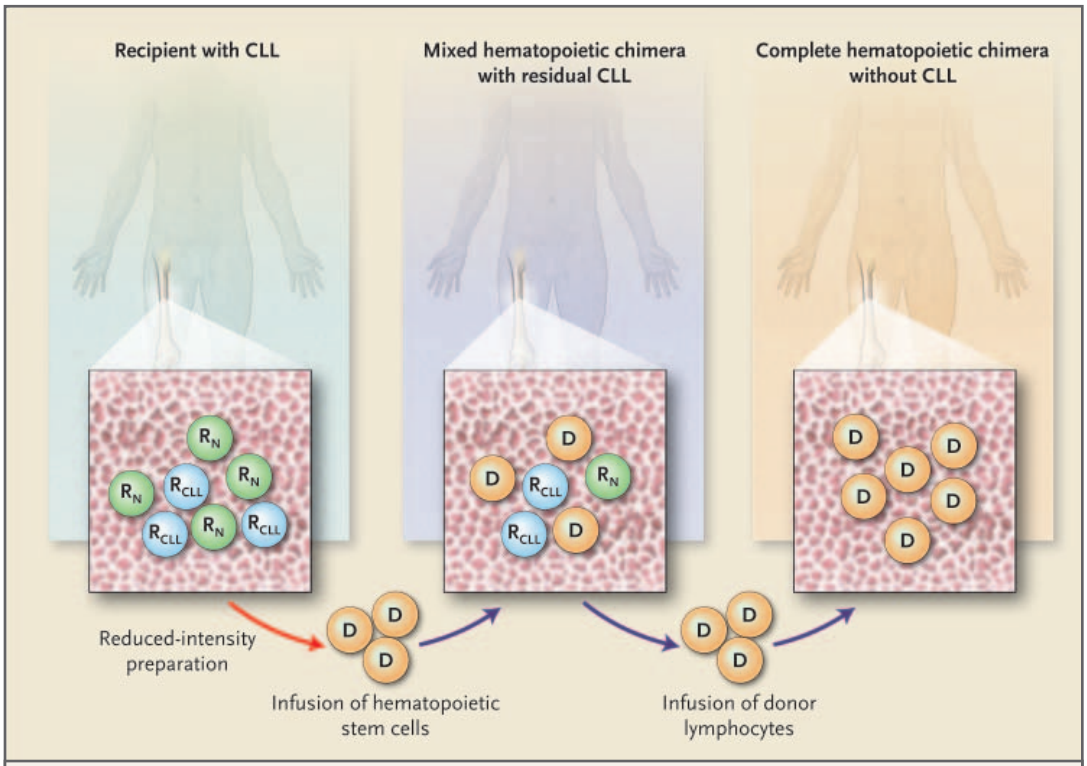

Figure 3. Transplantation Involving Reduced-Intensity Preparative Regimens.

A recipient with chronic lymphocytic leukemia (CLL) has normal (R_N) and malignant (R_{CLL}) cells in the marrow. A reduced-intensity regimen provides sufficient immunosuppression to permit the engraftment of hematopoietic stem cells from an allogeneic donor (D). Mixed hematopoietic chimerism results: normal donor cells and normal and malignant recipient cells coexist. The extent of donor chimerism can be ascertained by molecular analysis. Infusions of donor lymphocytes are given to eradicate residual recipient normal and malignant cells for complete donor chimerism.

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SOURCES OF STEM CELLS

Bone marrow obtained by repeated aspiration of the posterior iliac crests while the donor is under general or local anesthesia was the first source of hematopoietic stem cells. Discomfort from the harvesting procedure usually disappears within two weeks, and serious effects are rare (two deaths in 8000 collections).[42]

Because marrow stem cells detach continuously, enter the circulation, and return to the marrow, peripheral blood is a convenient source of hematopoietic stem cells and has replaced marrow for autologous and most allogeneic transplantations. As compared with marrow, peripheral-blood stem cells obtained with currently used techniques produce more rapid hematopoietic reconstitution. In allogeneic transplantation, however, peripheral-blood stem cells, which contain more T cells than marrow does, increase the incidence[43] and prolong the treatment[44] of chronic GVHD. The number of peripheral-blood stem cells is estimated with use of the cell-surface molecule CD34 as a surrogate marker. The number of CD34+ cells in blood can be increased by mobilizing them from the marrow with granulocyte colony-stimulating factor (G-CSF), which causes the proliferation of neutrophils and the release of proteases. Proteases degrade the proteins that anchor the stem cells to the marrow stroma and, together with protease-independent mechanisms, free the cells to enter the circulation.[45] The mobilization of CD34+ cells is increased when G-CSF is given after chemotherapy. The combination of G-CSF and AMD3100 — a small-molecule reversible inhibitor of CXC chemokine receptor 4 (CXCR4), a receptor on CD34+ cells that mediates signals to potentiate the adhesion of CD34+ cells to marrow — is superior to G-CSF alone in mobilizing CD34+ cells.[46] Leukapheresis in an adult, performed through the antecubital veins, can process up to 25 liters of blood in four hours, which usually yields enough CD34+ peripheral-blood stem cells to ensure rapid engraftment.

Studies performed during the 1980s showed that autologous transplantation cured some lymphomas after conventional chemotherapy failed to do so.[47] Autologous transplantation was applied successfully to treat many other diseases and is now used more often than allotransplantation. For autotransplantation, hematopoietic stem cells are usually frozen at temperatures below –120°C and are used within a few weeks, although, when frozen, they are viable for years. Because autologous transplantation does not induce GVHD, it can be used in older patients. Mortality is considerably lower with autotransplantation than with allotransplantation, but the absence of graft-versus-tumor activity in autotransplantation reduces its effectiveness. The contamination of grafts with tumor cells contributes to relapse in hematologic cancers,[48] but the purging of tumor cells from grafts immunologically or with the use of other techniques does not appear to improve survival.[49] Indeed, the failure to eradicate cancer in the patient is the primary cause of relapse.

Less than 30 percent of potential recipients of hematopoietic stem cells have HLA-identical siblings. Thus, the use of other sources of these cells has been an important advance. For example, the use of unrelated donors has increased, and the rates of success of such procedures have improved as better methods of gene definition and matching have been developed. These methods involve DNA typing to identify HLA alleles and the most closely matched donor, since the use of a closely matched donor increases the chances of successful engraftment and reduces the risk of GVHD.[50] How well a recipient tolerates HLA mismatches depends on the particular epitopes present, and young recipients tolerate mismatches better than older recipients do. The number of matched unrelated donors is limited by the extensive polymorphism of HLA genes. International registries now list more than 9 million potential donors and find acceptable donors for more than 50 percent of patients. However, identifying unrelated donors and then procuring the stem cells usually take more than three months. Largely because of this delay, less than half the donors who were matched to patients in this way are used.[51]

CORD-BLOOD TRANSPLANTATION

If transplantation is urgent or if suitable donors are not found, cord blood, which can be procured both easily and safely, can be used. First used in a child with Fanconi's anemia,[52] cord blood from mostly unrelated donors has since been transplanted into more than 6000 patients. Blood from the umbilical cord and the placenta is rich in hematopoietic stem cells but limited in volume. It is collected immediately after birth and then frozen. Because hematologic and immunologic reconsti-

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tution is slow in transplanted cord blood, infection is common soon after transplantation. The transplantation of cord blood requires less-stringent HLA matching than does the transplantation of adult peripheral blood or marrow, because mismatched cord-blood cells are less likely to cause GVHD, without losing the graft-versus-leukemia effect.[53] The results are better with fewer HLA mismatches and greater numbers of CD34+ cells.[53] The use of additional grafts from different donors may improve engraftment, particularly when the first graft contains few cells.[54]

The ex vivo expansion of cord-blood stem cells[55] and the transplantation of cord blood along with HLA-haploidentical peripheral-blood stem cells[56] are under study. Cord-blood banks in 21 countries currently store about 170,000 units. Bone Marrow Donors Worldwide (www.bmdw.org) collects and lists HLA types for cord-blood and adult registries. The less-stringent HLA requirements for cord-blood transplantation would permit a smaller donor pool to serve virtually all potential recipients. Members of minority populations, who are underrepresented in adult registries and often lack matches, would benefit from an increase in the number of cord-blood donors. For many children, cord blood is now transplanted instead of peripheral blood or marrow from unrelated adults. For adults, cord blood is currently used when suitable adult donors cannot be found quickly. Data from the Center for International Blood and Marrow Transplant Research indicate that 5 percent of transplants from unrelated donors into adult recipients consist of cord blood (Horowitz M: personal communication). Improving matches and increasing cell doses should extend the usefulness of cord-blood transplantation.

TRANSPLANTATION INVOLVING A HAPLOIDENTICAL DONOR

The transplantation of stem cells from a parent, sibling, or child of a patient with only one identical HLA haplotype was initially associated with high rates of engraftment failure and GVHD — complications that predictably caused death soon after transplantation. In the past decade, however, technical advances have improved the outcomes of this approach.[57] This type of transplantation involves another alloreactive mechanism involving natural killer cells, which express combinations of activating and inhibitory killer-cell immunoglobulin-like receptors that interact with class I HLA epitopes. The balance of signals determines the cytolytic activity of the natural killer cells, a process that is inhibited by the recognition of self-epitopes by the immunoglobulin-like receptors. Alloreactivity improves the chances of engraftment and reduces the risk of GVHD; it also reduces relapse in patients with acute myeloid leukemia.[58] Because half of transplants from unrelated donors are mismatched for one or more HLA alleles, alloreactivity of natural killer cells could be used for choosing donors and improving the outcome; however, retrospective studies have been inconclusive.[59,60]

Originally a treatment of last resort, hematopoietic stem-cell transplantation is now used early in the course of many diseases. Its appropriate use requires full knowledge of its outcomes and complications and those of other treatments.

COMPLICATIONS

EARLY EFFECTS

Mucositis is an important problem of hematopoietic stem-cell transplantation. In the short term, it is the most common complication of myeloablative preparative regimens and methotrexate (used to prevent GVHD). Oropharyngeal mucositis is painful and can involve the supraglottic area and require intubation. Intestinal mucositis causes nausea, cramping, and diarrhea and may require parenteral nutrition. A recombinant human keratinocyte growth factor, palifermin, reduces the incidence of oral mucositis after autologous transplantation.[61] In mice, keratinocyte growth factor protects the gut, which reduces the severity of GVHD,[62] and protects the epithelium of the thymus, which improves immune reconstitution.

The second most common acute adverse effect is a potentially fatal syndrome of painful hepatomegaly, jaundice, and fluid retention, traditionally called hepatic veno-occlusive disease. However, the term "sinusoidal obstruction syndrome" is more accurate,[63] because damaged sinusoidal endothelium sloughs and then obstructs the hepatic circulation, injuring centrilobular hepatocytes. In severe sinusoidal obstruction syndrome, renal and respiratory failure may occur. Total-body irradiation, busulfan, cyclophosphamide, and many other preparative agents cause sinusoidal obstruction syndrome, which limits maximal doses. Risk factors for the syndrome include chronic liver disease and the presence of the C282Y allele

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of the *HFE* hemochromatosis gene.[64] Common variants of the glutathione *S*-transferase gene alter the metabolism of busulfan and cyclophosphamide and are associated with an increased incidence of sinusoidal obstruction syndrome after the use of these drugs in the preparative regimen.[65] Because there is no effective treatment for the syndrome, its prevention is critical. The substitution of fludarabine for cyclophosphamide[66] and the use of reduced-intensity regimens[67] appear to decrease the risk of sinusoidal obstruction syndrome.

Transplantation-related lung injury occurs within four months after the procedure, and the mortality rate exceeds 60 percent. Risk factors include total-body irradiation, allogeneic transplantation, and acute GVHD, suggesting that donor lymphocytes target the lung.[68] Along with neutrophils and lymphocytes, tumor necrosis factor — induced by GVHD and the lipopolysaccharide that enters the circulation through damaged intestinal mucosa — contributes to lung injury; treatment with etanercept, which inhibits tumor necrosis factor, combined with corticosteroids, may reduce injury if used promptly.[69]

Transplantation-related infections result from damage to the mouth, gut, and skin from preparative regimens as well as from catheters, neutropenia, and immunodeficiency. Reduced-intensity regimens are associated with a lower rate of early infections than are myeloablative regimens, but the risk of late infection seems to be the same. Prolonged neutropenia, GVHD, and the administration of corticosteroids predispose patients to fungal infection, a life-threatening complication of allogeneic transplantation. Cytomegalovirus pneumonia, once fatal to 15 percent of recipients of allogeneic transplantation,[70] has become rare with the use of techniques involving antigens or the polymerase chain reaction that detect subclinical cytomegalovirus infection and make early treatment possible. Better prevention and treatment of transplantation-related infections have improved outcomes of transplantation.

GVHD is the most important complication of allogeneic transplantation. Acute GVHD damages the skin, gut, and liver. A pruritic micropapillary rash can affect the palms, soles, or face and may become generalized. Nausea, vomiting, abdominal pain, diarrhea, bloody stool, and jaundice may occur. GVHD and its treatment with corticosteroids cause profound immunodeficiency, predisposing the patient to fatal infection. The principal risk factor is HLA mismatch, but GVHD may occur despite an HLA-matched donor and the use of preventive measures. If prophylaxis is not provided, serious acute GVHD affects almost every recipient.[71] The risk of GVHD is greatly reduced by short-term treatment with methotrexate plus treatment with cyclosporine for several months.[72] The incidence of GVHD can be reduced by in vitro T-cell depletion of the graft before transplantation, but this does not improve disease-free survival, because the rates of graft rejection and relapse increase. A reduced-intensity regimen of total lymphoid irradiation and antithymocyte globulin may decrease the incidence of GVHD.[73] (The results of studies in mice suggest that repeated low-dose lymphoid irradiation spares natural killer T cells that prevent acute GVHD.)[74] Gene modification of donor T cells is a potential means of treating GVHD. Viral genes that are capable of converting drugs into lethal products have been expressed in donor T cells, which can then be eliminated if severe GVHD develops.[75] It is difficult, however, to transduce and eliminate sufficient numbers of lymphocytes. Current studies use human proteins to induce lymphocyte apoptosis.[76]

DELAYED EFFECTS

Most survivors of transplantation are active and healthy, but some delayed complications, particularly chronic GVHD, can be serious. The risk increases with recipient and donor age and is increased for peripheral-blood grafts or grafts from unrelated donors. Chronic GVHD is associated with loss of self-tolerance[77] and often resembles scleroderma or Sjögren's syndrome. Chronic GVHD can cause bronchiolitis, keratoconjunctivitis sicca, esophageal stricture, malabsorption, cholestasis, hematocytopenia, and generalized immunosuppression. Treatment with corticosteroids may be needed for two years or longer.[44] Corticosteroids can cause a variety of complications, including aseptic necrosis of bone and osteoporosis, and may predispose the patient to fatal infections. If severe hypogammaglobulinemia occurs, treatment with intravenous immune globulin can reduce infections.[78]

Most women fail to ovulate after undergoing transplantation. Hormonal suppression of the ovaries before the preparative regimen is administered might permit the recovery of ovulation after trans-

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plantation.[79] Some women who have undergone transplantation have become pregnant using cryopreserved embryos or oocytes. Men usually become infertile after transplantation, but younger men may recover their fertility, and if sperm are present before transplantation, the semen can be cryopreserved and used later. Even low-quality sperm can result in pregnancy by means of in vitro fertilization, particularly with intracytoplasmic injection.[80]

Children who undergo transplantation have special problems. Growth and development are impaired by myeloablative preparative regimens, but growth hormone therapy can increase height in children who have undergone hematopoietic stem-cell transplantation.[81]

The frequency of secondary cancers is increased after transplantation. After allotransplantation, the incidence of cancers of the skin, oral mucosa, brain, thyroid, and bone is increased.[82] Myelodysplasia and acute leukemia are complications of autologous transplantation for Hodgkin's and non-Hodgkin's lymphomas.[83] The type and intensity of the pretransplantation chemotherapy used affect this risk.[84] Survivors of transplantation must avoid carcinogens, particularly tobacco. They should be followed indefinitely to detect early cancer or precursor lesions. They should also be observed for other conditions that have been reported: hypothyroidism, sexual problems, depression, and anxiety.[85]

USES AND RESULTS

The diseases most often treated with autologous and allogeneic hematopoietic stem-cell transplantation are listed in Table 1. Outcomes vary according to the type and stage of disease, the age and functional level of the patient, the source of the stem cells to be transplanted, and the degree of HLA mismatch. Because transplantation is costly (at present, generally exceeding $80,000 for autologous transplantation and $150,000 for allogeneic transplantation) and the resulting morbidity

Table 2. Outcomes of Hematopoietic Stem-Cell Transplantation in Selected Diseases.*

Disease	Most Common Preparative Regimen	100-Day Mortality Rate	5-Yr Event-free Survival
		percent	
Autologous transplantation			
Diffuse large-cell non-Hodgkin's lymphoma	Carmustine, cyclophosphamide, and etoposide		
First chemotherapy-sensitive relapse		3–5	45–50
Second chemotherapy-sensitive relapse		5–8	30–35
Refractory		10–20	5–10
Allogeneic transplantation†			
Acute myeloid leukemia	Cyclophosphamide and total-body irradiation		
First complete remission		7–10	55–65
Second complete remission		10–20	30–40
Refractory		30–40	15–20
Chronic myeloid leukemia	Busulfan and cyclophosphamide		
Chronic phase <1 yr after diagnosis		5–10	70–80
Chronic phase >1 yr after diagnosis		10–15	50–60
Accelerated		15–20	30–35
Blastic		35–45	5–15

* The estimated ranges of data are based on recent reports.
† This category refers to the transplantation of hematopoietic stem cells from an HLA-identical sibling donor.

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and mortality are substantial, the goal of transplantation is usually to cure the disease. However, although autologous transplantation does not cure multiple myeloma, it does improve survival.[86] Two autologous transplantations in succession may further improve survival among patients with myeloma, especially if the response to the first is limited.[87]

Hematopoietic stem-cell transplantation has resulted in sustained remission in patients with autoimmune disease.[88] Autologous transplantation has resulted in remissions in patients with refractory rheumatoid arthritis and multiple sclerosis, and allotransplantation after reduced-intensity preparative regimens may prove to be curative.

Hematopoietic stem-cell transplantation cures many genetic diseases, including severe combined immunodeficiency, the Wiskott–Aldrich syndrome, sickle cell anemia, and thalassemia. The outcome is better among younger patients and patients with less organ damage. For example, in patients with thalassemia, the amount of preexisting liver damage from iron overload affects the outcome of transplantation.[89] For Krabbe's disease — a rare, fatal neurologic disorder caused by an enzyme deficiency — transplantation has usually been performed in symptomatic older children, but transplantation in asymptomatic newborns yielded better results in a recent study.[90]

Early transplantation is critical in patients with hematologic cancers (Table 2), but the proper time to perform the procedure is difficult to ascertain and is the subject of controversy. Recognized prognostic factors, particularly cytogenetics, are used to determine the time of transplantation for patients with acute leukemia. Allotransplantation during the first remission usually offers the best chance for a cure for patients with a poor prognosis with conventional chemotherapy alone. Allogeneic transplantation is used after relapse in patients who had a favorable prognosis with chemotherapy. In patients with chronic myeloid leukemia, allotransplantation is the only curative treatment, and it is safest when performed early. Although transplantation is an appropriate first-line therapy in some patients, imatinib therapy is favored for most patients, owing to the large number of long remissions and minimal toxic effects associated with the agent. Transplantation is then performed in patients who do not have a cytogenetic remission or after relapse.

Autologous transplantation is substantially better than chemotherapy for treating the first relapse of large-cell non-Hodgkin's lymphoma that is sensitive to chemotherapy.[91] Nevertheless, data from the Center for International Blood and Marrow Transplant Research show that many patients undergo transplantation belatedly, when a cure is less likely (Horowitz M: personal communication). Other data from the center and data from the National Cancer Institute (available at http://seer.cancer.gov) suggest that only a minority of patients with a relapse responsive to chemotherapy ever undergo autologous transplantation. This finding agrees with that of a report from 2001[92] and with the expert opinion that transplantation is broadly underused.[93] The General Accounting Office estimates that in the United States, only one third of patients who need transplants from unrelated donors have preliminary searches requested from the National Marrow Donor Registry.[51] Socioeconomic factors contribute to the decision,[94-96] but all too often transplantation is considered too late or not at all. Obviously, the potential benefit of transplantation must be balanced against its risk, and patients must be fully informed of both.

THE FUTURE

At present, hematopoietic stem-cell transplantation provides the best chance for a cure for many diseases. Future work will determine the best ablative regimens for specific conditions, and technical advances will improve the effectiveness of reduced-intensity regimens. The use of cytokine antagonists or suicide genes or the infusion of regulatory T cells[97,98] may reduce the severity of GVHD, and a better understanding of the genetic polymorphisms involved in its development may help prevent the disease.

Embryonic stem cells may become a source of hematopoietic stem cells.[99] Histocompatibility problems may be solved by establishing comprehensive banks of embryonic stem-cell lines or by creating genetically matched stem-cell lines individually. The bioengineering of embryonic stem cells might eliminate the need for HLA typing, procurement of hematopoietic stem cells, and even preparative therapy.

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