This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations.

LONG-TERM CARE AFTER HEMATOPOIETIC-CELL TRANSPLANTATION IN ADULTS

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A 35-year-old man who had undergone allogeneic hematopoietic-cell transplantation two years earlier for acute myeloid leukemia recently moved to a new town. He comes in for a general checkup because he tires easily and has frequent bouts of sinusitis. Physical examination reveals small central cataracts, some patches of vitiligo, and a dry mouth. Blood counts and the results of chemical analyses are normal. What are the major issues in the long-term follow-up and care of patients after successful hematopoietic-cell transplantation?

THE CLINICAL PROBLEM

The success of bone marrow transplantation in the late 1960s and early 1970s engendered a tremendous growth in the use of allogeneic and autologous hematopoietic-cell transplantation. Improvements in the outcome of transplantations have resulted in an increasing number of patients who are cured of the underlying disease and who are thus no longer followed by transplantation physicians. In the United States, there are now more than 20,000 patients who have survived for more than five years after transplantation, and this number should continue to grow.

There is an unfortunate tendency for patients and doctors alike to be so relieved that a dangerous procedure was successful that they deemphasize the importance of routine health maintenance. Having been so closely tied to medical care in the peritransplantation period, patients may welcome being freed from clinic visits, or they may assume that they do not need to see any health care providers other than the transplantation physician. However, after successful transplantation, patients remain at risk for diseases common in the general population, as well as for health problems directly related to transplantation. Primary care physicians will care for many of these patients. This review covers major health issues relevant to this population.

STRATEGIES AND EVIDENCE

Graft-versus-Host Disease

When allogeneic cells are transplanted, donor T cells can recognize either major histocompatibility, or HLA, antigens or minor histocompatibility antigens, small host peptides presented to T cells by the HLA molecules. This recognition leads to the activation of the T cells, which then attack target organs. The resultant clinical manifestations constitute graft-versus-host disease (GVHD). By convention, GVHD that occurs within 100 days after transplantation is defined as acute and that occurring after 100 days is considered chronic. Both types of GVHD are more frequent in older patients and after the receipt of HLA-mismatched hematopoietic cells or hematopoietic cells from an unrelated donor, an older donor, a cytomegalovirus-positive donor, a female donor, and a donor who has been sensitized by previous pregnancy or transfusion.

Clinically significant GVHD develops in approximately 30 to 50 percent of recipients of allogeneic hematopoietic cells. Acute GVHD occurs primarily in the skin, liver, and gut. Affected patients may have one or more organs involved to various degrees. The severity of acute GVHD is graded on a five-point scale on which a grade of 0 indicates the absence of GVHD and a grade of IV the presence of life-threatening GVHD. Acute GVHD is treated with corticosteroids, tacrolimus, cyclosporine, or investigational agents.

Primary care physicians are more likely to see patients with chronic GVHD than those with acute GVHD. The incidence of chronic GVHD ranges from 30 percent among recipients of fully histocompatible transplants to 60 to 70 percent among recipients of mismatched hematopoietic cells or hematopoietic cells from an unrelated donor. The incidence is probably higher if peripheral blood, rather than bone marrow, is the source of hematopoietic cells. Typically, GVHD appears between 3 months and 1.5 years after transplantation; however, it may begin as late as 2 or more years after transplantation.
rences may be triggered by an infection, such as herpes zoster, or by a sunburn. Chronic GVHD may evolve from acute GVHD soon after transplantation, it may occur after the resolution of acute GVHD, or it may occur without prior acute GVHD.

Common manifestations of chronic GVHD are lichenoid changes of the skin and mucous membranes, vitiligo, periorbital hyperpigmentation, odynophagia, nail dysplasia, keratoconjunctivitis sicca, xerostomia, alopecia, scleroderma or morphea, cholestasis, and most important, susceptibility to infection (Fig. 1 and 2). In women, vaginal strictures and dyspareunia can be the sole presenting features. Less common manifestations are polyserositis, bronchiolitis obliterans, and malabsorption. There may be insidious weight loss, and joint contractures may limit mobility. The identification of any of these problems warrants a discussion with the transplantation team, and the identification of problems in the oral cavity warrants the involvement of a dentist with expertise in this area. Chronic GVHD itself is not usually life-threatening; however, it is associated with defects in both cellular and humoral immunity that can result in severe infections.5,6

Most patients with GVHD require therapy with corticosteroids and often tacrolimus or cyclosporine. Organ injury may be slow to resolve, necessitating long courses of immunosuppressive therapy. Attempts to taper the dose of immunosuppressant agents as soon as the symptoms improve often result in a flare and a need for another course of therapy. Therefore, treatment of chronic GVHD should be slowly tapered no earlier than four to six months after all manifestations have resolved. The use of newer agents, such as mycophenolate mofetil, may allow treatment with lower doses of corticosteroids.7 Prophylaxis against in-

Figure 1. Lichenoid Lesions of Chronic Graft-versus-Host Disease.
Panel A shows mucosal ulcerations, white plaques, and striae on the hard palate. Panel B shows white plaques and striae on the tongue. The mouth of an affected patient is often dry, and the teeth are subject to caries. (Photographs courtesy of Dr. Sook-Bin Woo.)
Infection is a critical component of care, since infections are the primary cause of death in patients with GVHD.

**Immunologic Dysfunction**

Increased susceptibility to infection is a characteristic complication of hematopoietic-cell transplantation. Immediately after the transplantation, the primary risks are loss of barrier integrity and agranulocytosis. Later, after the neutrophil count has recovered, defects in both cell-mediated and humoral immunity predominate. Even in the absence of immunosuppressive therapy, it can take two years or longer for immunologic reconstitution to be complete. Continued treatment of GVHD exacerbates defects in immunity. Immunologic function usually recovers more rapidly after autologous hematopoietic-cell transplantation than allogeneic procedures; however, both approaches may result in prolonged immunocompromise, thus increasing the risk of infection\(^a^\)\(^b^\) (Table 1).

A low threshold for treating fevers in hematopoietic-cell recipients with antibiotics is warranted, since infections may progress rapidly.

Periodic assessment of basic measures of immunologic function can be useful. It is reasonable to obtain the CD4 cell count every three to four months for a year after transplantation, an approach that is also common in patients with human immunodeficiency virus infection.\(^a\)\(^b\) A similar schedule can be used for gamma globulin measurements. However, normal or near-normal gamma globulin levels do not necessarily indicate the presence of protective levels of immunity. Many patients who have seemingly normal levels have serious deficiencies in immunoglobulin subclasses needed to clear encapsulated organisms.

Loss of splenic function can be related either to prior splenectomy or to chronic GVHD. Deficiencies of secretory IgA are difficult to measure routinely, but they may increase susceptibility to infections such as conjunctivitis, sinusitis, and bronchitis. Chronic sinusitis and bronchiectasis may occur and may require prolonged courses of antibiotics and close follow-up. Patients with chronic GVHD or hypogammaglobulinemia (defined by an IgG antibody level of less than 400 mg per deciliter) require long-term prophylaxis with antibiotics designed to prevent pneumococcal disease; as the prevalence of antimicrobial resistance increases, this task is becoming increasingly problematic.\(^a\)

Viral infections are also a concern (Table 1). The incidence of varicella–zoster reactivation after transplantation is 20 to 50 percent, and it requires prompt therapy with an antiviral agent to minimize the risk of dissemination and postherpetic neuralgia.\(^b\) Reactivation of cytomegalovirus is a serious risk in the early period after hematopoietic-cell transplantation,\(^a\)\(^b\) but it becomes less likely with time. *Pneumocystis carinii* infection is a risk for at least a year after transplantation and for far longer in patients who continue to receive immunosuppressive therapy. Daily use of trimethoprim–sulfamethoxazole should prevent *P. carinii* infection and simultaneously reduce the risk of pneumococcal sepsis and, probably, reactivation of toxoplasmosis.\(^b\)

Most patients are vaccinated as described in Table 2.\(^b\) Live vaccines such as that against measles, mumps, and rubella are not administered until two years after hematopoietic-cell transplantation and only in the absence of chronic GVHD and immunosuppressive therapy. Family members may receive routine vaccines including influenza virus vaccine; however, patients should avoid contact with a child who has received oral poliovirus vaccine for about a month after vaccination. Susceptibility to infection with the virus used in the vaccine may last up to two years, or longer if the patient has chronic GVHD. This risk can be avoided by the use of inactivated poliovirus vaccine. These vaccines, especially unconjugated vaccines such as the pneumococcal vaccine, may not induce protective immunity in immunodeficient patients.

**Endocrine Dysfunction**

Hypothyroidism is common after hematopoietic-cell transplantation and occurs in up to 25 percent of adults, as a result of the effects of total-body irradiation. The risk of thyroid dysfunction is increased by irradiation of the head and neck as a primary therapy for the disease.\(^a\)\(^b\) Thyroid adenomas and carcinomas may occur at rates that are higher than expected.\(^a\)\(^b\) Adrenal and pituitary function is not affected, although secondary hypoadrenalism can result from corticosteroid therapy for GVHD.
§ A heat-inactivated vaccine is currently under study.

‡The administration of meningococcal vaccine may be indicated in areas where meningococcal disease is endemic.

†Famciclovir and similar agents are also effective. Patients who are receiving ganciclovir for cytomegalovirus prophylaxis probably do not need concomitant therapy.

¶Intravenous ganciclovir, cidofovir, and foscarnet can also be used.

∗The recommendations are modified from those of the Centers for Disease Control and Prevention.15

†Hepatitis B virus vaccine is recommended for adults with risk factors for infection.

‡The administration of meningococcal vaccine may be indicated in areas in which there are outbreaks of meningococcal disease.

§A heat-inactivated vaccine is currently under study.24

CLINICAL PRACTICE

Table 1. Common Late Infections in Recipients of Allogeneic or Autologous Hematopoietic Cells.

- Reactivation of Cytomegalovirus Infection
  - Period of Highest Risk after Transplantation: 1 mo to 2 yr
  - Treatment or Prophylaxis: Valganciclovir, 900 mg orally twice daily, for therapy

- Reactivation of Varicella-Zoster Infection
  - Period of Highest Risk after Transplantation: First yr
  - Treatment or Prophylaxis: Acyclovir, 400 mg orally three times daily, for prophylaxis

- Recurrent Sinusitis or Bronchitis
  - Period of Highest Risk after Transplantation: 3 mo to lifetime
  - Treatment or Prophylaxis: Haemophilus influenzae type b and pneumococcal vaccine, prophylactic antibiotics, immune globulin

- Pneumocystis Carinii Infection
  - Period of Highest Risk after Transplantation: First year or during immunosuppressive therapy
  - Treatment or Prophylaxis: Trimethoprim-sulfamethoxazole, 1 double- or single-strength tablet daily or 1 double-strength tablet three times per week; atovaquone, 750 mg twice daily; dapsone, 100 mg daily

- Useful Monitoring Tests
  - Tests for cytomegalovirus antigenemia, hybrid-capture assay, or polymerase-chain-reaction assay
  - Measurement of IgG and IgG subclass levels

- None

Table 2. Recommended Vaccinations for Recipients of Allogeneic and Autologous Hematopoietic-Cell Transplants.

- Inactivated Vaccine or Toxoid
  - Time after Transplantation: 12, 14, or 24 mo

- Measles, Mumps, and Rubella
  - Time after Transplantation: 24 mo

- Varicella-Zoster Virus
  - Contraindicated

- Live Attenuated Vaccine

- Diphtheria, Tetanus Toxoid
  - Time after Transplantation: 12, 14, or 24 mo

- Haemophilus influenzae Type b Conjugate
  - Time after Transplantation: 12, 14, or 24 mo

- Hepatitis A Virus
  - Time after Transplantation: 12 or 24 mo

- Influenza Virus
  - Time after Transplantation: Routine administration not indicated

- Hepatitis B Virus
  - Time after Transplantation: 12, 14, or 24 mo

- Meningococcal
  - Time after Transplantation: Routine administration not indicated

- Pneumococcal
  - Time after Transplantation: 12, 14, or 24 mo

- Poliovirus
  - Time after Transplantation: Routine administration not indicated

- *The recommendations are modified from those of the Centers for Disease Control and Prevention.15

- †Hepatitis B virus vaccine is recommended for adults with risk factors for infection.

- ‡The administration of meningococcal vaccine may be indicated in areas in which there are outbreaks of meningococcal disease.

- §A heat-inactivated vaccine is currently under study.24

Gonadal dysfunction is typical after transplantation if the doses of chemotherapy and radiation are high, and men are usually azoospermic after such therapy. Most men have relatively normal testosterone and luteinizing hormone levels; however, women are typically anovulatory and have high levels of both follicle-stimulating hormone and luteinizing hormone. Infertility is not a universal consequence of transplantation, however, and recovery of fertility can occur.21-23 Osteoporosis is an increasingly recognized problem after hematopoietic-cell transplantation. Osteopenia occurs in 50 to 60 percent of hematopoietic-cell recipients, and osteoporosis develops in as many as 20 percent of patients.24 Clinically significant bone loss often occurs before transplantation. This is in part due to the direct effects of hematologic cancers on the integrity of bone. The chemotherapeutic regimens used in primary treatment, which often include corticosteroids, also are contributing factors. The use of chemotherapy and, to a lesser extent, radiation therapy as part of the pretransplantation regimen exacerbates bone loss, owing in part to gonadal suppression. Physical inactivity further compounds these effects.

Avascular necrosis may occur in up to 5 percent of patients, often long after transplantation.25,26 It is usually related to the use of corticosteroids; even brief courses of high-dose therapy have been implicated. Hips are the most commonly affected joints, but ankles and shoulders may also be involved.

Secondary Cancers

Large-scale, retrospective studies have confirmed that the risk of secondary cancers is 3 to 13 times as high among patients who have undergone hematopoietic-cell transplantation as among an age-matched control population. Risk factors include the receipt of ionizing radiation or chemotherapy and immunoincompetence. The risk increases with both age and the presence of chronic GVHD.27-30 No single type of can-
<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>GROUP OF HEMATOPOIETIC-CELL RECIPIENTS AT HIGHEST RISK</th>
<th>DURATION OF INCREASED RISK AFTER TRANSPLANTATION</th>
<th>TRANSPANTATION-RELATED CAUSE</th>
<th>TREATMENT OR PROPHYLAXIS</th>
<th>SUGGESTED MONITORING INTERVAL AND TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>Recipients of allogeneic transplants</td>
<td>3 mo to 2 yr</td>
<td>Chronic GVHD</td>
<td>Immunosuppressants, topical lubricants (cevimeline or oral pilocarpine), oral fluoride rinse</td>
<td>Every 1 to 3 mo</td>
</tr>
<tr>
<td>Symptoms of sicca syndrome</td>
<td>Recipients of allogeneic transplants</td>
<td>Life long</td>
<td>Chronic GVHD</td>
<td>Immunosuppressants, topical lubricants (cevimeline or oral pilocarpine), surgery to alleviate lacrimal duct obstruction</td>
<td>Every 1 to 3 mo for GVHD</td>
</tr>
<tr>
<td>Eyes</td>
<td>Recipients of allogeneic transplants</td>
<td>Life long</td>
<td>Chronic GVHD</td>
<td>Immunosuppressants, topical lubricants (cevimeline or oral pilocarpine)</td>
<td>Eye examinations at least every 6 mo if there is corneal damage</td>
</tr>
<tr>
<td>Heart</td>
<td>Atherosclerotic cardiovascular disease</td>
<td>Years</td>
<td>Diabetes mellitus, hyperlipidemia, or hypertension related to drugs; premature ovarian failure; possibly radiotherapy</td>
<td>Standard therapy</td>
<td>Screening for cardiac risk factors, exercise testing</td>
</tr>
<tr>
<td>Lungs</td>
<td>Bronchiolitis obliterans</td>
<td>6 mo to 2 yr</td>
<td>Chronic GVHD</td>
<td>Immunosuppressants, possibly bronchodilators</td>
<td>Pulmonary-function tests</td>
</tr>
<tr>
<td></td>
<td>Bronchitis and bronchiectasis</td>
<td>6 mo to 2 yr</td>
<td>Defects in immunity and possibly ciliary function</td>
<td>Prophylactic antibiotics and immune globulin replacement for recurrent infections and bronchiectasis</td>
<td>No specific monitoring of pulmonary function usually required in an asymptomatic patient, shortness of breath and cough should trigger an infectious disease workup, increasing symptoms or the absence of improvement should prompt chest radiographs and pulmonary function tests</td>
</tr>
<tr>
<td>Liver</td>
<td>Chronic GVHD</td>
<td>First month</td>
<td>GVHD</td>
<td>Immunosuppression</td>
<td>Liver-function tests every 12 mo</td>
</tr>
<tr>
<td></td>
<td>Recipients of allogeneic transplants</td>
<td>6 mo to 2 yr</td>
<td>Hepatitis B and C virus</td>
<td>Antiviral therapy</td>
<td>Liver biopsy if warranted</td>
</tr>
<tr>
<td></td>
<td>Viral infection</td>
<td>Varies</td>
<td>Multiple causes</td>
<td>Phlebotomy or deferoxamine infusions</td>
<td>Viral testing as indicated, base-line ferritin measurement</td>
</tr>
<tr>
<td>Kidney</td>
<td>Recipients of allogeneic transplants</td>
<td>First month</td>
<td>Drugs (e.g., corticosteroids, cyclosporine), hemolytic–uremic syndrome</td>
<td>Antihypertensive agents, alterations in immunosuppressant regimen in patients with hemolytic–uremic syndrome, plasmapheresis</td>
<td>Annual monitoring of creatinine is probably sufficient, unless an abnormality is identified</td>
</tr>
</tbody>
</table>
**AREAS OF UNCERTAINTY**

There is no consensus on the optimal frequency of measurements of immunoglobulin levels and CD4 cells or the optimal duration or type of antibiotic prophylaxis after hematopoietic-cell transplantation. The usefulness of screening for secondary cancers in these patients also remains unclear.

**GUIDELINES**

The Centers for Disease Control and Prevention is the best comprehensive source of information on prophylaxis against and therapy for infection (available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910al.htm). With the exception of these guidelines, there are no formal recommendations for the long-term care of these patients. A useful set of guidelines for cancer screening in the general population has been published by the American Cancer Society; these guidelines are probably also applicable to transplant recipients.

**CONCLUSIONS AND RECOMMENDATIONS**

Hematopoietic-cell transplantation is a lifesaving procedure for many patients; however, because of the long-term risks of the conditioning regimen and altered immunity, these patients require close follow-up and attention (Table 3). The patient described in the case vignette has mild chronic GVHD, most likely involving reduced mucosal immunity and recurrent infections with encapsulated organisms. He needs to be monitored by a dentist and an internist in order to detect and treat sicca syndrome and recurrent infections. His cataracts will probably require surgery eventually. Exercise should be encouraged to improve the patient’s sense of well-being.
Patients with severe chronic GVHD should be followed by a physician who is skilled in the management of this disorder. A critical role for the primary care physician is to recognize manifestations of GVHD and devise a plan for evaluating the patient before serious disability develops. Attention to the possibility of pneumococcal sepsis is critical, since the interval between the onset of symptoms and shock may be brief. Patients with fewer than 200 CD4 cells per cubic millimeter, patients receiving immunosuppressive therapy for prolonged periods, and patients with chronic GVHD should receive prophylaxis against *P. carinii* infection. Immune-globulin—replacement therapy is typically administered to patients with IgG levels of less than 400 mg per deciliter, but it may also be warranted in some patients who have recurrent infections or low levels of IgG subclasses.

Although the total number of cases of new cancers among hematopoietic-cell recipients is low, these patients must be closely monitored. At a minimum, screening tests should be performed according to the guidelines of the American Cancer Society.

Regular skin and thyroid examinations are warranted. Furthermore, strong counseling to avoid exposure to carcinogens such as sunlight and tobacco is extremely important.

REFERENCES