Clinical Practice

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.[1]

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.

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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.[2,3] 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.[4] 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. Late occur-

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-

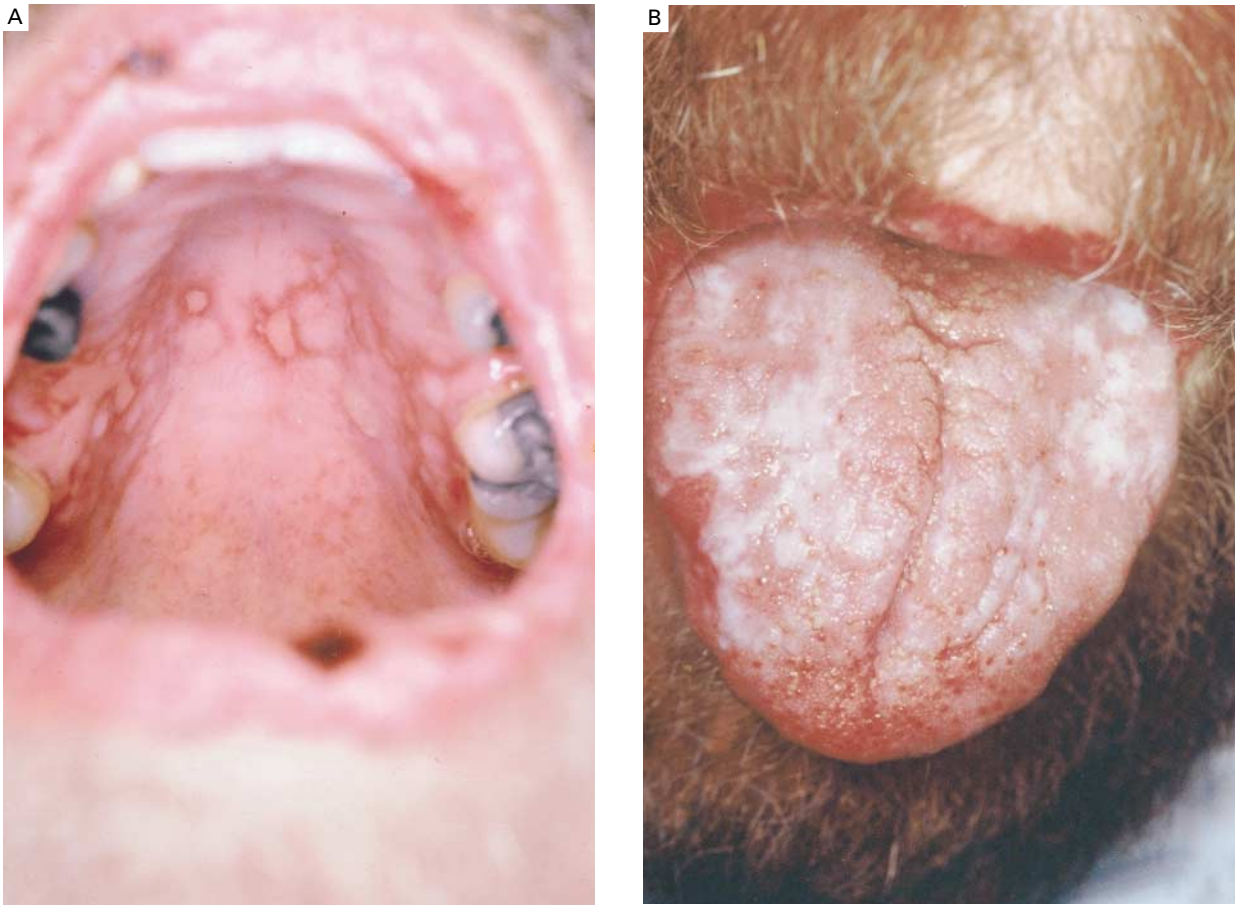

Figure 1. Lichenoid Lesions of Chronic Graft-versus-Host Disease.

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.)

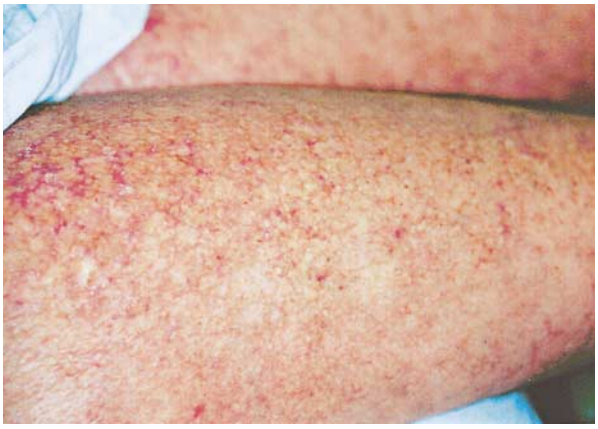

Figure 2. Graft-versus-Host Disease of the Skin.
There is hyperpigmentation and hypopigmentation of the skin, cutaneous atrophy, telangiectasia, and ulcerations. (Photograph courtesy of Dr. Paul Nghiem.)

fection 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[8,9] (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.[10] 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.[11]

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.[12] Reactivation of cytomegalovirus is a serious risk in the early period after hematopoietic-cell transplantation,[13,14] 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.[15]

Most patients are vaccinated as described in Table 2.[15] 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 influenzavirus 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.[17,18] Thyroid adenomas and carcinomas may occur at rates that are higher than expected.[17,19,20] Adrenal and pituitary function is not affected, although secondary hypoadrenalism can result from corticosteroid therapy for GVHD.

TABLE 1. COMMON LATE INFECTIONS IN RECIPIENTS OF ALLOGENEIC OR AUTOLOGOUS HEMATOPOIETIC CELLS.

TYPE OF INFECTION	PERIOD OF HIGHEST RISK AFTER TRANSPLANTATION	TREATMENT OR PROPHYLAXIS	USEFUL MONITORING TESTS
Reactivation of cytomegalovirus infection	1 mo to 2 yr	Valganciclovir, 900 mg orally twice daily, for therapy*	Tests for cytomegalovirus antigenemia, hybrid-capture assay, or polymerase-chain-reaction assay
Reactivation of varicella–zoster infection	First yr	Acyclovir, 400 mg orally three times daily, for prophylaxis†	None
Recurrent sinusitis or bronchitis‡	3 mo to lifetime	*Haemophilus influenzae* type b and pneumococcal vaccine, prophylactic antibiotics, immune globulin	Measurement of IgG and IgG subclass levels?
Pneumocystis carinii infection	First year or during immunosuppressive therapy	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	None

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

†Famciclovir and similar agents are also effective. Patients who are receiving cytomegalovirus prophylaxis probably do not need concomitant varicella–zoster prophylaxis. Vaccination is currently not recommended.

‡Such infections usually involve encapsulated organisms.

TABLE 2. RECOMMENDED VACCINATIONS FOR RECIPIENTS OF ALLOGENEIC AND AUTOLOGOUS HEMATOPOIETIC-CELL TRANSPLANTS.*

VACCINE OR TOXOID	TIME AFTER TRANSPLANTATION
Inactivated vaccine or toxoid	
Diphtheria, tetanus toxoid	12, 14, or 24 mo
Haemophilus influenzae type b conjugate	12, 14, or 24 mo
Hepatitis B virus†	12, 14, or 24 mo
23-Valent pneumococcal polysaccharide	12 or 24 mo
Hepatitis A virus	Routine administration not indicated
Influenzavirus	Lifelong, seasonal administration, beginning before transplantation and resuming six months after transplantation
Meningococcal‡	Routine administration not indicated
Inactivated poliovirus	12, 14, or 24 mo
Live attenuated vaccine	
Measles, mumps, and rubella	24 mo
Varicella–zoster virus	Contraindicated§

*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 meningitis.

§A heat-inactivated vaccine is currently under study.[16]

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 3. RECOMMENDATIONS FOR LONG-TERM FOLLOW-UP AFTER TRANSPLANTATION.*

COMPLICATION	GROUP OF HEMATOPOIETIC-CELL RECIPIENTS AT HIGHEST RISK	DURATION OF INCREASED RISK AFTER TRANSPLANTATION	TRANSPLANTATION-RELATED CAUSE	TREATMENT OR PROPHYLAXIS	SUGGESTED MONITORING INTERVAL AND TESTS
Oral cavity					
Lichen planus	Recipients of allogeneic transplants	3 mo to 2 yr	Chronic GVHD	Immunosuppressants, topical lubricants (cevimeline or oral pilocarpine), oral fluoride rinse	Every 1 to 3 mo
Symptoms of sicca syndrome	Recipients of allogeneic transplants	Lifelong	Chronic GVHD Radiotherapy		Every 1 to 3 mo for GVHD
Eyes					
Symptoms of sicca syndrome	Recipients of allogeneic transplants	Lifelong	Chronic GVHD Radiotherapy	Immunosuppressants, topical lubricants (cevimeline or oral pilocarpine), surgery to alleviate lacrimal-duct obstruction	Eye examinations at least every 6 mo if there is corneal damage
Cataracts	Recipients of allogeneic transplants	≥6 mo	Radiotherapy and corticosteroids	Surgery when necessary	Every 12 mo
Heart					
Atherosclerotic cardiovascular disease	Recipients of allogeneic transplants	Years	Diabetes mellitus, hyperlipidemia, or hypertension related to drugs; premature ovarian failure; possibly radiotherapy	Standard therapy	Screening for cardiac risk factors, exercise testing
Lungs					
Bronchiolitis obliterans	Recipients of allogeneic transplants	6 mo to 2 yr	Chronic GVHD	Immunosuppressants, possibly bronchodilators	Pulmonary-function tests
Bronchitis and bronchiectasis	Recipients of allogeneic transplants	6 mo to 2 yr	Defects in immunity and possibly ciliary function	Prophylactic antibiotics and immune globulin replacement for recurrent infections and bronchiectasis	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
Liver					
Chronic GVHD	Recipients of allogeneic transplants	First month	GVHD	Immunosuppression	Liver-function tests every 12 mo
Viral infection	Recipients of allogeneic transplants	6 mo to 2 yr	Hepatitis B and C virus	Antiviral therapy	Liver biopsy if warranted
Iron overload	Recipients of allogeneic transplants	Varies	Multiple causes	Phlebotomy or deferoxamine infusions	Viral testing as indicated, base-line ferritin measurement
Kidney					
Hypertension	Recipients of allogeneic transplants	First month	Drugs (e.g., corticosteroids, cyclosporine), hemolytic–uremic syndrome	Antihyperintensive agents, alterations in immunosuppressant regimen in patients with hemolytic–uremic syndrome, plasmapheresis	
Azotemia	Recipients of allogeneic transplants	0 to 6 mo	Drugs, hemolytic–uremic syndrome	Cautious use of nephrotoxins, supportive measures designed to prevent the progression of renal failure, antihypertensive agents	Annual monitoring of creatinine is probably sufficient, unless an abnormality is identified

Endocrine					
Thyroid	Recipients of either allogeneic or autologous transplants	6 mo to many years	Radiotherapy	Levothyroxine replacement for hypothyroidism, aspiration or surgical excision of nodules	Measurement of thyrotropin and thyroid examination every 12 mo
Ovary	Recipients of either allogeneic or autologous transplants	First mo	Radiotherapy	Hormone-replacement therapy or alternative treatment for symptoms associated with low estrogen levels	Mammogram and breast and pelvic examinations every 12 mo, bone-density study
Testes	Recipients of either allogeneic or autologous transplants	First mo	Radiotherapy	Usually none Androgen patch if testosterone level is low	None
Osteopenia and osteoporosis	Recipients of either allogeneic or autologous transplants	Mo to yr	Corticosteroids, gonadal failure, chemotherapy and radiotherapy	Supplemental calcium and vitamin D, exercise, bisphosphonates or other antiresorptive agents	Initial bone-density study, repeated as indicated clinically
Secondary cancers	Recipients of allogeneic transplants	≥3 mo	Radiation, immunosuppressant agents	Disease-specific therapy	Physical examination, including skin and thyroid examinations, every 12 mo; mammogram and Papanicolaou smear at standard intervals; screening for colorectal cancer, possibly measurement of prostate-specific antigen
Skin cancer	Recipients of allogeneic transplants	Variable	Radiotherapy, chronic GVHD	Lifelong avoidance of exposure to ultraviolet light, local excision	6 to 12 mo

*GVHD denotes graft-versus-host disease.

cer predominates, although the risks of cancers of the skin (squamous-cell carcinoma, basal-cell carcinoma, and melanoma), oral mucosa (squamous-cell carcinoma), thyroid, bone or connective tissue, and central nervous system seem to be the highest. There is an increased risk of lymphoproliferative disorders due to Epstein–Barr virus infection after hematopoietic stem-cell transplantation, but these disorders tend to occur in the first year after the procedure.

Late Effects of Conditioning Regimens or Prophylaxis against GVHD

Overall, long-term survivors of hematopoietic-cell transplantation have an excellent performance status and are typically able to resume active lives.[31] However, complications of the high doses of chemotherapy and radiation therapy may occur years after the procedure. Programs of aerobic exercise may ameliorate fatigue and anxiety and improve the general sense of well-being.[32]

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[15,33] (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[34]; 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.[35] 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.[36]

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.[34,37] Regular skin and thyroid examinations are warranted. Furthermore, strong counseling to avoid exposure to carcinogens such as sunlight and tobacco is extremely important.

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