

Nonmalignant late effects after allogeneic stem cell transplantation

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Introduction

Large numbers of patients now survive long term following stem cell transplantation (SCT). The late clinical effects of SCT are thus of major concern in the 21st century. Secondary malignant diseases are of particular clinical concern as more patients survive the early phase after transplantation and remain free of their original disease.^{1,2} These malignant complications have been previously reviewed in *Blood*³ and recently updated.⁴ Nonmalignant late effects are heterogeneous, and although often not life threatening they significantly impair the quality of life of long-term survivors.⁵ The main aims of this review by the Late Effects Working Party of the European Study Group for Blood and Marrow Transplantation (EBMT) are to present physicians with an overview of these nonmalignant late complications and provide some recommendations regarding their prevention and early treatment. The major risk factors for nonmalignant complications after SCT are chronic graft-versus-host disease (cGVHD) and/or its treatment and the use of irradiation in the pretransplantation conditioning. The interrelationship between cGVHD, total body irradiation (TBI), and nonmalignant late effects are summarized in Figure 1.

Chronic GVHD, late infections, and immune deficiency

Chronic GVHD, and its associated immune-deficiency state, is the prime cause of transplant-related mortality late after marrow grafting and contributes directly or indirectly to most nonmalignant complications. Because cGVHD has recently been reviewed in *Blood*,⁶ only the main points relating to nonmalignant complications will be highlighted here. Following HLA-identical marrow transplantation, the 5-year probability of transplant-related mortality following discharge is more than 20% in patients with and around 5% in patients without chronic GVHD.⁷ Despite the advent of new treatment modalities, the incidence of cGVHD is being sustained by changes in clinical SCT practice as follows: (1) the expanded use of matched unrelated as well as mismatched related donors,^{6,8,9} (2) the increasing use of SCT in older patients, (3) the increasing use of donor lymphocyte infusions to treat relapsed disease or to achieve full donor chimerism after nonmyeloablative transplantation, and (4) current evidence that suggests patients

receiving allogeneic peripheral blood stem cell transplants have an equally high or a higher incidence of chronic GVHD compared with patients receiving marrow grafts. Long-term follow-up data from Seattle indicated that, although the cumulative incidence of chronic GVHD at 3 years was similar in patients whose stem cells came from marrow versus peripheral blood, cGVHD after peripheral blood SCT was more protracted and less responsive to treatment than cGVHD after marrow SCT.¹⁰

Whereas the prophylactic use of multiagent immunosuppression has reduced the incidence and severity of acute GVHD, the incidence of chronic GVHD remains unchanged. The incidence of chronic GVHD after sibling-matched related, unrelated, and peripheral blood stem cell transplantation lies between 27% to 50%, 42% to 72%, and 54% to 57%, respectively.¹¹ Factors that increase the development of chronic GVHD include increased donor and recipient age, prior acute GVHD, use of alloimmune female donors, type of GVHD prophylaxis, and history of recipient herpes virus infection. There are several grading schemes that predict survival of patients with chronic GVHD. In these grading schemes, poor prognostic variables include lichenoid skin changes, extensive skin involvement (> 50% body surface area), elevated bilirubin, progressive onset, thrombocytopenia, and prior steroid refractory/dependent acute GVHD (reviewed in Lee et al¹¹).

Immune reconstitution has a pivotal role in the long-term issue of allogeneic SCT. Several studies have characterized the immune reconstitution in the few months following allogeneic SCT, but data on long-term immune reconstitution involving large numbers of patients are scarce.¹²⁻¹⁵ A large number of variables related to patient or transplant characteristics, such as age of recipients, stem cell engineering, type and duration of their disease, or conditioning regimen, may influence the recovery of immunity after SCT. Other posttransplantation variables, and in particular chronic GVHD and the consequent administration of immunosuppressive drugs, also have an effect. Chronic GVHD is the major factor affecting immune reconstitution of B cells and CD4⁺ and CD8⁺ T cells. Donor source (marrow versus peripheral blood), unrelated versus sibling transplant, and the degree of HLA compatibility between donor and recipient also affect the pace of immune reconstitution. Low B-cell count, inverted CD4/CD8 ratio, and a decreased immunoglobulin A (IgA) level are all risk factors associated with

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A complete list of the members of the Late Effect Working Party of the European Group for Blood and Marrow Transplantation appears in the "Appendix."

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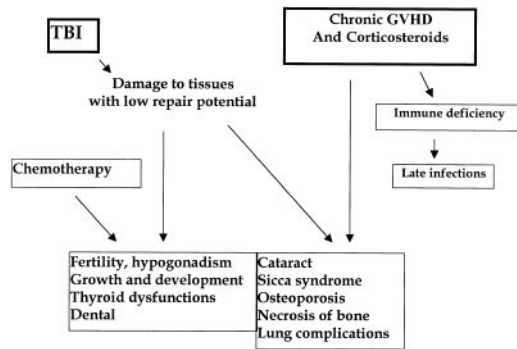


Figure 1. Interrelationship between total body irradiation, chronic graft-versus-host disease in the genesis of late complications after allogeneic stem-cell transplantation.

late infections. The role of slow B-cell reconstitution on the susceptibility to infections occurring in the years following SCT has been pointed out in 2 recent studies.^{12,14} Factors contributing to the immune deficiency post-SCT are summarized in Figure 2. Recent immunologic methods such as repertoire analysis or the identification of recent thymic emigrants are currently being used as tools to evaluate immune reconstitution following SCT. Using these new tools, it has recently been suggested¹⁵ that the immune system could regain normal functioning in the long term post-SCT. However, because most of the patients in the latter study were treated for severe aplastic anemia and did not have cGVHD,¹⁵ it still remains to be proven whether leukemic survivors who have undergone TBI-conditioned SCT and developed cGVHD are also able to recover normal immune function 15 to 20 years post-SCT.

Late bacterial and viral infections have been extensively reviewed, and guidelines for preventing and treating these opportunistic infections after SCT are proposed in a document published under the hospice of the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation.¹⁶ Susceptibility to encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*) has been well documented, especially in patients with current or previous chronic GVHD. Late (> 2 years) fungal or cytomegalovirus (CMV) infections are rare and almost invariably occur in patients with ongoing immune suppression for GVHD. Varicella-zoster, in contrast, is extremely frequent even in patients without GVHD, but it usually occurs within several months of SCT after acyclovir prophylaxis has been discontinued. Finally, of the parasitic infections, late *Pneumocystis carinii* pneumonia (PCP) and *Toxoplasma gondii* infections are more common in patients receiving active treatment for cGVHD. Because PCP prophylaxis with trimethoprim-sulfamethoxazole is highly active, this regimen should be given to all patients receiving treatment for cGVHD and/or those with CD4⁺ cells less than $0.2 \times 10^9/L$. Probably, PCP prophylaxis should be continued for several weeks after the cessation of immunosuppressive therapy given the long-lasting T-cell defects characteristic of patients who have developed cGVHD.

Late ocular effects

Ocular complications of the posterior segment

These complications can be divided into microvascular retinopathy, optic disk edema, hemorrhagic complications, and infectious

retinitis.¹⁷ Fungal infections typically occur within 120 days of SCT, whereas herpes zoster, CMV, and toxoplasmic retinitis occur later. Ischemic retinopathy with cotton-wool spots and optic-disk edema has been described in 10% of patients following SCT.¹⁸⁻²⁰ Microvascular retinopathy occurs mainly after TBI-conditioned allogeneic SCT in patients receiving cyclosporine as GVHD prophylaxis. Visual acuity is decreased in most patients but recovers when cyclosporine is withdrawn. Atypical retinal microvasculopathy, without cotton-wool spots, has also been described.²¹ Radiation may provoke an occlusive microangiopathy but only if the radiation dose exceeds 35 Gy. Thus, TBI alone cannot explain ischemic retinopathy in patients who have received a transplant, and additional factors, such as cyclosporine, may lower the threshold for radiation retinopathy.²² Ischemic retinopathy has been reported in patients conditioned with busulfan and cyclophosphamide without irradiation,²³ or in patients receiving Campath-1G for GVHD prophylaxis.²⁴ In most cases, retinal lesions resolve with withdrawal or reduction of immunosuppressive therapy, and resolution has even been described in a case associated with complete blindness.²⁵ Although ischemic retinopathy is still an enigma, these data suggest that the development of ischemic eye lesions is a multifactorial process leading to capillary damage of the eye fundus. These endothelial changes might not be restricted to the eye but may reflect a generalized process within the microvasculature.

Ocular complications of the anterior segment

The 2 most common late complications affecting the anterior segment are cataract formation and keratoconjunctivitis sicca syndrome. Cataract formation, particularly posterior subcapsular cataracts, has long been recognized in recipients of SC transplant as one of the most frequent late complications of TBI.^{26,27} After single-dose TBI almost all patients develop cataracts within 3 to 4 years, and most if not all need surgical repair. Although the probability of developing cataracts after fractionated TBI lies around 30% at 3 years, the incidence may reach more than 80% in 6 to 10 years post-SCT^{27,28} (Table 1; Figure 3A). In a multivariate analysis, the use of TBI, fractionation of its dose (Figure 3B), and the use of steroid treatment for longer than 3 months were associated with a significant risk of cataract development.²⁷ The effect of the dose rate of irradiation on the subsequent development of cataracts is also established.^{29,30,32} In the largest series evaluating a cohort of 1064 patients,³⁰ factors independently associated with an increased risk of cataracts were older age (> 23 years), higher dose rate (> 0.04Gy/minute), allogeneic SCT, and steroid administration. Finally, in prospective studies comparing cataract incidence rate and risk factors it has been shown that patients who receive

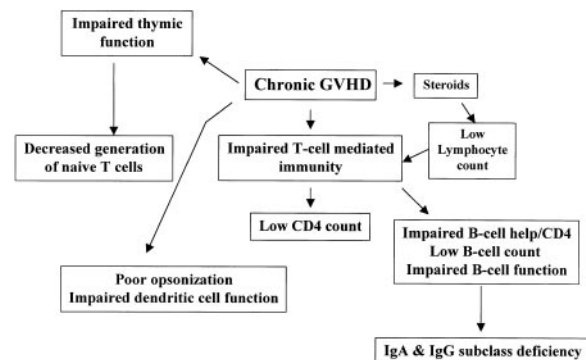


Figure 2. Factors contributing to late immune deficiency and late infection following allogeneic stem cell transplantation.

Table 1. Cataract after stem cell transplantation

Reference	Type of study	Patients (N)	Probability of cataract formation			Remarks
			sTBI	fTBI	No TBI	
Deeg et al ²⁶	Single center (Seattle)	277	80% at 6 y	18% at 6 y	19% at 6 y	Sparing effect of fTBI
Tichelli et al ²⁷	Single center (Basel)	197	100% at 3.5 y; surgery 96%	29% at 3.3 y	—	TBI
Benyunes et al ²⁸	Single center (Seattle)	492	85% at 11 y	83% at 6 y Risk at 11 y 50% (> 12 Gy) 34% (12 Gy)	19% at 11 y	Single dose Corticosteroids > 3 mo Need of surgical repair 59% sTBI 33% fTBI 23% no TBI Highest yearly hazard of cataract formation earlier with sTBI than fTBI
Belkacemi et al ²⁹	Single center (Paris)	494	34% at 5 y	11% at 5 y	—	High dose rate, main risk factor
Belkacemi et al ³⁰	EBMT registry	1063	Risk at 10 y 60%; 32% surgery	Risk at 10 y 43%; 3% surgery	—	Risk factors Older age Higher dose rate Allogeneic SCT No heparin
Socié et al ³¹	4 randomized studies	488	—	Risk at 7 y AML, 12.4% CML, 47%	Risk at 7 y AML, 12.3% CML, 16%	Comparison TBI versus BuCy Increased risk for CML patients with TBI

TBI indicates total body irradiation; sTBI, single-dose TBI; fTBI, fractionated TBI; BuCy, conditioning with busulfan/cyclophosphamide; Gy, Gray; —, not applicable.

cyclophosphamide and TBI (Cy/TBI) have a higher incidence of cataract formation than those treated with busulfan and cyclophosphamide (BuCy).³¹ Although the total dose of TBI is the most important factor for cataract formation, the incidence, severity, and time course of cataract formation differ depending on the number of fractions, dose rate of irradiation, the age of the patient, and the use of steroids. The only treatment for cataract is to surgically remove the opacified lens from the eye to restore transparency of the visual axis. Today, cataract surgery is a low-risk procedure and improves visual acuity in 95% of eyes that have no other pathology. Results of surgical repair in patients who have received a transplant are not yet available.

Keratoconjunctivitis sicca syndrome is usually part of a more general syndrome with xerostomia, vaginitis, and dryness of the skin.³³ All these manifestations are closely related to cGVHD³⁴ that may lead in its most extensive forms to a Sjögrenlike syndrome.³⁵ The ocular manifestations include reduced tear flow, keratoconjunctivitis sicca, sterile conjunctivitis, corneal epithelial defects, and corneal ulceration.³⁶⁻⁴⁰ The incidence of late-onset keratoconjunctivitis sicca syndrome may reach 20% in 15 years after SCT⁴¹⁻⁴³ but reaches nearly 40% in patients with cGVHD, compared with less than 10% in those without GVHD. Risk factors for late-onset keratoconjunctivitis include cGVHD, female sex, age older than 20 years, single-dose TBI, and the use of methotrexate for GVHD prophylaxis.⁴¹ Treatment is based on the management of cGVHD with repeated use of topical lubricants. Topical corticosteroids may improve symptoms but can cause sight-threatening complications if used inappropriately in herpes simplex virus or bacterial keratitis. Topical retinoic acid may also be used.⁴⁴

Pulmonary late effects

Significant late toxicity involving both the airways and lung parenchyma affects at least 15% to 40% of patients after SCT. Most of the studies have been performed in adult patients, and results are still conflicting because of varying selection and evaluation criteria, limited sample size, and short follow-up. Moreover, clinical syndromes are not well defined or definable because of overlapping

mechanisms and/or because they represent a continuum rather than a distinct disorder. Sensitivity to cytotoxic agents and irradiation, infections, and immune-mediated lung injury associated with GVHD are the most prominent factors that contribute to late respiratory complications.⁴⁵ Impaired growth of both lung and chest can be an additional factor in children.

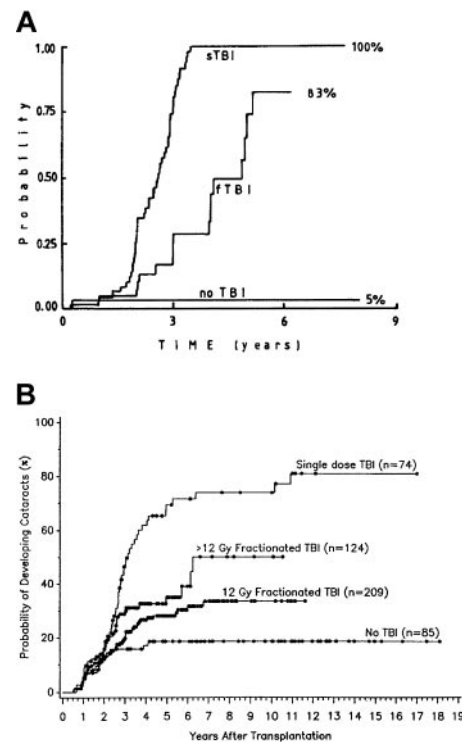


Figure 3. Cataract formation after TBI. (A) Cataract formation occurs earlier after single dose than after fractionated dose total body irradiation (reprinted from Tichelli et al²⁷ with permission). (B) Fractionated TBI is associated with a significant, dose-dependent risk of cataract formation (reprinted from Benyunes et al²⁸ with permission, nonexclusive world English rights only).

Restrictive lung disease

Abnormal pulmonary function tests (PFTs) with loss of lung volume and diffusing capacity may exist prior to SCT as a result of the intensification of front-line treatment.⁴⁶ Although the relevance of pretransplantation PFTs is still debated, some studies indicate that PFTs can be predictive of complications and outcome after SCT and should, therefore, be included within the pretransplantation investigation program.⁴⁷⁻⁴⁹ Restrictive lung disease is frequently observed 3 to 6 months after SCT in patients conditioned with TBI and/or receiving an allogeneic SCT, but in most cases it is not symptomatic. Restrictive disease is often stable and may recover, partially or completely, within 2 years.^{46,50,51} However, some patients do develop severe late restrictive defects and may eventually die of respiratory failure.⁵²

Chronic obstructive lung disease

Chronic obstructive pulmonary disease with reduced forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) and FEV₁ can be detected in up to 20% of long-term survivors after SCT.⁵³⁻⁵⁵ Its pathogenesis is not yet well understood. It has been mainly associated with cGVHD, but other potential risk factors, including TBI, hypogammaglobulinemia, GVHD prophylaxis with methotrexate, and infections, have been described. Although direct immune-mediated damage by donor T lymphocytes and cytokines is classically the main mechanism, airflow obstruction can also be due to indirect consequences of cGVHD, for example aspiration secondary to esophageal GVHD, sicca syndrome, abnormal mucociliary transport,⁵⁶ and recurrent infections. Mortality is high among these patients, particularly in those with an earlier onset and rapid decline of FEV₁. Symptoms consist of nonproductive cough, wheezing, and dyspnea; chest radiography is normal in most cases. High-resolution computed tomography (CT) scanning may reveal nonspecific abnormalities.⁵⁷ Symptomatic relief can be obtained in some patients with bronchodilators; however, in most cases obstructive abnormalities are not improved by this treatment. Patients with low IgG and IgA levels should receive immunoglobulins to prevent infections, which may further damage the airways. Immunosuppressive therapy may be of benefit, but typically improvements occur in less than 50% of cases probably because the damage has already become irreversible or because other pathogenic factors persist. Asymptomatic patients with abnormal PFTs should be closely monitored for the development of respiratory symptoms; an early recognition of airflow obstruction allows the initiation of treatment at a potentially reversible stage.

Obliterative bronchiolitis (OB), the best characterized obstructive syndrome, has been reported in 2% to 14% of allogeneic SC transplant recipients and carries a mortality rate of 50%.^{56,58-61} OB is strongly associated with cGVHD and low levels of immunoglobulins. GVHD is probably responsible for the initial epithelial injury to the small airways⁶² with further damage caused by repeated infections. Initial symptoms often resemble those of recurrent upper respiratory tract infections, and then persistent cough, wheezing, inspiratory rales, and dyspnea appear. PFTs gradually deteriorate with severe and nonreversible obstructive abnormalities. Chest radiographs and CT scanning may reveal hyperinflation with or without infiltrates and vascular attenuation; however, radiologic findings do not correlate with lung function changes probably because of the patchy nature of the disease.⁶³ Bronchoscopy with transbronchial biopsy can help to rule out infection and may reveal obliteration of bronchioles with granulation tissue, mononuclear cell infiltration, or fibrosis. It is not clear to what

extent combined immunosuppressive treatment can be effective in the treatment of this disease, which typically does not respond to treatment with steroids. Azathioprine and mycophenolate may lead to improved symptoms in some cases. Prophylaxis and prompt treatment of infections are the most important elements of clinical management and may help to alter the clinical course of a disease whose pace can vary from slow progression to rapidly fatal respiratory failure. Single or double lung transplantation has been suggested for patients with advanced disease,⁶⁴ although the transplanted lung may also be a target for immune-mediated damage.

Late liver complications

Unraveling the cause of liver dysfunction can pose difficulties, first, because several causes of liver disease may coexist and, second, because patterns of viral serology may be atypical. Furthermore, in addition to the most important hepatotropic viruses, other agents, like herpesviruses (including CMV), adenoviruses, and Epstein-Barr virus, may be implicated, sometimes leading to life-threatening fulminant hepatitis.⁶⁵ Useful tools for differential diagnosis are timing posttransplantation, type of clinical and biochemical deterioration, previous evidence of liver complications, including veno-occlusive disease (VOD), acute or chronic GVHD, and infection. Liver biopsy is often difficult to interpret, but histologic examination can be helpful in discriminating between an acute exacerbation of viral hepatitis and an episode of GVHD.

Hepatitis B and hepatitis C infections

Hepatitis B (HBV) or hepatitis C (HCV)⁶⁶ may be nonsymptomatic or may progress to fulminant hepatitis or evolve to chronic active hepatitis and cirrhosis. Today, the risk of acquiring HBV and HCV infection from blood transfusion is greatly reduced. A recent prospective study of the EBMT, which included patients transfused in the "post-screening" era, showed that the prevalence of serum hepatitis B surface antigen (HBsAg)- and HCV-RNA-positive SCT patients was 3.1% and 6.0%, respectively. The prevalence of "de novo" infection in patients receiving HBsAg and HCV-RNA-negative SC transplant was 2.0% and 7.4%, respectively; the prevalence of donors positive for HBsAg and HCV-RNA, was found to be 2.6% and 3.6%, respectively.⁶⁷ Chronic viral hepatitis still remains an important clinical problem in this setting.^{68,69}

Patients infected with HBV generally show mild to moderate liver disease on long-term follow-up, but cirrhosis as a result of chronic hepatitis B has not been reported to date. Chronic hepatitis C is often asymptomatic with fluctuating transaminases levels and no signs or symptoms of uncompensated liver disease at least during the first decade following SCT.⁶⁸⁻⁷⁰ Progression to cirrhosis or advanced liver disease in patients surviving more than 10 years does occur, however⁷¹ (G.S., unpublished observations, 2003). These observations indicate that, although the outcome of chronic hepatitis was thought to be benign, it may represent an important clinical problem in very long-term survivors. Careful tapering of immunosuppressive therapy posttransplantation, with monitoring of biochemical parameters and viral load, is crucial to prevent and allow early treatment of hepatitis reactivation. Increasing HBV viral load may need treatment with lamivudine.⁷² However, prolonged therapy with this drug is followed by the emergence of HBV DNA polymerase mutants. As the selection of these mutants is a function of time, the indication for long-term therapy should be

reviewed. The combination of lamivudine and anti-HBs immunoglobulins may also be of value. In patients with active chronic HCV, hepatitis treatment with interferon, with or without nucleotide analogues, is indicated.⁷³

Iron overload

On the basis of serum ferritin levels, the diagnosis of iron overload can be made in up to 88% of long-term survivors of SCT.⁷⁴ Prolonged dyserythropoiesis and increased iron absorption both contribute to the accumulation of iron. Liver biopsies performed early after SCT show siderosis in most patients.⁷⁵ Autopsies performed in patients dying early after SCT show iron accumulation in a range equivalent to that of patients suffering from hereditary hemochromatosis.⁷⁶ Iron deposition has also been demonstrated in other tissues, such as the myocardium or bone marrow.^{76,77} Iron overload may be associated with a number of clinical consequences, but these consequences have not been extensively evaluated in patients posttransplantation. A clear correlation exists between iron deposition and persistent hepatic dysfunction, probably as a consequence of intracellular iron accumulation and the toxic effect of free radicals. In heavily transfused patients, such as those with thalassemia, iron can contribute to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma as well as to cardiac dysfunction.^{77,78} Hepatic iron overload may also worsen the natural course of chronic hepatitis, in particular hepatitis C, and the response to antiviral therapy.⁷⁹ Finally, iron overload increases the risk of opportunistic infections in immunocompromised patients, mucormycosis being the infection most usually observed in SCT.⁸⁰ Although iron overload spontaneously decreases in the years following SCT,⁷⁸ the true effect of iron overload on post-SCT complications such as diabetes mellitus, impotence, hypogonadism, or growth retardation has not yet been established. All survivors (even if asymptomatic) should, therefore, be assessed for iron overload by measuring serum ferritin. Iron overload should be treated by means of phlebotomy and/or chelation therapy, especially when iron overload coexists with chronic viral hepatitis. Phlebotomy has the advantage over chelation of better compliance, fewer side effects, and lower costs. The use of recombinant human erythropoietin may facilitate this strategy in patients who have low hemoglobin levels.^{81,82}

Late complications of bones and joints

Avascular necrosis of bone (AVN)

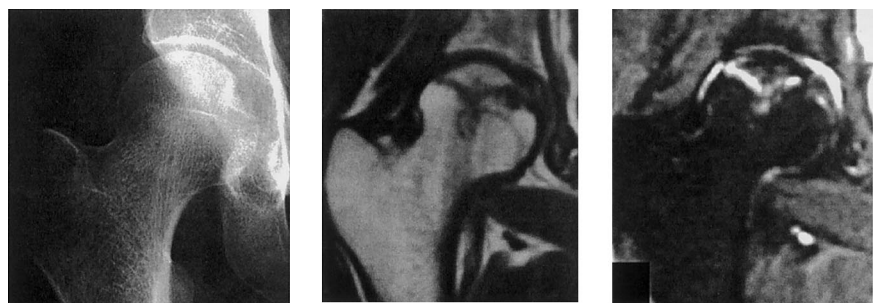
The published incidence of AVN varies from 4% to more than 10% in the largest series.⁸³⁻⁸⁷ The mean time from transplantation to AVN is 18 months (range, 4-132 months), and pain is usually the first sign. Early diagnosis can rarely be made using standard

radiography alone, and magnetic resonance imaging is the investigation of choice (Figure 4). The hip is the affected site in more than 80% of cases, with bilateral involvement occurring in more than 60% cases. Other locations described include the knee (10% of patient with AVN), the wrist, and ankle. Symptomatic relief of pain and orthopedic measures to decrease the pressure on the affected joints are of value, but most adult patients with advanced damage will require surgery. The probability of total hip replacement following a diagnosis of AVN is approximately 80% at 5 years.^{88,89} Although short-term results of joint surgery are excellent in the majority (> 85%) of cases, it is clear that long-term follow-up of the prostheses are needed in young patients who have a long life expectancy. Studies evaluating risk factors for AVN have clearly identified steroids (both total dose and duration) as the strongest risk factor. Thus, unnecessary long-term low-dose steroids for nonactive chronic GVHD should be avoided. The second major risk factor for AVN is TBI, the highest risks being associated with receipt of single doses of 10 Gy or higher or more than 12 Gy in fractionated doses.⁸⁷ Finally, some underlying conditions may predispose a patient to develop AVN after SCT, in particular patients receiving transplants for severe aplastic anemia⁹⁰ or acute lymphoblastic leukemia.

Osteoporosis

Hematopoietic SCT can induce bone loss and osteoporosis via the toxic effects of TBI, chemotherapy, and hypogonadism (reviewed in Weilbaecher⁹¹ and Schimmer et al⁹²). Osteopenia and osteoporosis are both characterized by a reduced bone mass and increased susceptibility to bone fracture. These conditions are further distinguished by the degree of reduction in bone mass and can be quantified by T and Z scores on dual photon densitometry. The Z score is similar to the T score but uses mean bone mass from an age- and sex-matched control population as a reference value. The relative risk of fracture doubles for every standard deviation below the control adult peak bone mass. The incidence and clinical course of bone mineral density (BMD) abnormalities following hematopoietic SCT have been studied in 2 large series.^{93,94} In both, the cumulative dose and number of days of glucocorticoid therapy and the number of days of cyclosporine or tacrolimus therapy showed significant associations with loss of BMD. Nontraumatic fractures occurred in 10% of patients. These results indicate that loss of BMD after allogeneic SCT is common and is accelerated by the length of immunosuppressive therapy and cumulative dose of glucocorticoid. With the use of World Health Organization (WHO) criteria, nearly 50% of the patients have low bone density, a third have osteopenia, and roughly 10% have osteoporosis, 12 to 18 months posttransplantation. The true incidence and morbidity rate of osteoporosis in very long-term SCT survivors is currently unknown. Preventative measures of osteoporosis must include sex-hormone replacement in patients with gonadal failure; the

Figure 4. Avascular necrosis of the hip. Standard radiography versus MRI as a tool for the diagnosis of avascular necrosis. These panels illustrate that standard radiography could be strictly normal at the first clinical sign while MRI is already highly abnormal. The top panel shows the normal appearance of the hip using standard radiography. The middle and bottom panels show 2 different MRI sequences showing that, although the femoral head is still spherical, the adjacent bone is already affected with necrosis, with even cartilage modification.



efficacy of new treatments for osteoporosis in long-term survivors of SCT requires evaluation.

Dental late effects

Both TBI-based regimens and those without irradiation can result in severe damage to the enamel organ and developing teeth. These defects may be prolonged or permanent.^{95,96} After TBI in children, underdevelopment of the mandible and anomalies in the mandibular joint may also occur.⁹⁶ In children, long-term clinical and radiologic follow-ups reveal hypoplasia and microdontia of the crowns of erupted permanent teeth and thinning and tapering of the roots of erupted permanent molars or incisors.⁹⁷⁻¹⁰⁰ Caries are found more frequently in patients who have received a transplant compared with age-matched healthy children. The defects in dental elements post-SCT may occur at any age of tooth development, and only the severity seems to depend on age at SCT.

Recommendations to minimize this adverse effect aim to preserve the enamel layer and prevent, by active oral hygiene, dental plaque, periodontal and oral mucosal infections, and xerostomia, all of which contribute to the development of caries. Specialist dental consultation before SCT and yearly posttransplantation examinations should be requested to register any specific dental problems, to provide treatment, and to give instruction on oral and dental care. In the long-term, 3 key elements to reduce dental complications are brushing teeth, application of fluoride, and the use of antiseptic mouthwashes. Brushing teeth should be done twice daily, with a soft brush and fluorinated toothpaste.

Endocrine function after SCT

Thyroid dysfunction

Thyroid dysfunction has long been recognized as one of the most frequent late complications of SCT.¹⁰¹ The most common thyroid abnormalities can be classified into 3 distinct patterns: subclinical-compensated hypothyroidism, overt hypothyroidism, and autoimmune thyroid disease.

Subclinical-compensated hypothyroidism. Between 7% and 15.5% of patients will develop subclinical hypothyroidism (slightly high serum thyroid-stimulating hormone [TSH] and normal free-T4 levels) in the year post-SCT.¹⁰²⁻¹⁰⁴ It is not yet clear if patients who develop subclinical hypothyroidism should be treated with L-thyroxin because most of these cases are mild, compensated, and may resolve spontaneously.^{102,105,106} Furthermore, treatment with L-thyroxin might induce early osteoporosis, especially if given to those women after SCT with gonadal failure. It is also not clear if a relationship exists between high TSH levels and carcinogenesis.¹⁰⁷ One possible approach is to monitor TSH and free-T4 levels twice yearly and to consider L-thyroxin treatment only if TSH concentration remains high or is increasing.¹⁰⁸

Overt hypothyroidism. The great majority of cases of overt hypothyroidism following SCT are due to direct damage to the thyroid gland. Secondary hypothyroidism, caused by pituitary damage, is rare following SCT. Hypothyroidism is usually diagnosed after a median period of 50 months posttransplantation. The frequency of hypothyroidism requiring L-thyroxin replacement therapy is highly variable,^{109,110} depending to a large extent on the type of pretransplantation conditioning applied as follows: nearly

90% in patients who have received 10 Gy single-dose TBI,¹¹⁰ 14% to 15% of patients following fractionated TBI,¹⁰³ and smaller numbers after conditioning with BuCy.^{32,109-111} Treatment with L-thyroxin is indicated in all cases of frank hypothyroidism (elevated TSH with low free-T4 blood levels). Thyroid hormone levels should be measured 4 to 6 weeks after commencement of replacement therapy, and dosage should be tailored thereafter to the individual patient and adjusted according to thyroid function evaluation every 6 months. Elderly patients should have an electrocardiogram (ECG) prior to commencing treatment to exclude associated ischemic heart disease and/or arrhythmias.

Autoimmune thyroid disease. Autoimmune thyroiditis, presumably transferred via donor cells, has been reported.¹¹² This same autoimmune mechanism can also lead to hyperthyroidism if the donor is affected with Grave disease.¹¹³

Growth

Linear growth is an intricate process that may be affected by several systems, including genetic (ie, midparental height), nutritional, hormonal, and psychological factors. Intensive anticancer therapy during childhood may influence all or some of these factors resulting in decreased growth. Children who undergo SCT form a heterogeneous group because of the different treatment protocols used. In addition, posttransplantation factors such as GVHD and its treatment, especially the use of long-term steroids, may induce growth failure in childhood.^{104,114-119}

Final height achievement has been reported in some studies.^{115-117,120-122} Decreased growth has been described in patients who underwent SCT during childhood. The mean loss of height (as estimated by the standard deviation score [SDS]) is estimated to be approximately 1 height SDS (equivalent to 6 cm) compared with both the mean height at the time of SCT and mean genetic height.^{115-117,120,121,123} Nevertheless, nearly 80% of the children will achieve adult height values above the 3rd percentile (or -2 height SDS) for the healthy general population.¹¹⁶ Growth deficiency is more pronounced in children who receive transplants at a younger age (< 10 years) and in those who have received irradiation. In contrast, children who are conditioned with non-TBI regimens, such as cyclophosphamide or busulfan-cyclophosphamide, usually grow normally. Patients who have been exposed to cranial radiotherapy (CRT) prior to conditioning with TBI show a greater decline in growth.¹²⁴ The role of growth hormone (GH) deficiency as a cause of growth failure and its substitution in children after SCT is still controversial. Although some reports show some benefit of GH treatment in children after SCT,^{125,126} others have failed to document GH deficiency.^{106,121,122} Furthermore, some studies have failed to demonstrate any correlation between growth rate and the GH secretion level after pharmacologic provocative tests.^{116,127} In a study involving children who had survived more than 5 years after SCT for severe aplastic anemia (SAA),¹¹⁷ the decrease in growth observed in a population of 11 children who had received thoracoabdominal irradiation in their pretransplantation conditioning was significantly higher than seen in a group of 27 children who had received cyclophosphamide only. The decrease in growth found in the irradiated group cannot be explained by impaired secretion of growth hormone because thoracoabdominal irradiation spares the hypothalamus and pituitary gland. The reduction in growth observed in the irradiated group may, however, be explained by the direct effect of irradiation on the gonads, the thyroid gland, and/or the bone epiphyses.

Puberty and gonadal failure

Gonadal failure (both testicular and ovarian) is a common long-term consequence of the chemotherapy given prior to SCT and of the pretransplantation conditioning. The major cause of gonadal damage leading to hypergonadotropic-hypogonadism is irradiation.^{128,129} Similar damage can also be caused by busulfan. Among patients who have received a transplant, it is uncommon to find either a condition of hypogonadotropic-hypogonadism or precocious puberty because of irradiation damage to the hypothalamic-pituitary area.^{120,130}

In males, the testicular germinal epithelium (Sertoli cells) where spermatogenesis occurs is more vulnerable to radiation and chemotherapy than the testicular Leydig cell component, which is involved in testosterone secretion. Therefore, testosterone levels are usually normal even when spermatogenesis is reduced or absent. The serum follicle-stimulating hormone (FSH) is typically elevated, whereas luteinizing hormone (LH) levels may remain in the normal range. The great majority of patients will not, therefore, require testosterone replacement to ensure sexual activity, libido, erection, and ejaculation. Furthermore, boys transplanted during childhood will usually spontaneously start and complete puberty. Patients transplanted before puberty, however, might achieve a reduced testicular volume as a result of damage to the germinal epithelium.¹³¹ Sex hormone replacement therapy (SHRT) with testosterone derivatives in males is indicated in patients with severe uncompensated hypogonadism.

In females, the ovaries are more vulnerable to irradiation and chemotherapy than the testes, and hypergonadotropic-hypogonadism is almost the rule. Busulfan is one of the most gonadotoxic agents, whereas cyclophosphamide is usually associated with only minor effects on gonadal function.

Prepubertal patients conditioned with cyclophosphamide alone for SAA usually have normal puberty.¹¹⁴ The age at transplantation is of major importance because the younger the age, the better will be the chances for gonadal recovery. In fact, ovarian failure in adult women is usually irreversible, whereas in prepubertal girls, although uncommon, there is still a greater possibility for a subsequent spontaneous recovery and achievement of spontaneous menarche.¹³¹⁻¹³⁴ Fractionation of the irradiation reduces the effect on the ovaries^{114,135}; girls treated with 12 Gy fractionated TBI are 5 times more likely to have a spontaneous recovery to normal ovarian function than girls receiving single-dose TBI. With the increasing utilization of BuCy in pediatric pretransplantation conditioning, it becomes clear that most girls of any age at transplantation develop ovarian failure.^{136,137}

Most females will need SHRT, both for the induction of puberty in girls who have had SCT prior to the menarche and for maintaining menstrual cycles and bone turnover/mineralization in adult women. In prepubertal girls who do not undergo puberty spontaneously post-SCT, estrogen treatment should be started at the age of 12 to 13 years to promote breast and uterine development and the pubertal growth spurt. The dose of estrogen treatment will need to be gradually increased, and a combination of cyclical estrogen-progesterone treatment introduced after 1 to 2 years to initiate menstruation and to reduce the risk of future osteoporosis. SHRT can be interrupted once every 2 to 3 years, for a period of 6 months, to evaluate possible spontaneous recovery of ovarian activity, which occurs in a minority of women. Because of the high incidence of gonadal dysfunction and early menopause in patients after SCT, an annual clinical and biologic gynecologic assessment is recommended.

Fertility following stem cell transplantation

Despite the potential gonadotoxicity of pretransplantation conditioning (see "Puberty and gonadal failure"), gonadal recovery and pregnancies following SCT are well described (Tables 2 and 3). The precise incidence of fertility following SCT is hard to establish. Unpublished data from the EBMT Late Effects Working Party (LEWP) pregnancy database relating to incidence of pregnancy in patients transplanted prior to 1994 who survived for a minimum of 2 years is given in Table 2. These data are not comparative because the patients within the groups were not age matched. Nonetheless, it is clear that the overall incidence of pregnancy is low (< 2%) except for patients transplanted for SAA and this is in accordance with the available literature. Such data are limited in their ability to accurately predict the likely return of fertility post-SCT, however, because many patients do not wish to become parents following the diagnosis of a potentially life-threatening illness.

Other studies have looked at clinical and laboratory indicators of gonadal function in post-SCT patients. In women these include amenorrhea, menopausal symptoms, raised gonadotrophin levels, and low estrogen. In men, sperm quality (motility and morphology) and quantity can be assessed, and the typical biochemical profile would be raised FSH with normal LH and normal/low testosterone levels.

Fertility following SCT for nonmalignant disease

Return of gonadal function following cyclophosphamide conditioning for SAA was noted in 56 of 103 adult female survivors in Seattle (as indicated by return of menstruation and normal gonadotrophin and estradiol levels); 28 (27%) women subsequently conceived.¹³⁸ Of 109 adult male survivors in the same study, 61% had return of sperm production and 28 (26%) subsequently fathered children. Previous data from this and from other centers indicated that gonadal recovery is usual in women younger than the age of 25 years at the time of transplantation but sharply decrease thereafter.^{135,142,143} In thalassemia, gonadal failure is common as a result of both transfusional hemosiderosis and conditioning with BuCy. Approximately 40% enter puberty, but pregnancies are very rare.^{144,145}

Fertility following SCT for malignant disease

Most of the patients given TBI conditioning experience gonadal failure. Recovery of gonadal function occurs in 10% to 14% of the

Table 2. Incidence of pregnancy following stem cell transplantation

	Female		Male	
	Survivors*	Pregnancies n (%)	Survivors*	Pregnancies n (%)
Total	7615	113 (1.5)	10 467	119 (1.1)
Allografts	3695	74 (2)	5 124	93 (1.8)
Autografts	3920	39 (1)	5 343	26 (0.5)
Acute leukemia	2632	24 (0.9)	3 685	33 (0.9)
Chronic leukemia	1081	8 (0.7)	1 467	26 (1.8)
Lymphoma	1641	29 (1.8)	2 666	17 (0.6)
Aplastic anemia	385	47 (12.2)	605	32 (5.3)
Myeloma/amyloid	323	1 (0.3)	485	2 (0.4)
Other	1553	4	1 559	9

Data from EBMT LEWP database.

*The number of patients surviving more than 2 years following SCT.

Table 3. Gonadal recovery following SCT

Type of SCT	Conditioning	Sex	n	Gonadal recovery	Reference
Allogeneic	Cy	F	43	74% (100% < 26; 31% > 26)	Spinelli et al ¹³³
Allogeneic	Cy	F	103	54%	Sanders et al ¹³⁵
Allogeneic	Cy	M	109	61%	Sanders et al ¹³⁵
Allogeneic	BuCy	F	73	1%	Sanders et al ¹³⁵
Allogeneic	BuCy	M	146	17%	Sanders et al ¹³⁵
Allogeneic	TBI	F	74	13.5% (100% < 18; 15% > 18)	Bakker et al ¹³¹
Allogeneic	TBI	F	532	10%	Sanders et al ¹³⁸
Allogeneic	TBI	M	463	17.5%	Sanders et al ¹³⁸
Autologous	BEAM	F	10	60%	Salooja et al ¹³⁹
Autologous	BEAM	M	13	0	Jacob et al ¹⁴⁰
Autologous	BEAM	M	10	0	Jackson et al ¹⁴¹

women, and the incidence of pregnancy is less than 3%.^{133,138,139} In men, recovery of gonadal function has been reported in less than 20% of patients, and use of increasing doses of TBI may be associated with considerably lower recovery.^{138,140} Parenting a child following administration of TBI is a rare event in men. We have identified 27 men who fathered children naturally following TBI,¹³⁹ and 5 such patients have been reported by the Seattle group.¹³⁸

The use of busulphan and cyclophosphamide (BuCy) is also associated with a high incidence of gonadal failure in women, and there have been no pregnancies reported using BuCy for patients with leukemia.^{138,139} In men, this conditioning appears to be associated with return of gonadal function in approximately 17% of cases, which is similar to the recovery after TBI conditioning. Few patients have subsequently fathered children naturally; 20 patients were identified by the EBMT LEWP¹³⁹ and 2 patients were reported by the Seattle group.¹³⁸ Melphalan alone or associated with VP16 or cyclophosphamide in SCT conditioning is compatible with return of fertility in up to 50% of cases.^{141,146}

Fewer studies have evaluated gonadal function following autologous SCT, and most of these studies have involved small numbers of patients. The use of BEAM (bischoleorethynitrosourea, etoposide, ara-C, melphalan) conditioning for autografts may be associated with a high incidence of gonadal recovery in women,¹⁴⁷ but in men azoospermia is almost always the rule.^{148,149} The EBMT LEWP has retrospectively identified 7 male patients who have fathered children naturally following BEAM, however.¹³⁹

Pretransplantation counseling and treatment options

Ideally, the pretransplantation counseling process should include data on the chance of gonadal failure and should assess the relevance of this situation to the patient. If the patient is of reproductive age and wishes to parent a child following SCT, it may be possible to alter the choice of conditioning protocol without compromising other factors such as survival. Clearly, this is not always an option, and discussion of management options for gonadal failure is thus essential. This should include discussion of assisted conception techniques and in women management of a premature menopause. In women with no residual ovarian function following SCT, implantation of embryos cryopreserved prior to SCT is currently the only option for parenting a woman's own genetic child. This option, however, requires that prior to SCT the underlying disease can tolerate a minimum 4- to 6-week delay in treatment for controlled stimulation of the ovary and egg collection. It also requires that the patient have a committed partner to provide sperm. In situations in which treatment cannot be delayed or there is no committed partner, consideration can be given to

freezing ovarian tissue prior to SCT. Centers in some countries will provide this service for young women, but the patients need to be aware that currently this is a research rather than clinical tool and that to date there have been no successful pregnancies in human subjects using this methodology. Although the incidence of assisted conception increases annually, there are few published reports of pregnancy outcome following assisted conception in SC transplant recipients.¹⁵⁰⁻¹⁵² In the pregnancy outcome study published by the EBMT LEWP, a high incidence of relapse was noted in female patients with chronic myelocytic leukemia (CML) who had conceived using assisted techniques.¹³⁹ On this basis we recommended that women with CML who wish to have assisted conception wait for 2 years post-SCT and are demonstrated to be bcr-abl negative before implantation.

Sperm cryopreserved prior to SCT may be used post-SCT for artificial insemination, in vitro fertilization (IVF), and embryo transfer or for in vitro injection into the cytoplasm of the oocyte (ICSI). Semen collection should ideally occur at diagnosis before chemotherapy has been given. Concurrent administration of chemotherapy is not an absolute contraindication to storage, but the patient must be informed of potential risks.

Posttransplantation management should routinely include symptomatic and biochemical monitoring of gonadal function. Although the patient should be prepared for infertility, a possible need for contraception soon after SCT must also be emphasized, particularly in women who resume menstruation or patients who do not wish to become parents. Patients have conceived within 6 months of SCT, and unexpected pregnancy may result in requests for termination. Distressing vasomotor symptoms may commence acutely post-SCT, but this situation may be prevented by initiating SHRT. Alternatively, SHRT can be initiated at the onset of symptoms or when gonadotrophin levels indicate ovarian failure. SHRT does not suppress ovulation and will not, therefore, prevent recovery of gonadal function or pregnancy. It is, therefore, important to intermittently withdraw HRT and assess gonadotrophin levels. If there are signs of gonadal recovery, patients may benefit from contraceptive advice. Alternatively, because recovery in women is likely to be followed by a premature menopause, this period may be perceived by the patients as a window of opportunity to conceive naturally. Only regular follow-up will identify this point in time.

Quality of life and neuropsychological functioning

Quality of life (QoL) has become an essential outcome criterion for treatment strategies.¹⁵³ QoL assessment can identify rehabilitation needs and can facilitate the initiation and evaluation of rehabilitation programs. When SCT is an alternative competing therapeutic option for a disease, eg, chronic myelogenous leukemia or acute myeloid leukemia, QoL may be integrated in the pre-SCT counseling, in an often-complex clinical decision-making process. Finally, psychosocial and QoL indices may have a predictive value for survival in SCT.¹⁵⁴

Despite a clear definition of health by the World Health Organization in 1948, as a "state of complete physical, mental and social well being, and not merely the absence of disease," QoL remains difficult to measure. It can be considered to be a multidimensional, time-dependent concept, which is both individual and subjective. Furthermore, there is poor correlation between symptoms and signs and overall QoL. Self-evaluation by

the patient rather than reporting by observers is thus of central importance when assessing QoL.

Two main approaches can be used for self-evaluation of QoL: (1) psychometric tests (questionnaires) and (2) utility/preferences measures. These approaches should include items concerning physical functioning, disease/treatment-related symptoms, psychological and social functioning, sexual functioning and body image, satisfaction with health care and the doctor-patient relationship, and, more recently, spiritual concerns. Psychometric measures can be generic, disease specific, and site or therapeutic specific. Many instruments have been developed, for example the Sickness Impact Profile (SIP)¹⁵⁵ or SF-36¹⁵⁶ for generic assessment and the European Organization for Research and Treatment of Cancer Core Quality of Life (EORTC QLQ-C30)¹⁵⁷ or FACT¹⁵⁸ (Functional Assessment of Cancer Therapy Scale) for cancer patients. For SCT patients, a specific questionnaire has been validated, the FACT-BMT.¹⁵⁹ These instruments are patterned around a similar concept: a core questionnaire consisting of several subunits for specific life domains, in combination with disease- or treatment-specific modules. The psychometric measures provide a descriptive profile as to how each patient is feeling, and it can be used to describe groups of patients for comparative purposes in clinical trials. However, for decision making, it may be desirable to formally compare the therapeutic benefit versus the changes in QoL for a given clinical management strategy. For example, if the more efficacious therapy is associated with poorer QoL, is it worthwhile? Various methods are available for determining patients' preferences. The utility approach, combining survival and QoL (like quality adjusted time without symptoms or toxicity, Q-TWiST) enables a comparison of different policies of management when both survival and QoL vary simultaneously by combining QoL and survival into a single summary score. These tools have been mainly used in patients with cancer, but to date there has been only one published study¹⁶⁰ comparing patients who underwent SCT with patients treated by chemotherapy alone.

Overall, studies^{161,162} have reported good levels of function and well-being in long-term survivors of SCT. Despite this level of functioning, there are increased reports of fatigue, lack of energy, sleep problems, and sexual dissatisfaction. Risk factors identified for impaired QoL post-SCT include older age and advanced disease at SCT, lower level of education, and the development of cGVHD.

Fatigue and sleeping disorders have been reported in up to 65% patients post-SCT,^{154,163,164} and these changes may persist for several years following SCT.¹⁶⁴⁻¹⁶⁷ Problems with sexuality and intimacy after SCT are reported in approximately 25% of patients. Changes in sexual experience and lower level of sexual satisfaction have been reported in addition to disorders of sexual functioning.^{165,168-171} Some data suggest that women have higher prevalence rates than men.^{168,172} Neuropsychological deficits have also been investigated in patients undergoing allogeneic SCT.¹⁷³⁻¹⁷⁵ Problems with memory can be found in nearly 20% of patients within the first year after SCT; this problem is unrelated to the patient's emotional status or intake of psychoactive drugs. However, neuropsychological examination prior to SCT also reveals cognitive impairments in 10% of patients.^{163,164,176} Patients with a history of central nervous system (CNS) disease seemed to be at higher risk of cognitive deficits, especially children treated with cranial radiation or the combination of cytotoxic drugs and irradiation.^{166,173-175,177-180} Lower IQ levels have been described in children 1 year following SCT, but this decrease remained stable at the 3-year follow-up.¹⁸¹ Changes in IQ were minimal, however, in children transplanted at a very young age (< 3 years).¹⁷⁸

Conclusion

Allogeneic SCT has been able to cure thousands of patients with otherwise lethal diseases. In this century our aim is not only to cure a patient's underlying disease but also to minimize the incidence of post-SCT complications and ensure the best possible QoL. The 2 main risk factors (pretransplantation conditioning and chronic GVHD) have hitherto been poorly amenable to modifications. The advent of reduced intensity conditioning for SCT and new immunosuppressive drugs will hopefully open the door for a curative procedure with relatively few late effects.

Acknowledgments

We realize that numerous reports and publications have not been included in the present review. We would like to express our excuses to authors not cited in the present manuscript because of lack of space (limited by *Blood* requirements for reviews).

Note from G.S.: while on the way to Seattle on September 11, 2001, my plane was obliged to land in Newfoundland (Canada), for obvious security reasons. The Memorial University of Newfoundland then hosted me for 6 days. The goal of my trip was a lecture on Late Effect after SCT. I would thus dedicate this review to Memorial University and the individuals who hosted me during those never-forgotten days.

Appendix: members of the Late Effects Working Party of the European Group for Blood and Marrow Transplantation

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