LATE EFFECTS OF HEMATOPOETIC STEM CELL TRANSPLANTATION

Late effects of hematopoietic stem cell transplantation

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Introduction

Hematopoietic stem cell (HSC) transplantation has evolved into a modern therapeutic modality for variety of life-threatening hematologic, neoplastic and immunologic diseases. Around the world thousands of patients are currently alive more than 5 years following stem cell transplantation and increasing data have been collected for the long term complications [1,2].

Long term complications of hematopoietic stem cell therapy are categorized as regimen related toxicity, immunodeficiency, infection, chronic graft-versus host disease (GVHD), bone disease, relapse of malignancy and secondary malignancies (Table I).

Regimen-related toxicities

Late complications after allogeneic and autologous HSC transplantation may arise from chemotherapy and/or radiotherapy associated organ toxicity [3]. These potential late effects of high-dose conditioning regimens include cataracts, neurological problems, gonadal conditions, endocrine conditions, growth and development problems (Table I). These regimen-related complications are briefly reviewed below.

Cataracts

Cataract formation is a well-known consequence of corticosteroid use and total body irradiation (TBI). In the analysis of 492 adults followed for a median of 6 years after bone marrow transplantation, cataracts developed in 159 patients (32%). [4]. The probability of cataract formation at 11 years after transplantation was 85% for patients receiving 10 GY single dose TBI, 50% for the patients receiving more than 12 GY and was 19% for the patients who were not conditioned with TBI [4]. In the cohort developing cataracts, the severity was greater in patients given single-dose TBI than those given 12GY (33%) or no TBI (23%) [4].

Steroids administered given after Day 100 also appeared to increase the risk of cataracts seen after TBI. Patients who were treated with steroids post-transplantation had a significantly higher probability of cataracts (45%) than those who did not receive steroids (38%). In these studies cataract formation appeared to reach a plateau phase at 7 years after transplantation with a median time of 2 to 5 years [4].

Neurological complications

Late neurological complications may result from previous cranial radiation, recurrence of the primary disease, intrathecal therapy and other drug toxicities. Leukoencephalopathy may develop in patients who receive intrathecal methotrexate and cranial irradiation and risk may increase in young patients who receive more than six doses of I.T. methotrexate after the transplant [5]. Late neurologic abnormalities may also be seen in patients receiving nitrogen mustard as part of the preparative conditioning regimen [6,7].

Endocrine and growth abnormalities

Myeloablative conditioning regimens may also affect the endocrine system, growth and development. In adult bone marrow transplant patients two-thirds of the recipients may have elevated TSH with normal blood T4 and T3 levels [6]. In the same study it was also shown that 20 to 25% of the patients will develop definite hypothyroidism [6]. Thyroid deficiency was reported in 31 to 43% of patients after single fraction of TBI [7]. In children who were given conditioning regimens with fractionated irradiation developed less frequent hypothyroidism [7]. Thyroid hormone replacement should be administered if the diagnosis of hypothyroidism has been confirmed.
Graves’ disease has not been commonly seen in the bone marrow transplant recipients. In view of these clinical studies mentioned, thyroid function studies must be done annually in all bone marrow transplant recipients.

Growth hormone deficiency has also been reported following TBI [8]. It may be higher than 90% in the pediatric patients conditioned with TBI and also had a history of cranial irradiation for CNS leukemia [8]. In some children who were treated with corticosteroids for chronic graft-versus-host disease (cGVHD) growth rate may be lower compared to the period during which steroids are discontinued. Finally, children who are prepared with busulfan may also develop growth hormone deficiency and may require growth hormone replacement therapy [8].

Some children who received pre-transplant cranial irradiation may exhibit learning disabilities within the period of 24 to 42 months post-transplant. In addition, some patients may develop variety of coping mechanisms to deal with intensive medical care and life-threatening illnesses. Concurrent drug therapies such as prednisone may cause emotional problems, rarely psychosis and cyclosporine may cause tremors, seizures, muscle cramps and lethargy.

Gonadal dysfunction

Gonadal function abnormalities are quite frequently observed as a result of myeloablative chemotherapy and radiotherapy. Gonadal dysfunction has been closely associated with alkylating agents, may be related to patient’s age and intensity of the chemotherapy regimen. Female patients may have anovulation, low estrogen levels and elevation of serum gonadotropins [9]. Patients who were conditioned with TBI containing preparative regimens rarely have return of their fertility [10].

Children who are eight years and older should be examined annually and assessed by Tanner Development Scores for grading secondary sexual development [11].

Hormone replacement with cyclic estrogen/progesterone therapy to prevent osteoporosis and its complications of early menopause. Most women prefer Premarin 0.625 mg to 1.25 mg per day (P.O) and Provera 2.5 to 5.0 mg days 1–14 (P.O.). Both of these medications are well-tolerated. Provera should not be given to women who had hysterectomy.

Gynecological and obstetric conditions

Post-pubertal female patients who received TBI containing regimes have been shown to have climacteric abnormalities [12]. Appropriate and early hormone replacement with estrogen and progestrone may reduce the risk of osteoporosis and eliminate the unnecessary discomfort. Although pre-term delivery and low-birth weight children were reported to be increased than expected in the bone marrow recipients, the incidence of congenital abnormalities did not appear to be different than the rates observed for the population [12].

Immunodeficiency

Both allogeneic and autologous hematopoietic stem cell recipients experience impaired immunological changes for 6 to 12 months post-transplant [13]. HLA–disparity of the allogeneic donor and presence of chronic GVHD will also play a very significant role in the evolution of both cellular and humoral immunodeficiency [14]. Low levels of CD4+ T-helper lymphocytes may stay low within the first six months after transplantation. Normal numbers of peripheral blood B-cells can be quantified one to two months after bone marrow transplantation. In general, the patients are expected to reach normal levels of serum IgG within 2–3 months, serum IgM in 9–12 months and IgA levels in 2 to 3 years. If the patients develop chronic GVHD the normalization of the serum immunoglobulin levels will be significantly prolonged [15]. During the first three months after transplant the recipients with hypogammaglobulinemia (serum IgG levels less than 400 mgdl−1) should receive I.V. immunoglobulin therapy which ultimately will reduce the risk of infection.

Infection

All marrow transplant recipients undergo a time of immune deficiency which is most severe in the first 6–12 months post-transplant. It is during this time that most bacterial fungal and viral infections occur. After 12 months post-transplant most patients will achieve adequate immune reconstitution. However, the tempo of immune recovery is delayed in patients who develop chronic GVHD.

Fever of unknown origin

Fever in a marrow transplant recipient should be considered a sign of infection until proven otherwise. Prompt and thorough evaluation of fever in an
immunocompromised host should include blood cultures (and other sites of culture as indicated), chest radiograph and serial physical examination. If sudden, overwhelming sepsis syndrome (with pneumococci or other encapsulated organisms) has been observed, empiric antibiotics may be indicated after obtaining cultures. Empirical antibiotic coverage for a broad-spectrum of bacteria to include gram-negative and encapsulated organisms. Organisms should be tested for antibiotic sensitivities. Initial therapy of the febrile neutropenic patient should be directed by clinical findings and concurrent antimicrobial therapy. A combination of third generation cephalosporin with an aminoglycoside is commonly utilized for the initial treatment but physicians should make their choices depending upon the microbial sensitivities of their individual institutions.

If fungal infection is presumed, consideration should be given to CT of the sinuses and lungs. Especially in patients with cGVHD, empirical addition of Pneumocystis carinii specific treatment (i.e., trimethoprim-sulfamethoxazole or pentamidine isethionate) is advised if the clinical presentation is consistent with this diagnosis and prophylactic treatment is not being administered.

Empirical antibiotic therapy regimen should be modified or discontinued depending on the culture and diagnostic procedure results.

Pneumonia

Approximately half of pneumonias after BMT are due to infection. The true incidence of bacterial bronchopneumonia is unknown but estimates range from 2% (documented by open lung biopsy) to over 25% (from clinical response). Aspergillus infection most often involves lung and is seen in approximately 10%.

Cytomegalovirus pneumonia

Late cytomegalovirus (CMV) pneumonias occur in around 10% of transplant patients who had positive CMV-serologies before transplant or whose donor was CMV-seropositive. This incidence is highest in patients with chronic GVHD. Pneumonia usually occurs concurrent with evidence of CMV reactivation in blood, documented either through antigenemia or PCR. Weekly blood monitoring for re-activation is very helpful in diagnosing end-organ CMV disease. Importantly, if pneumonia develops, the risk of mortality increases to 50%. CMV pneumonia is diagnosed by lung biopsy. Cytological, immunofluorescent monoclonal antibody or viral culture evidence of CMV infection with clinical evidence of pneumonia is considered CMV pneumonia. The preferred treatment is intravenous ganciclovir. An immunoglobulin regimen is combined with the antiviral ganciclovir.

Pneumocystis carinii pneumonia (PCP)

It occurs in 7% of recipients not receiving adequate prophylaxis. All patients are to receive Pneumocystis Carinii pneumonia (PCP) prophylaxis through day 120 post transplant, or longer if they continue on prednisone treatment. PCP prophylaxis should continue beyond 6 months if patients is still on immunosuppressives, during treatment for chronic GVHD and for 6 months after discontinuation of treatment. Systemic intravenous therapy should be initiated with either trimethoprim-sulfamethoxazole or pentamidine isethionate. Trimethoprim-sulfamethoxazole should be given 15–20 mg kg⁻¹ per day of the trimethoprim component, in divided doses every 6–8 hours, for 14–21 days.

Varicella zoster

Varicella zoster virus (VZV) infection develops in 40–50% of marrow transplant recipients within the first year after transplant (peak risk 2–8 months). Importantly, around 10% of patients present with back or abdominal pain before the skin lesions, and 30–50% of patients develop disseminated infection. Patients with suspected prodromal Zoster or documented Zoster during the first year after transplant should start I.V. acyclovir (ACV) therapy immediately and have whole blood sent for VZV PCR (cutaneous lesions may not even occur). ACV is given at 10 mg/kg/1 dose as a 1 hour infusion every 8 hours for 7 days or until the lesions crust over. Dose adjustment of ACV is needed, if renal function is impaired.

Reactivation of VZV is being seen with increasing frequency after BMT, especially among those with unrelated donors and prolonged immunosuppression. All BMT recipients should avoid exposure to persons with chickenpox or shingles. Recurrent VZV may be seen in 10–20% of ACV-treated patients, and these patients should be retreated.

Transplant patients who have been exposed to active chickenpox infections or other patients with zoster need to be observed for the development of lesions if they were VZV-seropositive pretransplant or if they have already had an episode of zoster after transplant. For VZV-seronegative exposed patients, VZV immune globulin (VZIG) prophylaxis should be administered within 96 hours of the exposure.

When patients return to home community, recurrent exposures to varicells are expected. In selected individual patient situations, multiple or high risk exposures may occur for patients who are not likely to be immediate candidates for the vaccine. To prevent infection from occurring in these patients, two approaches can be utilized. One is the use of oral prophylactic acyclovir or valaciclovir until eligible for the vaccine, unless patient is receiving other medications with activity against the herpesviruses.
(e.g., ganciclovir, foscarin, or cidofovir). The other approach is to administer monthly injections of VZIG.

**Infection prevention**

Patients should avoid frequent contact with anyone with viral infections or other communicable disease. Handwashing is crucial in the prevention of communicable diseases. Patients who are receiving treatment for chronic GVHD should continue antibiotic prophylaxis for 6 months after discontinuing all immunosuppression.

**Antibiotic prophylaxis**

All patients should receive PCP prophylaxis throughout their immunosuppressive regimen. Those patients who are on corticosteroids should remain on PCP prophylaxis until steroids discontinued. Patients on treatment regimen for chronic GVHD should follow recommendations for antibiotic coverage. Patients will receive prophylaxis with daily penicillin and once-a-day double-strength Trimethoprim-sulfamethoxazole.

Patients not able to receive trimethoprim sulfamethoxazole should receive PCP prophylaxis with dapsone (50–100 mg, 3–7 times a week, P.O.) or intravenous Pentamidine (4 mg kg\(^{-1}\) up to 300 mg per dose) every 2 weeks *not to exceed total dose of 3 grams*.

Post-transplant vaccinations of seronegative transplant recipients should be done after 2 years post-transplant or 12 months after discontinuation of all immunosuppression, whichever occurs later. VZV vaccine should be given concurrently with MMR vaccine or at least 4 weeks apart from the MMR vaccination.

**Immunizations**

During the first year, patients are generally unable to develop antibody responses to such immunizations as pneumococcal polysaccharide antigen (Pneumovax) or other inactivated vaccines. Beyond 1 year post-transplant, patients free of chronic GVHD develop specific IgG antibody titers to recall antigens such as tetanus toxoid, and measles virus, but titers will drop over time without re-immunization. Most recipients with chronic GVHD fail to develop titers to these antigens at all. Although patients with chronic GVHD may have an inadequate immune response, we recommend a complete vaccination series because this cohort is at highest risk for development of some of the preventable diseases.

We recommend vaccination after the first year post-transplant for optimal antibody response. Booster immunization should include; influenza (yearly), pneumococcal, Haemophilus influenza, hepatitis B, diphtheria, pertussis (only for patients <7 years old), tetanus and inactivated polio. Whether patients with chronic GVHD will develop an antibody response is not known in all cases. Therefore, antibody titers can be helpful if drawn before and 4 weeks following vaccinations to evaluate antibody response. If antibody response is low or unknown, repeat vaccinations up to 2 times in 2 month intervals, except for influenza and pneumococcus.

Should the oral polio vaccine (OPV) be given to family infants or others in close contact with the patient within the first year after transplantation, the patient should be isolated from the person vaccinated for 8 to 12 weeks which is the period of potential live virus shedding.

**Chronic graft-versus-host disease**

**Incidence**

Chronic GVHD is a clinicopathologic syndrome which is the major determinant of long-term outcome (mortality) and quality of life (morbidity) after allogeneic bone marrow transplantation. Chronic GVHD may develop within 3 to 18 months after allografting and occurs in approximately 33% of HLA-identical sibling recipients and 50 to 70% of recipients of unrelated or mismatched-related marrow grafts (Sullivan et al.1991). Increasing patient age and degree of prior acute GVHD are known risk factors for developing chronic GVHD, 20–30% have adenovirus late onset without preceding acute GVHD. In addition, allogeneic peripheral blood stem cell recipients appear to have a higher incidence of chronic GVHD than bone marrow recipients (Storek et al.1997).

Chronic GVHD may manifest in two ways: “Limited disease” is defined as the presence of signs and symptoms of GVHD limited to skin and/or liver involvement. “Extensive disease” is defined as the presence of signs and symptoms consistent with GVHD involving multiple organ system with at least one biopsy showing characteristic pathological GVHD findings. Individuals with the extensive chronic GVHD have an unfavorable natural history (18% disability -free survival without immuno-suppressive treatment (Sullivan et al. 1981; Sullivan et al. 1981; Sullivan 1994).

There are three typical patterns of onset of chronic GVHD. Progressive chronic GVHD is defined as direct continuation of signs and symptoms of acute GVHD and it is associated with the highest mortality rate. Quiescent onset of chronic GVHD is observed after the complete resolution of prior acute GVHD. De novo onset of chronic GVHD is defined as onset of the disease without any prior history of acute GVHD. De-novo onset of chronic GVHD has the best prognosis (Sullivan et al. 1981; Wingard et al. 1989; Atkinson 1990).
Chronic GVHD is a pleiotropic disease with clinical and pathological signs and symptoms similar to several naturally occurring autoimmune disorders. Organ involvement in extensive and chronic GVHD includes the skin, mouth, eyes, sinuses, gastrointestinal tract, lungs, muscles, tendons, serous surfaces and vagina (Sullivan et al. 1981; Sullivan 1994).

Clinical manifestations

**Dermal.** Dermal involvement is the most frequent clinical feature of chronic GVHD. Erythema, dyspigmentation, poikiloderma, and violaceous papules resembling lichen planus may be observed. Lichenoid lesions can be generalized and coalesce to form plaques. If no therapeutic intervention is given, the skin becomes progressively indurated and sclerotic, leading to joint contractures and profound disability. The sclerosis can be associated with skin ulcers, alopecia and anhidrosis. Progressive hair loss with scarring alopecia can be observed in patients with chronic GVHD.

**Oral.** Oral lesions include erythema, atrophy and lichen planus-like findings. Severe mucous membrane involvement with chronic GVHD may lead to a Sjogren's syndrome-like disease findings with xerostomia and xerophthalmia. Presence of "oral sicca" syndrome in these patients may lead to poor oral hygiene and dental caries.

**Ocular.** Abnormalities include kerato-conjunctivitis sicca, conjunctivitis and uveitis. Schirmer's testing of lacrimal gland function may show wetting < 5mm at 5 minutes or < 10 mm with signs of keratitis diagnosed with slit-light examination. Other symptoms will include blurring, dryness, "gritty eyes" and/or photophobia. Artificial tear replacements may be required to prevent corneal abrasion.

**Pulmonary.** Chronic GVHD may be associated with recurrent sinopulmonary infection and progressive obstructive lung defects. Clinical and pathologic features are characterized by the presence of bronchiolitis obliterans (Clark et al. 1987; Clark, Crawford, Madtes, and Sullivan 1989). Progressive bronchiolitis obliterans affects 5–10% of all patients with active chronic GVHD.

**Hepatic.** Liver function abnormalities are common and are predominantly cholestatic in nature but hepato-cellular dysfunction may make it difficult to distinguish chronic GVHD from viral or drug-induced hepatitis. Ursodeoxycholic acid may be of benefit as bile displacement therapy. (Fried et al. 1992).

**Musculo-Skeletal.** Arthralgias, synovial effusions, arthritis, tendonitis and fasciit have been associated with chronic GVHD (Janin et al. 1994). Proximal muscle weakness with increased CPK, aldolase and EMG findings are consistent with myositis. Muscle cramping can also occur. Muscle biopsy may be required to confirm the diagnosis if the muscle is the only organ involved.

**Gastro-Intestinal.** Chronic GVHD rarely involves the intestine. Weight loss often is related to loss of appetite and increased metabolic needs. Esophageal complications may include desquamative esophagitis causing web formation and gastro-esophageal reflux. Classic findings of malabsorption may be noted due to bacterial overgrowth in the gut, pancreatic or hepatic disease.

**Other sites.** Vaginal stenosis, dryness and inflammation can all be seen during the course of chronic GVHD. Peripheral neuropathy and myaesthenia gravis are less common manifestations.

**Infections.** Due to prolonged time to immunologic recovery, infections may be common in patients with chronic GVHD. Chronic GVHD, its treatment with corticosteroids and associated hypogammaglobulinemia contribute to this risk. Infections with encapsulated Gram-positive bacteria are most common and require daily penicillin or trimethoprim-sulfamethaxazole prophylaxis (Sullivan et al. 1986).

**Outcome.** In an analysis of 164 consecutive patients with extensive chronic GVHD, older patient age, progressive onset of GVHD, failure to respond to 9 month therapy and continued thrombocytopenia (platelets < less than 100,000 μl−1), hyperbilirubinemia and lichenoid histology have been reported to be associated with an increased non-relapse mortality and poor prognosis. Among unrelated donor marrow transplants a prolonged course of interferon-alpha given before transplant in patients with chronic myeloid leukemia (CML) resulted in poorer survival due to chronic GVHD which was refractory to immunosuppressive treatment (Morton et al. 1997a; Morton et al. 1997b).

**Treatment**

As noted above, without treatment only 18% of patients with extensive chronic GVHD survived free of major disability. In standard-risk patients (i.e., those with a platelet count greater than 100,000 μl−1, de novo or quiescent type of onset) early treatment with prednisone alone significantly...
improved outcome (21% mortality) compared to prednisone and azathioprine (40% mortality) (Sullivan et al. 1988). In high-risk patients (i.e., those with platelet counts less than $<100,000 \, \mu l^{-1}$ or progressive type onset) survival after prednisone treatment was only 10 to 26%. Subsequently, the addition of cyclosporine to an alternating-day regimen of prednisone has improved the survival to 52% in high-risk patients (Sullivan et al. 1988). However, transplant-related mortality still continues to be higher (35%) in high-risk patients than in standard-risk patients (20%) due to increased rates of infection.

New treatment approaches include the use of FK506, thalidomide, mycophenolate mofetil and rapamycin (Vogelsang et al. 1992; Nash et al. 1997). Supportive care includes correction of hypogammaglobulinemia and administration of trimethoprim-sulfamethoxazole to reduce the risk of infection include the use of (Sullivan et al. 1996).

**Bone disease**

Bone disease is a well-known complication of solid organ transplantation, however the development of avascular necrosis, osteoporosis and fractures following stem cell transplantation is less well characterized (Kelly et al. 1990; Socie et al. 1994). Recently, adult patients treated with prednisone and cyclosporine for chronic GVHD and who were evaluated for biochemical factors associated with skeletal turnover at initiation of immunosuppressive therapy and 9 months later (Stern et al. 1996). Single and dual photon absorptiometry of the wrist and spine and dual energy x-ray absorptiometry (DEXA) were used to evaluate bone mineral density. Results showed a significant bone mineral density (greater than 2.5 times the test precision) decrease over 9 months in bone mineral density in three of five evaluable males and all three females who were receiving prednisone and cyclosporine treatment. The results of the study indicated increased collagen and bone turnover, increased urinary magnesium and calcium excretion, and a significant risk of osteoporosis in patients receiving corticosteroids for chronic GVHD.

**Secondary malignancy**

Secondary neoplasms may arise in the oncogenic milieu of genetically determined factors, infection, immunodeficiency and cytotoxic conditioning regimens, including TBI (Witherspoon et al. 1989; Witherspoon et al. 1992). The Seattle team reported the cumulative incidence of secondary cancers in 330 patients with aplastic anemia who received cyclophosphamide alone as pre-transplant conditioning (Witherspoon et al. 1992). The cumulative incidence at 5 years was 0.4% (95% confidence interval 0 to 1.1), at 10 years was 1.4% (0 to 3.4), and at 15 years was 4.2% (0.9 to 8.6). The rate was less than reported by the Paris team in patients with aplastic anemia given cyclophosphamide and thoraco-abdominal irradiation as conditioning (N=147).

European studies confirm that pre-transplantation irradiation is a major determinant of late malignancies in patients with aplastic anemia (Socie et al. 1993). To further define these interactions, 700 patients with severe aplastic anemia treated with allogeneic marrow transplantation in Seattle or in Paris were reviewed (Deeg et al. 1996). A malignancy developed in 23 patients 1.4 to 221 (median 91) months after transplantation, for a Kaplan-Meir estimate of 14% (confidence interval 4 to 24%) at 20 years. Proportional hazards models indicated that azathioprine therapy ($P<0.0001$) and the diagnosis of Fanconi’s anemia ($P<0.0001$) were significant factors for development of secondary malignancies for all patients. Irradiation was a significant factor ($P=0.004$) only if the time-dependent variable azathioprine was not included in the analysis. If only non-Fanconi patients were considered, azathioprine ($P=0.0043$), age ($P=0.025$), and irradiation ($P=0.042$) were independent risk factors for development of late secondary neoplasms.

In a recent report, a multi-institutional data base including 19,229 recipients of allogeneic marrow transplants was analyzed to determine the risk of developing late solid cancers (Curtis et al. 1997). The risk of new solid cancers was 8.3 times higher than expected for the general population among those who survived 10 or more years after transplantation. The cumulative incidence rate of solid cancers was 2.2% (95 percent confidence interval, 1.5% to 3.0%) at 10 years and 6.7% (3.7 to 9.6%) at 15 years. In this study, the risk of developing a new solid cancer was also found to be higher for recipients who were younger at the time of transplantation. Radiogenic tumors (especially of brain and thyroid) were noted in children, most of whom had cranial irradiation given before referral for transplantation.

**Recurrent malignancy**

Prior experience has indicated poor survival after recurrence of the original malignancy after marrow cell transplantation (Mortimer et al. 1989). In some patients recurrent leukemia has been successfully treated with second transplantations, but resistant disease and regimen-related toxicities contribute to high mortality (Radich et al. 1993). In recent years, the development of highly sensitive molecular biology techniques has helped detect minimal residual disease. For patients with CML, long-term monitoring includes cytogenetics for the Philadelphia chromosome and bone marrow and peripheral blood molecular determinations for the BCR/ABL transcripts every 6 months after transplantation through Year 3,
then annual evaluations through Year 5. Positive BCR/ABL studies six months or more after transplantation appears to predict risk of subsequent hematologic relapse (Radich et al. 1995). Patients with residual disease could be eligible for treatment with alpha-interferon during early molecular or cytogenetic relapse (Higano et al. 1992). Recurrent leukemia following stem cell transplantation may also be successfully treated with donor leukocyte infusions. This beneficial effect derives from an apparent graft-versus-leukemia (GVL) effect associated with allogeneic stem cells that recognize and destroy host histocompatibility antigens and/or tumor-associated antigens (Weiden et al. 1981; Sullivan et al. 1989). Donor leukocyte infusions have been used successfully to treat patients with recurrent leukemia and Epstein-barr virus-associated lymphoproliferative disorders (Kolb 1990; Papadopoulos et al. 1994).

Quality of life

Recovery from transplantation is a dynamic process blending physical and psychosocial aspects. Quality of life is a multi-dimensional construct composed of at least four domains: physical function, psychological function, social role function and disease and treatment symptoms. Recent studies examining the medical and psychosocial sequelae of stem cell or marrow transplantation have reported that most survivors do relatively well, while a smaller group continues to experience less than optimal quality of life (Wingard, Curbow, Baker and Piantadosi 1991; Chao et al. 1992; Schmidt et al. 1993). We conducted a prospective analysis of 67 adults with “Quality of Life” measures taken before and after allogeneic transplantation (Syrjala et al. 1993). Physical function was most impaired at 90 days post-transplant, with a return to pre-transplant levels of functioning in most areas by one year. By two years, 68% of patients had returned to full-time work and only 9% of 4-year survivors failed to return to full-time occupations. Before transplantation 27% of patients reported elevated anxiety. Mean levels of anxiety and depression did not change over the first year. In a multivariate analysis greater emotional distress at 1 year was predicted by pre-transplantation family conflict and non-married status. Impaired physical recovery at 1 year was predicted by more severe chronic GVHD, pre-transplant physical impairment and family conflict. Family relationships therefore appear to be important determinants of recovery.

A recent study used a cross-sectional analysis of 125 adults surviving a mean of 10 (range 6 to 18) years after allogeneic (87%) or autologous /syngeneic (13%) transplantation (Bush, Haberman,Donaldson, and Sullivan 1995). Seven wide-ranging tests measured physical, psychological, social functioning, and disease and treatment symptoms. Eighty percent of individuals rated their quality of life as good to excellent, and 5% rated it as poor. The most frequently cited problem during recovery was a perceived lack of social support from family and friends. Although complaints such as fatigue, sexual dysfunction and sleep disturbances were noted, most survivors judged these to be of low severity and 88% of the 125 patients said the benefits of transplantation outweighed the side-effects.

Summary

Bone marrow and peripheral blood stem cell transplantation is now considered the treatment of choice for a variety of non-malignant and malignant disorders. In some patients, the impact of late complications determines the success of the procedure and efforts directed at preventing rare events are vital. Knowledge of late complications and follow-up care by the specialist and general practitioner will enhance the outcome of recipients of allogeneic and autologous hematopoietic cell transplantation.