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Impact of chronic GVHD on late complications after hematopoietic cell transplantation

H. JOACHIM DEEG & MARY E.D. FLOWERS

Fred Hutchinson Cancer Research Center and the University of Washington School of Medicine, Seattle, WA, USA

Current results with transplantation of marrow or blood derived hemopoietic stem cells (HCT) in patients with aplastic anemia and patients who do not develop chronic graft-versus-host disease (GVHD) show life expectancies similar to age-matched controls. However, patients with advanced malignant diseases and patients who develop chronic GVHD after transplant are at risk of late disease recurrence and delayed, potentially fatal complications [1]. Major complications associated with chronic GVHD are listed in Table I.

Infections

Late infections due to bacterial, viral and fungal organisms occur most commonly in patients with chronic GVHD. Early post-transplant prophylaxis may result in an increased incidence of late infections (see e.g., acyclovir/ganciclovir and late CMV infections). It is standard practice to give prophylaxis for infections caused by Pneumocystis carinii, varicella zoster and encapsulated bacteria (and, more recently, fungal organisms) during the first year post-transplant, or longer, for patients with chronic GVHD.

Airway and pulmonary disease

The bronchial tree may be involved by GVHD [2], and immunosuppression related to GVHD or its therapy may enhance pulmonary infection. Late onset interstitial pneumonia usually occurs in patients with chronic GVHD [3]. Restrictive pulmonary changes do not appear to correlate with chronic GVHD.

The pathogenesis of air flow obstruction (AFO) after HCT is not fully understood [4], but recurrent aspirations, possibly associated with GVHD of the esophagus or purulent sinus drainage, contribute to airway inflammation and the development of obstructive lung disease. A recent study analyzed AFO in 1049 patients who received an allogeneic HCT at FHCRC [5].here were 257 patients (25%) with significant AFO as defined by a decline in pFEV1 by more than 5% per year. In multivariate logistic regression analysis, patients with quiescent (relative risk [RR] 1.5, 95% CI 1.2–1.7) or progressive onset (RR 2.5, 95% CI 1.4–3.1) of chronic GVHD, among other factors, were at an increased risk, and those with chronic GVHD and AFO had a higher risk of mortality (hazard ratio 1.9, $P=0.002$) than patients without AFO. Thus, AFO had a significant independent effect on long-term survival.

Progressive bronchiolitis obliterans has been reported to occur in 10% of all patients with chronic GVHD [6] from 3 months to 2 years after HCT. Clinical and pathological findings are similar to those seen after lung or heart-lung transplants [6]. Histological changes are thought to be due to a graft-versus-host reaction, possibly aggravated by infections. Pulmonary infections develop in more than 60% of allogeneic HCT recipients with GVHD compared to about 20% of patients without chronic GVHD.

A recent analysis of results in 6523 patients transplanted at FHCRC revealed 51 cases of bronchiolitis obliterans organizing pneumonia (BOOP), all but two after allogeneic transplants. BOOP was diagnosed at 5–2,819 (median 108) days after HCT. The disease was significantly associated with acute and chronic GVHD. The disease progressed in 22% of patients and resolved or was stable in the remaining patients [7].

Correspondence: H. Joachim Deeg, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., D1-100, PO Box 19024, Seattle, WA 98109-1024. Tel: 206-667-5985. Fax: 206-667-6124. E-mail: jdeeg@fhcrc.org

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Table I. Chronic GVHD and delayed complications

Immunodeficiency and infections
Airway and pulmonary disease
Autoimmune disorders
Neuroendocrine dysfunction
Impairment of growth and development
Infertility
Cardiac disease
Ocular problems
Musculo-skeletal disease
Dental problems
Dysfunction of the genitourinary tract
Gastrointestinal and hepatic complications
Post-transplant malignancies
Central and peripheral nervous system impairment
Psychosocial effects

Dysregulation of immunity

All currently used conditioning regimens are associated with immunosuppression of the transplant recipient. The presence of thymic damage, due to transplant conditioning and GVHD, interferes with the negative selection of autoreactive cells and thereby facilitates the development of cellular and, via $CD4^+$ cells, humoral autoreactivity [8]. However, while autoantibodies occur frequently, particularly in patients with chronic GVHD, a correlation with GVHD activity is uncertain.

Hematologic problems

GVHD can also affect the marrow, and persistent thrombocytopenia is a poor prognostic factor in chronic GVHD [9]. Immunosuppressive treatment of GVHD is often successful [10].

Endocrine dysfunction

Adrenal glands

Many HCT patients receive glucocorticoid therapy in the pre-, peri- or post-transplant period and show the classic side effects of steroid therapy, including cushingoid features, myopathy, and bone loss. Endogenous cortisol production is suppressed, and any superimposed stress may cause a relative adrenal insufficiency. For the same reason, prolonged glucocorticoid therapy for GVHD should be given on alternate days and must be tapered very gradually.

Gonadal function, puberty and fertility

Impairment of gonadal function, fertility, and growth and development are primarily related to cytotoxic therapy. However, the presence of chronic GVHD and its treatment, in particular with glucocorticoids, may add to these problems. Local complications, such as vaginitis, may interfere with normal sexual relationships [11].

Pancreas

Prolonged therapy of GVHD with glucocorticoids, alone or combined with calcineurin inhibitors, may result in iatrogenic diabetes mellitus. It tends to resolve with discontinuation of steroid therapy.

Cardiovascular disease

Treatment of GVHD with calcineurin inhibitors, rapamycin and glucocorticoids may result in hyperlipidemia, hyperglycemia (see above), and hypertension, thereby compromising cardiovascular function. Coronary artery disease and thrombotic events have been reported at various time intervals after HCT [12].

Ocular problems

The most common problem affecting the eyes after HCT is ocular sicca, usually related to chronic GVHD, and treatment of GVHD with steroids carries the risk of capsular cataracts. The treatment of choice is lens extraction and implantation of an artificial lens. Contact lenses can be used but may be difficult to wear in patients with ocular sicca, which is often irreversible [13]. Chronic GVHD involving the eyes can result in scar formation (e.g., in the tarsus) and lead to synechiae, ectropion, corneal damage and, potentially, perforation if not treated meticulously and aggressively. Keratoconjunctivitis sicca also occurs in patients without chronic GVHD, although the possibility that it represents a sequel of prior GVHD or a form fruste of GVHD must be considered [14].

Obstruction of the nasolacrimal duct, related either to GVHD or conditioning-induced fibrosis, has been observed [15], but is infrequent.

Musculofascial problems

The most common muscular complication is corticosteroid-induced myopathy, most frequently in the context of chronic GVHD. Occasionally patients with chronic GVHD have involvement of muscle, fascia, and serous membranes, including the synovia [16]; joint effusions may occur in patients without any other sign of GVHD. Involvement of fascia or tendons by an eosinophilic infiltrate (early) or fibrosis (late) frequently preceded by edema and often resulting in joint contractures of the wrists (most common), fingers, shoulders, elbows, ankles and occasionally knees may be manifestations of chronic GVHD.

Skeletal complications

Osteoporosis/osteopenia

Bone loss after HCT is related to several factors, including irradiation, glucocorticoid therapy, inactivity, and iatrogenic hypogonadism. Monitoring and

management have been discussed extensively elsewhere [17]. In view of recent data on potential adverse effects of estrogen replacement in women, the overall risk and benefits of hormone replacement must be discussed individually before starting therapy and again at yearly intervals.

Avascular necrosis

Avascular necrosis, especially in weight-bearing joints, is a classic side effect of glucocorticoid therapy and has been reported in 4 to 10% of allogeneic HCT survivors at a median of 12 (range 2–132) months after transplant [18,19]. The hip is most frequently affected (two-thirds of all cases), and in most patients more than one joint is involved. A multi-institutional study from France, including 4,388 patients, found 77 patients with avascular necrosis for a 5-year incidence of 4.3% [18]. Symptoms developed at 2–132 months, and 1–7 (mean 1.9) joints were affected. The hip joint was affected in 88% of cases, and 48% of these patients required joint replacement. Type of GVHD prophylaxis, and acute or chronic GVHD, among other factors, were associated with an increased risk of avascular necrosis.

Dental problems

An oral sicca syndrome related to conditioning therapy or chronic GVHD may lead to poor oral hygiene with recurrent infection and periodontitis. Dental decay occurs because of a lack of cleansing by saliva, which is of altered consistency and reduced volume [20].

Genitourinary dysfunction

Patients receiving immunosuppressive therapy for chronic GVHD, particularly women with GVHD of the vagina, are at risk for recurrent urinary tract infections which require prompt antibiotic therapy.

Kidneys

There is very little evidence of renal involvement with GVHD, although proteinuria has been reported. Important, however, is the fact that several agents used for treatment of GVHD, in particular calcineurin inhibitors, may induce chronic renal failure. Renal failure associated with hemolytic uremic syndrome or microangiopathic hemolytic anemia can occur even in patients who are not heavily pre-treated and are not conditioned with TBI. The mechanism is not fully understood. The syndrome may become manifest either during or following discontinuation of therapy with CSP or FK506 [21].

Genital organs

Complications related to chronic GVHD may also involve the genital organs, in particular the glans penis and vagina. Vaginitis may be severe and cause considerable distress and dyspareunia. Prolonged treatment, topically with estrogens and systemically, e.g., with glucocorticoids, is indicated to prevent the development of atrophic vaginitis and adhesions. The vulva has also been a site of post-transplant malignancies (see below).

Gastrointestinal and hepatic complications

Gastrointestinal (GI) tract

The GI tract is a frequent target of acute transplant-related complications. Chronic problems are less common and generally related to GVHD. Involvement of the esophagus by chronic GVHD may lead to strictures and web formation [22,23]. Chronic GVHD of the small bowel may result in malabsorption.

Liver

Liver function abnormalities related to the conditioning regimen, and GVHD or infections, in particular viral infections, are frequent in the early post-transplant period. At 3 or more months after transplant, the most frequent cause for enzyme or bilirubin elevations is chronic GVHD. However, viral hepatitis has to be considered at any time after HCT. Some cases of hepatitis after HCT were diagnosed upon tapering of immunosuppressive drugs given for GVHD prophylaxis or therapy [24].

Post-transplant malignancies

Lymphoid malignancies

Lymphoproliferative disorders after HCT (post-transplant lymphoproliferative disorder [PTLD]), generally of B-cell lineage, occur mostly in allogeneic transplant recipients [25–27]; T-cell PTLD, non-Hodgkin lymphoma and Hodgkin disease have also been reported. Risk factors include the use of antithymocyte globulin (ATG) or anti-CD3 monoclonal antibodies for acute GVHD prophylaxis, treatment, or in the preparative regimen.

In a study of 18,531 transplant recipients (covering more than 42,000 patient years), 8 cases of Hodgkin disease were identified at 2.9 to 9.1 years after HCT (observed/expected ratio 6.2) [28]. Five cases (67%) showed mixed cellularity subtype, and 5 of 6 cases studied contained the EBV genome. Two patients were also positive for HIV. Patients who developed Hodgkin disease were more likely than matched

controls to have acute GVHD and to require therapy for chronic GVHD (RR in one study 4.0).

Hematologic malignancies

No association between GVHD, acute or chronic, and secondary hematologic malignancies has been reported.

Solid tumors

A spectrum of tumors, including glioblastoma, melanoma, squamous cell carcinoma, adenocarcinoma, hepatoma, and basal cell carcinoma, has been reported. A collaborative study analyzed results in 28,874 patients($<$1–72 years of age, 74% with leukemia, 76% transplanted from an HLA identical sibling, 59% given TBI was part of the conditioning regimen) transplanted from 1964–1996. Among 10-year survivors, the O/E ratios for cancers were 26.5 for buccal cavity, 32.3 for liver, 18.3 for thyroid, 6.0 for melanoma, and 3.3 for breast. The rates of excess cancers/10,000 patients per year were highest in patients $<$17 years (16.06), and lowest for patients $>$40 years of age (2.42). A case control study based on the same cohort showed that the duration and severity of chronic GVHD were major risk factors, in particular for the development of squamous cell carcinomas of the skin and mucous membranes [29].

Nervous system

The possibility of CNS involvement by GVHD has been debated but generally rejected. However, HCT results in patients with Hurler disease show that the patient's microglia is being replaced by donor cells and, hence, donor/host interactions might take place in the CNS [30]. Others have described cerebellar and pyramidal signs correlating with GVHD activity [31]. Also, Padovan et al. [32] and Takatsuka et al. [33] described periventricular white matter lesions and vasculitis or an angiitis-like syndrome which they attributed to GVHD in several patients. Some patients improved on treatment with CY or glucocorticoids.

Several clearly documented cases of peripheral neuropathy with reduced nerve conduction velocity related to chronic GVHD have been reported [34]. Destruction of Schwann cells seems to be responsible for this phenomenon, and patients respond to glucocorticoid therapy.

Patients with chronic GVHD are also prone to develop septicemia and meningitis caused by encapsulated organisms and invasive fungal infections [35]. Patients with chronic GVHD who receive immunosuppressive therapy should, therefore, also be given prophylactic antibiotics.

Psychosocial effects and rehabilitation

An estimated 75% of patients are back to pretransplant physical function by one year post-transplant [36,37]. However, at least in one study, 20% of HCT recipients had failed to return to full-time employment 40 months after transplantation [38], whereas another group reported that only 9% of 4-year survivors had failed to return to full-time occupation [39]. The development of chronic GVHD after transplant predicts a delay in physical recovery.

Summary

Most patients who recover from the immediate post-transplant problems become healthy long-term survivors and return to normal activities of life. Some patients, however, develop chronic or delayed complications. Major factors contributing to these problems are pretransplant therapy, intensive conditioning regimens and chronic GVHD. Ongoing studies are expected to provide a better understanding of the psychosocial adjustment of patients. Effective therapy or preemptive treatment for some complications is available. Thus, systematic long-term follow-up is recommended for all post-transplant patients. Further refinement of conditioning regimens, prevention of GVHD, especially in its chronic form, and accelerated immunoreconstitution should reduce complications and improve quality of life of HCT recipients.

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