Life after allogeneic bone marrow transplant

Introduction

Bone marrow transplantation has become an increasingly common treatment both for haematological malignancies and bone marrow failure syndromes. While patients undergoing bone marrow transplantation will do so in highly specialized units, these patients experience a unique array of complications after transplantation engraftment. The arrival of such a patient can be daunting for the junior doctor in an acute setting. This article gives an overview of the complications relating to allogeneic bone marrow transplant in the immediate post-transplant period, to aid a more educated differential diagnosis for common presenting complaints in these patients.

Bone marrow transplantation

There are two main types of bone marrow transplant: autografts and allografts. Autologous transplantation involves a course of myeloablative chemotherapy and/or radiotherapy to eradicate the malignant cell population, and subsequent 'rescue' using the patient's own previously harvested stem cells. These are infused post chemotherapy to resume normal haematopoiesis (engraftment). Allogeneic transplantation uses a stem cell graft from a human leucocyte antigen (HLA)-matched donor: this may be a sibling, an unrelated donor or from umbilical cord harvests. Induction chemotherapy before an allogeneic transplant may not necessarily destroy the patient's entire bone marrow. The treatment instead relies on the genetic differences between donor and patient (via unmatched minor histocompatibility antigens; mHAgs) which have a beneficial graft *vs* tumour effect to eradicate residual host malignant cells.

Advances in supportive care and reduced intensity induction regimens have significantly reduced transplant-related mortality, so more patients may benefit from its use as a potentially curative therapy, such as older recipients, patients with additional comorbidities and those for whom an exact HLA-matched donor cannot be found.

The risk of mortality associated with these transplants continues post-engraftment, and a greater understanding of and vigilance for common complications can ensure optimum outcomes.

Dr Catherine Hockings *is Haematology Registrar and* **Dr Karl Peggs** *is Consultant Haematologist in the Department of Haematology, University College London Hospital, London NW1 2BU*

Correspondence to: Dr C Hockings (chockings@nhs.net)

Graft *vs* host disease

Graft *vs* host disease is the one of the most common complications following allogeneic bone marrow transplantion. Immunocompetent donor T cells are triggered to target recipient tissues by mHAgs expressed by these tissues. Clinicians try to find the best HLA match available to minimize the risk of graft *vs* host disease, currently screening for 10 major histocompatibility (MHC) loci. Sibling donors will show a greater degree of similarity as unmatched minor antigens tend to be inherited alongside those that are matched, and so in broad terms will experience less graft *vs* host disease. Where only a mismatched donor can be found, the risk of graft *vs* host disease can be modulated by depleting the T-cell component (which mediates potential graft *vs* host disease).

Graft *vs* host disease can be either acute or chronic. Acute disease typically occurs 2–10 weeks post bone marrow transplant, but can occur after 100 days if a patient has been given donor lymphocyte infusions (see below). It may present with various symptoms, classified from stage I–IV based on clinical or biochemical criteria. The severity and incidence of graft *vs* host disease will be influenced by other factors, including histoincompatibility, older patient, greater intensity of transplant preconditioning, donor/recipient sex mismatch (female donor, male recipient) and use of donor lymphocyte infusion.

Cutaneous

This is the most common manifestation of graft *vs* host disease, varying from localized erythema to severe confluent blistering. Coincidence with engraftment and involvement of the palms and soles is strongly suggestive of acute graft *vs* host disease but not necessary for diagnosis. Milder forms may respond to topical steroid creams or ointments.

Liver

This may show either an obstructive pattern of liver function tests or a transaminitis. Recipients are screened for chronic hepatitis as part of their pre-transplantation work-up to differentiate graft *vs* host disease from hepatotrophic viral reactivation, and Epstein–Barr virus and cytomegalovirus (CMV) titres are also monitored. Toxicity from immunosuppressive or anti-infectious drugs must also be considered.

Gastrointestinal

In most cases this manifests as diarrhoea. Cramping abdominal pain is associated with severe disease. Stool cultures for microscopy and bacterial culture, *Clostridium difficile* toxin and enteropathic viral polymerase chain reaction (PCR) should be sent to exclude infectious diarrhoea. This is especially prudent given the immunosuppressive therapy used to treat graft *vs* host disease. Biopsy of involved gut mucosa via sigmoidoscopy or colonoscopy may be useful to show typical histological features of graft *vs* host disease.

Chronic graft *vs* host disease can affect any organ, with symptoms generally more insidious than in acute graft *vs* host disease and often mimicking systemic autoimmune conditions such as scleroderma or systemic lupus, e.g. dry mouth and eyes. In patients who present with pancytopenia post-transplant, stromal bone marrow graft *vs* host disease should be considered. This is a diagnosis of exclusion where other potential causes such as relapse or drug toxicity have been investigated.

Most patients are started on immunosuppressants at transplantation with ciclosporin or an equivalent. These are dosed according to serum drug levels and renal function to minimize post-transplant graft *vs* host disease. It is important to regularly monitor levels to prevent calcineurin toxicity. Patients presenting with typical symptoms of tremor, hypertension, or new onset or worsening renal impairment require urgent drug levels to exclude the possibility of drug toxicity.

The main treatment for acute graft *vs* host disease is steroids, with methylprednisolone 2 mg/kg the optimum dose in severe cases (Van Lint et al (1998) showed no advantage with higher doses). Patients who are clinically refractory to this may benefit from extra agents such as mycophenolate mofetil, anti-thymocyte globulin or anti-tumour necrosis factor therapy (particularly useful in gastrointestinal graft *vs* host disease). Enhancing immunosuppression significantly increases the risk of opportunistic infections and CMV reactivation.

Cytomegalovirus reactivation

CMV is a DNA herpesvirus, which is common in the general immunocompetent population, achieving lifelong latency following primary infection. Before transplantation, the recipient and potential donors are serotyped for evidence of prior infection. Where either the recipient or donor is CMV seropositive, post-haematopoietic stem cell transplant patients will be at risk of viral reactivation, which can lead to significant clinical disease. If the recipient and donor are both seronegative for CMV, all blood products given to the recipient should be CMV negative to prevent primary infection via transfusion.

CMV-related disease most often presents as pneumonitis or gastrointestinal symptoms, but reactivation can also cause a hepatitis or encephalitis. CMV retinitis should be considered in any post-transplant patient presenting with visual changes. Even with prevention of clinical disease using potent antiviral drugs (*Table 1*), CMV reactivation significantly affects transplant-related mortality (Broers et al, 2000).

Risk factors for CMV reactivation include use of high-dose steroids for graft *vs* host disease, T cell-depleted transplantation and repeated previous CMV reactivation. Although CMV reactivation is common, antiviral chemoprophylaxis has not shown significant survival benefit, perhaps because of the toxicities of antiviral drugs. Instead, most centres adopt a surveillance strategy, monitoring for CMV DNA with quantitative PCR to discover any increasing CMV viral load and initiate virus-specific treatment according to local thresholds before any clinical evidence of disease develops. Such testing is usually performed less frequently as time from transplantation increases, but this varies according to the presence of risk factors as above.

CMV is the most common single infectious agent requiring treatment in haematopoietic stem cell transplant patients as a result of its seroprevalence (45–100% dependent on the population investigated; Cannon et al, 2010). However, a wide variety of other infectious agents can cause morbidity and mortality in these patients.

Transfusion requirements

An important consideration when reviewing a haematopoietic stem cell transplant recipient is the patient's specific transfusion requirements. Owing to the risk of transfusion-associated graft *vs* host disease all post-allogeneic haematopoietic stem cell transplant patients must receive irradiated products while they receive graft *vs* host disease immunosuppression or until lymphocytes are >1x10^9/litre (Treleaven et al, 2010). In these patients any blood donor T cells, i.e. contaminating the red blood cells or platelets from the blood transfusion donor, can target as foreign both the recipient's native tissue and his/her stem-cell graft. As well as the manifestations above, transfusion-associated graft *vs* host disease destroys the recipient's graft causing bone marrow failure and a mortality exceeding 90% (Williamson et al, 2007), as well as a high incidence of severe haemorrhage and infection.

Practically, all post-allogeneic haematopoietic stem cell transplant patients should receive CMV-negative irradiated products until their requirements can be confirmed with their transplant centre. These requirements should be documented by the local transfusion laboratory to aid appropriate allocation of blood products. To ensure compliance by other members of staff it is useful to document transfusion requirements clearly, e.g. on the drug allergy section of the patient's drug chart.

Opportunistic infections and routine prophylaxis

Infections can occur either as early or late complications, although the pattern of pathogens varies. Bacterial infections are prevalent during the early neutropenic phase before primary engraftment, while fungal and viral infections become more common over subsequent weeks and months. They are an important cause of post-transplant mortality, particularly in patients with extensive chronic graft *vs* host disease. *Pneumocystis jirovecii* pneumonia also occurs (Bjorklund et al, 2007) and pneumococcal septicaemia is a significant risk in patients following total body irradiation. Prophylaxis against both these pathogens is usually given for extended periods.

Various factors may increase the risk of late infection, such as acute and chronic graft *vs* host disease, CMV reactivation and mismatched or unrelated graft donor (Robin et al, 2007). The type of pre-conditioning and graft also affects the risk and array of opportunistic infections depending on the level of suppression or depletion of various lymphocyte and myeloid populations. For example, patients who have undergone a T cell-depleted transplant regimen to minimize graft *vs* host disease have a greater risk of most viral infections.

Owing to the high burden of infection-related morbidity, transplant centres use their own guidelines for routine prophylaxis of various infectious species.

Fungal infection

As well as CMV reactivation, Aspergillus and *P. jirovecii* infections are significant risks in early post-engraftment (30–100 days post-transplant) (Afessa and Peters, 2006).

Table 1. Treatment for cytomegalovirus reactivation

Ganciclovir	A nucleoside analogue, generally first-line treatment. This may be given via a portable infusion pump as an outpatient. Its myelosuppressive effects may prevent its use in those patients with fragile engraftment
Foscarnet	A competitive inhibitor of viral DNA polymerase. Less myelosuppressive than ganciclovir, but glomerulotoxic. It also causes significant electrolyte derangement requiring frequent monitoring +/- replacement in an inpatient setting
Cidofovir	Given as a weekly infusion with pre- and post-hydration. Often used in concurrent adenovirus and cytomegalovirus reactivation or where other treatments have failed
Cytomegalovirus immunotherapy	Clinical trials are currently underway for the use of cytomegalovirus-specific cytotoxic T lymphocytes to prevent and treat cytomegalovirus reactivation

Patients with CD4 counts <200/mm^3 should receive *P. jirovecii* prophylaxis. Monthly pentamadine nebulizers are a non-myelosuppressive alternative to co-trimoxazole in adults immediately post-engraftment. Non-compliance or intolerance of prophylaxis, chronic graft *vs* host disease and relapse increase the risk of *P. jirovecii* infection (De Castro et al, 2005).

Invasive fungal infection can be difficult to diagnose. It may be suspected on the basis of high-resolution chest computed tomography findings, galactomannan assays or treated for empirically in febrile patients not responding to broad spectrum antibiotics. As most fungal exposure is via airborne spores inhaled before hospital admission, it is extremely difficult to prevent. Patients are most at risk of invasive fungal disease during the neutropenic period before engraftment, so antifungal prophylaxis should be routinely given throughout prolonged neutropenia. Owing to variable absorption, tolerability, cost and sensitivities of the various potential agents there is no general consensus on antifungal choice (McCoy et al, 2009).

Epstein–Barr virus and post-transplant lymphoproliferative disorder

Epstein–Barr virus reactivation post-haematopoietic stem cell transplant is specific linked to post-transplant lymphoproliferative disorder. As with CMV reactivation, early diagnosis with viral DNA quantitative PCR can decrease morbidity and mortality by detecting early reactivation before overt clinical presentation (Meijer and Cornelissen, 2008). Endogenous Epstein–Barr virus reactivation in severe immunosuppression leads to B lymphocyte proliferation, which may progress to non-Hodgkin's lymphoma. If left untreated post-transplant lymphoproliferative disorder can cause fevers, fatigue, cytopenias and lymphadenopathy. The monoclonal antibody rituximab is frequently used to lyse infected B cells if post-transplant lymphoproliferative disorder is suspected. Any possible reduction of immunosuppression is encouraged to facilitate T cell recovery.

Encapsulated bacteria

These can include *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitides*. Prophylaxis with antibiotics such as penicillin V is recommended for as long as patients receive treatment for management or prevention of graft *vs* host disease. Those who have received total body irradiation are generally treated as if hyposplenic.

Bone marrow-related complications

As well as immunosuppression for graft *vs* host disease, problems with the graft may increase or prolong infectious complications.

Secondary graft failure

Patients are managed in their specialist transplantation centre until primary engraftment has occurred. However, several factors may cause peripheral cell counts to drop after initial engraftment, including bone marrow stromal graft *vs* host disease, viral infection, e.g. parvovirus, and concurrent medications, e.g. ganciclovir for CMV reactivation. Reversible causes should be sought and if necessary 'top-up' infusions of donor haematopoietic cells can be organized. An important differential in patients with a prominent low platelet count, especially with neurological or renal pathology, is the haematological emergency of post-transplant microangiopathy. If suspected, urgent blood film examination should be performed and expert haematology advice sought.

Relapse of primary diagnosis

The highest cause of death in allogeneic transplant in both sibling and unrelated grafts is relapse of primary disease (van den Brink et al, 2010). Patients are closely monitored post-transplantation, and the range of presentations associated with relapse varies according to the primary diagnosis. The initial strategy used to treat relapse in those without significant graft *vs* host disease is to enhance the graft *vs* tumour effect of the allogeneic population of donor T cells. This may be by reducing immunosuppression or by infusing further donor lymphocytes, with a subsequent increased risk of graft *vs* host disease. Patients can also undergo a second allogeneic transplant, although this is of limited benefit owing to the risk of a secondary relapse and of transplant-related mortality.

Patients who have populations of both host and donor blood cells after transplantation (mixed chimerism) may be at higher risk of relapse, since stable chimerism suggests bidirectional immune tolerance. Such patients can be treated by donor lymphocyte infusion. Infusing non-tolerant donor T cells can break the state of tolerance in the patient, but risks inducing graft *vs* host disease.

Psychological impact

Owing to the significant transplant-related mortality and subsequent morbidity all patients must be thoroughly counseled before transplantation. Psychologists and specialist nurses are invaluable in providing support and education to patients. As well as being important for informed consent, educating patients about expected complications will aid compliance with preventative measures and lower the risk of post-transplant morbidity and recurrent hospital admissions. Patients considered high risk for non-compliance on initial psychosocial assessment may be refused transplantation if potential elevated transplant-related mortality outweighs their chances of benefitting from the transplant.

Many patients who choose a haematopoietic stem cell transplant hope for a 'cure' and a return to their original state of health. While appropriate stem cell transplantation gives patients a better chance of prolonged remission from the original diagnosis, complications may lead them to feel more unwell and spend more time in hospital than when originally diagnosed. This often has a negative impact on their mood and their relationships with family members, and health-care professionals need to support this as well as their physical state. Even when patients have a prolonged remission, they are at risk of long-term complications such as secondary malignancy, endocrine dysfunction, organ toxicity and repeated infections and infertility. A more detailed discussion of these risks is beyond the scope of this article.

Conclusions

Allogeneic haematopoetic stem cell transplantation is a highly specialized treatment, which is largely managed in centres with a great deal of experience. However, while a high proportion of transplant-related mortality is experienced in the pre-engraftment phase, many late complications contribute to haematopoietic stem cell transplant patient mortality and impaired quality of life. These are often specific to haemato-

poietic stem cell transplant because of its manipulation of the host's immune system or may be the result of cytotoxic chemotherapy regimens they have undergone before transplantation (*Table 2*). General physicians should understand the theory, presentation and management of these patients, although this is no substitute for the experience and expertise of the specialist centre, who should be contacted promptly for support and advice. BJHM

Conflict of interest: none.

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Table 2. Differential diagnosis and investigation of common presenting complaints in the bone marrow transplant patient

Presenting complaint	Differential diagnosis	Investigations
Deranged liver function tests	Drugs, e.g. azoles (transaminitis), Total parenteral nutrition, ciclosporin (obstructive) Infection – fungal, viral or bacterial sepsis Graft *vs* host disease – obstructive or hepatic picture Veno-occlusive disease	Blood cultures Ultrasound of the liver +/- Doppler Viral PCR for hepatitis A/B/C, Epstein–Barr virus, cytomegalovirus, adenovirus, varicella zoster virus, herpes simplex virus Liver biopsy – may need to be performed via a transjugular approach if low platelets or deranged clotting
Pyrexia	Fungal disease Bacterial sepsis Cytomegalovirus reactivation PTLD Relapse	Blood + urine cultures Chest X-ray +/- CT chest +/- PET Cytomegalovirus, Epstein–Barr virus, adenoviral PCR
Diarrhoea	Graft *vs* host disease Total body irradiation or chemotherapy related (early) Infection – parasitic, bacterial or viral Drug-induced – metoclopramide, foscarnet, antibiotics	Stool samples for *C. difficile* toxin, bacterial microscopy, culture and sensitivities, PCR for norovirus and adenovirus Serum cytomegalovirus, adenovirus PCR Inflammatory markers Sigmoidoscopy or colonoscopy +/- biopsies Abdominal X-ray Ciclosporin levels
Rash	Graft *vs* host disease Drug reaction Thrombocytopenia Post-transplant microangiopathy Sepsis, viral infection Secondary skin cancer (late)	Full blood count, clotting screen Blood cultures Ciclosporin levels Blood film
Shortness of breath	*Pneumocystis* pneumonia Bacterial pneumonia Invasive fungal chest infection Pulmonary embolism	Oxygen saturations on exercise Arterial blood gas sampling Chest X-ray +/- CT chest +/- CT pulmonary angiogram Sputum culture Bronchoscopy with bronchoalveolar lavage
Visual disturbance	Drug-related, e.g. ciclosporin Cytomegalovirus reactivation CNS event – haemorrhage, infarct, relapse or microangiopathy	Ophthalmology review Cytomegalovirus PCR CT head Blood film
Lymphadenopathy	Relapse PTLD Secondary malignancy (late)	Viral PCR, including Epstein–Barr virus CT/PET Histological sampling

CT = computed tomography; PCR = polymerase chain reaction; PET = positron emission tomography; PTLD = post-transplant lymphoproliferative disorder

KEY POINTS

- Allogeneic bone marrow transplantation is a growing field.
- The differential diagnosis of presenting complaints in these patients is unusual because of the manipulation of their immune system.
- Appropriate transfusion of irradiated +/- cytomegalovirus negative blood products is mandatory.
- A clear understanding of what is involved in allogeneic bone marrow transplantation and the common complications patients undergo will help prevent transplant-related mortality.
- Early liaison with the patient's specialist transplant centre is essential to ensure appropriate specialist advice and help prevent patient morbidity.