Review Article

Anaesthetic implications for bone marrow transplant recipients

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Bone marrow transplantation (BMT) has become an accepted form of therapy for the treatment of a broad range of haematological, immunological, and inherited metabolic diseases.¹⁻⁴ In many cases it offers the opportunity for cure in previously incurable disease states. Examples include refractory leukaemias, aplastic anaemia, primary immunodeficiency syndromes, several inborn errors of metabolism and, more recently, selected solid tumours. Table I contains a more comprehensive list of diseases which may be cured via BMT.

Over the past 30 yr the number of transplants performed annually as well as the number of centres participating in bone marrow transplantation have gradually increased. In the last five years, however, there has been a marked increase in the number of transplants, rising to approximately 2500 to 3000 cases registered yearly with the International Bone Marrow Transplant registry.⁴ As supportive care, including antibiotic and immunosuppressive therapies, has improved so also has the success rate of the procedure. Often during the post-transplant course, these patients may require diagnostic and therapeutic manoeuvres facilitated by regional or general anaesthesia. The BMT recipient may present many unusual challenges to the anaesthetist.

This article will review the principles of BMT and its applications, describe the unique features and idiosyncrasies of this group of patients pertaining to anaesthesia, and

review the anaesthetic management of transplant recipients at the University of Kentucky Medical Center.

Types of BMT

Bone marrow transplants can be categorized into three major groups. The first is the *syngeneic* transplant, performed between identical twins.⁵ The second is the *autologous* transplant, wherein the patient donates his or her own marrow for cryopreservation and subsequent reinfusion.^{6,7} The third group falls under the general heading of the *allogeneic* transplant. In this instance, the donor and recipient are identified according to the major histocompatibility complex (HLA) loci A, B, and D/Dr.⁹ Each locus contains two alleles; thus three pairs of alleles must be accounted for to fulfill the criteria for an histocompatible match.¹⁰ If all six alleles match and the donor and recipient are siblings, this is termed a genotypic (genetic) match. An unrelated patient and donor who

TABLE I Indications for bone marrow transplantation

Aplastic anaemia
Genetic disorders of the bone marrow
– Hurler's syndrome
– Lipidoses
– Mucopolysaccharidoses
– Osteopetrosis
– Sickle cell anaemia
– Thalassemia
Haematological malignancies
– Acute lymphocytic leukaemia
– Acute non-lymphocytic leukaemia
– Chronic myelogenous leukaemia
Other malignant disorders
– Breast cancer
– Ewing's sarcoma
– Lymphoma (Hodgkin's and Burkitt's)
– Multiple myeloma
– Myelofibrosis
– Small-cell lung cancer
– Neuroblastoma
– Testicular cancer
Paroxysmal Nocturnal Haemoglobinuria
Severe Combined Immunological Deficiency

Key Words

ANAESTHESIA: transplantation, bone marrow;
IMMUNE RESPONSE.

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share the same alleles are termed phenotypically matched (an unrelated matched transplant).^{11,12} A mismatched (haploidentical) transplant is one in which disparity exists between the HLA antigens, whether the patients are or are not related.¹³

Currently the most common type of transplant is the genotypic, HLA identical, sibling transplantation. There is, however, an increasing utilization of autologous transplants, both for solid tumours and haematological malignancies.⁷

Pre-transplant evaluation

The candidate for bone marrow transplantation must meet a number of criteria to be approved for the procedure. One important concern is that the primary disease process must be remittable. In the case of a marrow-based disorder, neoplastic or genetic, remission can be achieved by ablation of the bone marrow. For solid tumours, the attempt at cure may secondarily result in marrow failure. Regardless of the diagnosis, the common feature is the necessity for bone marrow transplantation to restore haematological and immunological function. Another concern in the evaluative process is the patient's general health. The prospective BMT recipient should, apart from the primary diagnosis, be healthy and without major organ dysfunction. This stipulation arises because a number of sequelae may be incurred as a result of the procedure. Major pre-existing disease, such as congestive heart failure, chronic obstructive pulmonary disease, or renal insufficiency, could be exacerbated to preclude a favourable outcome. A strategy for bone marrow donation must be composed. The autologous donor should be free of active disease and have functioning bone marrow. Allogeneic recipients must be paired with the donor to provide the best HLA match. This may entail screening multiple individuals. Ultimately, the donor must agree to undergo a procedure which is not without risk. Finally, the psychological and social mechanisms necessary to support the endeavour must be verified. The patient and close family must understand the nature of the procedure and commit the energies needed to ensure success.

Screening of the patient may take several weeks. The formal protocol includes a variety of tests and other evaluations. A summary of the required data may be found in Table II. This is reviewed by a committee which is usually staffed by transplant haematologists/oncologists, a blood-bank pathologist, an immunologist, psychologists and social workers, and nursing personnel. When the results of the evaluation are sufficient, preparations for transplantation can be initiated.

Bone marrow harvesting and transplantation

The bone marrow harvest is a procedure requiring either

TABLE II Pre-transplantation evaluation

Cardiac
– Electrocardiogram
– Nuclear ejection fraction
Dental
– Evaluation and indicated therapy
Haematological
– Bone marrow biopsy and aspirate
– Complete blood count
Hepatic
– Liver function tests
Neurological
– Cerebrospinal fluid analysis
– Magnetic resonance imaging – Brain
Psycho-social
– Evaluation
Pulmonary
– Chest radiograph
– Pulmonary function tests
Renal
– Serum electrolytes
– Twenty-four hour creatinine clearance
– Urine analysis

general tracheal or spinal anaesthesia. Rarely, the harvest may be completed utilizing analgesia and local anaesthesia.¹⁴ After initiation of adequate anaesthesia, the patient is placed in the prone position. The procedure may take as little as 15 minutes or as long as several hours. Up to 1.5 L of marrow may be harvested via multiple aspirations obtained from the posterior iliac spines and iliac crests. Clinical experience indicates that the larger the quantity of marrow harvested the greater the amount of peripheral blood coincidentally extricated. Thus, sizeable volumes of fluid replenishment are often required and the use of two large bore peripheral IV's is recommended. Blood replacement may also be necessary, either with autologous blood transfusions or via reinfusion of separated red cells obtained during the harvest.¹⁵ The decision to place a Foley catheter would be predicated on the donor's general health, the anticipated duration of the procedure, and the estimated volume of bone marrow to be harvested. Various descriptions of bone marrow harvesting have been published.^{16,17}

After the marrow is harvested, any of several processing techniques may be used. In the case of an autologous donation, monoclonal antibody may be incorporated to facilitate eradication of malignant cells.¹⁸ T-cell depletion may be carried out in allogeneic transplants to reduce graft-versus-host effects.¹⁹ Red cells may have to be extricated in the case of ABO incompatibility.²⁰ Processing may take from two to twelve hours. The marrow, if manipulated, will be condensed usually to a volume of less than 200 ml. Unmanipulated marrow volumes may include quantities up to 1000 to 2000 ml. After the

material is prepared for transplantation it is infused through an indwelling central venous line. From the central circulation the marrow stem cells will pass to various bone marrow beds which provide the microenvironment necessary for maturation and differentiation.

Regardless of the type of transplant performed, the recipient must undergo a preparative regimen designed to achieve functional bone marrow ablation. This is carried out over 7–10 days, traditionally utilizing combinations of chemotherapy and radiation.² Rescue with the transplanted marrow is then initiated. Protective isolation is continued through the immediate post-transplant period. Time to engraftment is generally 10–28 days. Engraftment is confirmed by following daily peripheral cell counts and verified with bone marrow aspiration and biopsy, usually at two and four weeks. Haematological support is necessary while awaiting engraftment. Platelet transfusions, often daily, may be required to maintain a minimum value of $20,000 \cdot \text{mm}^{-3}$. Red blood cells (leukocyte poor, irradiated) are transfused as necessary to maintain a haematocrit of at least 25 per cent.

Complications of BMT

Complications associated with transplantation are varied. Many disturbances are specific to the BMT population, while some effects are more general and are associated with other immunodeficiency and oncological processes. Multiple sequelae are incurred as a result of the preparative regimen. Another complicating factor is the inherent immunodeficiency associated with the procedure.²¹ The majority of untoward effects, however, pertain to graft-versus-host disease (GVHD).²²

The preparative regimen consists of total body irradiation (TBI) administered in combination with one or more chemotherapeutic agents. TBI readily leads to gastrointestinal toxicity, including oral mucositis, nausea/vomiting and diarrhoea. Pulmonary fibrosis, restrictive cardiomyopathy, and cataract formation are later sequelae of radiation exposure. Chemotherapeutic agents can cause several side-effects (Table III). Cardiac, pulmonary, gastrointestinal and haematological insults may be identified. The transplant protocol utilized for each patient will specify the total radiation dosage and chemotherapeutic agent(s) to be administered. All transplant recipients have longstanding immunodeficiency²¹ and are susceptible to infection. T-cell deficiency may lead to viral and fungal infestation and B-cell incapacitation may result in immunoglobulin deficiency and the risk of gram-positive bacterial infection.²⁵ Table IV contains descriptions of the commonly encountered pathogens and the most likely times during the transplantation process when these may be seen.^{26,27}

Graft-versus-host disease is a constellation of signs and

TABLE III Preparative chemotherapeutic agents and associated sequelae*

Busulfan (Myleran)
– Diarrhoea
– Nausea/vomiting
Carmustine (BCNU)
– Diarrhoea
– Interstitial pulmonary fibrosis
– Nausea/vomiting
Cisplatin
– Central and peripheral nervous system toxicity including ototoxicity
– Nausea/vomiting
– Renal insufficiency
Cylophosphamide (Cytosan)
– Dilated cardiomyopathy
– Haemorrhagic cystitis
– Interstitial pulmonary fibrosis
Cytosine arabinoside (ARA-C)
– Nausea/vomiting
Daunorubicin (Daunomycin)
– Congestive cardiomyopathy
– Dysrhythmias
– Nausea/vomiting
Etoposide
– Diarrhoea
– Nausea/vomiting
Melphalan (L-PAM)
– Interstitial pulmonary fibrosis
Mitomycin-C
– Diarrhoea
– Interstitial pulmonary fibrosis
– Nausea/vomiting
– Renal insufficiency
Thiotepa
– Nausea/vomiting

*All agents possess the potential for bone marrow suppression (leukopenia, thrombocytopenia, anaemia) and oral mucositis.

TABLE IV Infective agents

Early (day 0 – day 21)	Staphylococcus aureus Staphylococcus epidermidis Streptococcus species Escherichia coli Klebsiella pneumoniae Pseudomonas aeruginosa Herpes simplex
Middle (day 22 – day 100)	Corynebacterium species *Cytomegalovirus *Pneumocystis carinii Staphylococcus epidermidis
Late (after day 100)	Streptococcus pneumoniae Haemophilus influenzae Neisseria meningitidis Varicella zoster

*Interstitial pneumonitis.

symptoms which comprise the hallmark side-effect of allogeneic transplantation. It occurs when immunocompetent T-lymphocytes are injected into an immunosuppressed host. The reaction involves both cytotoxic injury to target organ systems as well as the release of various lymphokines. It is divided into acute and chronic forms.²⁹ The acute disease is present most commonly between days 10 and 100 after transplantation. It represents a more aggressive and cytotoxic reaction than chronic graft-versus-host disease which either follows the acute disease or appears *de novo*, and tends to occur between days 100 and 400 after transplantation. It has the characteristics of an autoimmune disease.^{29,30} GVHD can involve any organ system, although skin, liver, and the alimentary canal are classically affected. In addition, graft-versus-host disease is immunosuppressive, which further increases the risk of infection.²⁵ Initial therapy with high-dose corticosteroids can often attenuate the GVHD response. Anti-rejection drugs such as azathioprine and cyclosporine have a proven role in the prophylaxis and treatment of this disorder.³¹ Table V contains a list of the clinical effects associated with GVHD.²⁸

Other risks associated with BMT include graft failure and recurrence of malignancy. Venocclusive disease of the liver (VOD) is a unique complication of high-dose chemoradiotherapy.³² Its primary features are direct

hyperbilirubinaemia, right upper quadrant pain, and weight gain. Fever, often unremitting and to levels of 105° F, may be a sign of infection, GVHD, or an immunological reaction. Cytokines, including Interleukin-1 and Tumour Necrosis Factor, may prove to be the cause of an immunologically mediated febrile response.³³ Intravenous access is often not a problem because a central venous indwelling catheter is usually maintained for six to twelve months after transplantation. This provides the route for extended transfusion, antibiotic, and immunosuppressive therapy as indicated by clinical progress.

Pre-operative assessment and anaesthetic management

These patients have a complicated medical history, may be taking a variety of medications (steroids/immunosuppressives, antibiotics, sedatives/anxiolytics), and may have multiple organ system dyscrasias. Thus, a methodical review of the history and a carefully directed physical examination will allow for the planning and delivery of a safe anaesthetic.

The standard historical information pertinent to any anaesthetic should be reviewed. The imminent surgical diagnosis and all facts critical to this must be known. Drug allergies, current medications and dosages, previous anaesthetics, past medical and surgical histories, and significant social data should be recorded. A review of systems is essential and should incorporate all historical data which are specific to the BMT population. The primary diagnosis which necessitated transplantation as well as all past treatment for the disease should be reviewed. The protocol utilized for the preparative regimen and the total dosages of all agents employed are important. The relationship between examination and transplantation is important because sequelae may arise during the preparative phase, or early and late post-transplantation phases (see Complications of BMT).

The physical examination should begin with assessment of vital signs, including blood pressure, pulse, respiratory rate, and temperature. Orthostatic haemodynamic changes should be anticipated. Febrile patients require 100–150 ml additional fluid per day for each degree greater than 37° C.³⁴ Quantification of recent intake (oral, IV) and output (emesis, stool, urine) is important. The examination should be directed to all major organ systems. Surveillance for complications arising from the primary diagnosis and treatment, the preparative regimen, and graft-versus-host disease must be kept in mind.

Gastrointestinal dyscrasias may present at any time during the transplant process and may have an impact on anaesthesia. They may arise from radiation exposure, chemotherapy, or GVHD and include oral mucositis,

TABLE V Graft versus host disease

Cutaneous
– Impaired thermoregulation
– Scleroderma-like syndrome
– Ulceration and infection
Eye
– Cataracts
Gastrointestinal
– Diarrhoea with fluid/electrolyte/blood loss
– Oesophageal infection and ulceration
– Oral ulceration and mucositis with propensity for invasive oral candidiasis
Hepatic
– Acute and chronic hepatitis with coagulopathy
– Impaired drug metabolism
Marrow
– Early
– pancytopenia and immunodeficiency (preparative regimen versus acute GVHD)
– Late
– pancytopenia and immunodeficiency (viral infection versus chronic GVHD)
Pulmonary
– Bronchiolitis obliterans
– Interstitial pneumonitis
– Pulmonary fibrosis
Renal
– Insufficiency with electrolyte abnormalities
– Renal tubular acidosis

oro-pharyngeal candidiasis, and oesophageal ulcerations and infection.^{35,36} Persistent nausea and vomiting may also be present. Peptic ulcer disease can develop in the chronically ill patient and GVHD gastrointestinal effects may potentiate this. GVHD of the colon may precipitate intractable diarrhoea and haematochezia. Parenteral hyperalimentation is often utilized in the presence of active gastrointestinal disease. During the preoperative evaluation careful examination of the oro-pharynx is recommended. If oesophageal disease is present, one may be advised to avoid oesophageal stethoscopes. Active peptic ulcer disease should warrant antacid use and airway protection during induction of anaesthesia and at tracheal extubation. Rectal temperature probes should not be used. Emesis and diarrhoea may result in intravascular volume depletion and electrolyte abnormalities. Therefore, a preoperative review of the haematocrit and serum electrolytes is necessary.

Hepatic insufficiency is often encountered, from graft-versus-host or venocclusive disease. The tests of liver function assess cellular integrity (alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase), detoxification (ammonia, direct bilirubin), excretion (total bilirubin), and synthesis (albumin levels, cholesterol levels, prothrombin time).³⁷ Hyperbilirubinaemia (direct) will be found with active VOD. Hepatic GVHD may alter transaminases, albumin levels, and the prothrombin time. In the patient with active hepatic disease, any medication utilized for anaesthesia which is metabolized and excreted via the liver may have prolonged effects. Coagulopathy should be anticipated when planning regional anaesthetics. A preoperative review of the liver function tests and the coagulation profile is warranted.

While the integument may be affected by radiation exposure, the most prominent changes will result from GVHD. Incapacitating chronic pruritus, necessitating antihistamine, anxiolytic, and narcotics, may be seen. All ulcers must be protected and any other sites prone to breakdown should be secured. Impaired thermoregulation should be anticipated, and the means for maintaining an acceptable body temperature must be available.

The cardiac insults associated with BMT are almost exclusively attributable to the preparative regimen. Congestive cardiomyopathy may result from specific chemotherapeutic agents and is dose-dependent.² The restrictive cardiomyopathy arising from radiation exposure is also dose-related. The signs and symptoms of these types of cardiac dysfunction are well known.³⁴ If there is evidence to incriminate any preparative agent, an electrocardiogram and/or echocardiogram may be needed. The haemodynamically unstable patient may require invasive monitoring perioperatively.

Pulmonary deficiencies arising during transplantation can be important with regard to anaesthesia. An obstructive defect developing from GVHD-incited bronchiolitis obliterans may lead to CO₂ retention.³⁸ The restrictive pulmonary sequelae which develop as a result of exposure to radiation therapy or specific chemotherapeutic agents could also lead to difficulty with anaesthesia.³⁹ The threat of pulmonary infection, bacterial or viral, is continuous. During the preoperative examination, auscultation of the lungs is necessary to identify localized findings. If tachypnoea, dyspnoea, or abnormal auscultatory findings are found, a preoperative chest radiograph, arterial blood gas analysis, and pulmonary function testing should be considered.

Renal insufficiency, while not a direct result of BMT *per se*, is encountered and usually develops as other complications arise. A hypotensive insult may occur secondary to overwhelming sepsis or hypovolaemia. Nephrotoxic antimicrobial drugs, including aminoglycosides and amphotericin B, are often utilized to combat various infections. Acute urinary tract obstruction may develop as a result of cyclophosphamide-induced haemorrhagic cystitis. On this basis, a review of the serum electrolytes, the blood urea nitrogen and serum creatinine, and analysis of a urine specimen is advised. Careful assessment of volume status is important.

Bone marrow deficiency will be evident at any time after initiation of the preparative regimen. Attenuation of both haematopoietic and immunologic reserves will be seen. These defects can impact anaesthetic planning and management. Pancytopenia can arise from the preparative regimen, viral infection, or GVHD.²⁹ Thrombocytopenia may preclude regional anaesthesia. Anaemia may be clinically important and, if perioperative transfusions are necessary, leukocyte-poor irradiated blood products should be used. Exogenous white blood cell exposure is potentially detrimental as this may exacerbate graft-versus-host disease. Thus the use of washed red blood cell preparations and/or commercially available white blood cell filters is advised. Preoperatively, a complete blood count including platelets is indicated.

Bone marrow immunodeficiency demands extreme measures to prevent exposure to and transmission of infective agents. Operating room personnel having direct contact with these patients should use gloves, masks, and caps. Unnecessary nasal, rectal, and urethral probes should be avoided. Temperature monitoring should be carried out via oro-pharyngeal or axillary probe placement. The use of bacterial filter attachments for anaesthesia machines is controversial.³⁷ The risk of infection from invasive monitoring must be weighted against the benefits to be gained.

The use of inhalational anaesthetic agents in patients

with bone marrow dysfunction is debated. Various studies have shown both cell-mediated and humoral attenuation arising from volatile agent exposure.⁴⁰⁻⁴² Further, the debate regarding the bone marrow suppressive effect of nitrous oxide is unresolved.⁴³ As no definitive information is presently available, the clinician is left to decide which of the inhalational agents are to be used.

Basic laboratory data (complete blood count and serum electrolytes) are reviewed daily and liver function studies once a week. Patients receiving amphotericin B have the serum magnesium concentration measured periodically. All patients with ongoing fever have cultures of blood, sputum, and urine regularly and x-rays of the chest and sinuses.

The choice of anaesthesia technique is based on the usual standards of clinical practice. Most types of anaesthesia can be used. It should be remembered that the bone marrow recipient is immunosuppressed and, potentially, has multi-system disease.

Anaesthetic review

Pertinent data gathered from all available records in our institution included age and gender, date, procedure, ASA classification, anaesthetic techniques and agents, and pre- and post-anaesthetic course. A total of 160 patient records was reviewed, covering the period from September 1982 through December 1987. In this series, 42 patients (25 male, 17 female) underwent a total of 58 anaesthetics. Ages ranged from one year to 55 years.

Procedures varied widely and involved all surgical specialties. Table VI depicts a complete review. Of the 58 anaesthetic cases evaluated, general tracheal anaesthesia was utilized in all but four. Mask general anaesthesia was employed on two occasions, once for bladder cystoscopy and once for manipulation of a Hickman catheter in a child. Regional techniques were used twice. One tetracaine subarachnoid block was performed for cystoscopy and one lidocaine epidural anaesthetic was utilized for Caesarean section. Induction agents for general anaesthesia included thiopentone, ketamine, diazepam, lorazepam, midazolam, alfentanil, and fentanyl. To facilitate intubation, muscle relaxation was achieved variably with atracurium, pancuronium, succinylcholine, or vecuronium. Maintenance inhalational agents included enflurane, halothane, isoflurane, and nitrous oxide. Invasive monitoring was used infrequently. Only two patients required placement of radial and pulmonary artery catheters. These were necessary because of haemodynamic instability arising from overwhelming sepsis in one case, and intravascular volume depletion secondary to a bleeding gastric ulceration in the other. Following the completion of surgery, most patients recovered either in a protective isolation room in the Post-Anaesthesia Care Unit (PACU)

TABLE VI Operative procedures

Cardiothoracic
- Open lung biopsy
- Pericardial biopsy
ENT
- Incision and drainage of peritonsillar abscess
- Nasal septum debridement/Caldwell Luc procedure
- Tracheal intubation for epiglottitis
General surgery
- Cholecystectomy
- Hemicolectomy
- Hickman catheter
- Laparoscopic liver biopsy
- Open liver biopsy
- Tenckhoff catheter
- Tracheostomy
- Vagotomy with ulcer oversewing
Neurosurgery
- Craniotomy for intracerebral haematoma
- Omax reservoir
- Open brain biopsy
- Paediatric cerebral angiography
OB-GYN
- Caesarian section
- Ovarian cystectomy
Urology
- Cystoscopy
- Open renal biopsy
- Percutaneous nephrostomy tube

or in their own room on the Bone Marrow Transplant Unit. Patients transported directly from an intensive care unit to the operating room generally recovered in the ICU of origin.

No intraoperative deaths occurred. All patients survived a minimum of 72 hr after the procedure. Four patients died within one week of an operation from overwhelming sepsis which was not related to the operative/anaesthetic procedures. Aetiological agents included bacterial, viral, and yeast species. No major anaesthetic complications were noted on any anaesthetic records nor were any identified in the post-anaesthetic notes.

Conclusion

The bone marrow transplant recipient is unique. Multiple sequelae may arise as a result of the procedure and many of these effects may be pertinent to the planning and administration of anaesthesia. The results indicate that knowledge of these idiosyncrasies accompanied by careful and directed evaluation of each patient should permit the delivery of safe anaesthesia.

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