Editorial

Bone marrow transplantation and the lung

Bone marrow transplantation is a remarkably easy technical procedure with enormous therapeutic potential, which is as yet only partially tapped because of a paucity of suitable donors and a high complication rate. Nevertheless the procedure offers the hope of curing the many and diverse clinical disorders that result from malfunction of the progeny of haemopoietic pluripotential stem cells. The technique is capable of restoring normal haematological function in primary red cell, white cell, or platelet disorders after ablation of aberrant cells and can be used to rescue patients with marrow failure secondary to chemical or radiation insult. Immunological competence can be restored as grafted haematological stem cells are able to differentiate into T and B lymphocytes. Possibly many immunological disorders will be treated with bone marrow transplantation in the forseeable future. Bone marrow transplantation is also being studied as a form of treatment for metabolic disorders, including mucopolysaccharidoses, Gaucher’s disease, and adenosine deaminase deficiency. By means of a graft of normal stem cells into an affected patient erythrocytes, granulocytes, and macrophages are produced and normal enzymes are manufactured, which then diffuse into enzyme deficient tissues. In 1986 two major difficulties, graft versus host disease and pulmonary damage, limit the widespread exploitation of bone marrow transplantation.

Graft versus host disease is thought to result because donor T lymphocytes recognise the recipient’s tissues as foreign and, by mounting an immune response, damage them. In the first 100 days acute graft versus host disease presents as a rash, often accompanied by evidence of damage to the gut and liver, in 25–75% of patients. Later, chronic graft versus host disease may present by mimicking multiorgan autoimmune disease with rash, oral and ophthalmic sicca syndrome, hepatic damage, immune deficiency, and opportunistic infections. This may follow acute graft versus host disease or may occur de novo. For the accurate diagnosis of graft versus host disease biopsy and histological examination of the affected organ is required. Despite increasing understanding of histocompatibility determinants and recent advances in manipulating T cell function, in most centres bone marrow transplantation is confined to patients who have sibling donors who are HLA-AB-Dr identical and whose lymphocytes are non-reactive in mixed lymphocyte culture. But even when it becomes commonplace to transplant from unrelated histocompatible donors lung damage will continue to complicate and prejudice the clinical course of the patient with a bone marrow transplant. The lung complications described in patients with bone marrow transplant are very diverse (table). The greatest threat after transplantation is interstitial pneumonitis, which in both American and European series has complicated recovery in up to one third of all patients treated and has had a mortality rate of nearly 75%. In over a half of all these patients active cytomegalovirus infection has been present.

Bone marrow transplantation is at present generally performed for patients with aplastic anaemia and haematological malignancies, acute lymphoblastic leukaemia, acute myeloid leukaemia, and chronic granulocytic leukaemia. Where appropriate these conditions are treated by allotransplant. Marrow is harvested from a histocompatible sibling and transplanted into the patient, who is preferably aged less than 45 years since the incidence of graft versus host disease increases substantially with age. The best results in acute lymphoblastic and acute myeloid leukaemia are obtained when the patient is in haematological remission with no overt disease in bone marrow or

Early complications (within 100 days of bone marrow transplantation)

1 Pulmonary oedema
   (a) Fluid overload
   (b) Myocardial damage
   (c) Acute haemorrhagic—cyclosporin toxicity
2 Adult respiratory distress syndrome
   (a) Septicaemia
   (b) Idiopathic
3 Bronchopneumonia
   (a) Bacterial
   (b) Fungal
4 Interstitial pneumonitis
   (a) Idiopathic (perhaps due to effect of cytotoxic drugs and irradiation)
   (b) Infective—cytomegalovirus, pneumocystis, etc
5 Pulmonary embolism

Late complications (after 100 days from bone marrow transplantation)

1 Bronchopneumonia
2 Interstitial pneumonitis
3 Restrictive lung disease
4 Bronchiolitis obliterans

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cerebrospinal fluid. In chronic granulocytic leukaemia bone marrow transplantation is undertaken in the early stable phase when little cytotoxic treatment has been used. Immediately before transplantation the patient is conditioned with high doses of cytotoxic treatment, which in aplastic anaemia may include horse or rabbit antihuman antithymocyte immunoglobulin, to which is added in most cases of haematological malignancy total body irradiation. With adequate preparation, graft rejection and continuing marrow failure are not seen. After two to three weeks of peripheral blood pancytopenia marrow engraftment ensues. Respectable peripheral blood counts become self sustaining after about one month. Restoration of full immunocompetence may take several years, T cells remaining phenotypically and functionally immature, immunoglobulin concentrations low, and antibody levels reduced. The major threat of infection, however—from various bacterial, fungal, viral, and protozoal organisms—comes within the first six months. Prophylaxis against graft versus host disease with methotrexate administration was pioneered in Seattle, although in recent years many centres have used cyclosporin. Recently encouraging results have been claimed for T cell depletion of donor marrow.

Pretransplantation pulmonary function

In any attempt to assess the importance of pulmonary complications after bone marrow transplantation it is important to recognise that despite the absence of clinical disease patients with leukaemias and aplastic anaemia often have abnormal pulmonary function before transplantation. In addition, the very different diseases treated with bone marrow transplantation have widely different clinical courses before bone marrow transplantation. For example, a patient with acute myeloid leukaemia may have had a very large number of episodes of both septicaemia and pneumonia before bone marrow transplantation. In contrast, a patient who has a marrow transplantation because of chronic granulocytic leukaemia may never have had an infection. The extent and nature of antibiotic treatment before transplantation varies widely between different disorders and between individuals. Blood component treatment may or may not have been substantial and in some diseases cytotoxic chemotherapy needs to be considered as a possible cause of lung disorder in its own right. Busulphan is used extensively in the treatment of chronic granulocytic leukaemia and was first reported to cause pulmonary fibrosis in 1961. Acute myeloid leukaemia is treated with anthracyclines (daunorubicin and adriamycin), which are associated with cardiac rather than pulmonary toxicity; and the antimetabolites cytosine arabinoside and thioguanine are infrequently implicated as pulmonary toxins. Acute lymphoblastic leukaemia is treated with vincristine and prednisolone, which cause little lung damage by themselves; but to these drugs are added the pulmonary toxic antimetabolites mercaptopurine and methotrexate. In the conditioning programme immediately before bone marrow transplantation large doses of the alkylating agents cyclophosphamide or melphalan are used. Such drugs in small, long term doses have been associated with substantial subclinical lung damage, but the effects of acute dosing remain to be determined. Cytotoxic agents damage pulmonary endothelial cells, which make up 40% of the lung cells and have a turnover rate of 1% a day in the steady state, with a potential for accelerated growth when damaged. It is thus imperative, when the occurrence of pulmonary toxicity after bone marrow transplantation is being assessed, that previous cytotoxic treatment and radiation are taken into account.

Total body irradiation with doses of the order of 10 Gy (1000 rads) is used to condition patients for bone marrow transplantation. In animal studies radiation of this order is associated with increased vascular permeability, alveolar wall oedema, and alveolar protein leak, with gross loss of lung surfactant. Seven to 28 days after irradiation alveolar macrophages become reduced in number, pneumocytes degenerate, and hyaline membranes form. Several months later cellular hyperplasia and fibrosis develop. Attempts to minimise radiation damage have centred on fractionating the treatment and using low dose rates. High dose pulmonary irradiation results in considerably reduced diffusing capacity for the first three months followed by possible minor improvements over a couple of years. When cytotoxic chemotherapy has not been used, as with some solid tumours, radiation to the lungs is rarely associated with appreciable changes in lung volume, forced vital capacity (FVC), forced expiratory volume in one minute (FEV1) or the FEV1/VC ratio. But in the long term survivors of bone marrow transplantation who have been conditioned with high dose chemotherapy and irradiation restrictive and obstructive lung disease is being described (see below).

In studying the effect upon pulmonary morbidity of allograft transplantation between histocompatible siblings and even unrelated donors it will be important to take into account the experience being gained by using conditioning regimens in which irradiation is replaced by additional chemotherapy.

Complications after transplantation

Perhaps the earliest pulmonary complication of bone marrow transplantation is the rapid onset of pul-
monary oedema associated with volume overload and cardiac dysfunction attributable to previous anthra-
cycline and cyclophosphamide treatment and irra-
diation. These causes must be distinguished from
acute haemorrhagic pulmonary oedema associated
with reduced central venous pressure, fluid retention,
hypoalbuminaemia, hypotension, and incipient renal
failure.\textsuperscript{14,32} Histologically, intra-alveolar and occa-
sonally interstitial oedema fluid is seen with red cells
and fibrin exudation, but no pneumocyte abnormal-
ities are recognisable. This complication has a high
mortality rate and occurs characteristically in patients
receiving mismatched transplants and high doses of
cyclosporin. The adult respiratory distress syndrome
has also been described in allogeneic matched sibling
transplants for chronic granulocytic leukaemia.\textsuperscript{33}
What causes the pulmonary endothelial damage in
these severely neutropenic patients remains unclear
as, in this context, neutrophil derived oxidant pro-
ducts seem unlikely to play a part in adult respiratory
distress syndrome.

Any patient with pancytopenia and immuno-
suppression is susceptible to infection\textsuperscript{34} and almost
all of these patients have indwelling central venous
catheters and many receive parenteral nutrition.
Bronchopneumonia associated with few radiological
signs when neutrophil counts are low is generally bac-
terial in origin\textsuperscript{35} and Gram positive organisms often
sensitive only to vancomycin are surprisingly com-
mon. Pneumonias developing in the neutropenic
patient receiving broad spectrum antibiotics may be
due to fungi, among which \textit{Candida albicans}, \textit{Asper-
gillus fumigatus}, and the fungi causing mucormycosis
are the most common. Recently lobar pulmonary
aspergillosis has been linked with sinusitis.\textsuperscript{36}

**INTERSTITIAL PNEUMONITIS**

Dyspnoea, non-productive cough, fever, widespread
crackles, bilateral fluffy infiltrates on the chest radi-
ograph, and hypoxia suggest interstitial pneu-
monitis.\textsuperscript{9–13} Diagnosis has been improved by cyto-
logical, bacteriological, and virological examination
of bronchial lavage fluid\textsuperscript{37} to exclude an infectious
cause, which is demonstrable in half of all cases.
Pathologically, interstitial pneumonitis has been
divided into three types depending on the presence
of cytomegalovirus inclusion bodies and type II
pneumocyte atypia and hyperplasia.\textsuperscript{14}

Cytomegalovirus is the major concern. It accounts
for most cases of infective interstitial pneumonitis
after bone marrow transplantation and character-
istically presents six weeks after grafting. It has an
alarmingly high mortality rate of about 90\%.\textsuperscript{9,10} We
must hope that with improvements in early diagnosis
afforded by detection of the expression of early cyto-
megalo virus antigens\textsuperscript{38} and the development of inno-
vative antiviral agents\textsuperscript{39} improvements in outlook
will occur. The major source of infection is almost
certainly reactivation of latent cytomegalovirus in the
profoundly immunosuppressed recipient of a bone
marrow graft but the contribution of exogenous
infection from donor marrow and blood products
should not be overlooked.\textsuperscript{40} Ideally the recipient
negative for cytomegalovirus antibody should receive
marrow and concentrates negative for cytomegalo-

\textit{...
to eight equal fractions, to a total of 12–15 Gy (1200–1500 rads) overall are delivered as opposed to a single dose of 10 Gy. In the larger registry series such discriminants were not evident, but high radiation dose rates in patients receiving methotrexate seem to be harmful.9

PULMONARY EMBOLISM
During marrow harvest fat and bone fragments will inevitably be collected and subsequently infused. Transient hypoxia may occur but no long term parenchymal damage seems to ensue.46 47 Nevertheless abnormalities of pulmonary vasculature are being recognised with endothelial changes and intimal thickening predisposing to thrombosis of the arterioles, capillaries, and venules that presumably reflects radiation damage.14 Pulmonary veno-occlusive disease may masquerade as interstitial pneumonitis48 and, intriguingly, fat embolisation has been seen as a late complication of bone marrow transplantation.49

RESTRICTIVE AND OBSTRUCTIVE LUNG DISEASE
Among the later complications of bone marrow transplantation restrictive and obstructive defects of ventilatory function have been reported in subjects who have had pretransplantation conditioning with high dose chemotherapy and irradiation. In over 300 patients with marrow transplants studied in Seattle a mean loss of 0.81 litres of total lung capacity, 0.54 l of vital capacity, and 4.4 ml/min/mm Hg of diffusing capacity (1.5 mmol min⁻¹ kPa⁻¹ of transfer factor) was evident one year after transplantation.15 In most patients these changes improved over the next three to four years. Obstructive lung disease seems to become more prominent with the passage of time. Reduction in FEV₁/VC to less than 50%, 60%, and 70% predicted was seen in 0%, 2%, and 11% at three months but in 8%, 18%, and 29% by three years. Unfortunately the pathological findings in patients reported in this study are unknown. What is causing such lung damage remains something of an enigma, since severe obstruction was not attributable in this series to previous whole body irradiation, interstitial pneumonitis, or chronic graft versus host disease.

GRAFT VERSUS HOST DISEASE AND BRONCHIOLITIS OBLITERANS
The relationship between graft versus host disease and the lung remains uncertain. Although several pulmonary entities have been linked with graft versus host disease, definite evidence that these are true manifestations of graft versus host disease is lacking. Lymphocytic bronchitis with the histological demonstration of lymphocytic infiltration of the bronchial mucosa, loss of cilia and goblet cells, and even necrosis of mucosa and submucosa has been described as a postmortem finding in 25% of patients dying after bone marrow transplantation.50 Many patients having had cough and dyspnoea. Recent studies suggest that these findings relate poorly if at all to the presence of graft versus host disease and are probably due to earlier chemotherapy.51 Lymphocytic interstitial pneumonitis has also been reported as a late complication of bone marrow transplantation,52 but the relationship of such an entity to graft versus host disease is uncertain and further studies of the lungs of patients with no other evidence of graft versus host disease are needed. In 1982 the first cases of severe irreversible airways obstruction occurring within five months of bone marrow transplantation and in the context of chronic graft versus host disease were reported.53 The chest radiograph may be normal, but hyperinflation flat diaphragms and pneumothoraces have been reported, in association with reduced elastic recoil pressure. Histological appearances are those of bronchiolitis obliterans. The clinical course is variable. Treatment with corticosteroids and azathioprine may be of benefit, although the mortality rate remains high.53–58 Workers in one centre contend that as many as 13% of all recipients of marrow grafts have this complication.54 Its aetiology may be multifactorial, and it may not necessarily be directly attributable to graft versus host disease itself but may result from recurrent infection or recurrent gastrooesophageal regurgitation. Others contend that it is related to the fibrotic chronic mucositis of the mouth and oesophagus seen in many cases of chronic graft versus host disease.

The contributions, if any, of graft versus host disease and its prophylaxis to pulmonary sequelae after BMT may become clearer by studying the patient who has received an autotransplant. Here marrow is harvested from the patient himself, preserved, and reinfused after intensive chemotherapy or radiation therapy (or both) has been used to control resistant disease. The patient is rescued from bone marrow failure by his own marrow. Such treatment is of potential use in the treatment of solid tumours and is being explored in haematological malignancies, particularly where resistant disease is present in sanctuary sites.

The seriousness of pulmonary damage to patients who have bone marrow transplantation must not be underestimated. Many further studies are needed. Sufficient numbers of patients with similar underlying disorders must be studied. Investigations must detail pretransplant pulmonary function, previous infections, chemotherapy, radiotherapy, transfusions, and smoking history. Sequential assessment of pulmonary function must be performed in relation to clinical events and combined with detailed bacteriological and virological monitoring. Episodes of graft versus
host disease need to be defined in terms of biopsy changes in relevant tissues. Many more reports of lung biopsy material studied by histological and immunohistochemical means are needed in conjunction with evidence of intensive search for infective organisms, particularly viruses. In this way the causes of pulmonary morbidity may be determined more precisely and the way prepared for prevention and the realisation of the wider application of bone marrow transplantation.

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