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EDITORIAL

Obliterative bronchiolitis in haematopoietic stem cell transplantation: can it be treated?

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Allogeneic and autologous haematopoietic stem cell (HSC) transplantation are now both established as principal forms of treatment for patients with acute or chronic leukaemia, aplastic anaemia and various immunodeficiency syndromes, as well as various nonhaematological malignancies and auto-immune disorders [1–3]. However, major limitations to the successful use of HSC transplantation include respiratory complications and graft *versus* host disease. Lung dysfunction occurs in up to 50% of subjects after HSC transplantation, and pulmonary complications are among the most common causes of morbidity and mortality after this procedure [4].

Obliterative bronchiolitis (OB) is the most common noninfectious respiratory complication after HSC transplantation [5, 6], and usually develops as a late complication (after the first 100 days) and at the same time as chronic graft *versus* host disease develops. The onset of OB is usually 6–12 months post-transplant, with the clinical severity ranging from asymptomatic to fulminant and fatal. The lack of a precise definition and uniform diagnostic criteria has led to variations in the reported incidence, between 0 and 50%, with commonly quoted figures being between 5 and 20% [7, 8]. Although OB has been described after autologous HSC transplantation [9], this is a rare complication, a fact usually attributed to the absence of chronic graft *versus* host disease after autologous HSC transplantation.

The most commonly identified risk factor for OB after HSC transplantation is chronic graft *versus* host disease, but other risk factors include human leukocyte antigen mismatch or use of an unrelated donor, use of busulfan or methotrexate, increased age, male sex, cigarette smoking and the presence of airflow limitation prior to transplantation [6, 8, 10]. The pathophysiology is incompletely understood, but, given its strong association with chronic graft *versus* host disease, it is believed that the disorder occurs as a result of an alloimmune process, with donor T-lymphocytes being the likely mediators of the response [11], which is characterised histopathologically by a predominantly lymphocytic bronchiolar and peribronchiolar inflammatory infiltrate, as well as concentric bronchiolar fibrosis [6]. This mechanism is supported by a murine model [12]. Similar long-term complications have been reported after lung transplantation, indicating that OB is a manifestation of lung rejection, as well as part of the chronic graft *versus* host syndrome that occurs after allogenic HSC transplantation. OB after HSC transplantation is an earlier and less common complication than in patients after lung transplantation [7]. However, a recent study in subjects after lung transplantation has provided a new insight into the natural history of OB in that clinical setting, and suggests that repetitive low-grade acute cellular rejection episodes have a cumulative effect on the airways, leading to clinically relevant alloimmune-mediated airway injury, which results in the OB syndrome [13]. HOPKINS *et al*. [13] also point out that other sources of nonalloimmune injury (such as gastro-oesophageal reflux and lower respiratory infection) may have an additive affect. In the light of the irreversible nature of established OB, it is, therefore, hoped that controlling both alloimmune and non-alloimmune epithelial injury after transplantation may provide an opportunity for reducing pulmonary complications and improving survival [14].

A definitive diagnosis of OB is based on a histological examination of lung tissue, which, because of the patchy nature of the process, generally requires surgical lung biopsy. Transbronchial lung biopsies generally provide an insufficient sample and have an unacceptably high false-negative diagnostic rate [6, 8]. However, a presumptive diagnosis can be made in the appropriate clinical setting. In a patient >100 days post-transplant, who develops breathlessness and bronchodilator nonresponsive airflow limitation, and who has moderate-to-severe chronic graft *versus* host disease, with a clear chest radiograph and a high-resolution computed tomography scan showing thickened or dilated small airways with mosaic attenuation, the diagnosis of OB is highly probable [6].

The clinical course is variable, but the median mortality rate is in excess of 60%, with most authorities agreeing that improvement in lung function occurs infrequently and that stabilisation, which occurs in no more than one third of subjects, is usually the best outcome that can be achieved [15, 16]. In controlled clinical trials, no agents have been shown to be of proven efficacy in the management of OB after HSC transplantation. Current recommendations are derived from the opinions of experts in the field and from anecdotal reports. Treatment is usually directed at the exclusion and treatment of any secondary infection, the control of any asthmatic contribution and the augmenting of immunosuppression [16, 17]. Worsening of the patient's condition is likely to occur, particularly following lower respiratory tract infection, and, for this reason, the threshold for investigation and treatment in this group of subjects should be low.

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Therefore, prevention, early detection and effective treatment for OB after HSC transplantation remain prime objectives if patient outcomes are to be improved. Due to their association, improved measures to prevent and treat chronic graft *versus* host disease will undoubtedly be of major importance in helping to prevent OB. Although the use of cyclosporine has led to a reduction in the rates of chronic graft *versus* host disease, and of OB, additional immunosuppression measures will need to be balanced against an increase in the rates of opportunistic infection.

There have been several recent studies in animal models looking at other agents that may be helpful in preventing the development of OB. These include inhibition of Janus kinase (JAK) 3, with a resulting effect on platelet-derived growth factor, the modulation of transforming growth factor (TGF)-β_1 and of agents influencing vascular endothelial growth factor all in rat transplant models [18, 19]. Studies in the murine model using pirfenidone, which also affects TGF-β_1, have demonstrated a delay in the onset, as well as a reduction in the severity, of OB when administered early in the post-transplant period, suggesting that pirfenidone may be a candidate drug to be evaluated in human subjects [20].

Of particular interest are recent studies of the use of azithromycin for patients with OB after transplantation procedures. A recent open-labelled study of eight human subjects after lung transplantation suggests that azithromycin, in a dosage of 250 mg·day^{-1} for 5 days, followed by 250 mg every other day, when added to the patient's pre-existing immunosuppressive therapy, results in a significant improvement in the degree of airway narrowing [21]. KURDOWSKA *et al*. [22] postulated that azithromycin may have produced this improvement by the inhibition of interleukin-8 release by human alveolar macrophages [23] or by an increase in the apoptosis of neutrophils. In this issue of the *European Respiratory Journal*, KHALID *et al*. [24] have produced further evidence to suggest that there is a potential role for azithromycin in the treatment of OB. Theirs is an observational study of eight patients out of 153 subjects undergoing allogeneic HSC transplantation. The eight patients with OB were given azithromycin 500 mg daily for 3 days, then 250 mg three times per week for 12 weeks. Clinically significant improvement was achieved in both forced expiratory volume in one second and forced vital capacity with the average improvement being 21%. KHALID *et al*. [24] postulate that macrolide antibiotics may have a beneficial effect in patients with OB after HSC transplantation, by virtue of a range of anti-inflammatory effects, not all of which are well understood.

In the light of the results of KHALID *et al*. [24], and in view of the poor prognosis of obliterative bronchiolitis in patients after haematopoietic stem cell transplantation, a larger scale randomised trial to assess the benefit of this form of treatment is needed. This study highlights the need for continued research in this important area and provides the exciting prospect of improved patient outcome for a complication that otherwise carries a grim prognosis. It goes without saying that a major challenge exists to understand more precisely the factors, both immune and nonimmune, which contribute to the development of obliterative bronchiolitis after haematopoietic stem cell transplantation. Although it is probable that each of these injuries is additive, current evidence indicates that the alloimmune injury is the critical insult, and that measures which offer the prospect of curtailing this injury, such as those reported in this Journal by KHALID *et al*. [24], offer the promise of improved survival for patients after haematopoietic stem cell transplantation.

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