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Allogeneic stem cell transplantation for rheumatic autoimmune diseases

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Abstract

Haematopoietic stem cell transplantation (HSCT) has evolved from an experimental concept to an effective treatment option for severe autoimmune diseases and has a unique ability to restore immune regulation. It is a complex multistep procedure involving the administration of high doses of immunosuppressive medication and transplantation of stem cells. Most HSCT procedures in autoimmune disease have involved autologous stem cells. In the case of allogeneic transplantation, stem cells are derived from peripheral blood or bone marrow of a healthy HLA-matched donor. Allogeneic HSCT has curative potential based on studies in experimental models of autoimmune disease, case reports, and a registry analysis but carries significant risks of rejection and graft-versus-host disease. Unless these risks become manageable, allogeneic HSCT should be offered only if all alternative treatment options have failed, if a patient has a suitable donor, and if a patient still has a chance to benefit significantly from the procedure.

Introduction and context

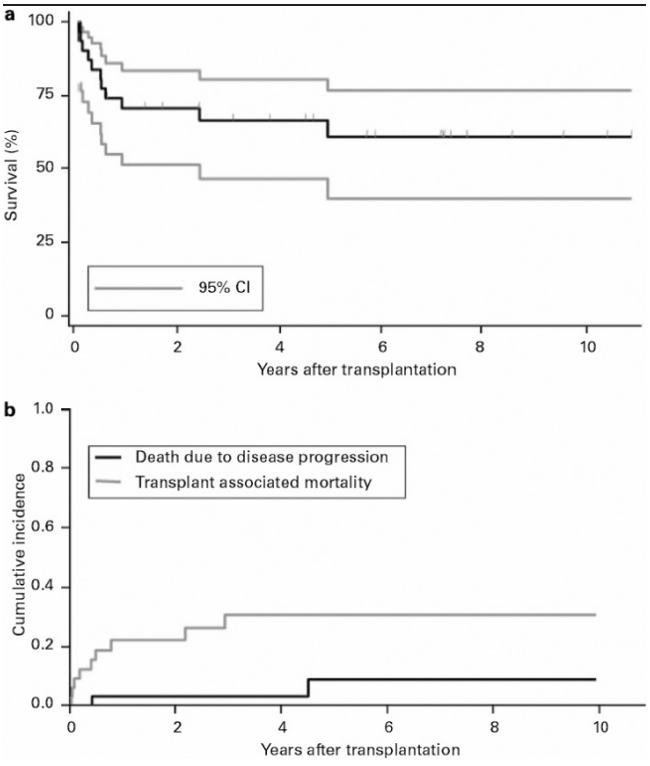
Allogeneic haematopoietic stem cell transplantation (HSCT), or 'allografting', is an established treatment for haematological malignancies and genetic defects, but not autoimmune diseases (ADs). The risk of graft-versus-host disease (GvHD) and the difficulties in finding a suitable donor have hampered clinical studies on allografting in AD. Yet there is a good scientific rationale for allografting in AD as it theoretically is the only treatment of AD with curative potential. Its main aim is to replace a patient's dysfunctional immune system with an allograft from a healthy donor so as to restore normal immune regulation. This is in contrast with autologous HSCT, in which a patient's own stem cells are re-infused after intensive immunosuppressive therapy. In patients with a haematological condition and concomitant AD such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), allografting resulted in long-term improvements of disease activity [1,2]. Extensive studies in different animal models of AD have confirmed the superiority of allografting in eliminating reactivity against autoantigens and inducing sustained clinical responses [3]. The term 'graft-versus-autoimmunity' (GvA) effect has been coined, in analogy to the 'graft-versus-leukaemia' effect observed in allotransplanted leukaemia patients, to describe the reactivity of donor T and natural killer cells against a patient's autoreactive lymphocytes [4]. Whether GvA can occur in the absence of (sub)clinical GvHD is a matter of debate but is an important issue as it would not make sense to exchange one AD for another.

Recent advances

Feasibility and safety of allografting have improved significantly since allogeneic bone marrow transplantation was first introduced in the clinic in the 1950s. This can be explained by the use of less intensive regimens and a switch from whole bone marrow transplants to T cell-depleted peripheral blood stem cell grafts [5]. Nowadays, so-called non-myeloablative preparative regimens that leave stem cells intact, permitting rapid reconstitution of innate immune cells and thus reducing

the risk of infection, are routinely employed [6]. The use of T cell-depleted allografts for haemato-oncological indications has reduced the risk of GvHD but at the expense of a higher risk of relapse. While undesirable, such an outcome is probably preferred over serious complications from GvHD in the case of AD. Despite its theoretical appeal, allografting is still used only incidentally to treat AD, and most cases have involved patients with multiple sclerosis, RA, SLE, vasculitis or systemic sclerosis (SSc). Both long-term remissions and relapses have been observed [1,7-9]. Remarkably, in two patients with severe SSc, non-myeloablative conditioning resulted in 10-15% donor chimerism yet was sufficient to achieve complete sustained remission for more than 3 years after HSCT [10,11]. This suggested that full ablation of the host immune system is not a precondition to induce effective immune regulation. Similar observations were made in a patient with severe refractory RA treated with non-myeloablative conditioning and HLA-matched CD34-selected HSCT [12]. This patient was in remission with 55% donor T cells and 70% donor myeloid cells in blood. Systematic studies in experimental animal AD have confirmed that low levels (>1%) of allogeneic haematopoietic chimerism are sufficient to treat AD effectively [13]. In a recent review of the EBMT (European Group for Blood and Marrow Transplantation) Database, the outcome reports of 35 patients who had haematological or non-haematological AD and who collectively had received a total of 38 allogeneic transplantations were analysed [14]. The group included two patients with Behçet disease, two with vasculitis, two with SLE, one with dermatomyositis, and four with RA. An impressive 55% of patients reportedly had a complete response and 23% had at least a partial response, with a median duration of response of 12.3 months after HSCT. This came at the expense of a treatment-related mortality at 2 years of 22.1%, however. The probability of survival at 2 years was 70% (Figure 1). No predictive factor of survival could be identified. Although based on a retrospective analysis of partly incomplete data, the induction of complete remission by allografting underscores the potential clinical effectiveness. A recent proof-of-principle study in mice showed that it is possible to achieve donor stem cell engraftment in bone marrow via antibody-based clearance of haematopoietic stem cell niches. If applicable in humans, this would bypass the need for preparative regimens based on chemotherapy and reduce toxicity [15].

Figure 1. Allogeneic haematopoietic stem cell transplantation in autoimmune disease



(a) Kaplan-Meier plot of survival for all patients with autoimmune disease (n = 35) treated with allogeneic haematopoietic stem cell transplantation. CI, confidence interval. **(b)** Cumulative incidence of death owing to disease progression versus transplant-related mortality. Originally published in Daikeler *et al.* [14], *Bone Marrow Transpl* 2009.

Implications for clinical practice

Allogeneic HSCT *may* be considered for poor-prognosis patients who have failed conventional treatment including biologicals (RA or juvenile idiopathic arthritis) or autologous HSCT (SSc or SLE), which is now being examined in prospective clinical trials. Nevertheless, the clinical evidence in favour of allografting is sparse and the risks are considerable. In our opinion, patients with end-stage disease or serious co-morbidities should not be transplanted. The risks of HSCT in general (both autologous and allogeneic) may be particularly high in patients who have been heavily pre-treated with different immunosuppressive drugs, including biologicals, or who suffer from severe organ damage (or both). Patient selection is therefore critical and patients should be offered HSCT only if they have treatment-resistant life-threatening disease yet a reasonable lifespan to allow logistical preparations for HSCT to be made. Patients should also have acceptable organ function to withstand unintended consequences of intensive immunosuppressive treatment and be willing to accept the risks of allografting. In terms of donor selection, sibling or matched unrelated donor transplants are preferred to minimise the risk of GvHD. There is no consensus (yet) about the optimal transplant regimen or even the source

of the graft [16]. Whether the benefits of allografting outweigh the risks can be investigated only through a prospective collaborative trial with standardised treatment regimens, uniform eligibility criteria and outcome measures, but whether such a trial is feasible remains to be seen. In the interim, it would probably be best to harmonise treatment protocols and outcome measures and collect outcome data from a comparator group of patients who are considered eligible but who do not have a suitable donor.

Abbreviations

AD, autoimmune disease; GvA, graft-versus-autoimmunity; GvHD, graft-versus-host disease; HLA, human leukocyte antigen; HSCT, haematopoietic stem cell transplantation; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Competing interests

The authors declare that they have no competing interests.

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