Unrelated donor haemopoietic stem-cell transplantation: ATG or not?

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Chronic graft-versus-host disease (GVHD) is a multisystemic syndrome involving tissue inflammation and fibrosis that shares many clinical manifestations with autoimmune diseases such as systemic lupus erythematous or systemic sclerosis.[1] Despite being associated with lower relapse rates, chronic GVHD is the main cause of late mortality after unrelated allogeneic haemopoietic stem-cell transplantation. Furthermore, chronic GVHD has a large effect on quality of life.[2]

Since the mid-1980s, the standard GVHD prophylaxis for patients transplanted following myeloabaltive conditioning has consisted of the combination of ciclosporine (or tacrolimus) with a short course of methotrexate.[3] This regimen has been relatively successful at preventing severe acute GVHD but largely failed to prevent chronic GVHD in patients receiving grafts from unrelated donors or in those given peripheral blood stem-cells rather than bone marrow.[4]

Rabbit anti-thymocyte globulins (ATGs) are polyclonal immunoglobulins obtained from hyperimmune sera of rabbits immunised with the human Jurkat leukemic T-cell line (anti-T-lymphocyte globulin, ATLG) or human thymocytes (thymoglobuline).[5] Five randomised studies have assessed the effect of ATLG or thymoglobuline on GVHD prevention in patients receiving bone marrow or peripheral blood stem-cells from unrelated donors, or peripheral blood stem-cells from HLA-identical siblings. Despite important differences in the setting of these five trials, all showed that ATG protected from severe chronic GVHD. Relapse and overall survival were not significantly affected by ATG in four of these trials, whereas preliminary data from the trial of Soiffer and colleagues[6] show worse 2-year survival in patients in the ATLG group due to higher relapse-related mortality. There are no obvious explanations for these discrepancies besides that immunosuppression after grafting consisted of tacrolimus plus methotrexate in the study by Soiffer and colleagues and ciclosporine plus methotrexate in the other four trials.

Aside from the GITMO study (which was done in an era when matching standards for unrelated donor grafts were less stringent), randomised trials of ATGs have had a relatively short median follow-up (1–3 years). In *The Lancet Haematology*, Finke and colleagues[7] report the final results of a randomised phase 3 multicentre trial (previously reported after a median follow-up of 2 years[8]) comparing standard GVHD prophylaxis with ciclosporine and methotrexate with or without additional ATLG (60 mg/kg total dose) in patients given grafts (mainly peripheral blood stem-cells) from unrelated donors. Median follow-up was 8·6 years. The main observations were that, at 8 years, the probability of being alive and free of immunosuppressive therapy was 11% (95% CI 5–18) in the non-ATLG group versus 47% (37–57) in the ATLG group (p=0·0002), while severe GVHD-free and relapse-free survival (which serves as a measure of cure without ongoing morbidity) was 13% (95% CI 7–21) in the non-ATLG group versus 34% (25–43) in the ATLG group (p=0·0003; figure 1). Relapse mortality was not increased by ATLG (adjusted HR 1·03, 95% CI 0·61–1·76; p=0·90), which is reassuring regarding the long-term safety of ATLG. Finally, 8-year overall survival was 37% (27–47) in non-ATLG patients versus 49% (39–59) in ATLG patients (p=0·3).

These findings are remarkable in several aspects. First, the study showed that only 11% of non-ATLG patients were alive and free of immunosuppressive therapy (a good marker for survival without ongoing severe chronic GVHD) 8 years after transplantation, which might seem insufficient. ATLG administration significantly improved this endpoint to 47%. Given the substantial effect of

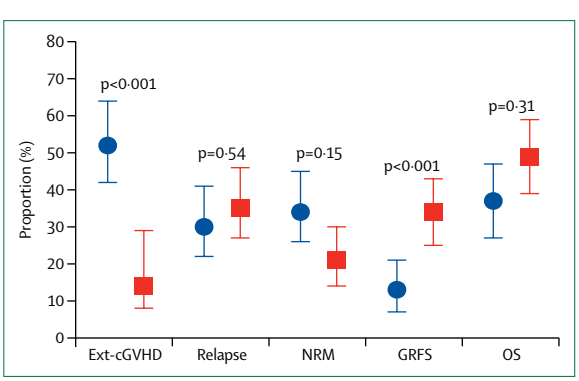

Figure 1: **Major transplantation outcomes at 8 years**
Blue circles=non-ATLG. Red squares=ATLG. Error bars show the 95% CIs. Ext-cGVHD=extensive chronic GVHD. NRM=non-relapse mortality. GRFS=GVHD-free and relapse-free survival. OS=overall survival. ATLG=anti-T-lymphocyte globulin.

chronic GVHD treatment on quality-of-life, these data should be taken in consideration for decision-making and patient counselling. Second, this study shows the long-term safety ATLG administration before transplantation with an 8-year incidence of relapse-related mortality similar in both groups and an overall survival at least as good in ATLG as in non-ATLG groups. However, the trial did not assess the effect of ATLG on long-term quality-of-life and other survivorship issues.

Although long-term data reported by Finke and colleagues suggest that ATLG could be the standard of care for patients receiving peripheral blood stem-cells from unrelated donors after myeloablative conditioning, it is unclear whether some subgroups of patients do not benefit or even could be harmed by ATLG administration. It is reassuring that no interactive effects between ATLG administration and disease status or stem-cell source could be detected in the study by Finke and colleagues, although the trial was not powered to adequately address these issues. Further, the trial included only patients receiving grafts after myeloablative conditioning and thus did not address the effect of ATG administration in patients who had reduced intensity conditioning allogeneic haemopoietic stem-cell transplantation, a transplantation approach that relies mainly on immune-mediated graft-versus-tumour effects to eradicate leukaemia. Another important question is whether the same dose of ATG per kg should be used for all unrelated recipients of peripheral blood stem-cells or whether the dose should be individualised according to other factors affecting ATG pharmacokinetics such as absolute lymphocyte counts at the time of ATG administration.[9]

Although long-term ATLG results reported by Finke and colleagues are impressive, several novel promising strategies for GVHD prophylaxis are under investigation.[3,10] Further prospective randomised trials are needed to compare ATG with these strategies.

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