Impact of Serotherapy on Immune Reconstitution and Survival Outcomes after Stem Cell Transplantations in Children: Thymoglobulin Versus Alemtuzumab

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The administration of antibodies targeting T cells and other immune cells (‘serotherapy’ or ‘in vivo T cell depletion’) to prevent graft-versus-host disease (GVHD) appears beneficial. For rabbit polyclonal ‘anti-T cell globulin’ (ATG), five randomized and multiple nonrandomized studies have shown that, in the setting of adult marrow or mobilized blood stem cell transplantation using myeloablative conditioning, ATG given with conditioning prevents GVHD without compromising relapse incidence or survival [1]. This leads to improved immunosuppression-free survival [2] and improved quality of life [3-5]. This is true in spite of the fact that ATG appears to increase viral infections, particularly Epstein-Barr virus (EBV)–driven post-transplantation lymphoproliferative disorder [1].

Alemtuzumab (humanized rat monoclonal antibody targeting CD52) may reduce GVHD to a greater degree than ATG [6,7]. The incidence of relapse has been reported to be not higher with alemtuzumab than it is with ATG [6,7]. Viral infections may occur more frequently with alemtuzumab than with ATG [8], except for EBV post-transplantation lymphoproliferative disorder, which may be more frequent with ATG. However, whether alemtuzumab can be substituted for ATG as GVHD prophylaxis is not known because only a few studies comparing ATG with alemtuzumab are available, and all are retrospective.

The study of Willemsen et al. [9] is a welcome addition to the group of retrospective studies. It showed that, compared with ~10 mg/kg ATG (Thymoglobulin, Sanofi, Paris, France), ~8 mg/kg alemtuzumab resulted in a trend toward less acute GVHD, as expected. Also as expected, adenoviral reactivation was more frequent in the alemtuzumab group, whereas EBV reactivation was more frequent in the alemtuzumab group. Surprisingly, relapse incidence was higher in the alemtuzumab group, which resulted in lower overall and relapse-free survival. This could not be attributed to the longer half-life of alemtuzumab (compared with ATG), as when patients with short alemtuzumab exposure (low area under the time-concentration curve) were compared with patients with long ATG exposure, the relapse incidence and survival were still significantly worse in the short exposure alemtuzumab group. This was true despite the similar relative exposure to antibodies for both groups. It should not be assumed that the increased relapse incidence and mortality with alemtuzumab applies to adults, who are more prone to develop GVHD than children (without serotherapy) and, thus, could theoretically derive a greater benefit (less GVHD-associated mortality and morbidity) from alemtuzumab.

The strength of the study is in its mechanistic components—immune reconstitution and pharmacokinetics. Reconstitution of virtually all immune cell subsets (neutrophils, monocytes, total and memory/effector CD4 T cells, total and memory/effector CD8 T cells, and NK cells, but not B cells) was delayed in the alemtuzumab group, compared with the ATG group. This was caused, at least in part, by the longer half-life of alemtuzumab, as when the patients with short alemtuzumab exposure were compared with the patients with long ATG exposure, the reconstitution of all the immune cell subsets was similar. As expected, among both alemtuzumab- and ATG-treated patients, T cell reconstitution was faster in patients with lower exposure to the antibody. Complete donor chimerism (among mononuclear cells) was achieved faster in the ATG group than in the alemtuzumab group, perhaps because of the longer half-life of alemtuzumab.

The weakness of the study is in the patient population studied, ie, pediatric patients. Whereas in adults the benefit of ATG (GVHD reduction) outweighs the risks (eg, viral infections), this may not apply to children, who are less likely to develop GVHD compared with adults (without serotherapy) [1]. ATG has become a new standard in GVHD prophylaxis in the setting of adult myeloablative marrow or mobilized blood stem cell transplantation. Investigations into whether another form of in vivo T cell depletion (eg, alemtuzumab) may be more advantageous than ATG should use patients in whom the favorable risk to benefit ratio of ATG has been documented.

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REFERENCES


