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Letters to the Editor

Reply to: Transient Grades Three to Four Acute Hepatitis Is a Common Complication of Rabbit Antithymocyte Globulin (Thymoglobulin) Administered before Allogeneic Stem Cell Transplantation

Mats Remberger*, Jonas Mattsson

Center for Allogeneic Stem Cell Transplantation, Karolinska University Hospital, Stockholm, Sweden

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To the Editor:

In a recent issue of *Biology of Blood and Marrow Transplantation*, Médiavilla et al. [1] explored incidence, characteristics, potential risk factors, and consequences of severe acute hepatotoxicity (SAH) associated with rabbit antithymocyte globulin (ATG, Thymoglobulin [Genzyme, Cambridge, MA]). *SAH* was defined as an aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN) within 1 week after administration of ATG. SAH was diagnosed in 55 (26%) patients. Of these 55 patients, 36 (17%) had 5 to 20 × ULN (grade 3) and 19 (9%) had >20 × ULN (grade 4). No deleterious impact of SAH on survival, nonrelapse mortality, relapse, or graft-versus-host disease was reported. Risk factors were blood systolic pressure < 90 mm Hg during administration of ATG and 2 previous autologous stem cell transplantations.

We have used rabbit ATG (Thymoglobulin, Genzyme) for many years and were not aware of this problem. This prompted us to study SAH associated with ATG infusion at our institution.

We studied 176 consecutive patients receiving their first allogeneic stem cell transplantations between 2012 and 2014 who received rabbit ATG as part of the conditioning. In this cohort of patients, SAH was seen in only 9 patients (5%). All 9 patients had grade 3 toxicity (5 to 20 × ULN of AST or ALT) and no grade 4 toxicity (>20 × ULN) occurred. The maximum median levels of AST and ALT among the 9 SAH patients were 6.6 × UNL (range, 3.4 to 17.8) and 8.7 × ULN (range, 2.3 to 17.0), respectively. In our material, we found a strong effect of SAH on survival (34% versus 84% at 1 year, $P < .001$) and treatment-related mortality (59% versus 9%, $P < .001$). Causes of death in the SAH patients were relapse in 1 and infection in 4. No effect on acute GVHD was seen. However, as only 9 patients developed SAH, this should be interpreted with caution.

The only factor associated to SAH in our cohort was a female patient; SAH did not occur in any male patient.

The reason for the discrepancy between Médiavilla et al. and our study is difficult to speculate, but 1 reason might be the administration of ATG. For many years, we have first administered a small test dose of 25 mg of ATG the day before the first full dose. This procedure has decreased the number and severity of side effects of ATG at our center. We give 2 mg/kg/day of ATG compared with 2.5 mg/kg/day in the French study. Furthermore, our patients receive premedication with antihistamine (klemastin) and methylprednisolone (500 mg + 250 mg) before infusion of ATG to reduce side effects.

In our opinion, liver toxicity during or within 1 week after conditioning is mainly due to the conditioning itself (busulfan) or other drugs given simultaneously, eg, ciprofloxacin, fluconazole etc. Most patients (n = 6, 67%) with SAH in our study received busulfan-based reduced-intensity conditioning. Furthermore, we practice dose adjustment of busulfan based on pharmacokinetic analysis in all patients (reduced and myeloablative conditioning), and patients with high busulfan concentrations are treated with acetylcysteine. With these strategies, liver toxicity is a rare event at our center and during the last 5 years, only 1 patient developed liver sinusoidal obstruction syndrome after busulfan and cyclophosphamide conditioning.

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* Correspondence and reprint requests: Mats Remberger, PhD, Center for Allogeneic Stem Cell Transplantation, Karolinska University Hospital, SE14186 Stockholm, Sweden.

E-mail address: mats.remberger@ki.se (M. Remberger).

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Autologous Hematopoietic Stem Cell Transplantation for Plasmablastic Lymphoma: The European Society for Blood and Marrow Transplantation Experience

Chiara Cattaneo [1], Herve Finel [2], Grant McQuaker [3], Elizabeth Vandenberghe [4], Giuseppe Rossi [1], Peter Dreger [2,5,*]

[1] *Hematology Unit, Spedali Civili, Brescia, Italy*
[2] *Lymhoma Working Party, European Society for Blood and Marrow Transplantation, Paris, France*
[3] *BMT Unit, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom*
[4] *Haematology Department, St. James's Hospital, Dublin, Ireland*
[5] *Department of Medicine V, University of Heidelberg, Heidelberg, Germany*

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To the Editor:

We read with interest the excellent review of Al-Malki et al. on hematopoietic stem cell transplantation (HSCT) for plasmablastic lymphoma (PBL) [1]. The authors conclude that autologous HSCT (autoHSCT) might be beneficial both in the salvage setting and for consolidation of first-line responses in this orphan lymphoma subset, which has a very poor prognosis with conventional chemotherapy [2]. As this suggestion is largely based on anecdotal data, we would like to substantiate the evidence supporting autoHSCT in PBL by reporting the European Society for Blood and Marrow Transplantation experience.

Between 2001 and 2011, data pertaining to 24 patients, who underwent autoHSCT for PBL and had a full MED-A (minimal essential dataset A) available were reported to the European Society for Blood and Marrow Transplantation registry. The patient population showed a male predominance (75%) and a relatively young age (median, 43 years; range, 16 to 63), typical for PBL [2]. The majority of transplantations were performed in first complete (50%) or partial (17%) remission, and in 71% of the patients BEAM (carmustine, etoposide, ara-C, melphalan) or modifications of BEAM were used as a myeloablative regimen. Human immune deficiency virus (HIV) status was available for only 8 patients and was positive in 7 of them.

Of the 24 patients, 7 relapsed after autoHSCT, translating into a 2-year relapse rate of 30% (95% confidence interval [CI], 8% to 57%). In these 7 patients, disease status at HSCT was first complete remission (CR) in 2, first partial remission in 2, third partial remission in 1, and refractory disease in 2 patients. Notably, no relapse was observed beyond 4 months from transplantation. Except a single patient who was lost to follow-up, all relapsed patients subsequently died, most of them within a short time period after disease recurrence. In addition, there were 3 nonrelapse deaths (1 from sepsis, 1 from progressive HIV infection, and 1 from a secondary T cell lymphoma), translating into a 2-year overall survival probability of 53% (95% CI, 28% to 73%). Patients who were autografted in CR had a significantly lower relapse risk (hazard ratio, 11.7; 95% CI, 1.98 to 68.9) and overall mortality risk (hazard ratio, 15.6; 95% CI, 2.62 to 92.5) than more advanced patients. In contrast, neither age, gender, interval from diagnosis to autoHSCT, performance status, high-dose regimen, nor calendar year of transplantation had a significant impact on survival.

Limitations of this analysis consist in its retrospective character, the small sample size, a paucity of information about pretransplantation treatment, and the median follow-up of survivors, which was only 30 months (range, 3 to 132; interquartile range, 3 to 63). However, as there were 11 patients who remained relapse free and survived 6 months or longer, our series supports the notion that autoHSCT might have the potential to induce sustained remissions in PBL given the extremely short interval to disease recurrence in all patients who experienced post-transplantation relapse. This implies that there is a rationale to consider autoHSCT as soon as a first CR is achieved. In conclusion, in the absence of effective treatment alternatives, autoHSCT deserves to be further explored as consolidation for first-line and salvage therapy of PBL both in the HIV^+ and HIV^- setting [3].

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* Correspondence and reprint requests: Dr. Peter Dreger, Department of Medicine V, University of Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany.

E-mail address: peter.dreger@med.uni-heidelberg.de (P. Dreger).

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