with an increased risk of postoperative infection. Therefore, as suggested by Pereira, the length of storage of the transfused RBCs should be investigated as a possible explanation for the disagreements among the available RCTs in any future IPD meta-analysis of these studies.

It is possible that future research will not corroborate the reported association between increased length of storage of the transfused blood components and an increased risk of postoperative infection. If the TRIM effects were mediated by immunologically active, intact allogeneic WBCs, as opposed to older blood components would be associated with an increased risk of infection. Table 1 presents 3 mechanisms that may underlie an association of ABT with postoperative infection as mutually exclusive hypotheses and shows the expected results from future observational comparisons of patients transfused before or after the implementation of universal WBC reduction, in the event that these 3 hypotheses were indeed mutually exclusive and only 1 of them was correct.

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To the editor:

Relationship between HLA alleles and cytomegalovirus infection after allogeneic hematopoietic stem cell transplant

Cytomegalovirus (CMV) infection remains associated with increased mortality in immunocompromised populations, particularly in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Risk factors for reactivation include serostatus and occurrence of graft-versus-host disease (GVHD). Identifying new factors that modify the immune response against CMV might be of importance in HSCT recipients. There has been one study on the association between HLA alleles and CMV pneumonitis after hematopoietic stem cell transplantation (HSCT), but no study has tested the influence of a large number of alleles on CMV reactivation. We initiated a retrospective study on the effect of HLA alleles on CMV reactivation in the 144 consecutive recipients with a positive CMV serostatus at the time of transplantation who received an allogeneic transplant in our unit between October 1, 1996, and August 31, 1999. The donor was related in 98 patients. Weekly monitoring started from engraftment until day 100 after transplantation or longer. CMV reactivation was defined as a CMV pp65 antigenemia of at least 2 in 2 × 10^5 leukocytes. CMV infection was treated with ganciclovir or foscarnet, for 2 to 3 weeks in 2 patients or until 2 consecutive negative tests. Because immunity recovers essentially from the graft, we studied the effect of the HLA alleles of the donor. HLA alleles were considered if their phenotype frequency exceeded 10%. Univariable and multivariable prognostic analyses, performed on SAS 6.12 software (SAS Institute, Cary, NC), were based on Cox models, and assessing the effect of acute grade II-IV GVHD as time-dependent. Multivariable prognostic analysis used a stepwise selection, introducing covariates either previously selected as associated with outcome at the 10% level or reported as prognostic factors from the literature.

As of December 1, 1999, the median follow-up was 20 months after transplantation (range, 2 to 38 months). Ninety patients had developed CMV reactivation; only 12 had developed a CMV disease. The estimated rate of CMV reactivation was 64% at 3 months after transplantation. The estimated median time to CMV reactivation for patients with CMV infection, using time-to-event methods, was 45 days (95% CI, 39-48 days). Seventy-two patients had experienced acute grade II-IV GVHD. The estimated median time to GVHD was 18 days (95% CI, 16-21 days). In univariable analyses, GVHD was associated with CMV reactivation (HR [hazard ratio] = 1.73, P = .01), and 5 HLA alleles were associated with outcome at a 10% level. HLA-A11 (HR = 0.40, P = .03) and HLA-B51 (HR = 0.59, P = .07) were potentially protective against CMV reactivation, while HLA-DR7 (HR = 1.48, P = .08), HLA-DR15 (HR = 1.56, P = .06), and HLA-A24 (HR = 1.56, P = .08) increased the risk of CMV reactivation. These 5 alleles were introduced into a multivariable Cox model, jointly with age, type of donor (related vs unrelated), T-cell depletion, donor CMV serostatus, and acute grade II-IV GVHD. The 2 factors that were selected with prognostic influence were GVHD (HR = 1.71, P = .01) and HLA-A11 (HR = 0.41, P = .04). The median peak of antigenemia was not significantly different between HLA-A11 recipients and non-HLA-A11 recipients (22 and 13 positive leukocytes, respectively, P = .50, Wilcoxon rank sum test). But none of the 17 HLA-A11 patients suffered from CMV disease.

References

Our results were not corrected for the number of studied alleles; so it is possible that significant results were due to random chance. Bonferroni correction is likely overly conservative, and there is no clear consensus on how one should control for multiple comparisons. As one answer to this problem, we found that other data from the literature are consistent with some of our findings, especially regarding HLA-A11, HLA-DR7, and HLA-DR15. HLA-A11 protects against skin cancer after kidney transplantation, which is often human Papillomavirus–related, and against Kaposi sarcoma in AIDS, a herpesvirus-related condition. An association between HLA-DR7 and CMV infection or disease has already been reported.4,5 We also corroborate a Japanese study, which suggested a deficient production of neutralizing antibodies against CMV in HLA-DR15 subjects.5

Therefore, our results, backed up with other findings from the literature, clearly prompt for more investigations of HLA polymorphism influences on CMV reactivation in the HSCT setting, either on other series or on a multicenter database, in order to achieve higher statistical significance. Furthermore, large-scale studies could investigate influences of HLA types on CMV disease. If confirmed, our findings could provide additional insights into CMV reactivation pathophysiology and be relevant for the design of immunotherapy-oriented strategies.

References
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