What are the probable reasons for the high rate of gastrointestinal complications and TRM? In contrast to the cohort of Bunjes the majority of our patients suffered from Philadelphia chromosome–positive ALL. Several studies demonstrated a high TRM in patients with this disease. However, this does not explain the high frequency of acute intestinal GVHD. The second obvious difference was the use of unmanipulated grafts or early incremental T-cell add backs. We therefore assume that the combination of anti-CD66 (a, b, c, e) mAb therapy and early exposure to allogeneic T cell might be the reason for intestinal toxicity. Since anti-CD66 (a, b, c, e) antibodies (clone BW250/183) bind intestinal epithelial cells, radioimmunotherapy might cause tissue damage in the bowel. This might also trigger intestinal GVHD. Moreover, the antigen CD66a is expressed on the surface of small intestinal intraepithelial lymphocytes (iIEL). Via cross fire radiolabeled intraepithelial T-cell binding, mAb might cause additional tissue damage.

In summary, allografting without T-cell depletion or with early T-cell add backs after conditioning regimens including 188Re-labeled anti-CD66 (a, b, c, e) mAb is associated with a high risk of severe intestinal acute GVHD and a high TRM. We therefore suggest that efficient T-cell depletion is strongly recommended for allogeneic hematopoietic cell grafts after a radioimmunotherapy conditioning with anti-CD66 (a, b, c, e) mAb. Furthermore, the anticipated benefit of early T-cell add backs should be weighed out carefully with the risk of severe intestinal GVHD.

Response:

Factors influencing gut GVHD after intensified conditioning with Rhenium 188–labeled anti-CD66 monoclonal antibody

We are grateful to Klein et al for emphasizing one aspect of our study that received comparatively little attention in the original publication, namely the fact that all patients but one received T-cell-depleted grafts. Therefore the conclusions with respect to organ toxicity and the incidence of graft-versus-host disease (GVHD) only apply to T-cell-depleted stem cell transplantations and cannot be transferred to patients receiving conventional GVHD prophylaxis. Klein et al report a high incidence of gut GVHD in a cohort of patients receiving non–T-cell-depleted grafts after intensified conditioning according to our radioimmunotherapy protocol. We cannot entirely exclude the possibility that the specificity of the anti-CD66 antibody used in our study could have contributed to the gut problems observed. However, we have never observed localization of the antibody to the gut in our dosimetry studies, and we have data demonstrating that the labeled antibody per se does not induce a systemic release of cytokines involved in GVHD (interleukin-1, tumor necrosis factor–alpha, gamma-interferon [Buchmann et al, unpublished observations, December 2001]). We have only observed localization of the antibody to the gut in rare patients with significant infectious complications such as severe appendicitis. We therefore feel that this high incidence of intestinal GVHD is due to the use of conventional GVHD prophylaxis, and in particular to the early application of donor lymphocyte transfusions.

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References


To the editor:

Discrepancy between antithrombin activity methods revealed in Antithrombin Stockholm: do factor Xa–based methods overestimate antithrombin activity in some patients?

Antithrombin is a single-chain glycoprotein of 432 amino acids. It is the most important endogenous coagulation inhibitor and inhibits several coagulation factors: IXa, Xa, XIa, and thrombin (of which the inhibition of thrombin probably is the most important). In 1992 Blajchman et al reported the Antithrombin Stockholm point mutation in codon 392 (Gly to Asp) as a reactive site (RS) type of mutation that results in a type II antithrombin deficiency. It was found in a young woman on oral contraceptives who presented with pulmonary embolism. The authors reported low antithrombin activity measured with thrombin inhibition–based (72%–74%) and factor Xa inhibition–based (53%–56%) methods using chromogenic peptide substrate assays. Several years later, much to our surprise, the proband and her 2 siblings had normal antithrombin activity in a routine factor Xa inhibition–based test. Her 2 siblings had previously presented with low levels but never suffered from any symptoms.
In the present study with the factor Xa–based method normal antithrombin activity was found in the patient with type II deficiency; her siblings also had low levels with the thrombin-based test. We would therefore like to stress that there is a possibility of not detecting all type II deficiencies with a factor Xa inhibition–based test, which is the most widespread routine method. In our investigation the factor Xa–based method overestimated antithrombin activity levels. According to our knowledge this has not previously been described and can cast some doubts about the validity of the use of this test as the test of choice when screening for antithrombin deficiency. Therefore we believe that both the bovine thrombin– and factor Xa inhibition–based tests, together with an antigen method, should be performed in patients with suspected antithrombin deficiency type II.

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References
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