Towards a rational graft-*versus*-host disease (GVHD) prophylaxis: rituximab should not be forgotten

Recently, Bucher *et al.*[1] addressed rational graft-*versus*-host disease (GVHD) prophylaxis (December 2012 issue of this Journal). The authors addressed calcineurin inhibition and T-cell immune modulation but fully overlooked the important results obtained with rituximab that have been reported in the prevention of acute and chronic GVHD.

Initial reports on the potential role of rituximab in chronic GVHD addressed the treatment of steroid refractory chronic GVHD.[2-10] Up to 100% response was reported, including responses in all organ systems affected.[11] Apart from a therapeutic effect, there is also evidence for a prophylactic effect of rituximab on acute and chronic GVHD.

In 2005, the author presented the hypothesis that the risk of chronic GVHD could be reduced by administration of rituximab at initial diagnosis of chronic GVHD. The aim would be to cure the initial manifestation and prevent development of new manifestations of chronic GVHD.[12] Since then, several papers have discussed the prophylactic use of rituximab for acute and chronic GVHD.

Khouri *et al.*[13] reported 11 patients with lymphocytic lymphoma who received cyclophosphamide and fludarabine conditioning. Nine patients also received rituximab on Days -6, +1, +8 and +15. GVHD prophylaxis consisted of tacrolimus and methotrexate. The cumulative incidence of grade II-IV GVHD was 20%; one patient developed grade III GVHD.

Kebriaei *et al.*[14] reported 35 patients who received an ablative allogeneic HLA-identical or unrelated donor transplant for acute lymphoblastic leukemia. Rituximab 375 mg/m^2 was administered four times starting Day -7. GVHD prophylaxis consisted of tacrolimus and methotrexate. The cumulative incidence of acute GVHD was 17% and there was 43% limited and extensive chronic GVHD at two years.

Khouri *et al.*[15] reported 47 patients with follicular lymphoma who received cyclophosphamide and fludarabine conditioning and rituximab on Day -13 (375 mg/m^2) and Days -6, +1 and +8 (1000 mg/m^2). GVHD prophylaxis consisted of tacrolimus and methotrexate. The cumulative incidence of grade II-IV acute GVHD was 11%. Five patients had grade II and one patient grade III GvHD. The incidence of limited and extensive chronic GVHD was 60% and 36%, respectively. Of the 28 patients who developed chronic GVHD, 20 (71%) had *de novo* onset. Infections were the major cause of death. No patients died as a result of GVHD.

Christopeit *et al.*[16] reported a retrospective study of 34 patients; 13 received rituximab 375 mg/m^2 in the conditioning regimen and 4 received 375 mg/m^2 on Days + 31, +49, +69 and +89 to prevent posttransplant lymphoma. Acute GVHD occurred in 18% of patients with and 82% without rituximab, and grade II-IV occurred in 18% and 53%, respectively. Rituximab added to ATG was more effective in preventing acute GVHD grade II-IV than ATG alone (0% *vs.* 30%).

Ratanatharathon *et al.*[17] reported a retrospective study of 179 patients who received rituximab in the conditioning regimen compared to 256 B-cell lymphoma patients who did not receive rituximab within the six months prior to transplantation. The rituximab cohort had a significantly lower incidence of treatment-related mortality (30% *vs*. 37%) and low grade of acute GVHD grade II-IV (36% *vs*. 48%) and grade III-IV (12% *vs*. 23%). There was no difference in the risk of chronic GVHD (56% *vs*. 53%), disease progression or relapse. Progression free survival (56% *vs*. 41%) and overall survival (57% *vs*. 44%) were significantly better in the rituximab cohort.

Van Dorp *et al.*[18] reported 173 patients who had not received rituximab within the six months prior to reduced intensity conditioning and allogeneic transplant. Rituximab significantly reduced extensive chronic GVHD from 45.8% to 20.1%.

Crocchiolo *et al.*[19] retrospectively analyzed 57 patients with lymphoproliferative disorders and showed that rituximab within three months prior to transplantation prevented acute GVHD grade II-IV: 10% *vs.* 48% in the non-rituximab group and acute GVHD grade III-IV in 0% and 24%, respectively. No impact on chronic GVHD was observed.

Dominietto *et al.*[20] retrospectively analyzed 55 patients who received rituximab 200 mg on Day +5 post allogeneic transplant to prevent EBV DNAemia. They observed that the cumulative incidence of grade II-IV acute GVHD was significantly reduced in rituximab patients (20% *vs.* 38%). There was no effect on chronic GVHD. As result of reduced treatment-related mortality, there was a trend towards improved overall survival: 46% in the rituximab cohort *versus* 40% in the non-rituximab cohort.

Arai *et al.*[21] evaluated prophylactic rituximab 375 mg/m^2 two months after transplantation (Day +65 through Day +77). Patients with lymphoid malignancies received TLI and ATG prior to allogeneic transplantation. The incidence of acute GVHD was 6% and the cumulative incidence of chronic GVHD was 20%. Non-relapse mortality was 3%. The authors concluded that rituximab significantly reduced B-cell allogeneic immunity.

In summary, this overview shows that pre- or peri-transplant rituximab has a prophylactic effect for acute GVHD but the results for chronic GVHD by rituximab administration at this time are not conclusive and, indeed, rather show no effect.[15,17-20] However, two months post transplant rituximab seems to reduce the incidence of acute and chronic GVHD.[21] Treatment of chronic GVHD does also prevent new manifestations and is curative.[9] Our hypothesis that rituximab at the time of initial diagnosis of chronic GVHD may cure the manifestation and may prevent development of other manifestations of chronic GVHD still holds and should be evaluated in a randomized study.[12] No editorial or perspective is complete without reference to the effect of anti-CD20 on B-cell allogeneic immunity.[1]

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