To the editor:

Prophylaxis with defibrotide prevents veno-occlusive disease in stem cell transplantation after gemtuzumab ozogamicin exposure

Gemtuzumab ozogamicin (GO; Mylotarg; Wyeth, PA) is a humanized anti-CD33 antibody conjugated to the cytotoxic agent calicheamicin. Although the efficacy of this agent is now being explored in phase 3 trials, there is significant concern about the risk of hepatic injury consequent on exposure to GO, particularly in relation to the incidence of veno-occlusive disease (VOD) after allogeneic stem cell transplantation (SCT). In a recent article in this journal, Wadleigh et al described 14 adults with AML who had received GO therapy prior to allogeneic SCT, of whom 9 (64%) developed VOD compared with only 4 (8%) of 48 who had not received GO.1 Regression analysis highlighted a short interval (< 3 months) between GO exposure and conditioning as conveying the greatest risk for the development of VOD after SCT. In an accompanying editorial it was suggested that, based on these data, allogeneic SCT should not take place within 3.5 months of GO therapy.2

In light of the above information, we wish to draw attention to our experience with 7 children who received GO within 2 months of transplantation, with emphasis on the occurrence and management of VOD. Between July 2001 and July 2003, 4 boys and 3 girls with a median age of 6 years (range, 1-12 years) with more than 30% CD33+ myeloid blasts in the marrow were treated with GO as a single agent as cytodestruction prior to SCT. Of these children, 2 (unique patient number [UPN] 2 and UPN 5) had primary refractory AML, having failed 2 courses of therapy as per AML XII3 and subsequent exposure to at least one course of FLAG4; 5 children with refractory relapse (all had a first complete remission [CR1] of < 12 months following therapy with AML XII) had failed 2 courses of fludarabine, Ara-C, G-CSF (FLAG) with or without Daunoxome (Gilead, Foster City, CA). Between 1 and 4 doses of GO were given in a dose of 9 mg/m² per dose. SCT from the best available donor was then undertaken with conditioning planned to commence 14 to 21 days after exposure to the final dose of GO. The median interval between GO exposure and day 0 of SCT was 32 days (range, 27-60 days). All patients except UPN 6 received full-intensity conditioning busulphan (20 mg/kg)/cyclophosphamide (120 mg/kg) (2 cases); cyclophosphamide (120 mg/kg) total body irradiation (TBI; 14.4 Gy) (3 cases); and TBI (13.2 Gy) melphalan (100 mg/m²) (1 case). UPN 6 received a reduced intensity conditioning (fludarabine 125 mg/m² and melphalan 100 mg/m²) due to concerns over anthracycline-induced cardiomyopathy. UPN 1 underwent SCT 27 days after a single dose of GO due to concerns over the risk of VOD. Ursodeoxycholic acid was given as VOD prophylaxis. No hepatic problems occurred. UPN 2 received 2 doses of GO for, last 28 days prior to day 0 of SCT. This patient developed severe VOD that was successfully treated with defibrotide (40 mg/kg per day in 4 doses). Subsequently, all patients who underwent SCT after GO received prophylactic defibrotide initially, at 10 mg/kg per day for UPN 3 and then at 20 mg/kg per day for UPN 4 to UPN 7 as VOD prophylaxis. Defibrotide was administered by infusion from the beginning of conditioning until day +30. No VOD was seen in these patients. No adverse effects of the defibrotide—in particular no excess of bleeding—were seen. As might be expected with such a high-risk cohort of patients, the overall clinical outcome is poor, with only 2 patients (UPN 6 and UPN 7) alive and in remission at 3 and 5 months after SCT. Four patients (UPN 1, UPN 3, UPN 4, and UPN 5) suffered relapse at 7, 5, 17, and 1 month after SCT, respectively; UPN 2 died in remission of disseminated adenovirus 7 months after SCT.

These limited early data suggest that defibrotide may have a role in preventing life-threatening VOD in patients undergoing SCT following recent exposure to GO. We do of course acknowledge that our experience relates to children primarily receiving T-cell–depleted alternative donor grafts, a group traditionally thought to be at low risk for VOD. Nevertheless, all of these children had received at least 3 courses of intensive therapy prior to GO and 6 of 7 received full-intensity conditioning. Thus, at present we believe that, at least in children, recent exposure to GO should not be seen as contraindication to SCT but rather as an indication for appropriate prophylaxis against VOD.

Brigitta Versluys, Rajat Bhattcharaya, Collin Steward, Jackie Cornish, Anthony Oakhill, and Nick Goulden

Correspondence: N. Goulden, Oncology Day Beds Bristol Children’s Hospital, Bristol, United Kingdom BS2 8BJ; e-mail: nick.goulden@ubht.swest.nhs.uk.

References


To the editor:

CD38 on B-cell chronic lymphocytic leukemia cells has higher expression in lymph nodes than in peripheral blood or bone marrow

We read with great interest the paper by Deaglio et al1 analyzing signaling through the CD38 molecule on B-lymphocytes in chronic lymphocytic leukemia (B-CLL). Their results suggest that CD38 is a receptor on B-CLL cells that transduces activation/differentiation signals. In B-CLL, CD38 expression can differentiate naïve from memory cells, and has prognostic impact with higher expression having inferior prognosis.2 Since CD38 can be differently expressed and can have different biologic functions during B-cell

To the editor:

Efficacy of alemtuzumab treatment for refractory T-cell large granular lymphocytic leukemia

T-cell large granular lymphocytic leukemia (T-LGL) is a clonal lymphoproliferative disorder representing approximately 2% to 3% of all lymphoproliferative diseases. Clonal lymphocytes express CD3, CD8, CD16, and CD5 and share a common rearranged T-cell receptor (TCR). Clinically, the bone marrow, spleen, and liver are extensively infiltrated by LGL, resulting in chronic neutropenia, anemia, and subsequent life-threatening infections. The pathogenesis of these cytopenias is thought to be immune-mediated immunosuppression. Thus, standard therapy utilizes immunosuppressive and/or chemotherapeutic agents. However, none have proven to be universally effective in achieving durable disease control.

References

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Ozren Jaksic, Mirjana Mariana Kardum Paro, Ika Kardum Skelin, Rajko Kusec, Vlatko Pejsa and Branimir Jaksic