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 cytoreduction 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 XII[3] and subsequent exposure to at least one course of FLAG[4]; 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/m^2 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/m^2) (1 case). UPN 6 received a reduced intensity conditioning (fludarabine 125 mg/m^2 and melphalan 100 mg/m^2) 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.

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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 al[1] 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 naive 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

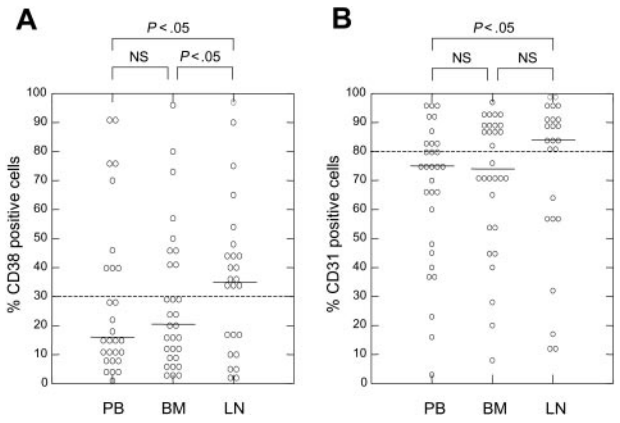

Figure 1. CD38 and CD31 expression by lymphoid compartments in patients with B-CLL. Results are presented as the percentage of (A) $CD38^+$ and (B) $CD31^+$ cells, and the medians are marked by solid lines. Dotted lines indicate arbitrary cutoffs. NS indicates not significant.

development in different lymphoid compartments, Deaglio et al[1] surmise that CD38 can be up-regulated in lymph nodes and bone marrow where interactions with other cells and cytokines take place. We would like to add on this issue by our analysis of the expression of CD38 and its ligand CD31 in bone marrow (BM) and lymph nodes (LNs) in addition to peripheral blood (PB).

In 33 untreated patients with B-CLL with typical immunophenotype ($CD5^+CD19^+CD23^+sIg^{dim}$), we analyzed by flow cytometry the expression of CD38 (detected by fluorescein isothiocyanate [FITC]–labeled monoclonal antibody [mAb; DAKO, Glostrup, Denmark]) and CD31 (detected by FITC-labeled mAb [Serotec, Oxford, United Kingdom]) on $CD19^+$ cells (detected by phycoerythrin-labeled mAb [DAKO]). Results were analyzed as mean fluorescence intensity (MFI) and standardized/quantified by determining molecules of equivalent fluorochrome (MEFs; Fluorospheres, DAKO) and expressed as percentage of positive cells. Fresh samples were taken on the same day from PB, BM, and LN (by fine needle aspiration biopsy in 28 patients). There were 18 men and 15 women (median age, 65 years); 11, 14, and 8 patients were in Binet stage A, B, and C, respectively.

We found significantly higher CD38 expression in LN compared with BM or PB (median percentage 35%, vs 20% or 16%, respectively; $P < .05$; Wilcoxon matched pair test; for percentage, MFI, and MEFs, see Figure 1A). No significant difference was found between PB and BM, similarly to Hamblin et al[3] and Arena et al,[4] whereas Ghia et al[5] found higher CD38 expression in BM in a subset of analyzed patients. We found expression of CD31 to be higher than expression of CD38 in all compartments. There was a higher percentage of $CD31^+$ cells in LN than in PB ($P < .05$; Fisher test; $> 80\%$ vs $\leq 80\%$ positivity, but not in other tests; Figure 1B). CD38 MEFs correlate with CD31 MEFs in each lymphoid compartment ($r = 0.55$; $P < .05$).

Higher CD38 expression in all compartments was associated with more advanced clinical stage ($P < .05$). The ratio of CD38/CD31 expression, especially in LN, has a more pronounced association with clinical parameters including BM insufficiency ($P < .05$), lymphoma-like tumor distribution[6,7] ($P < .05$), and clinical stages ($P < .05$), suggesting possible interactions with coexpressed CD31.[1,8] Patients with a higher CD38 expression ratio in LN relative to PB or BM have lymphoma-like tumor distribution ($P < .05$) and a diffuse BM infiltration pattern ($P < .05$), suggesting more aggressive disease irrespective of CD38 level.

Our results show that the levels of CD38 expression and to a lesser extent CD31 are significantly associated with lymphoid compartments. The higher expression in LN is probably related to different proliferation/activation status and up-regulation of CD38. It is of interest to stress that CD38 expression in LN as compared with PB or BM has a stronger relationship with clinical disease parameters.

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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 lymphocytic leukemias.[1] Clonal lymphocytes express CD3, CD8, CD16, and CD5 and share a common rearranged T-cell receptor (TCR).[2] 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.[3] However, none have proven to be universally effective in achieving durable disease control.[4]