Response:

BCL6 and outcome in diffuse large B-cell lymphoma: a work in progress

In patients with a median age of 69 years, we believe the results reported by Winter et al in patients receiving cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP) followed by maintenance rituximab for BCL6+ diffuse large B-cell lymphoma (DLBCL) will indeed be difficult to improve upon; the 2-year failure-free survival (FFS) for this specific subgroup was 82%. Dunleavy et al are contending that these results are an overestimation since they include only the patients that had a complete or partial response to induction therapy; however, this is not the case. The subset of patients enrolled in E4494 for the analysis by Winter et al was selected on the basis of the following: Southwest Oncology Group (SWOG)/Eastern Cooperative Oncology Group (ECOG) patients, tissue availability, and staining for BCL6. We agree, however, if one focuses on the patients treated with R-CHOP and analyzes the data by intent to treat, excluding the use of maintenance rituximab, then the results offer only a modest improvement over CHOP chemotherapy; the 3-year FFS is approximately 40% as suggested by Dunleavy et al. However, it is not valid to compare this study with that of the National Cancer Institute (NCI) single-center phase 2 study of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R), where FFS is 88% with all the well-known problems with selection bias in a small single-center trial involving a much younger patient population. If these study populations could be well balanced, a small difference in outcome would require a large randomized study to establish the superiority of either R-CHOP-21 with or without maintenance or DA-EPOCH-R. One may be able to look at this subgroup in the ongoing Cancer and Leukemia Group B (CALGB) phase 3 trial comparing R-CHOP-21 and DA-EPOCH-R, but we would predict that any improvement in this elderly cohort will be small.

We agree with Dunleavy et al that the BCL6+/− division in the Winter et al paper likely was at best a rough surrogate for cell of origin. BCL6 expression is seen in both germinal center (GC) and non-GC lymphoma, though more common in the former. Immunohistochemistry (IHC) classification of the samples with CD10, BCL6, MUM1, and possibly FOX P1 would provide a better definition of cell of origin. It would be interesting to see if the correlation of outcome was more closely related to cell of origin or BCL6 expression. Without these data, it is difficult to know if the benefit of rituximab was related to cell of origin or more specifically to BCL6 expression. Without these data, it is premature to speculate on the mechanisms by which rituximab may be acting in these tumors.

We agree that rituximab may not be needed in all subsets of DLBCL. However, before the practicing oncologist eliminates rituximab from the treatment of newly diagnosed DLBCL, we need to be certain that we can prospectively identify the patients who will not benefit from rituximab.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References


To the editor:

Hepatitis C virus and alanine aminotransferase kinetics following B-lymphocyte depletion with rituximab: evidence for a significant role of humoral immunity in the control of viremia in chronic HCV liver disease

The mechanisms involved in the clearance from plasma of approximately 10^12 copies of hepatitis C virus (HCV) produced daily are unclear. The use of the anti-CD20 monoclonal antibody rituximab, which reversibly depletes B cells, in HCV-related mixed cryoglobulinemia afforded an opportunity to study the potential role of humoral immunity.

We evaluated chronicologic changes in plasma HCV RNA, and alanine aminotransferase (ALT) levels, in a 40-year-old male with chronic genotype 1 HCV-related cryoglobulinemia after 2 courses of rituximab (375 mg/m^2 per week for 4 weeks, 70 weeks apart). Antiviral therapy, including pegylated interferon, reduced baseline viral load (VL) from 122 000 IU/mL to less than 7000 IU/mL. Therapy was maintained throughout. VL increased from less than 7000 IU/mL to 252 893 IU/mL within 2 weeks of starting rituximab infusions. It continued to rise progressively to 379 000 IU/mL by week 23 (Figure 1). B-cell markers, including CD20, CD19, CD21, IgM, IgD, IgG, and CD72, were absent from peripheral blood up to week 13. Thereafter, B-cell frequency increased to 8% by week 32. Although there is evidence for HCV replication in B cells, the continued rise in VL after B-cell depletion argues against this as a source of HCV RNA increase.

Following reappearance of B cells, VL decreased starting from week 23 to less than 615 IU/mL by week 63. A second 4-week course of rituximab infusions at week 70 similarly resulted in a prompt, more than 2-log rise in VL to 202 000 IU/mL (Figure 1).

On both occasions, rituximab increased ALT levels transiently. This suggests increased de novo infection and that B cells may play a protective role, thus accounting for the more rapid disease progression in immunodeficiency disorders. A second ALT level flare at week 27 coincided with the reappearance of B cells and HCV RNA decline. We speculate that this might indicate antibody-dependent cellular cytotoxicity.

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To the editor:

Are Erk, Btk, and PECAM-1 major players in GPIb signaling? The challenge of unraveling signaling events downstream of platelet GPIb

Several recently published studies in Blood have attempted to unravel the signaling events operating downstream of GPIb. One of these studies by Garcia et al examined the role of Erk in promoting VWF/GPIb-dependent activation of integrin αIbb3 in platelets. These investigators analyzed changes in Erk phosphorylation in VWF/ristocetin-stimulated platelets and examined the effects of a range of pharmacological signaling inhibitors on Erk activation and integrin αIbb3-dependent platelet aggregation. Based on these studies, the authors conclude that there is an important role for Erk in GPIb signaling and propose a model in which GPIb initiates a linear signaling cascade involving Src kinases → PLC → MEK → Erk → PLA2 that stimulates integrin αIbb3 and platelet aggregation through an indirect mechanism dependent on the generation of TXA2. Although the results presented are consistent with such a model, we have some concerns with the definitive nature of these conclusions.

The main concern is fundamental and relates to the individual contributions of GPIb and integrin αIbb3 to VWF-induced signaling. It is generally accepted that the VWF-GPIb interaction induces weak signals to initiate integrin αIbb3 activation, and the subsequent VWF binding to activated integrin αIbb3 in concert with released ADP and TXA2 triggers global platelet activation. Thus, many of the commonly used suspension-based functional assays to investigate signals downstream of soluble agonist receptors (ie, classical platelet aggregation, secretion, or ligand binding to activated integrin αIbb3) are not ideal for analysis of signals derived exclusively downstream of GPIb. In particular, when VWF/ristocetin or VWF/botrocetin induces biphasic platelet aggregation the authors need to consider that output signals are derived from both GPIb and integrin αIbb3, not solely from GPIb. These factors compound the analysis of the findings presented by Garcia et al and also those by Liu et al investigating a role for Btk in GPIb signaling and Rathore et al examining PECAM-1 regulation of GPIb signals.

It should be acknowledged that dissecting signaling events downstream of GPIb is difficult, mainly because GPIb-induced signals per se are weak regardless of the experimental approaches used. Elucidating GPIb-specific signaling events independent of...
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