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LETTER TO THE EDITOR

Impact of low-dose rituximab on splenic B cells: evidence for the shaving reaction

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We read with great interest the recent report in this journal by Toki *et al.* [1] on the use and demonstrated efficacy of low doses (15–150 mg/m^2) of rituximab (RIT) to eliminate splenic B cells in renal transplant patients. The authors noted that 'administration of low-dose RIT at <375 mg/m^2 has rarely been studied'. While this is indeed true with respect to the use of RIT in immunosuppressive paradigms, 3 years ago we demonstrated that low RIT doses (20 mg/m^2), given thrice weekly, could be quite effective in promoting rapid clearance of circulating malignant B cells in chronic lymphocytic leukemia (CLL) [2]. We initiated the low-dose approach in CLL because we observed that higher RIT doses promoted *loss of CD20* from targeted B cells ('shaving'), rendering the cells refractory to RIT treatment [3]. Under these latter conditions, B cell-bound RIT-CD20 complexes are transferred to and internalized by cells that express Fc receptors [4]. This process, formerly described as antigenic modulation, appears to be quite similar to trogocytosis [5,6]. We found that lower, more frequent doses of RIT preserved CD20 levels on CLL cells in the circulation, promoting their continued clearance as the cells re-equilibrated from other compartments [2]. The B cell burden in CLL can be quite high (approximately 100 000 cells per μl), and our observations that low doses of RTX could clear this large burden of circulating cells provided proof of principle for the following concept: at moderate RIT doses, the limiting factor(s) in B cell clearance is most likely the capacity of the body's effector mechanisms, mediated by macrophages, NK cells and complement, to eliminate RIT-opsonized cells [7]. The results reported by Toki *et al.* support the idea that lower RIT doses are indeed adequate for targeting the relatively low burden of normal B cells.

Toki *et al.* [1] also reported immunochemical analyses which revealed that CD79a$^+$CD20$^-$ cells, most likely B cells, were demonstrable in spleens of patients after RIT therapy. The authors suggested that these cells were immature B cells, or that the CD20 epitope was blocked on cells after RIT treatment. We suggest an alternative explanation, based on considerable precedence: Our work in a xenograft mouse model has revealed that high RTX doses can promote loss of CD20 from malignant human B cells in solid tumors, indicating that the shaving reaction can occur in tissues [8]. Moreover, as we have noted in a recent review, other groups have reported that treatment of patients with RIT can lead to generation of CD20$^-$ B cells in other compartments, including bone marrow and synovium [7]. In all of these cases, including the observations of Toki *et al.*, we suggest that as a consequence of local exhaustion of effector mechanisms, CD20 and bound RIT were removed from opsonized cells because of shaving. Several methods are available to demonstrate shaving [4,9], and it should be possible to determine if this mechanism explains the generation of CD20$^-$ cells reported by Toki *et al.*

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