To the editor:

Treatment of viral hepatitis B infection in patients receiving intensive immunosuppressive therapies

We read with great interest the paper written by Raymond Liang,[1] which represents an excellent and complete overview of the management of hepatitis B virus (HBV) infection during treatment of hematologic malignancies. Nevertheless, we would like to focus on the particular situation of HIV-HBV–coinfected patients. In our opinion, several points must be underlined because they lead to special attention when a hematologic malignancy, especially high-grade B lymphoma, is diagnosed in this population.

Prevalence of HBV infection is higher in HIV patients than in the general population. Moreover, in these cases, immunosuppression is generally more severe due to the coexistence of lymphoma and HIV. Addition of rituximab to the CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) regimen in HIV lymphoma patients has increased the response rate, but its immunosuppressive effects have, in some reports, led to an increase in infectious complications.[2]

Specific therapeutic considerations on the use of anti-HBV drugs must also be made. At first, it is important to remember that in HBV-HIV–coinfected patients, unlike HIV-negative patients, the use of 2 anti-HBV drugs is generally recommended.[3] Tenofovir and lamuvidine are generally the recommended choices. Furthermore, several anti-HBV drugs (lamuvidine, tenofovir, emcitrabine, and entecavir) also have a potent activity against HIV. So these drugs should be used not alone, but as part of a highly active antiretroviral therapy against HIV. To omit this important aspect could lead to the appearance of mutations in HIV genome and, finally, to resistance to antiretroviral therapy.

Philippe Genet, Tahar Touahri, and Veronique Morel

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

Correspondence: Philippe Genet, Department of Hematology, Centre Hospitalier Victor Dupouy, 69 rue du lieutenant colonel prudhon, Argenteuil, France 95100; e-mail: philippe.genet@ch-argenteuil.fr.

References

1. Liang R. How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood. 2009;113:3147-3153.
2. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood. 2006;106:1538-1543.
3. Rockstroh JK, Bhagani S, Benhamou Y. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. HIV Med. 2008;2:82-88.

To the editor:

When is a predose a dose too much?

We read with great interest the review by Sharkey and colleagues[1] that provides a fascinating and informative perspective on the practice of delivering a "cold" or predose of monoclonal antibody (mAb) before the delivery of the radioimmunconjugate in radioimmunotherapy (RIT) of B-cell lymphoma.

This review is important as it raises several clinically relevant questions to the application of RIT in the rituximab era. Predosing with unlabeled or "cold" anti-CD20 mAb has become standard practice in RIT targeting the CD20 antigen.[2,3] The predose has been shown to increase tumor targeting of the labeled mAb by blocking "nonspecific" binding sites such as circulating and splenic B cells and is used in both licensed RIT approaches (^{90}Y-ibritumomab tiuxetan [Zevalin] and ^{131}I-tositumomab [Bexxar]). It is indeed timely to readdress the question of the optimal approach to predose, as in contrast to the pioneering studies, the majority of patients who are currently suitable for RIT have received rituximab.

The recent publication of the FIT study has provided compelling evidence for the efficacy of ^{90}Y ibritumomab after induction chemotherapy with patients randomized to RIT enjoying more than a 2-year improvement in progression-free survival.[4] However, the majority of patients in this study did not receive rituximab containing regimens. Therefore an important question in current clinical practice is whether predose is necessary as part of an RIT consolidation therapy after rituximab containing chemotherapy. This issue comes into sharper focus, if as suggested by Sharkey and colleagues, repeated doses of rituximab may prevent subsequent binding of radiolabeled anti-CD20 antibody to tumor and thus potentially compromise tumor targeting and clinical efficacy. Further uncertainty arises when examining the relative paucity of data on which the current licensed RIT approaches are given.[2,3] The licensed predosing regimen for ^{90}Y-ibritumomab was based on just 6 patients with differences observed in the biodistribution between 125 mg/m^2 and 250 mg/m^2 of rituximab and the higher dose was selected on the basis of the potential increased clinical activity of large doses of rituximab.[3]

Sharkey and colleagues cite recent preclinical evidence supporting the view that rituximab, if given in high enough doses, blocks the binding of the anti-CD20 radioimmunoconjugate in a Burkitt lymphoma xenograft model.[5] In such xenograft models there is no cross-reactivity of the predose mAb targeting the normal host B-cell reservoir, leaving a finite antigen sink that is entirely limited to the small human tumors. In this context it is perhaps not surprising the tumors can be saturated with large enough doses of

rituximab. Perhaps these important questions must ultimately be addressed in well designed clinical studies?

Currently there is a lack of evidence from clinical studies that prior rituximab compromises subsequent anti-CD20 based RIT. In stark contrast to the preclinical data, recent phase II clinical data using several doses of induction therapy with rituximab alone or as part of Rituximab containing chemotherapy have led to excellent clinical efficacy with high rates of conversion from partial to complete response after RIT.[6] Our own recently published study attempts to address this predose question. We found that induction therapy with rituximab significantly increases the effective half-life of subsequent ^{131}I-rituximab and correlated with increased effective half-life of the ^{131}I-rituximab.[7] Importantly, we demonstrated that multiple doses of rituximab did not appear to compromise the clinical efficacy or increase the myelotoxicity of subsequent anti-CD20 targeted RIT.

Targeting another antigen such as CD45, as suggested in the review,[1] certainly bypasses the possible CD20 antigen competing effect from rituximab and is potentially an important approach to explore further. However, such an approach does not negate the predose issue, as the same dilemma remains as to how best to improve the targeting of radiolabeled anti-CD45 antibody targeting with a predose of anti-CD45.

The concern over excessive predosing adversely affecting tumor targeting in anti-CD20 based RIT remains an important theoretical concern. However decreased targeting leading to decreased efficacy of RIT has not thus far been observed in the clinic and if there is a deleterious effect with large amounts of mAb predosing, this does not appear to substantially affect the clinical efficacy.[7] Perhaps of greater concern in improving outcomes for patients with follicular lymphoma is the gross under usage of RIT. In an era where immunochemotherapy has substantially improved outcome, it is perhaps easier to become complacent that using such an effective treatment is not required in the treatment algorithm of follicular lymphoma. For those with low risk FLIPI disease that achieve long-lasting complete remission with rituximab containing regimens that may be so; however lest us not forget the heterogeneity of this disease, the toxicity associated with multiple courses of anthracycline based chemotherapy and the increasing number of patients who will in time become refractory to chemotherapy and rituximab. For the latter groups the unique mechanisms of action of RIT have resulted in high activity with durable remissions in both chemotherapy and rituximab refractory disease.[8,9] Perhaps what is currently required, as suggested by Sharkey and colleagues, is a "re-examination of radioimmunotherapy in the treatment of non-Hodgkin lymphoma" and an integration of this unique approach for some patient groups with follicular lymphoma. There is little doubt that RIT can be enhanced further by adopting the type of RIT/antibody combinations suggested and that such an approach could provide a viable alternative or enhance the responses for patients receiving immunochemotherapy regimens. By adopting such a considered re-examination this will ensure that the future is radiant for many patients with difficult to treat follicular lymphoma and potentially other NHL as well.

Tim Illidge and Yong Du

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

Correspondence: Dr Timothy M. Illidge, School of Cancer and Imaging Sciences, University of Manchester Christie Hospital, Wilmslow Rd, Manchester M20 4BX, United Kingdom; e-mail: tmi@manchester.ac.uk.

References

1. Sharkey RM, Press OW, Goldenberg DM. A re-examination of radioimmunotherapy in the treatment of non-Hodgkin lymphoma: prospects for dual-targeted antibody/radioantibody therapy. Blood. 2009;113:3891-3895.
2. Kaminski MS, Zasadny KR, Francis IR, et al. Radioimmunotherapy of B-cell lymphoma with [131I]anti-B1 (anti-CD20) antibody. N Engl J Med. 1993;329:459-65.
3. Witzig TE, White CA, Wiseman GA, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma. J Clin Oncol. 1999;17:3793-803.
4. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol. 2008;26:5156-5164.
5. Gopal AK, Press OW, Wilbur SM, Maloney DG, Pagel JM. Rituximab blocks binding of radiolabeled anti-CD20 antibodies (Ab) but not radiolabeled anti-CD45 Ab. Blood. 2008;112:830-835.
6. Jacobs SA, Swerdlow SH, Kant J, et al. Phase II trial of short-course CHOP-R followed by 90Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. Clin Cancer Res. 2008;14:7088-7094.
7. Illidge TM, Bayne M, Brown NS, et al. Phase 1/2 study of fractionated (131)I-rituximab in low-grade B-cell lymphoma: the effect of prior rituximab dosing and tumor burden on subsequent radioimmunotherapy. Blood. 2009;113:1412-1421.
8. Fisher RI, Kaminski MS, Wahl RL, et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. J Clin Oncol. 2005;23:7565-7573.
9. Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. J Clin Oncol. 2005;23:712-719.

To the editor:

APO866 activity in hematologic malignancies: a preclinical in vitro study

Nahimana and coworkers have recently reported that the nicotinamide phosphoribosyltransferase (NAMPT) inhibitor APO866 elicited massive cell death in primary leukemia cells and in numerous leukemia/lymphoma cell lines.[1] In particular, in 32 primary leukemias (including 12 B-cell chronic lymphocytic leukemias [B-CLLs]) these authors found that a 96 hour-exposure to 10 nM APO866 resulted in a median "fraction of dead cells" (fdc, annexin-V $[AV]^+$ cells) of 97%. Moreover, APO866 EC50, as measured by MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetratolium bromide] colorimetric assay in 45 established hematologic cancer cell lines ranged between 0.09 and 27.2 nM. Similar experiments were performed by our group on 29 primary leukemia cell samples (23 B-CLLs, 1 T-cell chronic lymphocytic leukemia [T-CLL], and 5 acute myeloid leukemias [AMLs]). We determined cell viability by AV–propidium iodide (PI) staining and flow cytometry. Specific cell death (scd) was calculated with the formula: $(x_t - x_m/100 - x_m) \times 100$, where x_t was the number of AV^+ cells in response to a given APO866 concentration and x_m were the AV^+ elements among the untreated cells. In our hands, susceptibility to APO866 among primary leukemia cells was heterogeneous (Figure 1A,B). Most cases exhibited a minor decrease in cell viability after a 96-hour exposure to APO866, while only in 1 B-CLL sample the scd was 89%. In almost all of our titration experiments (1 nM-1 μM),