

LETTER TO THE EDITOR

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Radioimmunotherapy consolidation and rituximab maintenance in the initial treatment of follicular lymphoma

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Abstract

Several reports have documented similar efficacies and tolerable toxicities of radioimmunotherapy (RIT) consolidation and rituximab maintenance after initial R-chemotherapy of follicular lymphoma. The relative merits of these two interventions are currently under discussion. We now raise the question whether both RIT consolidation and rituximab maintenance should be used together aiming to augment the results achievable with R-chemotherapy.

Keywords: Radioimmunotherapy consolidation, Rituximab maintenance, Follicular lymphoma

Letter to the Editor

The recent review of T.M. Illidge on radioimmunotherapy (RIT) of lymphoma highlighted the inherent potential of this particular treatment [1]. While convinced of the efficacy of RIT he regretted the low implementation of RIT in current clinical practice.

We would like to elaborate further on the biological agents that have shown efficacy in treatment of follicular lymphoma. In a small series of relapsed indolent lymphoma patients treated in Switzerland with ¹³¹I-tositumomab (Bexxar[®], GlaxoSmithKline, Brentford, UK), we experienced several long-lasting complete remissions with six of 12 patients (50%) reaching 10-years progression free survival without any further treatment [2]. Similar 10-year progression-free survivals after ¹³¹I-tositumomab in relapse have been reported by another group, though at a somewhat lower rate [3]. The Southwest Oncology Group (SWOG) has demonstrated that 67% of follicular lymphoma patients remained progression free more than 5 years after consolidation of CHOP chemotherapy with ¹³¹I-tositumomab [4]. Yet, another group has communicated a 50% complete response (CR) rate after 10 years following an initial treatment using abbreviated fludarabine combined with

¹³¹I-tositumomab [5]. A high number of persistent CRs at 5 to 6 years was also reported for ¹³¹I-tositumomab alone in the initial treatment of follicular lymphoma [6].

High efficacy of RIT with ⁹⁰Y-ibritumomab has also been reported repeatedly including a report demonstrating 5-year relapse free survival in about 20% of relapsed patients [7]; however, 10-year observations are currently not available to us.

⁹⁰Y-ibritumomab (Zevalin[®], Spectrum Pharmaceuticals, Henderson, NV, USA) is the only RIT currently approved in Europe, and its successful use in consolidation treatment following chemotherapy has been well documented [8]. On the other hand, rituximab (Mabthera[®], Rituxan[®], Roche Ltd., Genentech, Basel, Switzerland) maintenance treatment after R-chemotherapy was recently shown to improve the relapse-free survival in a large phase III study [9].

Several reports have documented similar efficacies of RIT consolidation and rituximab maintenance, though these approaches have not been formally tested in a randomized trial. Both complementary treatments have moderate and/or transient side effects. The mode of action of these two added therapies, however, are different. Rituximab maintenance is an immunotherapy while ¹³¹I-tositumomab and ⁹⁰Y-ibritumomab are targeted radiation therapies administered in combination with two injections of moderate amounts of unlabeled antibody. The latter approach is supported by long-standing

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evidence showing that radiotherapy may occasionally be curative when used as initial treatment for localized follicular lymphoma [10]. We envision a similar potential for RIT given in advanced disease either alone or combined with chemotherapy, as initial treatment or in relapse [2,3,5].

The 10-year progression-free survival as observed after ^{131}I -tositumomab either alone or combined with chemotherapy, upfront or at relapse of follicular lymphoma, appears to be an important milestone. It is anticipated that this approach might afford a low recurrence rate in subsequent years, analogous to that observed after external beam radiotherapy [10]. The low-energy electrons emitted by ^{131}I are also prone to eradicate microscopic disease, as has been shown by others and us in RIT of small-sized lung or liver metastatic disease, respectively [11,12].

Further improved biological efficacy in NHL might be achieved by combining anti-CD20 rituximab treatment with other antibodies directed against other antigens, such as anti-CD22 or anti-CD40, utilizing humanized antibodies, or novel anti-CD20 antibodies with modified Fc domains providing increased affinity for Fc receptors and improved effector functions as discussed previously [13,14].

In current practice, rituximab has appropriately assumed a dominant position in treatment of lymphoma both in combination with chemotherapy and as maintenance [9]. We now raise the question whether both rituximab and RIT should be used together as complementary methods to augment the results achievable with chemotherapy and whether this combined modality approach might afford additive or synergistic benefit. This strategy might also allow reducing chemotherapy as has been shown with abbreviated fludarabine combined with RIT [5]. An attenuated R-CHOP as recently described for elderly patients could possibly be envisaged in such a triple therapy approach [15].

We acknowledge that there is currently little published data demonstrating the efficacy of anti-CD20 RIT following rituximab-containing induction chemotherapy regimens. This information gap will be partially remedied by a phase II study investigating this combined approach that has recently been piloted by SWOG in the NCT00770224 trial, which is assessing the toxicity and efficacy of R-CHOP induction chemotherapy followed by ^{131}I -tositumomab consolidation and 4 years of rituximab maintenance. This study will assess the potential impact of administering rituximab anti-CD20 antibody with CHOP prior to anti-CD20 RIT [16], though in this trial rituximab was deliberately omitted from the last two cycles of CHOP chemotherapy, to minimize blocking of CD20 antigenic sites prior to RIT. If favorable results are achieved in this phase II trial, a phase III

randomized study comparing this “triple” approach with maintenance rituximab alone or consolidation RIT alone following induction with R-chemotherapy would be warranted.

List of abbreviations

RIT: radioimmunotherapy; R-chemotherapy: rituximab and chemotherapy; R-CHOP: combined rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SWOG (US): Southwest Oncology Group.

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Authors' contributions

Both authors express in this letter their opinion, edited and corrected this letter and approved its final version.

Competing interests

OWP declares a compensated consultant and advisory role and having received honoraria from Hoffmann-LaRoche/Genentech and Spectrum Pharmaceuticals as well as having received research funding from Hoffmann-LaRoche/Genentech. FB has no competing interest to declare.

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References

1. Illidge TM: Radioimmunotherapy of lymphoma: a treatment approach ahead of its time or past its sell-by date? *J Clin Oncol* 2010, **28**:2944-2946.
2. Buchegger F, Antonescu C, Helg C, Kosinski M, Prior JO, Bischof Delaloye AB, Press OW, Ketterer N: Six of 12 relapsed refractory indolent lymphoma patients treated 10 years ago with ^{131}I -tositumomab remain in complete remission. *J Nucl Med* 2011, **52**:896-900.
3. Kaminski MS, Zelenetz AD, Press OW, Saleh MN, Leonard JP, Fehrenbacher L, Lister TA, Horner TJ, Williams VC, Lin TS, Vleisides C, Knox SJ, Wahl RL, Vose MJ: Tositumomab and I-131 Tositumomab achieves complete remissions lasting > 10 years in patients with chemotherapy-refractory low grade and transformed B-cell lymphomas. *Blood* 2010, **116**:Abstract 3960.
4. Press OW, Unger JM, Brazier RM, Maloney DG, Miller TP, LeBlanc M, Fisher RI: Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol S9911. *J Clin Oncol* 2006, **24**:4143-4149.
5. Martin P, Coleman M, Furman RR, Vallabhajosula S, Kim DS, Edelstein A, Morrison J, Elstrom R, Ruan J, Goldsmith SJ, Leonard JP: Fludarabine plus I-131 tositumomab as initial treatment for follicular lymphoma: half of patients in remission at over 10 years median followup. *Blood* 2010, **116**: Abstract 1785.
6. Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, Regan D, Kison P, Fisher S, Kroll S, Wahl RL: ^{131}I -tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med* 2005, **352**:441-449.
7. Witzig TE, Molina A, Gordon LI, Emmanouilides S, Schilder RJ, Flinn IW, Darif M, Macklis R, Vo K, Wiseman GA: Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium-90 ibritumomab tiuxetan. *Cancer* 2007, **109**:1804-1810.
8. Morschhauser F, Radford J, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, Huijgens PC, Kolstad A, d'Amore F, Gonzalez GM, Petrini M, Sebban C, Zinzani PL, van Oers MHJ, van Putten W, Bischof-Delaloye A, Rohatiner A, Salles G, Kuhlmann J, Hagenbeek A: 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.
9. Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D, Xerri L, Feugier P, Bouabdallah R, Catalano JV, Brice P, Caballero D, Haioun C, Pedersen LM, Delmer A, Simpson D, Leppa S, Soubeyran P, Hagenbeek A,

- Casasnovas O, Intratumorachai T, Fermé C, da Silva MG, Sebban C, Lister A, Estell JA, Milone G, Sonet A, Mendila M, Coiffier B, Tilly H: **Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial.** *Lancet* 2011, **377**:42-51.
10. Mac Manus MP, Hoppe RT: **Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University.** *J Clin Oncol* 1996, **14**:1282-1290.
 11. Sharkey RM, Weadock KS, Natale A, Haywood L, Aninipot R, Blumenthal RD, Goldenberg DM: **Successful radioimmunotherapy for lung metastasis of human colonic cancer in nude mice.** *J Natl Cancer Inst* 1991, **83**:627-632.
 12. Vogel CA, Galmiche MC, Buchegger F: **Radioimmunotherapy and fractionated radiotherapy of human colon cancer liver metastases in nude mice.** *Cancer Res* 1997, **57**:447-453.
 13. Sharkey RM, Karacay H, Goldenberg DM: **Improving the treatment of non-Hodgkin lymphoma with antibody-targeted radionuclides.** *Cancer* 2010, **116**:1134-1145.
 14. Buchegger F, Press OW, Delaloye Bischof A, Ketterer N: **Radiolabeled and native antibodies and the prospect of cure of follicular lymphoma.** *Oncologist* 2008, **13**:657-667.
 15. Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, Castaigne S, Coiffier B, Haioun C, Bologna S, Fitoussi O, Lepeu G, Fruchart C, Bordessoule D, Blanc M, Delarue R, Janvier M, Salles B, André M, Fournier M, Gaulard P, Tilly H, for the Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigators: **Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial.** *Lancet Oncol* 2011, **12**:460-468.
 16. 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.

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