the almost universal negative perceptions of chemotherapy. The impact of direct-to-consumer advertising is unknown,⁴ but patients would presumably be attracted by the concept of supportive care options (such as growth factors) that promise reduced toxicity, even if the evidence does not support this. Finally, the strong social media presence of pharmaceutical companies⁵ highlights the emerging role of new Web-based technologies as a marketing strategy that targets patients and clinicians.

Our data strongly suggest that medical oncologists in Australia are not necessarily motivated by financial gain to the extent that the treatment received by patients is affected. The extent to which our results can be generalized is unknown, but we would argue that the many factors affecting therapy received do each need to be considered before concluding any direct link between financial incentives and changed clinical practice. Ultimately, although oncologists need to be cognizant of the rising costs of health care, it is critical that we as clinicians are allowed to provide the best possible care for our patients and are not made to feel guilty for prescribing expensive therapies when these are the best option.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** Hui-li Wong, Roche Australia; Kathryn M. Field, Roche Australia; Jeremy D. Shapiro, Roche Australia; Joseph J. McKendrick, Roche Australia; Peter Gibbs, Roche Australia **Expert Testimony:** None **Patents:** None **Other Remuneration:** None

REFERENCES

1. Malin JL, Weeks JC, Potosky AL, et al: Medical oncologists' perceptions of financial incentives in cancer care. *J Clin Oncol* 31:530-535, 2013
2. Field K, Shapiro J, McKendrick J, et al: Metastatic colorectal cancer and management in public versus private hospitals: Similarities and differences. *J Clin Oncol* 30, 2012 (suppl 34; abstr 497)
3. Spurling GK, Mansfield PR, Montgomery BD, et al: Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: A systematic review. *PLoS Med* 7:e1000352, 2010
4. Gellad ZF, Lyles KW: Direct-to-consumer advertising of pharmaceuticals. *Am J Med* 120:475-480, 2007
5. Liang BA, Mackey TK: Prevalence and global health implications of social media in direct-to-consumer drug advertising. *J Med Internet Res* 13:e64, 2011

DOI: 10.1200/JCO.2013.49.5457; published online ahead of print at www.jco.org on July 15, 2013

Long-Term Results of Autologous Hematopoietic Stem-Cell Transplantation After High-Dose ⁹⁰Y-Ibritumomab Tiuxetan for Patients With Poor-Risk Non-Hodgkin Lymphoma Not Eligible for High-Dose BEAM

TO THE EDITOR: The purpose of this correspondence is to provide a 5-year update of our previously published trial with high-dose yttrium 90 (⁹⁰Y) –ibritumomab tiuxetan conditioning regimen in order to definitively confirm our preliminary results.¹ High-dose chemotherapy and autologous hematopoietic stem-cell transplantation (ASCT) is standard procedure for poor-risk non-Hodgkin lymphoma (NHL), but a significant proportion of patients will never be considered for this approach because of age or comorbidities. Therefore, innovative conditioning regimens are required to improve remission duration and survival in patients not eligible for ASCT. ⁹⁰Y-ibritumomab tiuxetan is an effective radiolabeled monoclonal antibody in the treatment of NHLs,¹⁻⁸ and its favorable toxicity profile makes it a good candidate for dose escalation

with stem-cell support or in combination with carmustine, etoposide, cytarabine, and melphalan (BEAM).⁹⁻¹¹ As previously reported, the use of ⁹⁰Y-ibritumomab tiuxetan at twice to triple (0.8 to 1.2 mCi/kg) the standard dose in the conditioning setting is safe and successful.¹ The innovative feature of our study was split infusion of stem cells aimed at shortening the duration of the severe pancytopenia subsequent to myeloablation (Fig A1, online only). High-dose ⁹⁰Y-ibritumomab tiuxetan was used as consolidation therapy after an optimal cytoreduction.

Between December 2003 and July 2008, 60 patients with poor-risk CD20-positive NHL who were not eligible for BEAM were enrolled. Main inclusion criteria were diagnosis of relapsed or refractory CD20-positive NHL or a new diagnosis of poor-risk NHL and ineligibility for standard conditioning regimens. No upper age limit was established. Poor-risk NHL was defined as aggressive NHL with International Prognostic Index $\geq$ 3, mantle cell lymphoma (MCL), and transformed NHL. Main patient characteristics are reported in Appendix Table A1 (online only).

Patients were treated with rituximab-containing high-dose sequential chemotherapy followed by myeloablative ⁹⁰Y-ibritumomab tiuxetan (Z-HDS) and autologous peripheral blood stem-cell (PBSC) transplantation. Disease response was assessed according to Cheson criteria.¹² The study protocol was approved by the institutional review board and ethical committee.

Fig 1. Kaplan and Meier estimate of overall survival (OS) and progression-free survival (PFS) probabilities for patients who received high-dose sequential chemotherapy followed by myeloablative ^{90}Y -ibritumomab tiuxetan (Z-HDS).

All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki.

The primary objective of the study was tolerability and feasibility of the sequential program; secondary end points were progression-free survival (PFS) and overall survival (OS). At the end of treatment, 54 patients (90%) experienced a complete response (CR), and one patient experienced a partial response (PR), for an overall response rate of 92%. After a median follow-up of 5.9 years (range, 1–8.3 years), 44 patients are alive and 38 are in continuous complete remission: 5-year PFS and OS were 62.7% and 72.9% respectively (Fig 1). At study entry, 35 patients (58%) had bone marrow (BM) involvement, and appropriate measures were taken against the risk of lymphoma-contaminated grafts reinfusion such as molecular monitoring of stem-cell products with patient-specific probes and harvesting of stem cells after treatment with high-dose chemotherapy and rituximab.¹³ A molecular probe was available for 47 patients, including 32 with BM involvement. The molecular analysis of PBSCs harvested after cyclo-

phosphamide and/or cytarabine resulted in a positive signal in only one (3%) of the 32 patients with a positive BM. Thus, most patients received a tumor-free graft. Twenty-nine patients (93%) were negative for BM involvement at polymerase chain reaction (PCR) analysis before transplantation. Two of the three patients with a positive PCR reverted to negative after ^{90}Y -ibritumomab tiuxetan, for an overall BM molecular response rate of 97%.

The 5-year cumulative incidence of relapse was 32.5%, and nonrelapse mortality was only 1.7% (Fig 2). The antitumor activity of the program was noteworthy, and the tolerability of myeloablative radioimmunotherapy was remarkable for patients who were otherwise ineligible for chemotherapy-based autotransplant regimens.

A potential toxicity of concern with radioimmunotherapy is late toxicity, particularly secondary myelodysplastic syndrome (sMDS) and acute myeloid leukemia. In this study, we observed an 8-year cumulative incidence of sMDS of 9.4%, suggesting an increased risk compared with recently reported series of younger patients receiving high-dose therapy and autograft.^{14–16} However, when the sMDS occurrence was analyzed in the pair-matched group of patients treated with a conventional myeloablative regimen (HDS), a comparable 8-year cumulative incidence of sMDS of 10.3% was observed (Appendix Table A1 and Appendix Fig A2, online only). These results confirm the benefit of myeloablative radioimmunotherapy in transplant setting in patients who experience relapse after rituximab-containing regimens, overcoming in part the negative impact of rituximab failure.¹⁷

On the basis of these data, we conclude that Z-HDS is a well-tolerated regimen with a long-term toxicity profile comparable to other, more toxic, high-dose myeloablative regimens. Its high efficacy in this population of frail patients otherwise ineligible for high-dose chemotherapy would encourage randomized studies to confirm the favorable results reported here.

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Fig 2. Cumulative incidence of nonrelapse mortality (NRM) and relapse mortality for patients who received high-dose sequential chemotherapy followed by myeloablative ^{90}Y -ibritumomab tiuxetan (Z-HDS).

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ACKNOWLEDGMENT

Supported in part from Ministero dell'Università e della Ricerca (Rome, Italy), Ministero della Salute (Rome, Italy), Alleanza Contro il Cancro (Rome, Italy), and Michelangelo Foundation for Advances in Cancer Research and Treatment (Milano, Italy). Many thanks to Paolo Longoni e Marco Milanesi for technical assistance. Presented in part at the 2011 ASCO annual meeting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

- Devizzi L, Guidetti A, Tarella C, et al: High-dose yttrium-90-ibritumomab tiuxetan with tandem stem-cell reinfusion: An outpatient preparative regimen for autologous hematopoietic cell transplantation. *J Clin Oncol* 26:5175-5182, 2008
- Witzig TE, Flinn IW, Gordon LI, et al: Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 20:3262-3269, 2002
- Gordon LI, Molina A, Witzig T, et al: Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20+ B-cell lymphoma: Long-term follow-up of a phase 1/2 study. *Blood* 103:4429-4431, 2004
- Gordon LI, Witzig T, Molina A, et al: Yttrium 90-labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma. *Clin Lymphoma* 5:98-101, 2004
- Schilder R, Molina A, Bartlett N, et al: Follow-up results of a phase II study of ibritumomab tiuxetan radioimmunotherapy in patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma and mild thrombocytopenia. *Cancer Biother Radiopharm* 19:478-481, 2004
- Witzig TE, White CA, Gordon LI, et al: Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-hodgkin's lymphoma. *J Clin Oncol* 21:1263-1270, 2003
- Emmanouilides C, Witzig TE, Wiseman GA, et al: Safety and efficacy of yttrium-90 ibritumomab tiuxetan in older patients with non-Hodgkin's lymphoma. *Cancer Biother Radiopharm* 22:684-691, 2007
- 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* 17:3793-3803, 1999
- Krishnan A, Nademanee A, Fung HC, et al: Phase II trial of a transplantation regimen of yttrium-90 ibritumomab tiuxetan and high-dose chemotherapy in patients with non-Hodgkin's lymphoma. *J Clin Oncol* 26:90-95, 2008
- Shimoni A, Zwas ST, Oksman Y, et al: Yttrium-90-ibritumomab tiuxetan (Zevalin) combined with high-dose BEAM chemotherapy and autologous stem cell transplantation for chemo-refractory aggressive non-Hodgkin's lymphoma. *Exp Hematol* 35:534-540, 2007
- Shimoni A, Avivi I, Rowe JM, et al: A randomized study comparing yttrium-90 ibritumomab tiuxetan (Zevalin) and high-dose BEAM chemotherapy versus BEAM alone as the conditioning regimen before autologous stem cell transplantation in patients with aggressive lymphoma. *Cancer* 118:4706-4714, 2012
- Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579-586, 2007
- Magni M, Di Nicola M, Carlo-Stella C, et al: Efficacy and safety of high-dose chemotherapy with in vivo purged auto-SCT in relapsed follicular lymphoma: Long-term follow-up. *Bone Marrow Transplant* 45:1119-1120, 2010
- Armitage JO, Carbone PP, Connors JM, et al: Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. *J Clin Oncol* 21:897-906, 2003
- Lenz G, Dreyling M, Schiegnitz E, et al: Moderate increase of secondary hematologic malignancies after myeloablative radiochemotherapy and autologous stem-cell transplantation in patients with indolent lymphoma: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group. *J Clin Oncol* 22:4926-4933, 2004
- Bhatia R, Van Heijzen K, Palmer A, et al: Longitudinal assessment of hematopoietic abnormalities after autologous hematopoietic cell transplantation for lymphoma. *J Clin Oncol* 23:6699-6711, 2005
- Gisselbrecht C, Glass B, Mounier N, et al: Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 28:4184-4190, 2010

DOI: 10.1200/JCO.2013.50.2922; published online ahead of print at www.jco.org on July 15, 2013