

# The Role of Radiolabeled Monoclonal Antibodies as Part of the Conditioning Regimen for Non-Hodgkin's Lymphoma Autografts

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## BACKGROUND

High-dose therapy and autologous stem cell transplantation produces long-term disease-free survival in some patients with relapsed B-cell non-Hodgkin's lymphomas (NHLs). The results of the now updated PARMA study have confirmed the superiority of this approach over conventional-dose salvage chemotherapy for patients with diffuse large B-cell NHL still responsive to conventional-dose salvage chemotherapy.<sup>1</sup> The effectiveness of this approach in treating low-grade B-cell NHL has also been confirmed in several studies in which prolonged disease-free survival has been reported, although there are no current data to suggest that this approach is curative in patients with indolent disease.<sup>2,3</sup> Similarly in mantle cell lymphoma, although the use of high-dose therapy has been investigated in several studies, its role remains unclear, and there is little evidence of curative potential.<sup>4</sup>

Overall, the current data suggest that for patients with B-cell NHL, high-dose therapy and autologous stem cell transplantation is curative for approximately 20% to 30% of patients with chemosensitive, relapsed disease and that this curative potential is limited to patients with aggressive histologic subtypes.

## CD20-TARGETED THERAPY

The use of CD20-targeted monoclonal antibody therapy in B-cell NHL is now well established. Initial studies of the chimeric mouse/human anti-CD20 monoclonal antibody rituximab in patients with relapsed follicular lymphoma reported response rates of 50% to 60% with a median response duration of 12 to 15 months.<sup>5,6</sup> Subsequent studies have confirmed the activity of rituximab in treating other subtypes of B-cell NHL.<sup>7</sup> Although most studies to date have addressed the role of rituximab in treating patients with relapsed and refractory disease, this agent also has activity as first-line therapy for follicular lymphoma.<sup>8</sup>

The use of rituximab with combination chemotherapy has now been reported in several phase II studies. The combination of CHOP (cyclophosphamide, doxorubicin,

vincristine [Oncovin], and prednisone) with rituximab has been reported in the treatment of both follicular lymphoma and other B-cell NHL subtypes.<sup>9,10</sup> High complete response rates have been reported for CHOP/rituximab combinations in patients with relapsed follicular lymphoma. The activity of this combination as first-line therapy for aggressive B-cell NHL was reported in a phase II study of 33 patients.<sup>10</sup> A phase II study of the HyperCVAD (cyclophosphamide, vincristine, doxorubicin [Adriamycin], and dexamethasone)/high-dose cytarabine/methotrexate regimen in combination with rituximab has reported results in patients with mantle cell lymphoma comparable with those of the same chemotherapy regimen followed by high-dose therapy and autologous or allogeneic stem cell transplantation.<sup>11</sup>

A recent randomized trial from the GELA group in France that compared CHOP chemotherapy with the CHOP/rituximab regimen has reported superior event-free and overall survival rates for patients receiving combined chemoimmunotherapy compared with those of patients receiving CHOP chemotherapy alone.<sup>12</sup> Other randomized studies of chemotherapy/rituximab combinations are in progress.

### **RADIOLABELED ANTI-CD20 MONOCLONAL ANTIBODIES IN B-CELL NHL**

Several studies of radiolabeled anti-CD20 monoclonal antibodies at nonmyeloablative doses in treating B-cell NHL have been reported, and several are in progress. The agents for which most data are available are iodine I 131 (<sup>131</sup>I)-tositumomab (Bexxar) and yttrium Y 90 (<sup>90</sup>Y)-ibritumomab tiuxetan (Zevalin). These studies have reported response rates of 25% to 40% with a median response duration of 6 to 18 months in most studies and some very durable responses of more than 5 years' duration.<sup>13-16</sup>

### **HIGH-DOSE RADIOLABELED ANTI-CD20 MONOCLONAL ANTIBODIES**

Initial phase I and II studies of high-dose <sup>131</sup>I-tositumomab therapy followed by autologous stem cell transplantation in patients with relapsed and refractory B-cell NHL of various histologic subtypes reported overall response rates of 89% and complete response rates of 79%.<sup>17,18</sup> Although these results are encouraging, more than half of the patients in these studies relapsed after 5 years, and only 38% were disease free at the time of the most recent report. However, in view of the extensive prior therapy in these patients, the results of these studies are interesting and have been the basis for several subsequent studies of therapies with high-dose radiolabeled monoclonal antibodies, both as single agents and in combination with high-dose chemotherapy.

Very preliminary data have been reported for <sup>131</sup>I-labeled rituximab in 7 patients with mantle cell lymphoma, all of whom had relapsed after previous high-dose therapy and autologous stem cell transplantation.<sup>19</sup> Myeloablative doses of <sup>131</sup>I

were administered. Six of the 7 patients achieved a CR, 5 of whom were in continuing clinical complete remission after 5 years.

## **RADIOLABELED ANTI-CD20 MONOCLONAL ANTIBODIES COMBINED WITH HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION**

### **<sup>131</sup>I-Tositumomab-Based Regimens**

High-dose regimens including total body irradiation (TBI) have been in widespread use for more than 20 years as conditioning regimens for autologous and allogeneic stem cell transplantation. This usage is based on the marked radiosensitivity of NHLs. Despite its activity, the use of TBI is associated with significant toxicity, particularly pulmonary toxicity, which limits the total dose of external-beam radiation to 12 to 15 Gy. The potential benefit of radiolabeled monoclonal antibodies in this setting is the ability to deliver targeted radiation to sites of disease, with minimal radiation doses delivered to normal tissues.

An initial study of the combination of high-dose cyclophosphamide (Cytosan), etoposide, and <sup>131</sup>I-tositumomab was reported by Press et al.<sup>20</sup> In this study, 52 patients with relapsed B-cell NHL, 65% of whom had grade 1 or 2 follicular lymphoma, were treated with this drug combination. The end point of the main study was to determine the maximum tolerated dose of <sup>131</sup>I-tositumomab in this combination. Following administration of <sup>131</sup>I-tositumomab, patients were kept in radiation protection for a median of 11 days. Etoposide 60 mg/kg was given within 24 hours of release from radiation isolation, and cyclophosphamide 100mg/kg was given 48 hours after etoposide treatment. Purged autologous bone marrow or peripheral blood progenitor cells were given 36 to 48 hours after cyclophosphamide treatment, depending on the residual <sup>131</sup>I activity. Purging was performed with a combination of anti-B-cell monoclonal antibodies and complement. The results of this approach were compared with those of 106 historical control subjects who had received the same chemotherapy regimen but with external-beam TBI. Although follow-up was shorter in the group that received <sup>131</sup>I-tositumomab, both progression-free survival and overall survival rates were significantly higher in this group than in the historical controls. Results of this study were also analyzed according to the presence of indolent or aggressive histology. The apparent advantage of the <sup>131</sup>I-tositumomab-containing regimen over the TBI-based regimen was maintained for both indolent and aggressive histology (*P* values of <.002 for progression-free survival and <.004 for overall survival). Nine of 13 informative patients (69%) in this study with polymerase chain reaction (PCR)-detectable disease in the peripheral blood or bone marrow converted to PCR-negative after stem cell transplantation, although this test result did not appear to correlate with clinical response or outcome.

The results for patients with indolent lymphoma appear to be particularly impressive in this series, although these results should be interpreted cautiously. Sixty-four percent of the patients in this series had disease of low or low-intermediate risk according to the International Prognostic Index. The International Lymphoma Study Group has previously reported prolonged disease-free and overall survival rates for this patient group.<sup>21</sup> In addition, the group from Stanford University have previously reported a 10-year overall survival rate of greater than 90% for selected patients with follicular lymphoma who received high-dose cyclophosphamide, etoposide, and TBI with monoclonal antibody-purged autologous bone marrow transplantation in the first remission after induction chemotherapy.<sup>22</sup>

The excellent results from the Seattle group may therefore be at least partly explained by patient selection.

A recent study from Gopal et al. has reported the use of the same <sup>131</sup>I-tositumomab-containing conditioning regimen in the treatment of patients with relapsed mantle cell lymphoma.<sup>23</sup> Described was a small series of 16 patients with a median of 3 prior therapies, all of whom were treated with autologous peripheral blood progenitor cells purged with anti-B-cell monoclonal antibodies after an initial CD34 cell selection step. The 3-year overall and progression-free survival rates were 95% and 60%, respectively. These encouraging results must be interpreted in the context of equally encouraging results reported for the use of the HyperCVAD/high-dose methotrexate/cytarabine regimen followed either by a conventional high-dose conditioning regimen and stem cell transplantation or by rituxan therapy but without stem cell transplantation. Excellent results with this approach have been reported by Khouri et al.<sup>24</sup> and Romaguera et al.<sup>11</sup> at the M.D. Anderson Cancer Center. There is no clear evidence that the use of <sup>131</sup>I-tositumomab as part of a conditioning regimen in these patients produces results superior to those obtained with a more “conventional” high-dose approach.

### **<sup>90</sup>Y-ibritumomab Tiuxetan-Based Regimens**

Experience with <sup>90</sup>Y-ibritumomab tiuxetan in the high-dose setting with stem cell transplantation is limited compared with that reported for <sup>131</sup>I-tositumomab. Nademanee et al. have reported preliminary results from a phase I/II study using <sup>90</sup>Y-ibritumomab tiuxetan with high-dose cyclophosphamide and etoposide therapy in 28 patients with relapsed or refractory B-cell NHL.<sup>25</sup> Of 17 evaluable patients, 9 had follicular lymphoma, 7 had diffuse large B-cell lymphoma, and 2 had mantle cell lymphoma. Eleven patients were in complete remission at the time of transplantation (5 of whom were in the first complete remission). The reported 1-year progression-free and overall survival rates were both 92%. The short follow-up period and the heterogeneous patient population in this study limit its interpretation, although it is noteworthy that the therapy was apparently well

tolerated with hematopoietic engraftment comparable with that seen with the use of TBI-based regimens.

A recent study from Winter et al. has adopted a different approach, adding  $^{90}\text{Y}$ -ibritumomab tiuxetan to standard doses of a chemotherapy-only regimen, BEAM (carmustine, etoposide, cytarabine, and melphalan).<sup>26</sup> This approach is interesting in that it combines radioimmunotherapy with a standard high-dose regimen rather than using targeted radiation as a “substitute” for TBI. This approach is particularly interesting in view of the data (reviewed above) demonstrating that combined chemoimmunotherapy with unlabeled monoclonal antibodies may be associated with higher response and survival rates than chemotherapy alone.

In this phase I/II study, rituximab and Indium In 111 ibritumomab tiuxetan were given on day 22 for dosimetry. Rituximab therapy followed by  $^{90}\text{Y}$ -ibritumomab tiuxetan was given on day -14, and standard doses of BEAM chemotherapy given on days -6 through -1 were followed by autologous stem cell reinfusion. The primary end point of this ongoing study is the determination of the maximum tolerated dose of radioimmunotherapy that can be administered with the BEAM regimen. Response and survival rates are secondary end points. Fourteen patients with relapsed or refractory CD20<sup>+</sup> B-cell NHL (8 patients with diffuse large B-cell, 4 with mantle cell, and 2 with follicular NHL) had been treated at the time of this initial report. The patients had received a median of 2 prior therapies (range, 2–4). With a median follow-up period of 15 months, the 2-year overall and progression-free survival rates were 75% and 54%, respectively. Neutrophil and platelet engraftment occurred at a median of 9 and 21 days, respectively. The investigators concluded that this approach was feasible and that the engraftment data were comparable with the BEAM regimen alone.

## CONCLUSIONS

Current data regarding the use of radiolabeled monoclonal antibodies in the transplant setting are limited, especially with respect to the use of these agents as part of chemotherapy-containing high-dose regimens. The available data are mostly very preliminary and are based on short follow-up times with small numbers of patients and on studies in which the primary end points have been the determination of the maximum tolerated doses of radiation.

These studies have shown that the use of myeloablative doses of targeted radiation with high-dose chemotherapy is feasible and does not appear to produce major increases in the toxicity of this approach. However, the use of these antibodies lengthens the conditioning regimen by as much as 10 to 15 days and, in the case of  $^{131}\text{I}$ -based regimens, necessitates hospitalization and radiation isolation. Additionally, these protocols require dosimetric evaluation to determine eligibility for study therapy. It is not clear from the published data how many patients fail to meet the

eligibility criteria for these studies because of unfavorable biodistribution of the radiolabeled antibody, but in at least one of these studies, patients with splenomegaly and unfavorable biodistribution underwent splenectomy prior to study entry. This action almost certainly produces some degree of selection in favor of patients with higher performance status.

Studies to date have been heterogeneous with respect to patient populations, especially histologic subtype.

No comparative studies have been performed, and there is no clear evidence for the superiority of a specific radioimmunoconjugate.  $^{90}\text{Y}$ -based therapy has the potential advantage of increased patient convenience, because this agent is predominantly a  $\beta$ -emitter, and its use does not require radiation isolation. On the other hand, the bone-seeking propensity of this agent has raised concerns about the potential for the induction of secondary myelodysplasia and acute myeloid leukemia. To date, there is no clear evidence for this, although follow-up times in all series is short.<sup>27</sup> In the transplant setting in which secondary myelodysplastic syndrome and acute myelogenous leukemia are recognized complications, an additional effect from radioimmunoconjugates is likely to be difficult to detect.

The mechanism of action of radiolabeled monoclonal antibodies is not fully understood, and the relative contributions of antibody-mediated cell killing and radiation-induced cell death are not understood. The addition of radioimmunoconjugates to high-dose transplant regimens may have effects in addition to simply replacing TBI.

This consideration may have implications for the future selection of patients to undergo this therapy. Data emerging from the use of rituximab to treat patients with diffuse large B-cell NHL suggest that the survival benefit of this agent when used with chemotherapy may be restricted to patients whose tumors overexpress the *bcl-2* gene.<sup>28</sup> Overexpression of this gene is thought to confer chemotherapy resistance, which can be overcome by the addition of rituximab to combination chemotherapy. Such observations may also be true for radioimmunoconjugates. The growing use of gene expression profiling in treating these diseases may help to clarify this issue.<sup>29,30</sup>

In summary, the potential role of radiolabeled monoclonal antibodies as part of conditioning regimens for stem cell transplantation is unclear. The encouraging preliminary data will require confirmation in larger prospective studies analyzed by intent to treat and ultimately will need to be compared in a prospective fashion with more conventional high-dose regimens.

## REFERENCES

1. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *New Engl J Med* 333:1540–1545, 1995.

2. Freedman AS, Gribben JG, Neuberg D, et al. High-dose therapy and autologous bone marrow transplantation in patients with follicular lymphoma during first remission. *Blood* 88:2780–2786, 1996.
3. Apostolidis J, Gupta RK, Grenzeliias D, et al. High-dose therapy with autologous bone marrow support as consolidation of remission in follicular lymphoma: long-term clinical and molecular follow-up. *J Clin Oncol* 18:527–536, 2000.
4. Sweetenham JW. Stem cell transplantation for mantle cell lymphoma: should it ever be used outside clinical trials? *Bone Marrow Transplant* 28:813–820, 2001.
5. Maloney DG, Liles TM, Czerwinski DK, et al. Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. *Blood* 84:2457–2466, 1994.
6. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 16:2825–2833, 1998.
7. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing aggressive lymphoma: a multicenter phase II study. *Blood* 92:1927–1932, 1998.
8. Hainsworth JD, Litchy S, Burris HA, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. *J Clin Oncol* 20:4261–4267, 2002.
9. Czuczman MS, Grillo-Lopez AJ, White CA, et al. treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. *J Clin Oncol* 17:268–276, 1999.
10. Vose JM, Link BK, Grossbard ML, et al. Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 19:389–397, 2001.
11. Romaguera JE, Dang NH, Hagemester FB, et al. Preliminary report of rituximab with intensive chemotherapy for untreated aggressive mantle cell lymphoma (MCL) [abstract]. *Blood* 96:733a, 2000.
12. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. *N Engl J Med* 346:235–242, 2002.
13. Eary JF, Press OW, Badger CC, et al. Imaging and treatment of B-cell lymphoma. *J Nucl Med* 31:1257–1268, 1990.
14. Knox SJ, Levy R, Miller RA, et al. Determinants of the anti-tumor effect of radiolabeled monoclonal antibodies. *Cancer Res* 50:4935–4940, 1990.
15. Witzig TE, White CA, Wiseman GA, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20<sup>+</sup> B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 17:3793–3803, 1999.
16. Witzig TE, White CA, Gordon LI, et al. Prospective randomized controlled study of Zevalin (IDEC-Y2B8) radioimmunotherapy compared to rituximab immunotherapy for B-cell NHL: report of interim results [abstract]. *Blood* 94:631a, 1999.
17. Press OW, Eary JF, Appelbaum FR, et al. A phase II trial of <sup>131</sup>I-B1(anti-CD20) antibody therapy with autologous stem cell transplantation for relapsed B-cell lymphomas. *Lancet* 346:336–340, 1995.

18. Lui SJ, Eary JF, Petersdorf SH, et al. Follow up of relapsed B-cell lymphoma patients treated with I-131-labeled anti-CD20 and autologous stem cell rescue. *J Clin Oncol* 16:3270–3278, 1998.
19. Behr TM, Griesuinger F, Riggert J, et al. High-dose myeloablative radioimmunotherapy of mantle cell non-Hodgkin's lymphoma with the iodine-131-labeled chimeric anti-CD20 antibody C2B8 and autologous stem cell support: results of a pilot study. *Cancer* 94(suppl):1363–1372, 2002.
20. Press OW, Eary JF, Gooley T, et al. Phase I/II trial of iodine-131-tositumomab (anti-CD20), etoposide, cyclophosphamide and autologous stem cell transplantation for relapsed B-cell lymphomas. *Blood* 96:2934–2942, 2000.
21. Armitage JO, Weisenberger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol* 16:2780–2795, 1998.
22. Horning SJ, Negrin RS, Hoppe RT, et al. High-dose therapy and autologous bone marrow transplantation for follicular lymphoma in first complete or partial remission: results of a phase II clinical trial. *Blood* 97:404–409, 2001.
23. Gopal AK, Rajendran JG, Petersdorf SH, et al. High-dose chemo-radioimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma. *Blood* 99: 3158–3162, 2002.
24. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem cell transplantation: an active regimen for aggressive mantle cell lymphoma. *J Clin Oncol* 16:3803–3809, 1998.
25. Nademane A, Molina M, Forman SJ, et al. A phase I/II trial of high-dose radioimmunotherapy (RIT) with Zevalin in combination with high-dose etoposide (VP-16) and cyclophosphamide (CY) followed by autologous stem cell transplant (ASCT) in patients with poor-risk or relapsed B-cell non-Hodgkin's lymphoma (NHL) [abstract]. *Blood* 100:182a, 2002.
26. Winter JN, Inwards D, Erwin W, et al. Zevalin dose-escalation followed by high-dose BEAM and autologous peripheral blood progenitor cell (PBPC) transplant in non-Hodgkin's lymphoma: early outcome results [abstract]. *Blood* 100:411a, 2002.
27. Czuczman M, Witzig TE, Gaston I, et al. Zevalin™ radioimmunotherapy is not associated with an increased incidence of secondary myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) [abstract]. *Blood* 100, 2002. Abstract 1386.
28. Wilson WH, Pittaluga S, O'Connor P, et al. Rituximab may overcome *bcl-2*-associated chemotherapy resistance in untreated diffuse large b-cell lymphomas [abstract]. *Blood* 99, 2001. Abstract 1447.
29. Alizadeh AA, Elsen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 403:503–511, 2000.
30. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large B-cell lymphoma. *N Engl J Med* 346: 1937–1947, 2002.