
CHRISTIAN GISSELBRECHT, a JULIE VOSE, b AUAYPORN NADEMANEE, c ALESSANDRO M. GIANNI, d ARNON NAGLER e

aHôpital Saint-Louis, Paris, France; bUniversity of Nebraska Medical Center, Omaha, Nebraska, USA; cCity of Hope National Medical Center, Duarte, California, USA; dIstituto Nazionale Tumori, Milan, Italy; eBMT & CBB, Chaim Sheba Medical Center, Tel Hashomer, Israel

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ABSTRACT

High-dose chemotherapy (HDC) conditioning given in association with autologous stem cell transplantation (ASCT) or reduced-intensity conditioning (RIC) with allogeneic stem cell transplantation (alloSCT) are established treatment approaches for patients with chemotherapy-sensitive, relapsed, aggressive, or low-grade non-Hodgkin’s lymphoma (NHL). These approaches have been shown to be the only curative option for patients with relapsed NHL. Despite data suggesting that prolonged event-free survival can be achieved with SCT combined with HDC, there are problems that may limit the utility of this approach for a broad patient population. For example, older patients, who make up the majority of the NHL population, may not be able to withstand the toxicities associated with this intensive regimen, and this therapy combination, especially when it includes the use of total-body irradiation, has been associated with a greater risk for secondary malignancies. Furthermore, relapse is the most common cause of treatment failure after HDC with ASCT and there is a poor success rate for those patients with either chemotherapy-refractory or heavily pretreated, multiple-relapsed disease. Consequently, there is an urgent need for other effective and well-tolerated approaches that will eradicate the residual disease that may persist before SCT, thus improving outcomes for patients with this life-threatening disease. In addition, approaches with better safety profiles would allow older patients to benefit from this therapeutic option. Because lymphomas are highly sensitive to radiation, radioimmunotherapy (RIT) has been used with great success in consolidation therapy and, as a result, there is great interest in exploring the use of RIT, either as a single agent or as augmentation of HDC, as part of a conditioning regimen for ASCT. The flexibility of including RIT as part of conditioning therapy also allows it to be combined with RIC to reduce the toxic effects of HDC. This treatment option replaces any concomitant loss of chemotherapy efficacy with a gain in RIT efficacy. The data so far suggest that the use of RIT in the au-

Correspondence: Christian Gisselbrecht, Ph.D., Hôpital Saint-Louis, Hémato-oncologie, 1 Avenue Claude Vellefaux, Paris 75010, France. Telephone: 33-1-4249-9296; Fax: 33-1-4249-9641; e-mail: christian.gisselbrecht@sls.ap-hop-paris.fr Received March 27, 2009; accepted for publication June 1, 2009. ©AlphaMed Press 1083-7159/2009/$30.00/0 doi: 10.1634/theoncologist.2009-S2-41

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logous setting can improve clinical outcome with no added toxicity in these patients, whereas similar positive findings have been reported in preliminary stud-
ies of yttrium-90 ibritumomab tiuxetan combined with RIC and alloSCT in high-risk patients. The Oncologist 2009;14(suppl 2):41–51

INTRODUCTION
The principle of stem cell transplantation (SCT) is to eliminate residual disease, thus resulting in a complete response (CR). Elimination of residual disease can be achieved either by using a myeloablative approach, involving intensive (high-dose) immunochemotherapy with or without radio-
therapy followed by stem cell replacement from the patients themselves (autologous SCT [ASCT]), or with an immunological approach using stem cells from a matched donor (al-
logeneic SCT [alloSCT]). AlloSCT is usually performed with a reduced-intensity conditioning (RIC) regimen because it is the immunological process that eliminates resid-
ual disease. Although most patients with follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), the two most common types of non-Hodgkin’s lymphoma (NHL), achieve a partial response (PR) or a CR following primary combination chemotherapy, 15%–40% of patients with DLBCL treated with rituximab and almost all patients with FL relapse [1, 2]. Indeed, NHL is charac-
terized by continued relapse and shorter duration of re-
sponse, and high-dose chemotherapy (HDC) with SCT is the standard treatment approach in patients who have ag-
gressive types of NHL with high-risk features, or who have relapsed or are resistant to chemotherapy. The National Comprehensive Cancer Network guidelines [3] indicate that ASCT or alloSCT should be used in FL as second-line and subsequent therapy (Fig. 1) and in DLBCL as second-
line and first-line consolidation in patients with a poor prog-
nosis. However, these recommendations may not be the standard for all countries, and many patients do not qualify because of the intensity of treatment.

The survival benefit from both ASCT and alloSCT comes about by virtue of patients converting from a PR to a CR, and, historically, SCT has been the only therapy to achieve this and potentially offer a cure for younger NHL patients who have relapsed or are resistant to chemotherapy [4–7]. Randomized trials have demonstrated that both ASCT and alloSCT provide benefit to patients with either DLBCL or FL.

DLBCL
The PARMA trial demonstrated that ASCT in chemother-
apy-sensitive but incurable DLBCL provides a survival benefit over conventional chemotherapy [8]. Furthermore, long-term follow-up after ASCT shows that achievement of a CR in high-grade B-cell NHL (mainly DLBCL) correlates with longer progression-free survival (PFS) and overall survival (OS) times, and that the probability of relapse after achieving a CR is only 16% at 10 years [9]. Consequently, the introduction of SCT as a salvage regimen for NHL has provided a much-needed new and effective treatment approach for this challenging disease.

FL
The European Bone Marrow Transplantation Registry CUP trial also demonstrated that ASCT provides a survival ben-
efit in chemotherapy-sensitive FL patients [10, 11]. Long-
term follow-up of FL patients receiving HDC and ASCT also demonstrated that achieving a CR translated into a signif-
ificant event-free survival (EFS) benefit. At the 7-year fol-
low-up, the EFS rate among patients who achieved a CR was 56% (95% confidence interval [CI], 43%–69%), com-
pared with 36% (95% CI, 31%–43%) for patients who achieved a PR only (p < .001) [7]. In second-relapse FL, myeloablative therapy plus ASCT resulted in 48% of pa-
tients still in remission at 12 years, further supporting the beneficial effect of SCT regimens in controlling disease progression [12]. In addition, early intervention using ASCT resulted in a significantly longer survival duration for patients in second remission when compared with the survival time of patients who were treated later in the course of their treatment [12].

These data from both DLBCL and FL patients suggest that SCT can improve survival outcomes for patients with NHL, but an incomplete elimination of residual disease, or less than a CR, may be one reason for the high relapse rates that are still observed in the transplant setting.

Limitations of SCT
Despite significant advances in radiation therapy and che-
motherapy regimens over the past 25 years, few random-
ized studies have been carried out and no consensus has been reached to define the optimal conditioning regimen for leukemias or lymphomas. Relapses occur in many patients receiving HDC in conjunction with ASCT because of a con-
taminated graft or cancer cells remaining in the patient follow-
ing ablative chemotherapy [13]. Therefore, several approaches have been attempted to reduce relapse after ASCT for NHL by eliminating residual disease, including in vivo purging of the marrow graft [14], approaches to
manage side effects of HDC to maintain dose intensity [15], pre- and post-use of radiotherapy for bulky disease [16], and post-ASCT maintenance treatment with rituximab [13, 17]. Data from trials in mantle cell lymphoma (MCL) and FL have demonstrated that rituximab alone or added to chemotherapy can reduce the contamination of the graft given to the recipient [13].

HDC conditioning regimens (which typically contain strong alkylating agents and topoisomerase II inhibitors) are used in combination with ASCT for patients with aggressive or bulky lymphoma. Generally, the use of HDC is limited to younger and healthier patients, because many compromised and frail patients cannot withstand the toxicities associated with these HDC regimens. Therefore, to overcome the limitations of ASCT and improve survival, there is a need to purge residual disease in the graft and patient prior to administration, thus improving the efficacy of therapy without increasing the toxicity and enhancing treatment options for patients who are not traditional candidates for ASCT as a result of the toxicity associated with HDC.

### The Role of Radioimmunotherapy as a Pretransplant Conditioning Regimen

Radioimmunotherapy (RIT) is comprised of a monoclonal antibody conjugated to a radionuclide that targets a tumor-specific cell-surface antigen. RIT for NHL specifically targets cells expressing the CD20 antigen that is present exclusively on mature B cells and B-cell lymphomas [18]. Two agents are currently used for RIT of NHL [19]: yttrium-90 (90Y)-ibritumomab tiuxetan (Zevalin®; Spectrum Pharmaceuticals, Inc., Irvine, CA; Bayer Schering Pharma AG, Berlin, Germany) and iodine-131 (131I)-tositumomab (Bexxar®; GlaxoSmithKline, Research Triangle Park, NC). 90Y-ibritumomab tiuxetan received approval in the European Union (EU) in 2004 for the treatment of relapsed or refractory, low-grade NHL or FL, and more recently received regulatory approval in the EU for use as first-line consolidation of first remission in FL patients. 131I-tositumomab is only indicated in the U.S. as part of the treatment regimen for relapsed or refractory, low-grade NHL, FL, or transformed NHL.
There is a strong rationale for using RIT as a part of pre-conditioning treatment for SCT. For example, total-body irradiation (TBI) has traditionally been integrated into transplant regimens for many NHL patients, with the exclusion of the elderly who are unable to tolerate its toxicity. This is especially pertinent because the majority of patients with relapsed or refractory B-cell NHL are >60 years old, and yet are often denied potentially curative HDC and/or TBI and ASCT because of the risk for excessive treatment-related morbidity and mortality [20, 21]. In contrast to TBI, and by virtue of its targeted activity, RIT (conventional and high dose) can be used in elderly patients with comorbidities undergoing SCT, making it appropriate as a pretransplant regimen for a wider patient population [19]; as such, a dramatic decrease in TBI-containing regimens has been observed in data from the European Group for Blood and Marrow Transplantation registry since 2000 [22, 23]. In two studies, 90Y-ibritumomab tiuxetan was used to treat patients with NHL who were not eligible for HDC- and/or TBI-containing therapies prior to ASCT. Data demonstrated better disease control in relapsed and refractory FL and transformed B-cell NHL (such as DLBCL and MCL), with no unexpected additional toxicities [24, 25]. Because RIT delivers targeted radiation, it is feasible that any additional therapeutic benefit would be delivered without adding to the HDC-associated toxicity, which could increase the treatment options for older and frailer patients. In recent years, reduced-intensity regimens have been used in conjunction with alloSCT for the treatment of NHL in such patients [26]. Currently, there are two approaches to using RIT in the SCT setting. The first combines standard-dose, nonmyeloablative RIT with either conventional-dose chemotherapy (i.e., a reduced-intensity regimen) in the alloSCT setting, as mentioned above, or HDC prior to ASCT. The second is to use high-dose myeloablative RIT, with or without chemotherapy, mostly based on accurate dosimetry to ensure that enough radiation is delivered directly to the tumor sites while limiting radiation exposure to the rest of the body, particularly the critical organs.

By minimizing the levels of residual disease without increasing the toxicity of HDC, approaches that incorporate RIT in pretransplant conditioning may improve outcomes following SCT [27]. Information on the utility of RIT in the SCT setting is currently evolving and growing, and this paper summarizes data that were presented on this topic at the 6th meeting of the International Workshop on Nuclear Oncology.

**STANDARD-DOSE NONMYELOABLATIVE RIT IN COMBINATION WITH HDC**

The rationale for combining RIT and chemotherapy is to further minimize the risk for residual disease in SCT and to improve safety by targeting radiation exposure directly to the tumor site. Data from Lenz et al. [6] (German Low Grade Lymphoma Study Group), Deconinck et al. [5] (Groupe Ouest Est d’Etude des Leucémies et Autres Maladies du Sang), and Sebban et al. [7] (Groupe d’Etude des Lymphomes de l’Adulte [GELA]) show that chemotherapy as myeloablative conditioning prior to ASCT is beneficial in patients with FL in terms of PFS. However, the OS advantage remains uncertain because it is as yet unclear whether or not chemotherapy can sufficiently decrease tumor burden and the risk for relapse. Thus, new treatment approaches need to be developed that not only improve remission rates but are also better tolerated, in order to accommodate the older patient population [5–7].

Preliminary data suggest that RIT may be able to replace adjuvant radiotherapy or TBI as a conditioning regimen for SCT in B-cell lymphoma. Promising results from numerous trials (Table 1) suggest that incorporating RIT may significantly improve disease control with negligible added toxicity. Particularly in aggressive lymphomas, the high rates of OS with RIT and HDC seen in the studies below compare favorably with those from historical controls. The superior outcomes observed in the chemotherapy-sensitive NHL population are also attributed to the addition of RIT to SCT conditioning regimens [8]. Combining HDC regimens with 90Y-ibritumomab tiuxetan has produced impressive long-term OS rates of 81%–92% in chemotherapy-sensitive patients in preliminary trials in a variety of histologic lymphoma subtypes [28–30]. In the largest preliminary trial to date, in patients with low-grade lymphoma, the inclusion of 90Y-ibritumomab tiuxetan with HDC achieved an 80% PFS rate [23]. Recent reports investigating RIT in combination with HDC regimens in patients with chemotherapy-refractory disease have demonstrated higher OS rates of 55% and 87% at 38 months [31] and 30 months [32], respectively; a remarkable result considering that such patients have a 3-year estimated survival rate of <20% when treated with standard HDC and ASCT [27, 33]. Vose et al. [31] also reported an estimated 2-year OS rate of 67%, and another study investigating RIT and high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) chemotherapy with ASCT reported estimated 2-year OS and PFS rates of 67% (95% CI, 46%–87%) and 52% (95% CI, 31%–72%), respectively [34]. Altogether, such improvements in OS rates demonstrate the benefit of adding RIT to ASCT for patients with chemotherapy-refractory NHL. Such promising preliminary data have led to a number of studies investigating different, specific ASCT conditioning regimens that include RIT. The discussion below focuses...
on data from several key studies that have been reported recently.

**Table 1. Summary of available data for RIT with/without high-dose chemotherapy prior to autologous stem cell transplantation**

<table>
<thead>
<tr>
<th>Study</th>
<th>RIT</th>
<th>Chemotherapy</th>
<th>n of patients</th>
<th>Chemotherapy sensitive</th>
<th>Histology</th>
<th>Overall survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-agent high-dose RIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Swinnen et al. (2008) [42]</td>
<td>90Y-IT</td>
<td>None</td>
<td>24</td>
<td>S</td>
<td>M</td>
<td>NS</td>
<td>CR, 72%; median TTP, 9 mos</td>
</tr>
<tr>
<td>Vanazzi et al. (2008) [41]</td>
<td>90Y-IT</td>
<td>None</td>
<td>24</td>
<td>RE</td>
<td>M</td>
<td>NS</td>
<td>CR, 41%</td>
</tr>
<tr>
<td>Devizzi et al. (2008) [32]</td>
<td>90Y-IT</td>
<td>None</td>
<td>30</td>
<td>Mostly RE/RF</td>
<td>M (mostly FL and DLBCL)</td>
<td>4-yr, 87%</td>
<td>4-yr, 69%</td>
</tr>
<tr>
<td>Liu et al. (1998) [40]</td>
<td>131I-T</td>
<td>None</td>
<td>29</td>
<td>M</td>
<td>M (mostly FL)</td>
<td>4-yr, 68%</td>
<td>4-yr, 42%</td>
</tr>
<tr>
<td>Gopal et al. (2007) [39]</td>
<td>131I-T</td>
<td>None</td>
<td>24</td>
<td>M</td>
<td>M</td>
<td>3-yr, 59%</td>
<td>3-yr, 51%</td>
</tr>
<tr>
<td>Standard-dose RIT and high-dose chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Khouri et al. (2006) [28]</td>
<td>90Y-IT</td>
<td>BEAM</td>
<td>26</td>
<td>S</td>
<td>M (mostly A)</td>
<td>3-yr, 92%</td>
<td>3-yr, 83%</td>
</tr>
<tr>
<td>Shimoni et al. (2007) [34]</td>
<td>90Y-IT</td>
<td>BEAM</td>
<td>23</td>
<td>RF</td>
<td>A</td>
<td>3-yr, 67%</td>
<td>3-yr, 52%</td>
</tr>
<tr>
<td>Krishnan et al. (2008) [35]</td>
<td>90Y-IT</td>
<td>BEAM</td>
<td>41</td>
<td>M (mostly S)</td>
<td>M (mostly DLBCL)</td>
<td>2-yr, 89%</td>
<td>2-yr, 70%</td>
</tr>
<tr>
<td>Shimabukuro-Vornhagen et al. (2008) [36]</td>
<td>90Y-IT</td>
<td>BEAM</td>
<td>10</td>
<td>RE/RF</td>
<td>FL or DLBCL</td>
<td>NS</td>
<td>20% of patients relapsed (11 mos)</td>
</tr>
<tr>
<td>Gisselbrecht (2008) [23]</td>
<td>90Y-IT</td>
<td>BEAM</td>
<td>74</td>
<td>S</td>
<td>M (mostly FL)</td>
<td>NS</td>
<td>1-yr, 80%</td>
</tr>
<tr>
<td>Vose et al. (2005) [31]</td>
<td>131I-T</td>
<td>BEAM</td>
<td>23</td>
<td>RE</td>
<td>M (mostly A)</td>
<td>3-yr, 55%</td>
<td>3-yr, 39%</td>
</tr>
<tr>
<td>Vose et al. (2007) [37]</td>
<td>131I-T</td>
<td>BEAM</td>
<td>40</td>
<td>S</td>
<td>DLBCL</td>
<td>3-yr, 81%</td>
<td>3-yr, 70%</td>
</tr>
<tr>
<td>High-dose RIT and high-dose chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nademanee et al. (2005) [29]</td>
<td>90Y-IT</td>
<td>CTX + ETO</td>
<td>31</td>
<td>M (mostly S)</td>
<td>M</td>
<td>2-yr, 92%</td>
<td>2-yr, 78%</td>
</tr>
<tr>
<td>Nademanee et al. (2007) [30] (update of [29])</td>
<td>90Y-IT</td>
<td>CTX + ETO</td>
<td>42</td>
<td>M (mostly S)</td>
<td>M</td>
<td>4-yr, 81%</td>
<td>DFS, 65%</td>
</tr>
<tr>
<td>Winter et al. (2009) [56]</td>
<td>90Y-IT</td>
<td>BEAM</td>
<td>44</td>
<td>M (mostly RF)</td>
<td>M (mostly A)</td>
<td>3-yr, 60%</td>
<td>3-yr, 43%</td>
</tr>
<tr>
<td>Press et al. (2000) [57]</td>
<td>131I-T</td>
<td>CTX + ETO</td>
<td>52</td>
<td>M (mostly S)</td>
<td>M (mostly FL)</td>
<td>2-yr, 83%</td>
<td>2-yr, 68%</td>
</tr>
</tbody>
</table>

Abbreviations: 90Y-IT, yttrium-90 ibritumomab tiuxetan; 131I-T, iodine-131 tositumomab; A, aggressive; BEAM, high-dose carmustine, etoposide, cytarabine, and melphalan; CR, complete response; CTX + ETO, high-dose cyclophosphamide and etoposide; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; M, mixed; NS, not specified; RE, resistant; RF, refractory; RIT, radioimmunotherapy; S, sensitive; TTP, time to progression.

**Efficacy of 90Y-Ibritumomab Tiuxetan**

In a number of studies, the use of standard-dose 90Y-ibritumomab tiuxetan (0.4 mCi/kg) plus HDC (BEAM) has been evaluated as a conditioning regimen prior to ASCT in patients with relapsed/refractory NHL. In one study, 90Y-ibritumomab tiuxetan at this dose was well tolerated and effective in 41 older patients (median age, 60 years) undergoing ASCT for poor-risk NHL [35]. With a median follow-up of 18.4 months (range, 5.5–53.3 months), the estimated 2-year OS and disease-free survival rates were 88.9% and 69.8%, respectively (Fig. 2), and the rate and types of toxicities observed were similar to those with high-dose BEAM alone. Similar activity was reported in two other studies. In the GELA phase II trial, a conventional dose of 90Y-ibritumomab tiuxetan was combined with...
BEAM in 74 patients with low-grade B-cell lymphomas (68 with FL and six with marginal zone lymphoma [MZL]). At a minimum 1-year follow-up, the estimated 1-year EFS rate was 80% [23]. The second phase II trial, reporting data for the first 10 patients treated with standard-dose $^{90}$Y-ibritumomab tiuxetan and high-dose BEAM conditioning chemotherapy followed by ASCT, demonstrated that after a median follow-up of 11 months only two patients had central nervous system relapse, one of whom died [36]. From these data, the authors concluded that $^{90}$Y-ibritumomab tiuxetan in combination with BEAM and ASCT was an effective treatment option for relapsed/refractory NHL patients. Based on these data, further investigation of BEAM in combination with $^{90}$Y-ibritumomab tiuxetan prior to ASCT is continuing, with a randomized phase III trial currently recruiting patients.

**Efficacy of $^{131}$I-Tositumomab**

A phase I study of standard-dose $^{131}$I-tositumomab (0.30–0.75 Gy total-body dose) with BEAM followed by ASCT showed promising results in 23 patients (median age, 51 years) with chemotherapy-resistant, chemotherapy-relapsed, or chemotherapy-refractory B-cell NHL (FL, 4; DLBCL, 14; MCL, 5), with a 3-year OS rate of 55% [31]. In a subsequent phase II study of this regimen in chemotherapy-sensitive DLBCL patients, 40 patients received 75 cGy total-body dose of $^{131}$I-tositumomab with BEAM followed by ASCT. The addition of RIT was associated with a 3-year OS rate of 81%, without excess toxicity over BEAM [37].

The data above demonstrate that both $^{90}$Y-ibritumomab tiuxetan and $^{131}$I-tositumomab can significantly improve survival rates without additional toxicity when added to HDC and ASCT.

**Safety of Combination Regimens**

Secondary malignancies are observed in some patients treated with chemotherapy, and the addition of radiation may increase this risk; for example, a long-term follow-up of 693 FL patients undergoing HDC (including 378 patients receiving a TBI-containing regimen) demonstrated that of the 39 patients who developed these secondary malignancies, 34 had received TBI as the conditioning regimen ($p = 0.04$) [20]. Another recent report that retrospectively analyzed 563 patients with indolent lymphoma demonstrated a higher incidence of myelodysplastic syndromes/acute myeloid leukemia, which was associated with fludarabine-containing therapy after a 16-year follow-up [21]. Concerns that the incidence of secondary malignancies would increase with a combination of $^{90}$Y-ibritumomab tiuxetan plus BEAM followed by ASCT have not been settled [38]. However, data from a larger number of patients with a longer follow-up are needed to establish whether or not there is cause for concern. Interestingly, patients receiving RIT with HDC may be at no greater risk for secondary malignancies than those treated with HDC alone; this has been demonstrated in a number of studies in which the addition of RIT to HDC showed that adverse events were similar to those seen with high-dose BEAM alone and that there was no greater toxicity level [31, 37]. Furthermore, no secondary malignancies have been reported with standard-dose $^{90}$Y-ibritumomab tiuxetan [36].

**High-Dose Myeloablative RIT With or Without Chemotherapy**

Data from studies of high-dose RIT plus HDC and ASCT are promising, but the use of HDC in this setting may still be too aggressive for many patients who may benefit from ASCT. Therefore, high-dose, single-agent RIT prior to ASCT may be a promising new approach for patients with relapsed B-cell lymphoma. Because of the acceptable tolerability of RIT, a conditioning regimen that includes high-dose RIT but excludes HDC may be appropriate for a broader range of patients for whom myeloablative chemotherapy regimens are too toxic. This hypothesis has been, and still is being, evaluated in clinical trials [32, 39–42] (Table 1). In the following section, we review data that have recently emerged on the safety and efficacy of high-dose RIT prior to ASCT.

**Safety of High-Dose Myeloablative RIT**

At therapeutic doses, high-dose RIT is well tolerated [39, 40, 43, 44]. In dose-finding studies, the maximum-tolerated
dose and dose-limiting toxicities of RIT were defined. This approach provided the opportunity to identify doses that gave the highest radiation concentration in the tumor while minimizing total-body radiation exposure. For high-dose $^{90}$Y-ibritumomab tiuxetan prior to ASCT, 1.2 mCi/kg (45 MBq/kg) was defined as the maximum recommended dose because the radiation absorbed by non-hematologic critical organs approached the protocol-defined upper safety limit. In a recent publication by Devizzi et al. [32], the maximum dose given to 17 patients was 1.2 mCi/kg (45 MBq/kg), and no further dose escalation was attempted because 11 of these patients exhibited an absorbed dose close to the upper tolerance limits for the absorbed dose.

In phase I dose-escalation studies of $^{131}$I-tositumomab, 27 Gy was determined to be the maximum tolerated level of radiation that can be delivered to normal critical organs, with limited nonhematologic toxicity and maintained efficacy [40, 45]. These data established the optimal therapeutic dose as 2.5 mg/kg antibody labeled with 5–10 mCi $^{131}$I. However, in practice, and as a result of the fact that iodine is absorbed by the thyroid, the use of high-dose $^{131}$I-tositumomab treatment can be complicated for both health care professionals and patients, because therapeutic doses may have a long total-body residence time and patients may require radiation isolation in specialist hospital facilities [46]. When patients are released, they may also have to adhere to instructions outside their normal daily activities, for example, sleeping in a separate bed, minimizing close contact with others, and delaying their return to work [46]. In contrast, following treatment with $^{90}$Y-ibritumomab tiuxetan, patients are readily discharged with advice on how to properly manage bodily fluid spillages [47]. Furthermore, unlike treatment with $^{131}$I-tositumomab, patients are not required to minimize contact with others [48, 49].

**Efficacy of High-Dose $^{90}$Y-Ibritumomab Tiuxetan**

Preliminary data suggest that $^{90}$Y-ibritumomab tiuxetan, when used at two to three times the registered dose, is a well-tolerated and effective conditioning regimen prior to ASCT. In a very recent report, in 30 patients with CD20$^+$ NHL that was either relapsed/refractory or de novo high risk (FL, 12; DLBCL, 10; lymphocytic lymphoma, 2; MCL, 3; MZL, 2; Richter syndrome, 1), $^{90}$Y-ibritumomab tiuxetan administered at doses of 0.8 mCi/kg or 1.2 mCi/kg was well tolerated [32]. Hematologic toxicities were mild to moderate and of short duration. Only eight (27%) patients experienced infections, and only three (10%) patients required short hospital stays for grade 3 febrile neutropenia; no secondary myeloid malignancies/chromosomal abnormalities were evident after a mean observation time of 30 months. A disease-free status was achieved by 25 (83%) patients, two patients had a PR, and three had disease progression. The projected OS and EFS rates after a median follow-up of 30 months were 87% and 69%, respectively. These data are extremely promising because these patients are historically associated with an extremely poor prognosis [50]. The good tolerability of $^{90}$Y-ibritumomab tiuxetan demonstrated in that study suggests that the agent may be appropriate for the majority of NHL patients as an outpatient treatment [32, 43].

High-dose $^{90}$Y-ibritumomab tiuxetan plus HDC (high-dose etoposide and cyclophosphamide) was also investigated as a conditioning regimen before SCT in 42 patients (median age, 51 years) with poor-risk or refractory B-cell NHL [30]. The median dose of $^{90}$Y-ibritumomab tiuxetan used was 70.8 mCi. The regimen showed promising long-term efficacy, especially for FL and DLBCL patients, and an excellent safety profile without additional toxicity. At a median follow-up of 55 months (range, 25–84 months) for the surviving patients, the 4-year estimated OS and disease-free survival rates were 81% and 65%, respectively (Fig. 3). Engraftment was achieved in all but one patient, and the incidence of second malignancy (7%) with high-dose $^{90}$Y-ibritumomab tiuxetan plus HDC was similar to that of high-dose regimens that did not include RIT [30, 51].

**Efficacy of High-Dose $^{131}$I-Tositumomab**

Phase I/II data with high-dose $^{131}$I-tositumomab also show that RIT given with ASCT has high activity in relapsed NHL. A phase II study in patients aged $\geq$60 years with relapsed B-cell lymphoma histologies (DLBCL, 9; MCL,
who were treated with high-dose $^{131}$I-tositumomab with ASCT demonstrated 3-year OS and PFS rates of 59% and 51%, respectively, for the overall population. The authors hypothesize that the specific targeting of RIT to tumor sites underlies the good tolerability of RIT seen in these patients [39]. Similarly, follow-up in 29 patients (median age, 46 years) with relapsed B-cell lymphomas treated with $^{131}$I-tositumomab (5–10 mCi; 0.35, 1.7, or 7 mg/kg) revealed an objective response rate of 86%. Long-term follow-up at 42 months showed that remission was prolonged (OS rate, 68%; PFS rate, 42%) [40, 44].

The results from the studies above demonstrate that high-dose myeloablative RIT with or without chemotherapy and ASCT is a promising and effective treatment option for patients unable to tolerate HDC. Furthermore, the excellent tolerability demonstrated even by patients with poor-risk characteristics suggests that this approach may broaden the patient population who would benefit from SCT, thus offering a curative potential to a larger number of NHL patients.

**CAN RIT BE USED POST-TRANSPLANT?**

Currently, few data are available for the use of RIT in patients who have relapsed after HDC and stem cell transplantation (Table 2). However, these preliminary studies with $^{90}$Y-ibritumomab tiuxetan [52, 53] and $^{131}$I-tositumomab [54] suggest that RIT may be a viable option for some patients after ASCT failure. In a study by Vose et al. [53], 19 patients who failed transplant (DBLCL, 58%; FL, 32%; MCL, 5%; MZL, 5%) were treated with $^{90}$Y-ibritumomab tiuxetan (0.10–0.20 mCi/kg). The response rate was 47% and, at a median follow-up of 37 months, the 1-year EFS and OS rates were 26% and 57%, respectively. Although hematologic toxicities were dose limiting, the EFS and OS rates were higher with higher doses in the overall study population and also in the subset of patients with FL. In a second preliminary study ($n = 13$) of RIT ($^{131}$I-tositumomab, 45 cGy total-body dose) in chemotherapy-relapsed or chemotherapy-refractory B-cell lymphoma patients (histology not specified), the objective response rate was 50% (compared with 78% for nonperipheral SCT failures), and at 4.7 years, the median PFS time of responders had not been reached. Notably, 31% of patients were disease free at 3 years post-therapy [54]. Although these preliminary data are promising, further investigation is needed to clarify the appropriate dose of $^{90}$Y-ibritumomab tiuxetan and $^{131}$I-tositumomab to be used and the level of risk for myelodysplasia, acute myeloid leukemia, and hematologic toxicities in this setting.

**DOES RIT HAVE A ROLE IN NONMYELOABLATIVE CONDITIONING IN ALLOSCT?**

AlloSCT may be a therapeutic option for patients with chemotherapy-refractory, aggressive lymphoma and for patients failing prior ASCT. RIC can be used with alloSCT, but relapse rates are high when it is used in active disease because rapid tumor progression can occur before the graft-versus-lymphoma effect has time to be established [4]. Preliminary data suggest that RIT in combination with RIC in alloSCT may improve outcome, by better disease eradication and prevention of recurrence while maintaining the low toxicity of RIC. A small pilot trial evaluated the combination of $^{90}$Y-ibritumomab tiuxetan (0.4 mCi) with a fludarabine-based regimen in 12 patients (median age, 54 years) with chemotherapy-refractory NHL. Eighty-three percent of patients achieved a CR or a PR, and, at a median follow-up of 21 months, the 2-year PFS rate was 33% and the 2-year response rate was relatively low (25%). Toxicity was similar to that observed with similar regimens not containing $^{90}$Y-ibritumomab, once again indicating that adding RIT to chemotherapy does not increase toxicity [55]. The low incidence of relapse reported in this study will encourage further evaluation of $^{90}$Y-ibritumomab tiuxetan RIC and alloSCT in refractory NHL.

<p>| Table 2. Summary of available data for RIT in transplant failures following high-dose chemotherapy and stem cell transplantation |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>RIT</th>
<th>$n$ of patients</th>
<th>Histology</th>
<th>Overall survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs et al. (2005) [52]</td>
<td>$^{90}$Y-IT</td>
<td>8</td>
<td>Mostly DBLCL and FL</td>
<td>NA (CR, 1; MR, 1)</td>
<td>NA</td>
</tr>
<tr>
<td>Vose et al. (2007) [53]</td>
<td>$^{90}$Y-IT</td>
<td>19</td>
<td>Mostly DBLCL and FL</td>
<td>1-yr, 57%</td>
<td>1-yr, 26%</td>
</tr>
<tr>
<td>Kaminski et al. (2000) [54]</td>
<td>$^{131}$I-T</td>
<td>13</td>
<td>NS</td>
<td>NA (ORR, 50%)</td>
<td>Not reached at 4.7 yrs; 3-yr DFS, 31%</td>
</tr>
</tbody>
</table>

Abbreviations: $^{90}$Y-IT, yttrium-90 ibritumomab tiuxetan; $^{131}$I-T, iodine-131 tositumomab; CR, complete response; DFS, disease-free survival; DBLCL, diffuse large B-cell lymphoma; EFS, event-free survival; FL, follicular lymphoma; MR, mixed response; NA, not assessed; NS, not specified; ORR, objective response rate; RIT, radioimmunotherapy.
**90Y-Ibritumomab Tiuxetan Case Study**

A 90Y-ibritumomab tiuxetan case study (Fig. 4) illustrates the long-term effectiveness of RIT as a component of an RIC regimen for alloSCT in a 27-year-old patient with mediastinal large B-cell lymphoma (Dr. Dolores Caballero, Transplant Unit, University Hospital, Salamanca, Spain, personal communication).

**CONCLUSION**

Although HDC with ASCT is one curative option for eligible patients with chemotherapy-sensitive, relapsed, aggressive NHL leading to prolonged PFS, some patients who undergo this therapeutic option will eventually relapse. Additionally, it has limited success in chemotherapy-refractory disease or in heavily pretreated, multiple-relapsed patients and, because of its highly toxic nature, is unsuitable for elderly patients. AlloSCT is another curative option that may also be appropriate for elderly patients, but relapse rates are high in active disease. Consequently, there is much interest in evaluating new treatment regimens that can be used to improve the outcome with SCT in NHL without increasing the toxicity level of the existing regimens. In this paper, we reviewed the data supporting the safety and efficacy of RIT with 90Y-ibritumomab tiuxetan and 131I-tositumomab as part of the conditioning regimen before SCT. Two approaches have been explored relating to the use of RIT as a conditioning agent for ASCT: standard-dose, nonmyeloablative RIT with HDC and high-dose myeloablative RIT with or without chemotherapy. The data show that augmentation of these approaches appears to provide promising outcomes and disease control without greater toxicity. Interestingly, in both chemotherapy-sensitive and chemotherapy-refractory disease, augmentation of HDC with RIT prior to ASCT appears to provide better clinical outcomes than with historical data for pure HDC pretransplant conditioning regimens. Preliminary data from phase I/II trials show that RIT may be safely used as a single agent or added at either a high dose or standard dose to HDC preparative regimens for high-risk B-cell NHL histologies (DLBCL, FL, MCL, and MZL). Preliminary data also suggest that RIT in combination with RIC in alloSCT may improve outcome, by better disease eradication and prevention of recurrence, while maintaining the low toxicity of RIC.

All these studies indicate a promising role for RIT-based conditioning regimens for SCT, particularly in patients who cannot tolerate HDC and/or TBI. Based on these...
data, large-scale trials should be performed to investigate and further confirm these key observations.

**AUTHOR CONTRIBUTIONS**

**Conception/Design:** Auayporn Nademanee, Alessandro M. Gianni, Arnon Nagler  
**Provision of study materials:** Christian Gisselbrecht, Julie Vose, Auayporn Nademanee, Alessandro M. Gianni, Arnon Nagler  
**Collection/assembly of data:** Christian Gisselbrecht, Alessandro M. Gianni, Arnon Nagler

**REFERENCES**


**Data analysis:** Christian Gisselbrecht, Julie Vose, Auayporn Nademanee, Alessandro M. Gianni  
**Manuscript writing:** Christian Gisselbrecht, Julie Vose, Auayporn Nademanee, Alessandro M. Gianni, Arnon Nagler  
**Final approval of manuscript:** Christian Gisselbrecht, Julie Vose, Auayporn Nademanee, Alessandro M. Gianni, Arnon Nagler

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