Rationale for Consolidation to Improve Progression-Free Survival in Patients with Non-Hodgkin’s Lymphoma: A Review of the Evidence

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The article discusses 90Y-ibritumomab tiuxetan (Bayer Schering Pharma AG, Spectrum Pharmaceuticals, Inc., Irvine, CA) as consolidation at first remission in follicular lymphoma patients, as a therapy for nonfollicular NHL, and as first-line treatment for NHL patients not eligible for chemotherapy and rituximab (F. Hoffmann-La Roche) as maintenance therapy in previously untreated patients and as treatment for nonfollicular NHL.

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ABSTRACT

Non-Hodgkin’s lymphoma (NHL) comprises both indolent forms, including follicular lymphoma (FL) and marginal zone lymphoma (MZL), and aggressive forms, including diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). FL and DLBCL are the most common subtypes of indolent and aggressive NHL, respectively. Although these lymphomas exhibit different clinical behaviors and outcomes, the prognosis is negatively affected in both DLBCL and FL by the lack of a complete response (CR) with standard treatment options. The aim of therapy should therefore be achievement of a CR, which is not only associated with longer progression-free survival (PFS) and overall survival times, but is also a prerequisite for a cure, particularly in DLBCL.

Consolidation treatment with radioimmunotherapy (RIT) is an innovative treatment approach to increase CR rates. Phase II studies have indicated promising results with yttrium-90 (90Y)-ibritumomab tiuxetan and iodine-131 (131I)-tositumomab as consolidation following induction therapy for previously untreated patients with advanced FL. More recently, investigators reported a marked increase in CR rates and significant improvements in PFS using standard chemotherapy regimens followed by 90Y-ibritumomab tiuxetan in a phase III randomized trial in patients with previously untreated FL. Data also suggest that RIT may play a role in the treatment of high-risk DLBCL, with encouraging PFS results from a phase II trial of 90Y-ibritumomab tiuxetan consolidation following induction with rituximab plus chemotherapy in elderly patients with previously untreated DLBCL. With the higher CR rates and longer PFS times observed in patients with FL and...
TREATMENT APPROACHES FOR PATIENTS WITH NON-HODGKIN’S LYMPHOMA: THE ROLES OF INDUCTION, CONSOLIDATION, AND MAINTENANCE THERAPY

Induction therapy aims to produce a maximal initial response by reducing tumor burden, with the goal of prolonging progression-free survival (PFS) and overall survival (OS) times in patients with non-Hodgkin’s lymphoma (NHL). However, because disease recurrence is common [1], additional strategies have been sought to either maintain or improve the quality of the initial response with maintenance or consolidation therapy, respectively. Maintenance treatment is a long-term approach to delay relapse by stabilizing the best response to initial therapy. Because maintenance therapy is administered over a prolonged period of time, it must be well tolerated and cost-effective to be considered as a valid treatment strategy [2–4].

Traditionally, consolidation therapy was used to treat acute leukemia [5], in which the presence of residual disease is associated with a higher relapse rate. In contrast to maintenance treatment, the objective of consolidation therapy is to rapidly improve the response to induction therapy, not only by converting a partial response (PR) to a complete response (CR), but also by eradicating minimal residual disease to achieve a molecular response in patients with a clinical CR after initial treatment, thus reducing the relapse risk of responders [6–9]. In this review we examine the role of radioimmunotherapy (RIT) as consolidation treatment for patients with NHL, particularly focusing on follicular lymphoma (FL).

INDOLENT LYMPHOMA

Current Treatment Strategies

There are numerous strategies of care for patients with advanced (stage III/IV) FL, a low-grade (indolent) lymphoma that accounts for ~22% of newly diagnosed NHL cases [10]. Other indolent lymphomas include marginal zone lymphoma (MZL), an NHL subgroup comprising mucosa-associated lymphoid tissue (MALT), and nodal and splenic lymphomas [11]. Conventional therapy options for indolent lymphomas range from “watchful waiting” to chemotherapy, immunotherapy, and high-dose marrow-ablative treatment combined with autologous stem cell transplantation (ASCT), with *Helicobacter pylori* eradication also being employed in patients with gastric MALT [11–13].

Disease risk factors and patient characteristics are important parameters when selecting appropriate therapy, because prognosis and outcomes vary widely depending on these features [14, 15]. Evaluation of a large number of prognostic factors in patients with FL led to the development of the Follicular Lymphoma International Prognostic Index (FLIPI), a tool used by clinicians for the assessment of trial results, including those investigating more recent therapies such as rituximab [13, 16, 17]. However, investigators principally base patient selection or treatment decision-making in clinical trials on criteria from the British National Lymphoma Intergroup, the Groupe d’Etude des Lymphomes Folliculaires (GELF), the Ann Arbor staging system, and the Revised European-American Lymphoma/World Health Organization classification [12, 18–20].

Despite recent improvements in therapy, advanced FL is not considered curable, and most patients, including initial responders, undergo multiple relapses, presumably as a result of the persistence of residual disease. Investigators have long observed that, although patients who relapse following initial therapy may be induced to a second, third, or fourth remission, the duration of these remissions shortens with each subsequent treatment at recurrence [21, 22]. An additional threat to patients with FL is the possibility of transformation to diffuse large B-cell pathology, which is associated with a poor prognosis and shorter survival time [23].

Initial treatment of advanced FL has focused on the induction of a response, using chemotherapy or immunotherapy, alone or combined, in order to extend PFS and OS times (Fig. 1) [2, 24, 25]. However, despite noticeable improvements in the overall response rate with the addition of rituximab to chemotherapy, most initial treatment strategies for patients with FL result in high PR rates, whereas CR rates remain modest in the majority of trials (41%, including unconfirmed CR [CRu] cases [26], 50% [27], or 20% [28]), with higher CR rates being infrequently reported (67%, including CRu cases [18]).

Following induction, several treatments have been investigated as maintenance therapy to sustain the best initial response (Fig. 1). Maintenance therapy using interferon has been attempted in the past for patients with indolent lymphomas, although results were mixed and the impact on OS was minor [29]. A short course of rituximab following different chemotherapy regimens has been evaluated in patients with FL and MZL with encouraging results, although
rituximab is more frequently employed as a longer-term maintenance treatment [30, 31]. In relapsed FL, induction with chemotherapy plus rituximab followed by rituximab maintenance has led to longer PFS [32, 33] and OS [33] times, although CR rates after maintenance treatment remain low: 34% reported in one trial [32]. In a study using rituximab monotherapy, rituximab maintenance therapy did not result in higher OS rates than with rituximab treatment at relapse [34].

Various maintenance regimens with rituximab have been described, with no one method being clearly established as superior to the others [32–36]. The phase III Primary Rituximab and Maintenance trial (ClinicalTrials.gov trial identifier, NCT00140582), a prospective trial initiated in December 2004, should provide valuable information regarding the role of rituximab maintenance following first-line induction with rituximab plus chemotherapy in patients with FL.

The Role of Consolidation Treatment in Indolent Lymphoma

An alternative to simply maintaining the response achieved with induction therapy is the consolidation approach (Fig. 1). This strategy is supported by a recent long-term follow-up of the GELF86 trial, which showed that achieving a CR correlates with OS in FL [25], in addition to earlier reports of an association between survival and CR in lymphoma treatment [37, 38]. The PFS time for patients with FL who have achieved a PR has also been shown to be shorter, in many cases significantly shorter, than that for patients with a CR [26, 39, 40], and in one study, a longer PFS time following a CR was observed after, but not before, rituximab maintenance treatment [41]. Additionally, investigators have reported that minimal residual disease, which can be assessed by polymerase chain reaction (PCR) detection of bcl-2 gene rearrangement, is associated with a greater risk for relapse [6–9], whereby patients who consistently have bcl-2 PCR-undetectable disease have a lower likelihood of disease recurrence than patients with persistent bcl-2 PCR-detectable disease [42–45]. These reports emphasize the value of achieving the highest quality of initial response; therefore, future studies should focus on achieving higher CR and molecular response rates with the aim of prolonging PFS and OS.

Prior to the widespread use of rituximab, consolidation with marrow-ablative treatment followed by ASCT [46] was extensively studied in patients with FL, and PR to CR conversion rates of 38%–69% were reported from three large phase III randomized trials of ASCT consolidation following first-line induction with standard- or high-dose chemotherapy [39, 47, 48]. More recently, ASCT consolidation following induction with rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) resulted in a 5-year PFS rate of 79% [49]. Investigators recently evaluated consolidation with ASCT at second remission or later and reported improvements in both PFS and OS when patients undergo transplantation earlier in the course of the disease [50]. However, there are drawbacks to ASCT consolidation because of toxicity and the limited suitability of patients (only younger, fit patients are eligible) [47, 48]. ASCT has also been associated with a higher risk for myelodysplasia, acute myeloblastic leukemia, and infection [50, 51]. An alternative consolidation strategy has therefore been sought as a therapy option for a wider patient population, including those aged >60 years who account for ~50% of lymphoma patients [52]. Results from several trials evaluating RIT in patients with indolent NHL suggest that it may have an important role in the consolidation setting.

The Impact of RIT as Consolidation Therapy

RIT has been approved as a treatment for patients with relapsed FL for several years, following a number of trials that evaluated yttrium-90 (90Y)-ibritumomab tiuxetan (Zevalin®; Spectrum Pharmaceuticals, Inc., Irvine, CA; Bayer Schering Pharma AG, Berlin, Germany) or iodine-131 (131I)-tositumomab (Bexxar®; GlaxoSmithKline, Research Triangle Park, NC) [53–58]. A new 90Y-labeled anti-CD22 antibody, epratuzumab, is also being investigated in therapeutic trials in patients with NHL [59–61].
Whereas RIT is efficacious in relapsed or refractory disease, studies have shown that treatment earlier in the disease course produces significantly higher response rates and longer PFS times [62, 63]. RIT consolidation therapy after first-line induction with chemotherapy or chemoimmunotherapy has been evaluated in several phase I/II trials [64 – 68], and results of a phase III randomized study of 90Y-ibritumomab tiuxetan as front-line consolidation, the First-line Indolent Trial (FIT), were just published [69].

131I-Tositumomab
Several phase II trials have evaluated 131I-tositumomab as consolidation therapy following different induction schedules in previously untreated patients with FL, and PR to CR/CRu conversion rates have been in the range of 49%–84% [65, 70–72] (Table 1). A molecular response rate of 77% was achieved in 35 patients after fludarabine induction, and the median PFS time was not reached at a median follow-up of 58 months [70]. In a trial of cyclophosphamide, vincristine, and prednisone (CVP) induction followed by 131I-tositumomab consolidation (n = 30), a median PFS time was not reached after a median follow-up of 2.3 years [71]. A larger trial (n = 90) by the Southwest Oncology Group, in which CHOP induction was followed by 131I-tositumomab consolidation, reported that the estimated 5-year PFS and OS rates of 67% and 87%, respectively, were 23% higher than historical data for patients who had received induction chemotherapy alone [65, 72]. An important ongoing randomized phase III trial investigating the efficacy of 131I-tositumomab consolidation following CHOP induction compared with R-CHOP induction alone (ClinicalTrials.gov trial identifier, NCT00006721) should clarify which of these schedules is more effective.

131I-tositumomab requires dosimetry testing prior to treatment and thorough radioprotection measures because of the high-energy γ emission of 131I [73, 74]. According to radioprotection guidelines, treated patients should be isolated in specially equipped rooms for several days, although outpatient treatment with contact restrictions and contamination precautions is feasible in many cases [75].

90Y-Ibritumomab Tiuxetan
90Y-ibritumomab tiuxetan consolidation after induction with chemotherapy or chemoimmunotherapy was reported to be safe and effective in several phase II studies in patients with indolent lymphoma [64, 67, 76].

Table 1. Response rates from phase II trials evaluating radioimmunotherapy consolidation therapy after induction treatment in patients with previously untreated indolent lymphoma

<table>
<thead>
<tr>
<th>Study regimen</th>
<th>CR/PR rates after induction (%)</th>
<th>CR/PR rates after consolidation (%)</th>
<th>Conversion rate (≤PR to CR) after consolidation (%)</th>
<th>Reference (n of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>131I-tositumomab consolidation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVP (6 cycles) + 131I-tositumomab consolidation</td>
<td>50/50</td>
<td>80/NR</td>
<td>60</td>
<td>[71] (n = 30)</td>
</tr>
<tr>
<td>CHOP (6 cycles) + 131I-tositumomab consolidation</td>
<td>39%/49</td>
<td>67%/23</td>
<td>49a</td>
<td>[65] (n = 90)</td>
</tr>
<tr>
<td>Fludarabine (3 cycles) + 131I-tositumomab consolidation</td>
<td>9/80</td>
<td>86/14</td>
<td>84</td>
<td>[70] (n = 35)</td>
</tr>
<tr>
<td>90Y-IT consolidation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R (×4) + R-CHOP (3 cycles) + 90Y-IT consolidation</td>
<td>28/72</td>
<td>67/NR</td>
<td>54</td>
<td>[76] (n = 42)</td>
</tr>
<tr>
<td>FM (6 cycles) + 90Y-IT consolidation</td>
<td>50/30.5</td>
<td>100/0</td>
<td>100</td>
<td>[64]b (n = 26)</td>
</tr>
<tr>
<td>FM (6 cycles) + 90Y-IT consolidation</td>
<td>70/28</td>
<td>96.5/3.5</td>
<td>86</td>
<td>[77] (n = 61)</td>
</tr>
<tr>
<td>R-CHOP (3 cycles) + 90Y-IT consolidation + R (×4)</td>
<td>67%/NR</td>
<td>96%/NR</td>
<td>89</td>
<td>[67] (n = 60)</td>
</tr>
</tbody>
</table>

aIncludes unconfirmed CR.
bAll follicular lymphoma except nonfollicular indolent lymphoma.

Abbreviations: 90Y-IT, yttrium-90-ibritumomab tiuxetan; 131I, iodine-131; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; CVP, cyclophosphamide, vincristine, and prednisone; FM, fludarabine and mitoxantrone; NR, not reported; PR, partial response; R, rituximab.
sion to CR with $^{90}$Y-ibritumomab tiuxetan consolidation after short-course R-CHOP induction therapy was observed in 15 of 28 patients (54%) with an initial PR [76] and in 16 of 18 patients (89%) without an initial CR, as determined by positron emission tomography [67] (Table 1). In addition, all seven patients (100%) with non-FL lymphoma, including those with MZL, who achieved an initial PR after fludarabine and mitoxantrone induction were converted to a CR following $^{90}$Y-ibritumomab tiuxetan treatment [64]. A 2-year PFS rate of 77% was reported with $^{90}$Y-ibritumomab tiuxetan following R-CHOP induction [76], and estimated 3-year PFS and OS rates of 76% and 100%, respectively, were reported by Zinzani and colleagues after $^{90}$Y-ibritu-


momab tiuxetan consolidation following induction therapy consisting of fludarabine and mitoxantrone [77].

Based on promising phase II data, phase III FIT investigated $^{90}$Y-ibritumomab tiuxetan given as consolidation therapy versus observation in $>$400 patients with previously untreated stage III/IV FL, following induction with either chlorambucil, CVP, CHOP, a CHOP-like regimen, a fludarabine-based regimen, or rituximab combination therapy [69]. In total, 414 patients with a performance status score of 0–2 and a CR/CRu or PR following induction chemotherapy were randomized to receive either $^{90}$Y-ibritumomab tiuxetan consolidation therapy ($n = 208$) or no further treatment (control; $n = 206$). Randomization occurred 6–12 weeks after the final chemotherapy dose was administered. The primary endpoint was PFS, calculated from randomizing to first report of relapse, disease progression, or death from any cause.

In the group receiving consolidation treatment, low-, intermediate-, and high-risk FLIPI groups accounted for 37%, 39%, and 24% of patients, respectively, which was similar to the control group population (42%, 37%, and 21%, respectively). The most common first-line regimen received was CHOP (31% of patients), with 26% of patients receiving CVP and 15% receiving a CHOP-like regimen. The study began accrual in August 2001, which was prior to the standard use of rituximab as part of chemoimmuno-


therapy regimens. Therefore, patients receiving rituximab-based induction therapy were included in FIT only after a late protocol amendment in 2004, resulting in only 59 patients overall (14%) and 27 patients in the consolidation arm (13%) receiving rituximab–chemotherapy combinations as part of their induction regimen.

At a median observation time of 3.5 years, consolidation with $^{90}$Y-ibritumomab tiuxetan resulted in a statistically significant longer overall median PFS duration than in the control group (36.5 versus 13.3 months; $p < .0001$) (Fig. 2A). This superior PFS outcome was seen after $^{90}$Y-ibritu-


momab tiuxetan treatment both in patients who had achieved a CR/CRu with induction therapy (53.9 months versus 29.5 months; $p = .0154$) (Fig. 2B) and in those with a PR after induction (29.3 months versus 6.2 months; $p < .0001$), giving them an almost 2-year PFS advantage (Fig. 2C). The significant benefit observed even among patients with a CR after induction suggests that patients with a clinical CR following different induction regimens may have varying levels of residual disease, which is presumed to lead to relapse [78]. Longer PFS times were observed across all FLIPI subgroups, and reached statistical significance in the low- and intermediate-risk groups. In the high-risk group, the PFS time was extended to 23.8 months in the consolidation arm, compared with 6.5 months in the control group; however, this difference was not statistically significant, possibly, in part, as a result of low patient numbers. In addition to the strikingly longer PFS time, 77.2% of patients in PR after induction were converted to CR/CRu after $^{90}$Y-


ibritumomab tiuxetan consolidation, resulting in a final CR/CRu rate of 87% (Table 2).

PR to CR/CRu conversion rates after consolidation therapy were also higher for all induction groups and statistically significant in all but the rituximab induction schedule (Table 2). In all patient groups, except those receiving fludarabine or rituximab combinations as induction, the PFS time was significantly longer after $^{90}$Y-ibritumomab tiuxetan therapy (in the rituximab combination group, the median PFS time was not reached in either the control or the consolidation arm). It is important to note, however, that FIT was neither designed nor statistically powered to detect outcome differences according to first-line induction treatment. This is of particular relevance when considering outcomes in patients who received rituximab-based induction chemotherapy. Because of the late inclusion of patients who had received induction therapy including rituximab in FIT, resulting in a considerably shorter follow-up time and lower patient numbers than with the other induction treatment groups, conclusions cannot be drawn from the currently available outcome data for this patient population. Of note, recent data from a phase I/II study ($n = 16$) have shown that induction with multiple rituximab doses did not compromise the efficacy or tolerability of downstream RIT with $^{131}$I-rituximab therapy [79]. Furthermore, preliminary results from phase II studies have shown that $^{90}$Y-ibritumomab tiuxetan is highly active after prior exposure to rituximab (up to seven doses) with short-duration chemother-


apy [67, 76].

These phase II studies also indicate that $^{90}$Y-ibritu-


momab tiuxetan consolidation allows higher response rates with less aggressive induction therapy. This is supported by the superior outcomes in FIT after the CVP and chlorambucil induction regimens, and suggests that consolidation
therapy with $^{90}$Y-ibritumomab tiuxetan offers an effective option for patients who may not be able to tolerate aggressive induction regimens, such as the elderly.

The molecular conversion rate in FIT was considerable, with 90% of patients treated with $^{90}$Y-ibritumomab tiuxetan consolidation achieving PCR-undetectable $bcl-2$ sta-

Figure 2. Progression-free survival times of patients in the phase III First-line Indolent Trial investigating consolidation treatment with yttrium-90 ($^{90}$Y)-ibritumomab tiuxetan after induction treatment versus induction treatment alone (control). (A): All patients; (B): Complete response (CR)/unconfirmed CR patients; (C): Partial response patients. The median observation period was 3.5 years [69]. Adapted from 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. Reprinted with permission. ©2008 American Society of Clinical Oncology. All rights reserved.

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Conversion of response rates after 90Y-IT consolidation treatment versus no consolidation treatment (control) in the phase III First-line Indolent Oncology Trial with respect to induction treatment received [69].

<table>
<thead>
<tr>
<th>First-line induction regimen</th>
<th>Conversion rate (≤PR to CR/CRu) postrandomization (%)</th>
<th>90Y-IT consolidation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>17.5 (n = 97)</td>
<td>77.2 (n = 101)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>7.7 (n = 13)</td>
<td>84.6 (n = 13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CVP</td>
<td>10.3 (n = 29)</td>
<td>72.7 (n = 22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CHOP</td>
<td>25.0 (n = 32)</td>
<td>75.6 (n = 41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CHOP-like</td>
<td>0 (n = 8)</td>
<td>76.9 (n = 13)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Fludarabine combination</td>
<td>0 (n = 3)</td>
<td>100 (n = 5)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Rituximab combination</td>
<td>41.7 (n = 12)</td>
<td>71.4 (n = 7)</td>
<td>.34</td>
</tr>
</tbody>
</table>

Abbreviations: 90Y-IT, yttrium-90-ibritumomab tiuxetan; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; CRu, unconfirmed complete response; CVP, cyclophosphamide, vincristine, prednisone; PR, partial response.


Table 2.

The markedly better CR rate and PFS time in FIT, excellent PR to CR/CRu conversion rate, and a favorable tolerability profile led to the approval of 90Y-ibritumomab tiuxetan in April 2008 by the European Medicines Agency (EMEA) as consolidation therapy after remission induction in previously untreated patients with FL [83].

Role of RIT in the Treatment Algorithm for Patients with FL

Previous recommendations for the use of RIT have focused on its effectiveness in the treatment of patients with relapsed or refractory FL [84]. However, earlier treatment has been reported to be more beneficial in terms of increasing CR rates and prolonging PFS times [62], and investigators have reported encouraging data from trials of RIT in untreated patients, leading to the suggested inclusion of RIT in first-line treatment algorithms for FL [85, 86]. Based on these factors, and the results just published from FIT, we suggest that 90Y-ibritumomab tiuxetan may play an important role as first-line consolidation therapy in the treatment of patients with advanced FL (Fig. 3). For fit patients, the most effective strategy may be to use an intensive chemotherapy regimen followed by consolidation and maintenance [14]. The intensity of such a regimen could be reduced for frail patients, with less aggressive induction regimens followed by 90Y-ibritumomab tiuxetan consolidation therapy [69]. 90Y-ibritumomab tiuxetan may also have a role as first-line treatment in patients ineligible for chemotherapy [86, 87], although this approach is still under investigation and has not yet been approved. Further studies are required to establish the optimal use and dosing of rituximab as part of induction and/or maintenance therapy combined with 90Y-ibritumomab tiuxetan consolidation treatment. The role of RIT in ASCT and patient selection for RIT consolidation are discussed elsewhere in this supplement [14, 46].

Despite the benefit conferred by the addition of rituximab to first-line induction regimens, treatment outcomes are still considerably poorer for high-risk FLIPI patients than for other subgroups of patients [18], although a recent study showed a benefit with rituximab maintenance in patients with a high tumor burden (p = .03) [36]. The longer PFS time conferred by 90Y-ibritumomab tiuxetan consolidation in all FLIPI subgroups is an important observation [14]. Because the number of high-risk patients was low in FIT, additional studies should provide more data on 90Y-QoL-5D and European Organization for Research and Treatment of Cancer Core Questionnaire QLQ-C30 scores were similar in the control and consolidation groups, demonstrating that there was no adverse impact on quality of life with 90Y-ibritumomab tiuxetan treatment.
ibritumomab tiuxetan consolidation in these patients. Recently, promising results were reported from an ongoing phase II trial in high-risk FLIPI patients evaluating induction with rituximab, fludarabine, mitoxantrone, and dexamethasone followed by 90Y-ibritumomab tiuxetan consolidation and then rituximab maintenance for 1 year [68]. A CR was achieved in 29 patients, five of whom were converted from a PR after 90Y-ibritumomab tiuxetan consolidation and then rituximab maintenance for 1 year [68]. A CR was achieved in 29 patients, five of whom were converted from a PR after 90Y-ibritumomab tiuxetan consolidation and then rituximab maintenance for 1 year [68]. A CR was achieved in 29 patients, five of whom were converted from a PR after 90Y-ibritumomab tiuxetan consolidation and then rituximab maintenance for 1 year [68]. A CR was achieved in 29 patients, five of whom were converted from a PR after 90Y-ibritumomab tiuxetan consolidation and then rituximab maintenance for 1 year [68].

Figure 3. Proposed positioning of yttrium-90 (90Y)-ibritumomab tiuxetan as consolidation in the treatment algorithm for first-line therapy of patients with advanced follicular lymphoma. A patient selection algorithm for 90Y-ibritumomab tiuxetan consolidation can be found in Gregory et al. [14].

AGGRESSIVE LYMPHOMA

Treatment Challenges in Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive lymphoma, accounting for 31% of newly diagnosed NHL cases [10]. Management of this disease has largely been with chemotherapy and radiotherapy [88], although the use of external-beam radiotherapy is generally not supported in Europe and is not a standard of care in the U.S. [89, 90]. Despite markedly superior outcomes in first-line treatment following the addition of rituximab to the CHOP regimen, with dose-dense/dose-intensive regimens also playing a potential role [91–95], the prognosis remains poor for patients aged >60, with a 7-year OS rate of 53% reported in one study [91]. The standard of care for relapsed DLBCL is high-dose chemotherapy with ASCT consolidation, although it is not yet clear which conditioning regimen, including carmustine (BCNU), etoposide, cytarabine, and melphalan (BEAM), is the most effective [42, 96, 97]. There are some concerns that the combination of ASCT consolidation with BEAM conditioning may result in a higher incidence of secondary malignancies [98], a risk that has long been associated with whole-body radiotherapy in NHL [99, 100]. Alternative treatment approaches are therefore needed to reduce the risk for disease relapse by improving first-line therapy, particularly for older patients who are not eligible for ASCT. Effective first-line treatment relies on maximizing the benefits of induction therapy.

Emerging Evidence for the Role of RIT as Consolidation Treatment of DLBCL

Evidence for the Efficacy of RIT in DLBCL

Efficacy has been demonstrated with RIT for patients with relapsed/resistant aggressive DLBCL receiving 90Y-ibritumomab tiuxetan treatment, resulting in promising response rates and durable responses [56, 101, 102]. Phase II studies have found benefits with ASCT combined with 131I-tositum-
momab treatment [103, 104], and 90Y-ibritumomab tiuxetan treatment, given either alone or in combination with high-dose chemotherapy followed by ASCT, is reported to be safe and effective in heavily pretreated patients [105]. The potential efficacy of RIT in relapsed aggressive lymphoma, its emerging use as consolidation in the first-line treatment of FL, and reports that the use of RIT is more effective when administered earlier rather than later in the disease course provide a rationale for the investigation of RIT consolidation after first-line induction therapy in patients with DLBCL.

**RIT as Consolidation Therapy in DLBCL**

A phase II trial is currently investigating consolidation treatment with 90Y-ibritumomab tiuxetan following R-CHOP in elderly patients (≥60 years old) with high-risk, untreated DLBCL, because this patient group has a high relapse rate and significantly lower PFS and OS rates than younger patients [106]. Early results have indicated that 90Y-ibritumomab tiuxetan consolidation has a favorable tolerability profile, with low infection rates and manageable hematologic toxicities. In addition, responses improved after consolidation and OS and PFS rates were very encouraging after a median follow-up of 23 months, at 88% and 80%, respectively. Results are also awaited from two ongoing phase II trials investigating 90Y-ibritumomab tiuxetan consolidation in place of external-beam radiation after high-dose CHOP or R-CHOP (ClinicalTrials.gov trial identifiers, NCT00070018 and NCT00088881, respectively) [73], which will clarify the extent of the role of 90Y-ibritumomab tiuxetan in DLBCL treatment.

**Consolidation Therapy in Mantle Cell Lymphoma**

Mantle cell lymphoma (MCL) accounts for ~5%–10% of NHL cases and combines an aggressive clinical course with the lack of curability observed with available therapies for indolent lymphoma, resulting in a very poor prognosis [107, 108]. As with other types of NHL, ASCT has been employed as consolidation therapy in MCL patients, resulting in a significantly longer median PFS time than with interferon following CHOP-like induction in one trial (39 months versus 17 months; p = .0108) [109]. Patients with MCL have also received benefits from rituximab consolidation following high-dose chemotherapy and ASCT [110].

Many patients with MCL are not eligible for ASCT, however, and so RIT has been investigated as a treatment option in such cases. Pilot studies of 90Y-ibritumomab tiuxetan in patients with heavily pretreated MCL have shown promising results, but reports suggest that first-line RIT consolidation following induction chemoimmunotherapy may result in more durable responses [111, 112]. Similarly, investigators conducting a pilot study of 131I-tositumomab followed by CHOP chemotherapy in 24 patients with MCL concluded that minimal residual disease was not eradicated by this regimen and so proposed the evaluation of RIT consolidation following first-line induction therapy as an alternative option [113]. Subsequently, two phase II studies evaluating 90Y-ibritumomab tiuxetan consolidation after R-CHOP or other immunochemotherapy induction regimens have shown a higher quality of response (>50% PR to CR conversion rate), with an associated longer remission duration [114, 115]. Such emerging results suggest that RIT consolidation is also a potentially effective treatment approach for patients with MCL.

**Conclusions**

Data from clinical trials suggest that RIT consolidation therapy is an important treatment approach for patients with FL, with striking phase III results recently published for 90Y-ibritumomab tiuxetan consolidation following induction therapy in previously untreated patients. In particular, the high rates of CR observed may be a key factor in preventing the relapses that are characteristic of FL. Excellent rates of PR to CR/CRu conversion with RIT consolidation have led to significantly longer PFS times, with favorable tolerability and no unexpected toxicities. Following the release of the phase III 90Y-ibritumomab tiuxetan FIT data, the EMEA approved its use as consolidation therapy following remission induction in previously untreated patients with FL. Emerging data suggest that the RIT consolidation approach may also be effective in the treatment of other indolent lymphomas, such as MZL, and aggressive lymphomas, such as DLBCL and MCL. With such superior therapy options, the potential impact of RIT on the current and future treatment of both FL and aggressive NHL may include a shift in our approach to therapy and the adoption of RIT consolidation as a standard of care in the first-line setting.

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