Role of consolidation with yttrium-90 ibritumomab tiuxetan in patients with advanced-stage follicular lymphoma

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Abstract: Non-Hodgkin's lymphoma (NHL) accounts for 4% of all cancers diagnosed in the United States. Follicular lymphoma (FL) is the most common type of indolent NHL with a survival from 5 to 15 years. Although it is very sensitive to chemotherapy and radiotherapy, relapses are the main cause of therapeutic failure, and currently there is no consensus on the first-line treatment and optimal therapeutic strategies for patients with FL. Immediate treatment offers any survival benefit for asymptomatic and more indolent disease. In order to improve outcomes in FL, extend the remission, postpone the need for chemotherapy and improve OS, maintenance therapies with rituximab and consolidation treatments represent very attractive strategies. ^{90}Y -ibritumomab tiuxetan (^{90}Y -IT, Zevalin®) is approval as consolidation therapy in previously untreated FL patients who achieve response to first-line chemotherapy. Consolidation therapy with ^{90}Y -IT after initial induction treatment has shown improved activity compared with induction chemotherapy alone, even in patients previously treated with rituximab, in one phase III and several phase II trials, improving progression-free survival (PFS) and rate of conversion from partial response (PR) to complete response (CR). The phase III international FIT trial shows an improvement in PFS that is maintained after a median follow up of 7.3 years. Several phase II trials show high rate of conversion from PR to CR and a significant improvement in PFS. Treatment is feasible and well tolerated although myelodysplastic syndrome cases has been observed in some trials. ^{90}Y -IT should be considered for the initial treatment of FL in patients who are unable to tolerate standard chemotherapy, e.g., elderly or frail patients and otherwise in high-risk patients who achieve a PR or CR due to improvements in CR rate and PFS.

Keywords: ^{90}Y -ibritumomab tiuxetan, consolidation treatment, follicular lymphoma

Introduction

Non-Hodgkin's lymphoma (NHL) accounts for 4% of all cancers diagnosed in the United States, where more than 70,800 new cases (38,270 males and 32,530 females) and 18,990 deaths (10,470 males and 8520 females) are estimated for 2014. It represents an increasing incidence by 2–3% each year. The average American's risk of developing NHL during their lifetime is 2.4 (1 in 42) for males and for 1.9 (1 in 52) females and the risk of developing NHL increases throughout life, and about half of patients are older than 65. Death rates from NHL have been decreasing since the late 1990s, and there is a significant improvement in survival over the past three decades, with a trend in 5-year relative survival rate

from 47% to 71% (from period 1975–1977 to period 2003–2009) [Siegel *et al.* 2014].

Follicular lymphoma (FL) is the most common type of indolent NHL, the second most frequent lymphoma subtype, and comprises about 25% of all NHL. Nearly 15,000 new cases are diagnosed in the United States every year and for unclear reasons its incidence is increasing in the United States and Europe [Cartwright *et al.* 1999; Clarke and Glaser, 2002].

FL survival ranges from 5 to 15 years, depending on indices such as the Follicular Lymphoma International Prognostic Index (FLIPI) and the new FLIPI-2. Typically it is diagnosed at an

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advanced stage, with generalized lymphadenopathy and bone marrow involvement. World Health Organization (WHO) histologic grades 1 and 2 are considered the indolent subtypes, and grade 3 the more aggressive subtype (3a and 3b), and grade 3b FL is generally treated like diffuse large B-cell lymphoma (DLBCL).

Optimizing follicular lymphoma treatment options

Although it is very sensitive to chemotherapy and radiotherapy, relapses are the main cause of therapeutic failure. FL is characterized by initial responsiveness to single-agent or combination chemotherapy, with good response rates but frequent relapses that tend to be less responsive to chemotherapy and relapse-free survival last a shorter time, with a median survival of 4–5 years after first relapse. Advanced disease is still considered incurable with the treatments options we have nowadays, and despite the development of numerous treatment strategies to reduce the risk of progression, currently there is no consensus on the first-line treatment and optimal therapeutic strategies for patients with FL remain undefined.

As immediate treatment offers no survival benefit for patients [Ardeshtna *et al.* 2003; Young *et al.* 1988], some risk stratification classifications can be useful to decide which patients should receive front-line treatment upon diagnosis, such as: FLIPI [Solal-Céligny *et al.* 2004] and FLIPI-2 [Federico *et al.* 2009], although they do not predict when to initiate treatment and which treatment to use; the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria [Brice *et al.* 1997], which suggests that patients with ≥ 3 nodal sites with diameters of ≥ 3 cm or one mass ≥ 7 cm are not candidates for delayed therapy; and the British National Lymphoma Investigation (BNLI) criteria [Ardeshtna *et al.* 2003], which includes rapid, generalized disease progression in the preceding 3 months, life-threatening organ involvement, renal infiltration, bone lesions, presence of systemic symptoms including hemoglobin < 10 g/dl, white blood cell count (WBC) $< 1.5 \times 10^9/l$, or platelet counts $< 100 \times 10^9/l$, related to bone marrow involvement. In general, treatment is recommended for patients who are symptomatic or who have bulky disease.

There is no 'gold standard of therapy', and there are several treatment regimens or strategies that

have demonstrated efficacy in improving progression-free survival (PFS), time until treatment failure and even overall survival (OS), and can be considered when choosing which chemotherapy, immunotherapy, or chemo-immunotherapy use.

After the introduction of the anti-CD20 monoclonal antibody rituximab in 1997, overall response rates (ORRs), PFS, and OS have been improved, leading to rituximab chemotherapy becoming the standard induction treatment in first-line advanced FL [Fisher *et al.* 2005].

The more common regimens include cyclophosphamide-based treatments (cyclophosphamide, vincristine, and prednisone plus rituximab (R-CVP) [Marcus *et al.* 2008] and cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP) [Hiddemann *et al.* 2005]), bendamustine plus rituximab [Rummel *et al.* 2013], fludarabine-based treatments plus rituximab [Tsimberidou *et al.* 2002], or monotherapy with rituximab [Hainsworth *et al.* 2000].

In order to improve outcomes in FL, extend the remission, postpone the need for chemotherapy and improve OS, maintenance therapies with rituximab and consolidation treatments represent very attractive strategies.

Several randomized studies have analyzed the clinical benefit of rituximab maintenance treatment. The Primary Rituximab and Maintenance (PRIMA) study [Salles *et al.* 2011] evaluated rituximab maintenance in 1217 patients with previously untreated FL. Patients received induction regimen with chemotherapy plus rituximab (R-CHOP (75%), R-CVP (22%), or R-FCM (3%)) and those with complete response (CR) or partial response (PR) were randomized to observation or treatment with rituximab (375 mg/m² intravenously, one dose every 2 months for 2 years). PFS at 3 years was 75% in the rituximab maintenance and 58% for the observation group. Median time to disease progression has not been reached in the rituximab arm at a median follow up of 36 months. In a recently presented update [Salles *et al.* 2013], with a median follow up of 73 months from randomization, 6-year PFS was 42.7% in the observation arm and 59.2% in the rituximab maintenance. OS remains similar in both groups with a 6-year OS estimate in the observation arm of 88.7%, compared with 87.4% in the rituximab maintenance arm.

Other well-known studies using rituximab maintenance at different schedules have shown similar results [Hainsworth *et al.* 2005; Hochster *et al.* 2009; Forstpointner *et al.* 2006; Ghilmini *et al.* 2004; van Oers *et al.* 2006], and a meta-analysis [Vidal *et al.* 2009] demonstrated improvement in PFS and a small although significant increased risk of infections. However, the optimal duration and schedule of maintenance with rituximab is not known.

The idea that consolidation treatment after first line can be beneficial comes from the fact that patients with CR have greater survival than patients with PR, as we can observe how survival curves diverge early and maintained a significant difference over long follow up in the Bachy and colleagues [Bachy *et al.* 2010] analysis of OS for FL-treated patients. This idea has led to the development of strategies such as transplantation and radioimmunotherapy (RIT) as consolidation treatments.

Consolidation treatment with allogeneic transplantation and high-dose therapy with autologous stem cell rescue (HDT-ASCR) are effective treatment options, but due to the morbidity and mortality associated with these therapeutic options, it is not recommended as first-line therapy even for high-risk patients such as those with high-risk FLIPI [Montoto *et al.* 2013].

Radioimmunotherapy: role of consolidation with ^{90}Y -IT

Radioimmunotherapy

RIT is one of the most effective and infrequently utilized strategies in FL treatment. As relapse is the main cause of therapeutic failure in FL, RIT that aims to eradicate minimal residual disease (MRD) has been shown to be beneficial in patients with advanced stages of FL as consolidation treatment. It uses monoclonal antibodies bound to specific antigens marked by radioactive isotopes that release radiation directly into the tumor, combining the synergic effects of radiation and immunotherapy, handling well both the local and systemic effects [Charmarthy *et al.* 2011]. They utilize radionuclides that decay by releasing beta particles (high-energy electrons) producing lethal effects by causing double-strand DNA breaks. The anti-CD20 antibody binds to surface antigens and produces the death of lymphoma cells, inducing apoptosis and antibody-dependent

cytotoxicity, and the radiolabeled antibodies with the cytotoxic ionizing radiation can destroy antigen-negative cells within the tumors.

Two RIT agents have been approved by the FDA for the treatment of B-cell NHL. ^{90}Y -ibritumomab tiuxetan (^{90}Y -IT, Zevalin®) was granted accelerated approval by the US Food and Drug Administration (FDA) in 2002 for the treatment of patients with relapsed or refractory low-grade FL or transformed B-cell NHL, including patients with rituximab-refractory FL. In 2009, the FDA approved Zevalin® as consolidation therapy in previously untreated FL patients who achieve a PR or CR to first-line chemotherapy. In Europe, Zevalin® was initially approved in Europe in 2004, and in 2008 in first-line therapy after remission induction in previously untreated patients with FL. The other agent available (in United States and Canada) for the treatment of NHL is ^{131}I -tositumomab (Bexxar®), which was granted approval by the FDA in 2003 for the treatment of CD20-positive FL, with or without transformation, whose disease is refractory to rituximab and has relapsed following chemotherapy.

Consolidation with RIT of the response obtained after standard induction immunochemotherapy is a highly promising strategy for the treatment of FL patients, especially those with unfavorable prognostic factors or intermediate- and high-risk patients. Several studies have assessed the efficacy and safety of consolidation with ^{90}Y -IT in patients with advanced-stage FL in remission after first-line chemotherapy or chemoimmunotherapy.

The FIT trial

In the prospective, randomized, open-label, phase III international FIT trial (First-line Indolent Trial) [Morschhauser *et al.* 2008], ^{90}Y -IT was compared with no further therapy in 414 FL patients with CR or PR after standard front-line chemotherapy regimens. The induction therapy was chosen by investigators, and CVP/CHOP, CHOP, CHOP-like, fludarabine combinations, chlorambucil, and rituximab combinations were utilized. After completing induction therapy, patients were restaged and those achieving CR or PR were randomized to control or ^{90}Y -IT (standard dosage of 0.4 mCi/kg up to a maximum of 32 mCi) arms. The CR rate after induction therapy was 53% in the observation arm and 52% in the ^{90}Y -IT arm. In the ^{90}Y -IT arm, the final rate of CR after consolidation treatment was 87%, which

means a conversion rate of 77% from PR to CR. The same CR was achieved in all subgroups of chemotherapy after ^{90}Y -IT, despite the difference in CR after induction therapy. After 3.5 years, median PFS was significantly improved from 13.3 to 36.5 months. The increased of PFS was no significant in the patients that received rituximab chemotherapy, but it represented only a 14% of all patients. Patients in the ^{90}Y -IT had a greater 5-year improvement in the time to next treatment compared with control arm. No differences in OS were noted in the follow up, perhaps due to the indolent nature of FL.

After a median follow up of 7.3 years, results from the FIT study were updated [Morschhauser *et al.* 2013]. Median PFS was 4.1 years in the ^{90}Y -IT arm and 1.1 years in the control arm (hazard ratio [HR] 0.47; 95% confidence interval [CI] 0.37–0.60; $p < 0.001$), and the estimated 8-year overall PFS was 41% and 22%, respectively. The beneficial effect was superior for patients with PR after induction treatment compared with patients with CR. The time to next treatment was 8.1 years in the ^{90}Y -IT arm and 3 years in the control group, and treatment with ^{90}Y -IT did not rule out any second-line treatment, including autologous stem-cell transplantation. The rate of transformation to diffuse large B-cell lymphoma was similar in both arms (22 patients in the ^{90}Y -IT and 23 in the control arm). Although the number of second malignancies was not statistically different in both groups, the use of ^{90}Y -IT was associated with a higher annualized incidence rate of myeloid malignancies (0.50% *versus* 0.07%). Myelodysplastic syndrome (MDS) or acute myeloblastic leukemia (AML) was diagnosed in seven patients in the ^{90}Y -IT, after a median of 4.8 years and in one patient in the control group (that also was treated with ^{90}Y -IT in relapse).

As in the first report, there was no significant difference in OS, as only 28 patients have died in the ^{90}Y -IT arm (8-year OS, 84%) and 32 in the control arm (8-year OS, 81%). The main cause of death was progressive lymphoma disease, followed by second malignancies.

The main criticism of the FIT trial is that only 14% of subjects received rituximab during in the induction phase, because rituximab was not standard treatment when this study was designed. The trial was not powered to demonstrate a significant difference in the small rituximab subgroup, but it is important to considered that in

the last update of the trial the median PFS has not yet been reached (>7.9 years) for patients in the ^{90}Y -IT arm and it is 4.9 years in control arm. The authors concluded that first-line consolidation therapy with ^{90}Y -IT is a highly valuable treatment option for patients with advanced FL, conferring durable PFS benefit and significantly prolonged time to next treatment without unexpected toxicities or second malignancies.

There have been studies exploring various induction treatments, and several prospective trials of ^{90}Y -IT consolidation including rituximab in the induction regimens have been published, some of them with short duration chemotherapy.

R-CHOP or R-CVP trials

On the basis of preclinical studies, our GOTEL Group (Spanish Lymphoma Oncology Group) realized a phase II pilot, exploratory, open-label, controlled, multicenter study to assess the efficacy of an experimental regimen for patients with intermediate and high-risk FL [Provencio *et al.* 2014]. The treatment consisted in an abbreviated R-CHOP schedule (four cycles), followed by CHOP (two cycles) without rituximab, and consolidation in responding patients with ^{90}Y -IT. All 30 patients included in the trial received all the doses of CHOP-R, CHOP, and ^{90}Y -IT. There were no delays in treatment and there were no reductions in doses. After induction treatment, of the 30 eligible patients who were included in the study, 40% had a CR and 60% PR. After the consolidation treatment, the complete CR rate was 76.6%. The ORR after consolidation therapy was 93%. With a median follow up of 26 months, the means for PFS and OS were not reached and none of the patients in the trial died because of FL. Treatment was feasible, safe, and effective in patients with intermediate- and high-risk FL. The time to salvage treatment with the administering of a specific new treatment for lymphoma was a mean of 19.8 months (range 3–36), including treatment of seven of the nine patients with relapses or disease progression. As a final conclusion, our study can be added to the data supporting consolidation treatment with ^{90}Y -IT as an effective treatment, with manageable toxicity and it provides a long PFS and OS in first line after response to induction treatment in intermediate and high-risk FL patients.

On a phase II trial [Hainsworth *et al.* 2009] 41 untreated FL patients received rituximab for 4

weeks followed by three cycles of either R-CHOP or R-CVP, prior to ^{90}Y -IT consolidation 4–6 weeks after the end of chemotherapy. After induction therapy CR rate was 30%, and it improved to 72% following ^{90}Y -IT. After 67 months of follow up, the estimated 5-year PFS and OS rates were 64% and 96%, respectively.

In a similar study [Jacobs *et al.* 2008] treated 60 patients with symptomatic stages II to IV or with bulky FL in a phase II trial with R-CHOP for 3 cycles before ^{90}Y -IT followed by 4 weekly treatments with rituximab. A total of 55 patients completed all protocol therapy, with a mean follow up of 19.7 months. After RIT, the CR rate improved, from 46% to 89%, on restaging positron emission tomography (PET)/ computed tomography (CT). The failure to achieve an early PET CR after R-CHOP indicated high risk of relapse in this group of patients. On an intent-to-treat basis, the PFS and OS at 24 months were 73% and 94.8%, respectively. The PFS and OS for patients completing all protocol therapy at 24 months were 78.4% and 100%.

Fludarabine trials

Combinations with fludarabine in the induction regimen were also tested. A study published the results of a nonrandomized phase II study (FLUMIZ) of patients with indolent stage II or IV FL and untreated patients [Zinzani *et al.* 2008b]. They recruited patients with partial response to six cycles of fludarabine and mitoxantrone treatment. Following consolidation treatment, consisting of rituximab induction on day 1, they received on days 7–9 a second initial intravenous infusion with a dose of ^{90}Y -IT. ORR was 98% after chemotherapy, with 43 patients in CR. At the end of treatment, the CR rate was 55 out of 57 (96.5%). Mean follow up was 30 months (range 21–48) and 76% of patients were progression-free at 3 years, with 100% survival. And updated with data of long-term efficacy and toxicity results was reported [Zinzani *et al.* 2012a], and with a median follow-up of 64 months, the 6-year PFS and OS was 68.0% and 93.0%, respectively. Late hematological side effects such as MDS or AML did not occurred, and patients at progression could receive second-line chemotherapy and high-dose chemotherapy.

The same group [Zinzani *et al.* 2008a] reported a phase II trial with 26 indolent non-follicular NHL patients that received 6 cycles of fludarabine and

mitoxantrone followed by ^{90}Y -IT. CR was 50% after induction therapy and 100% in the evaluable patients at the end of consolidation treatment. After a median follow-up of 20 months, the estimated 3-year PFS and OS was 89.5% and 90% respectively.

The use of fludarabine and mitoxantrone with rituximab as an induction regimen, followed by consolidation with ^{90}Y -IT in previously untreated FL patients, gave a rate of conversion to complete response in 60% of the patients who reached only PR after FMR induction [Zinzani *et al.* 2012b]. In this study, 55 patients were treated with four cycles before consolidation, showing an ORR of 96%, with an 89% of CR by the end of the treatment. The estimated 3-year PFS was 81% and the 3-year OS 100%, after a median follow up of 21 months.

Another combination with fludarabine was presented [Karmali *et al.* 2011] in single-institution small phase II clinical trial with 20 FL patients and 2 patients with marginal zone lymphoma treated with FND and R-FND, for 4–6 cycles, followed by ^{90}Y -IT and R maintenance (375 mg/m² weekly $\times$ 4, repeated every 6 months for 2 years). ^{90}Y -IT converted 60% of PR to CR, resulting in an improved CR of 79%. At a median follow up of 49.6 months, median PFS was 47.2 months and median OS was not reached.

And in a report, also in a fludarabine combination [McLaughlin *et al.* 2008], 35 high-risk FL patients were treated with R-FND (fludarabine, mitoxantrone, dexamethasone) for four cycles, followed by ^{90}Y -IT and R maintenance. CR and PR was 83% and 14%. After a median follow up of 24 months, 3-year OS and failure-free survival (FFS) was 89% and 74%, respectively.

Upfront RIT trials

Another approach is to use ^{90}Y -IT as standalone first-line treatment. In the first clinical trial [Scholz *et al.* 2013] that used this strategy, 59 FL patients received ^{90}Y -IT. In the first radiologic evaluation (at 6 months according to protocol) 56% of patients achieved CR, 31% PR, and 10% showed progression. Minimal residual disease (MRD) was assessed, and patients with clinical CR but MRD positive, received consolidation with R. Median PFS was 26 months and median OS has not been reached. In this study, patients with increase lactate dehydrogenase (LDH) tend to relapse earlier.

The authors consider that ^{90}Y -IT was well tolerated and that the high percentage of CR resulting in a substantial median PFS and median time to treatment do this option attractive to older or comorbidity patients or those who refuse chemotherapy. In a similar study [Ibatici *et al.* 2013] treated 55 newly diagnosed advanced-stage FL patients with ‘upfront’ single-agent ^{90}Y -IT. CR rate was of 86% and ORR of 93%. After a median follow up of 38.8 months, 3-year estimated PFS and OS rate was 63.4% and 90%, respectively.

Fractionated ^{90}Y -IT trial

In order to improve biodistribution and tumor penetration, thought mainly for bulky disease, a phase II study [Illidge *et al.* 2013] tested fractionated ^{90}Y -IT as initial therapy of FL. A total of 76 patients requiring initial therapy were included. Treatment consisted of two doses of ^{90}Y -IT (11.1 MBq/kg) administered 8–12 weeks apart. Bone marrow infiltration >25% was not an exclusion criteria; and patients with pretreatment bone marrow involvement >20% received rituximab induction. A total of 12 (16.7%) patients did not receive the second infusion due to hematologic toxicity. ORR and CR were 95.8% and 69.4%. With a median follow up of 3.1 years, the estimated 3-year PFS was 58% (median PFS was 40.2 months), and OS 95%. Treatment was feasible, well tolerated, with few adverse events and manageable hematologic toxicity.

Consolidation and maintenance trial

The first report of a chemoimmunotherapy approach followed by both RIT consolidation and rituximab maintenance were presented [Fowler *et al.* 2011]. A total of 46 valuable patients, high-risk stage III or IV FL, most of them with bone marrow involvement, were treated with four cycles of R-FND followed by ^{90}Y -IT and rituximab maintenance (a single infusion every 2 months for 1 year) in the frontline setting. After R-FND, CR was 87% and following ^{90}Y -IT it increased to 91%. They reported a projected 5-year OS and PFS rate of 93% and 74%, respectively, after a median 50-month follow up. The use of rituximab in the induction treatment addressed the concerns arising in trials in which the good rate of improve PR to CR could be due to not use rituximab in the induction chemotherapeutic regimen, demonstrating high CR conversion rates in this high-risk patient population, despite rituximab being administered upfront.

Table 1. Upfront treatment options in follicular lymphoma.

Watch and wait
Chemoimmunotherapy
R-Bendamustine
R-CHOP
R-CVP
R- Fludarabine
R- Fludarabine combination such as
FND (fludarabine, mitoxantrone, and
dexamethasone) or FC
Chlorambucil
Immunotherapy alone
Radioimmunoconjugates
Chemoimmunotherapy plus maintenance
Chemoimmunotherapy plus consolidation
Chemoimmunotherapy plus consolidation plus
maintenance

Meta-analyses of RIT trials

A meta-analyses [Rose *et al.* 2012] analyzed 8 studies with a pool of 783 patients treated with RIT consolidation in the front line and at least 2-year follow up. CR rate and OR rate were 82.7% and 96.2%. The 2-year PFS rate was 77% and 5-year PFS and OS were 57.6% and 90.1%, respectively.

Discussion

One of the major challenges in the management of new diagnosed FL patients is to select the appropriate treatment as we have several options, ranging from no initial treatment (‘watch and wait’) to combine chemoimmunotherapy or immunotherapy alone, with the option of adding maintenance or consolidation therapy (Table 1).

One of the main principles should be increased survival without increasing toxicity. As in maintenance therapy, follow up of ^{90}Y -IT therapy is no longer enough to demonstrate a significant improvement in OS as happens in the maintenance trials.

^{90}Y -IT has demonstrated benefit in relapsed FL and safety and efficacy when moving forward into the front line where it has been studied as a single agent or as planned consolidation following standard chemotherapy or chemoimmunotherapy, with high rates of ORR and CR of 70–80%, and prolonging PFS, particularly for patients obtaining a CR. Consolidation therapy with ^{90}Y -IT after initial induction treatment has shown improved activity compared with induction

Table 2. Efficacy of ^{90}Y -IT in consolidation trials: complete response to induction and consolidation therapy of evaluated patients and progression free survival.

	CR after QT induction	CR after ^{90}Y -IT consolidation	PFS	
			Time (years)	%
Morschhauser <i>et al.</i> [2008], Morschhauser <i>et al.</i> [2013] (update)	52%	87%	3.5 ¹	13.3 months ^{1,3}
			3.5 ²	36.5 months ^{2,3}
			8 ¹	22
			8 ²	41
Provencio <i>et al.</i> [2014]	23%	76%	2.1	Not reached
Hainsworth <i>et al.</i> [2009]	30%	72%	5	64
Jacobs <i>et al.</i> [2008]	46%	89%	2	73
Zinzani <i>et al.</i> [2008b]	75%	96%	3	76
			6	68
Zinzani <i>et al.</i> [2008a]	50%	100%	3	89
Zinzani <i>et al.</i> [2012b]	69%	89%	3	81
Karmali <i>et al.</i> [2011]	45%	79%	4.1	47.2 months ³
McLaughlin <i>et al.</i> [2008]	78%	83%	3	74*
Fowler <i>et al.</i> [2011]	87%	91%	5	74
Scholz <i>et al.</i> [2013]	–	56%	2.5	25.9 months ⁴
Ibatici <i>et al.</i> [2013]	–	86%	3	63
Illidge <i>et al.</i> [2013]	–	69%	3	58

CR, complete response; QT, chemotherapy; ^{90}Y -IT, ^{90}Y -ibritumomab tiuxetan; PFS, progression-free survival.
¹Data from the control group arm.
²Data from the ^{90}Y -IT arm.
³Data from median progression-free survival.
⁴Data from failure-free survival.

chemotherapy alone, even in patients previously treated with rituximab, in one phase III and several phase II trials, improving PFS and rate of conversion from PR to CR (Table 2).

However, RIT is a treatment that as of today is underutilized, with low implementation in clinical practice [Illidge, 2010], perhaps because there are several other alternatives to choose from including alternative nonradioactive therapies, uncertainty regarding the place of RIT in the management of FL, limited knowledge of evidence showing the benefits of RIT, issues about the delivery and referral process and logistics of treatment, anxiety of patients related to radiopharmaceutical agents, economic concerns, and concerns about long-term secondary toxicity because of late radiation toxicity [Schaefer *et al.* 2010].

Moreover, from the patient's point of view, this treatment could be convenient because it is easy to administer, a dosimetry study for dose calculation is not needed nor required, and it only requires

two outpatient visits that allow high quality of life of patients to be maintained, without having to make as many visits to the hospital as those carried out during chemotherapy treatments. More importantly, toxicity does not appear to be a concern. Nonhematological toxicity such as asthenia, anorexia, and fever is low, especially when compared with the toxicity of anthracycline-based combination chemotherapy that includes emesis, alopecia, neutropenia, infection, neuropathy, and late toxicity with cardiomyopathy.

The main toxicity associated with RIT is myelosuppression, which lasts 6–8 weeks after the treatment and most patients recover spontaneously from RIT-induced myelosuppression after about 2–3 months. Because RIT implies radiation concerns regarding the risk of MDS/AML has raised. Analysis of data from 746 patients receiving ^{90}Y -IT in registration and compassionate-use trials suggests that the risks of MDS/AML are consistent with those expected in patients with NHL with extensive previous chemotherapy treatment and do not appear to

have increased. A total of 19 patients (2.5%) developed MDS/AML at a median follow up of 4.4 years [Czuczman *et al.* 2007]. The actuarial 8-year incidence of treatment-induced MDS or AML was 4.2% in the ^{90}Y -IT group, in the FIT trial [Morschhauser *et al.* 2013], and data analysis has not shown a statistically significant increase in either diagnosis among patients receiving RIT. Moreover, the SAKK 35/98 trial study testing single-agent rituximab showed a 3.3% incidence of MDS at a median follow up of 9.5 years [Martinelli *et al.* 2010]. However, in the FIT trial, all eight patients who developed MDS/AML had received ^{90}Y -IT, suggesting some role of ^{90}Y -IT in the risk of secondary MDS/AML, so these patients should be monitored closely.

Another concern regarding RIT is that it could limit the administration of more aggressive treatments, but it has not led to a limitation in subsequent stem-cell collection and transplantation, and no other chemotherapies have been compromised after the administration of ^{90}Y -IT as initial therapy. Autologous stem-cell transplantation was administered in 17% of patients in the ^{90}Y -IT arm of the FIT trial [Morschhauser *et al.* 2013].

Owing to this low toxicity of treatment, RIT as a single agent has been suggested as a relatively nontoxic alternative for use in elderly patients, who refuse chemotherapy or who are not suitable candidates for chemotherapy. When used as consolidation treatment after chemotherapy, it also allows a short chemotherapy induction trial [Hainsworth *et al.* 2009; Provencio *et al.* 2014]. However, RIT should not be considered as a treatment only for unfit patients, as it may be more useful for FL patients with more aggressive disease, who will benefit more given the high ORR and PFS obtained over standard treatment [Illidge *et al.* 2013; Jacobs *et al.* 2008].

One of the main alternatives to treatment with ^{90}Y -IT consolidation is maintenance therapy with rituximab, and although neither has demonstrated data on OS, maintenance therapy tends to be used more frequently than consolidation RIT. However, the benefits of administering ^{90}Y -IT consolidation, rituximab maintenance or observation after chemoimmunotherapy first-line induction in patients with previously untreated FL. Both strategies have demonstrated robust survival data: in the PRIMA study, with a median follow up of 6 years, 6-year PFS estimate was 42.7% in

the observation arm and 59.2% in the rituximab maintenance arm [Salles *et al.* 2013] and in the FIT trial with a median follow up of 8 years, overall PFS was 22% in the observation arm and 41% in the ^{90}Y -IT arm [Morschhauser *et al.* 2013].

A cost-effectiveness analysis of maintenance or consolidation therapy *versus* observation after front-line treatment from the United States payer's perspective showed that the incremental cost per QALY (quality adjusted life-year) gained for ^{90}Y -IT in the FIT trial, and rituximab maintenance in PRIMA and observation in ECOG 1496 trial [Hochster *et al.* 2009] were US\$57.975, US\$43.301, and US\$46.844, respectively. ^{90}Y -IT and rituximab maintenance had comparable incremental QALYs before first progression, while ^{90}Y -IT had higher incremental costs of adverse events due to the relatively high incidence of adverse events in the ^{90}Y -IT arm [Qiushi *et al.* 2013].

Both therapeutic strategies are being tested in comparative trials to clarify the best treatment options for these patients. The Spanish intergroup PETHEMA/GELTAMO/GELCAB [Lopez-Guillermo *et al.* 2013] compared, in a randomized phase II trial, the use of consolidation with ^{90}Y -IT *versus* rituximab maintenance in 146 FL patients that needed of treatment according to modified GELF criteria, and had responded to R-CHOP. A total of 124 patients were randomized, and after a median follow up of 37 months from randomization PFS was of 64% in the ^{90}Y -IT and 86% in the rituximab maintenance arm. With only five deaths, there were no differences in OS in this preliminary report.

Another treatment strategy can be the combination of both therapies: RIT consolidation and rituximab maintenance. Both treatments are well tolerated, with moderate toxicity and provide efficacy respect observation, mainly high PFS. RIT can help to reduce tumour mass, with its high ORR and CR, and also potentially reduce tumour-mediated immunosuppression and rituximab maintenance could have a chance to build up anti-tumor immune responses that lead to longer recurrence-free survival. The induction of CR by RIT may be important for the recovery of effective T-cell response, which can be inhibited in large tumors. This combination has the potential to be most efficient due to the preservation or stimulation of the patient's antitumor T-cell response [Buchegeger *et al.* 2013]. Although still preliminary,

the data presented by Fowler and colleagues [Fowler *et al.* 2011], with a 5-year OS and PFS rates of 93% and 74%, could corroborate this theory in clinical practice. The SWOG S0801 trial is an ongoing phase II study of R-CHOP, followed by consolidation with 131 I-tositumomab and rituximab maintenance in FL patients [ClinicalTrials.gov identifier: NCT00770224] that could clarify the feasibility, efficacy, and safety of the triple therapy.

The other approved RIT agent, 131 I-tositumomab, has been extensively studied in consolidation after chemotherapy and in upfront therapy in FL patients showing optimal efficacy [William and Bierman, 2010]. As single-agent upfront therapy, 131 I-tositumomab showed an ORR of 95% and a CR rate of 75% in 76 previously untreated patients with advanced-stage FL [Kaminski *et al.* 2005]. In consolidation, 131 I-tositumomab after induction CHOP showed 98% of ORR, 74% of CR, and an estimated 5-year OS rate of 87% and PFS of 67%, in 90 previously untreated advanced-stage FL patients after a median follow up of 5.1 years [Press *et al.* 2006]. However, the results comparing chemotherapy plus 131 I-tositumomab consolidation against chemoimmunotherapy alone were disappointing. In a phase III trial (SWOG S0016) [Press *et al.* 2013], 554 patients with newly diagnosed FL were random to receive R-CHOP for six cycles or CHOP for six cycles followed by 131 I-tositumomab. No significant differences in ORR or were observed. At a median follow up of 4.9 years, R-CHOP alone resulted in similar rates of PFS (76% *versus* 80%) and OS (97% *versus* 93%) survival at 2 years. 131 I-tositumomab consolidation seems to have the same efficacy as six infusions of rituximab.

To date, no randomized studies comparing 90 Y-IT and 131 I-tositumomab have been completed. In a retrospective trial of refractory NHL patients, 131 I-tositumomab caused significantly less severe thrombocytopenia and 90 Y-IT seemed a more appropriate choice for patients with limited bone marrow reserve [Jacene *et al.* 2007].

131 I-tositumomab (Bexxar®), currently approved in the United States and Canada for the treatment of certain types of NHL, is manufactured by GlaxoSmithKline. The company announced on 7 August 2013 the discontinuation of manufacture and sale of (Bexxar®) from 20 February 2014. See <http://us.gsk.com/html/media-news/pressreleases/>

2013/GSK-to-discontinue-manufacture-and-sale-of-the-BEXXAR-therapeutic-regimen.html

Conclusion

Consolidation treatment with 90 Y-IT after induction chemotherapy with or without rituximab has demonstrated improve the quality of remission by converting PR into CR and improve PFS, but it has not shown a significant improvement in OS. No therapy has been shown to have an effect on OS, which should be the gold standard, since the introduction of rituximab, and decisions have to be made based on clinical trial that use PFS as a endpoint, and no OS. Both the EMEA and the FDA have approved 90 Y-IT consolidation therapy following remission induction in previously untreated patients with FL, after the FIT trial data. The USA National Comprehensive Cancer Network has included RIT consolidation as a category 1 level of evidence and consensus as front-line treatment for FL.

Despite all of the data previously shown, perhaps only a close doctor–patient relationship could be the solution to the problem of choosing the first line in lymphoma. Although there are many points that are not clear, as which patients could benefit more (e.g. rituximab-naïve patients or those induced with a regimen that included rituximab, or those in a complete *versus* partial remission, fragile, elderly, or high risk), the role of RIT in patients already receiving chemoimmunotherapy, the role of rituximab maintenance in patients who receive RIT, the choice among consolidation, maintenance or both, it is clear that RIT is a highly effective and well-tolerated therapy for lymphoma patients that has shown benefits in frontline, consolidation and relapsed settings. 90 Y-IT should be considered for the initial treatment of FL in patients who are unable to tolerate standard chemotherapy, e.g. elderly or frail patients. It also is beneficial for consolidation after induction therapy in high-risk patients who achieve a PR or CR due to improvements in CR rate and PFS. There have been important advances in FL treatment over recent years, and today we have many therapies to choose as first and following lines of therapy, with new options (Table 3) to offer to our patients to continue improving their outcomes.

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Table 3. New treatments in follicular lymphoma.

¹⁷⁷ Lu-DOTA-rituximab
¹³¹ I- Anti-CD45
Galiximab (anti-CD80)
Epratuzumab (anti-CD22)
Bortezomib
Everolimus
Idelalisib
Ibrutinib
Lenalidomide
Ofatumumab
Panobinostat
Veltuzumab
Idiotype vaccine

Conflict of interest statement

The authors have no conflicts of interest to declare in preparing this article.

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