

Update on the rational use of ^{90}Y -ibritumomab tiuxetan in the treatment of follicular lymphoma

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Abstract: The development of radiolabeled antibodies against CD20 has facilitated targeted treatment of follicular lymphoma (FL). By using ^{90}Y -ibritumomab tiuxetan (Zevalin[®]), a radio-nuclide (yttrium-90, linked by the chelator tiuxetan to the antibody ibritumomab) is brought into the vicinity of lymphoma cells. By the so-called cross-fire effect, this beta emitter has the capacity to destroy not only the lymphoma cells having bound the antibody, but also neighboring lymphoma cells. Currently this antibody is licensed in the European Union for use in relapsed or refractory FL. It is anticipated that this drug will also be approved for use as consolidation therapy after successful first-line treatment. Here we first will review the published literature supporting the use of ^{90}Y -ibritumomab tiuxetan in the aforementioned indications and emerging data showing applicability of ibritumomab tiuxetan as sole first-line therapy for FL, as well as in the transplant setting. Possible strategies of incorporating ibritumomab tiuxetan into the treatment algorithm of FL are discussed.

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

Introduction

Follicular lymphoma (FL) is the most common indolent subtype and accounts for almost a quarter of non-Hodgkin lymphomas (NHL). The course of disease is characterized by a response to initial treatment, followed by multiple relapses. Although long-term survival has been seen in localized disease treated with involved field radiotherapy with curative intent, FL is incurable with conventional chemotherapy.¹ The main impact on survival occurred with the introduction of immunotherapy over the last 10 years.² Large randomized clinical studies confirmed the benefit of adding the anti-CD20 monoclonal antibody rituximab to combination chemotherapy regimes with highly significant improvement in progression-free (PFS) and even overall survival (OS).³⁻⁶ A helpful clinical advance has been the development of the FL international prognostic index (FLIPI).⁷ The FLIPI stratifies patients into risk groups. Based on five prognostic factors (age, Ann Arbor Stage, hemoglobin level, number of nodes involved and serum LDH level) three risk groups were defined. Low (0–1 risk factor), intermediate (2 risk factors) and high (>3 risk factors) with 10-year overall survival rates of 70.7%, 50.9% and 35.5%, respectively.

Dose intensified consolidation with myeloablative conditioning followed by autologous stem cell rescue also leads to an improvement in PFS,⁸ although this approach is only feasibly in younger patients and is associated with higher treatment related morbidity and a remarkable risk of secondary malignancies. In a trial of the German Low

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Grade Lymphoma Study Group, secondary hematological malignancies were observed in 5 out of 195 patients with indolent lymphoma after high-dose chemotherapy, yielding an estimated risk of secondary hematological malignancies after autologous stem cell transplantation of 3.8%.⁹ Radioimmunotherapy (RIT) represents another therapeutic approach that allows targeted delivery of a therapeutic dose of radiation to tumors at multiple sites in disseminated disease. Currently the only radiolabeled antibodies approved for treatment of follicular NHL are iodine-131-tositumomab (¹³¹I-T, Bexxar®; GlaxoSmithKline, Research Triangle Park, NC, USA), which is not approved within the European Union (EU) and yttrium-90-ibritumomab tiuxetan (⁹⁰Y-IT, Zevalin®; Bayer Schering Pharma AG, Berlin, Germany). Both ¹³¹I-T and ⁹⁰Y-IT are directed against the CD20 antigen. Radiolabeled immunotherapy (RIT) is an established treatment option for second relapse or later and ⁹⁰Y-IT has recently obtained a positive opinion of European Medicines Agency (EMA) about the use as consolidation therapy after first-line treatment.

Ibritumomab tiuxetan (Zevalin®)

The radioisotope 90-yttrium (⁹⁰Y) is linked to the monoclonal anti-CD20 antibody ibritumomab by the chelator tiuxetan. ⁹⁰Y is a high energy pure beta emitter (2.3 MeV) with a physical half-life of 64 hours. More than 90% of the emitted radiation is absorbed within 5 mm. This path-length corresponds to a diameter of 100 to 200 cells,¹⁰ thus allowing highly targeted delivery of radiation without a need for patient isolation or shielding. Radiation induces cellular damage in both, the targeted lymphoma cells and neighboring cells, a phenomenon referred to as crossfire or bystander effect, and might be effective even in case of poorly vascularized tumors and those with heterogeneous antigen expression.¹¹

⁹⁰Y-IT is currently approved for the treatment of adult patients with rituximab-relapsed or refractory CD20-positive follicular B-cell NHL in the European Union. Another radiolabeled anti-CD20 antibody (¹³¹I-tositumomab) is approved in the United States. Although there are differences in application and pharmacokinetics, the efficacy of both radiolabeled antibodies seems to be comparable in this indication.

Treatment schedule includes infusion of 250 mg/m² rituximab on day 1 and 8 followed by the therapeutic dose of ⁹⁰Y-IT on day 8 as intravenous push over 10 minutes.

Rituximab pretreatment is given to improve the biodistribution of the radionuclide and to reduce binding to CD20 on normal circulating B-cells and B-cells in bone-marrow and spleen.^{12,13} Because ⁹⁰Y is a pure beta emitter, indium-IT was used as a surrogate and chelated to ibritumomab tiuxetan

for studying biodistribution and biological clearance, using gamma camera imaging as part of the registration studies. The first rituximab infusion was followed by an application of 5 mCi of ¹¹¹In-IT for the purpose of imaging. Gamma camera scans were performed within 24 to 48 hours. The dosimetry studies showed that the application of ⁹⁰Y-IT results in a minimal radiation exposure of non-targeted organs, but it failed to demonstrate a significant correlation between biodistribution of the radioactive antibody and hematological toxicity.¹⁴ This lack of correlation has led to the approval of ⁹⁰Y-IT within the European Union without the necessity for imaging studies.

Recommendations for ibritumomab tiuxetan use

A phase I/II trial incorporating a comparison of two doses of unlabeled antibody showed an improvement of biodistribution of the radioimmunoconjugate after pretreatment with rituximab at a dose of 250 mg/m². Higher doses did not further improve the biodistribution of ¹¹¹In-IT. For increasing ⁹⁰Y-IT doses, myelotoxicity was found as dose limiting toxicity, and the maximum tolerated dose (MTD) was determined to be 0.4 mCi/kg (or 14.8 MBq/kg) for patients with platelet count over 150,000/μL and 0.3 mCi/kg (or 11.1 MBq/kg) for patients with mild thrombocytopenia (baseline platelet count <150,000/μL but >100,000/μL).¹² Another trial confirmed the safe treatment with ⁹⁰Y-IT in patients with mild thrombocytopenia at a dose of 0.3 mCi/kg.¹⁵ Patients with an increased risk of hematological toxicity or impaired bone marrow reserve should be excluded from treatment. Exclusion criteria are a >25% infiltration of the bone marrow with lymphoma cells, prior radiation therapy to >25% of marrow area and baseline platelet count <100,000/μL or neutrophil count <1500/μL. Despite initial concerns, preliminary data suggest that patients can be safely treated without a significant dose reduction of ⁹⁰Y-IT after myeloablative chemotherapy.¹⁶

In an early phase I/II study,¹⁷ 18 patients with recurrent B-cell lymphoma were treated with ⁹⁰Y-IT at doses between 13.5 and 50 mCi. Doses up to 40 mCi were not myeloablative; however, 2 patients treated at the 50 mCi level required stem cell support. This pivotal report also included ¹¹¹In-IT imaging studies. It was shown that preadministration of unlabeled antibody resulted in an improved biodistribution of the radiolabeled antibody with increased visualization of known sites of disease and reduced uptake by non-targeted organs (spleen, bone-marrow). In the absence of rituximab pretreatment, only 18% of known sites of disease were imaged. Rituximab administration at a dose of 1mg/kg body weight before ¹¹¹In-IT imaging studies resulted in detection

of 56% of known disease sites, with further improvement achieved (imaging of 92% of known disease sites) at higher rituximab doses (2.5 mg/kg body weight). Also the intensity of imaging tended to be higher following infusion of the unlabeled antibody.

It seems that the radioimmunoconjugate is confronted by a considerable antigenic sink, ie, by binding to CD20 on normal B-cells or nonspecific uptake by cells of the reticulo-endothelial system expressing Fc receptors. Splenomegaly and high tumor burden (bulky disease) adversely affect imaging in biodistribution studies, especially in the absence of rituximab pretreatment. Nevertheless, it has been argued recently that the routine rituximab application before RIT might also compromise the effectiveness of treatment by competition for binding sites on tumor cells.¹⁸ This view is supported by a preclinical lymphoma xenograft model, where indeed larger doses seem to block subsequent binding of the radiolabeled anti-CD20 monoclonal antibody.¹⁹ However, in a recently performed phase I/II study, higher pretreatment rituximab doses (4×375 mg/m² weekly) achieved a beneficial effect in terms of increasing the half-life of the radioimmunoconjugate. Also, neither clinical efficacy of RIT did appear to be compromised, nor toxicity increased.²⁰ Similarly, in 2 trials using rituximab + chemotherapy combination therapy before ⁹⁰Y-IT application,^{28,29} a significant rate of conversion from partial response (PR) to complete response (CR) was observed, again indicating that prior rituximab therapy does not hamper RIT.

Patient management

Since 2002, ⁹⁰Y-IT is approved in the United States (US) for patients with CD20+FL or transformed B-cell NHL, refractory to or relapsed after rituximab. Within the European Union (EU) the license is restricted to rituximab-relapsed or refractory CD20+FL. ⁹⁰Y-IT is the only therapy approved for the use after rituximab failure in the EU.

⁹⁰Y-IT is contraindicated in patients with known hypersensitivity to mouse antibodies or chelating agents (such as tiuxetan), as well as during pregnancy and lactation. Patients should be advised to wash their hands thoroughly after urination, to clean up spilled urine and body fluids immediately and to use condoms for sexual intercourse for at least one week after RIT as well as an effective contraception for up to a whole year after treatment.

Safety/tolerability/toxicity of ibritumomab tiuxetan

An integrated safety analysis for 349 patients treated with ⁹⁰Y-IT in 5 separate multicenter clinical trials showed

that the treatment with ⁹⁰Y-IT in an outpatient setting is well tolerated.²¹ Although 80% of patients reported non-hematologic adverse events (AEs), the majority of those AEs were mild or moderate and most frequently asthenia, nausea and chills were reported. Only 11% of all patients had grade 3 or 4 of non-hematological toxicity. The primary hematological toxicity was reversible myelosuppression which typically developed by week four to six, reached nadir at week seven to nine and recovered within 1 to 4 weeks. This pattern of myelosuppression differs from that experienced with myelosuppressive chemotherapy regimes which usually have a nadir at day eight to fourteen with recovery by day twenty-one. Neutropenia grade 1–2 occurred in 40%, grade 3 and 4 in 60% of all patients, respectively. Ninety percent of patients with grade 3–4 neutropenia recovered to $>1000/\mu\text{L}$ within 12 weeks after RIT. Thrombocytopenia grade 1–2 and grade 3–4 were observed in 37% and 63% of patients and 89% of patients with grade 3 and 4 thrombocytopenia recovered to $>50,000/\mu\text{L}$ during the 12 week period. Grade 3 and grade 4 anemia occurred in 13% and 4% of all patients. Of 211 patients, 20% received red blood cell transfusions and 22% received platelet transfusions. Patients with any involvement of bone marrow had a significant greater incidence of grade 4 hematological toxicity and incidence of severe thrombocytopenia and neutropenia increased with increasing lymphoma bone marrow involvement at baseline, underscoring the importance of excluding patients with $>25\%$ bone marrow infiltration. Despite the incidence of grade 4 neutropenia in approximately one third of the patients, the rate of severe infections is low. Infections of all severity occurred in 29% of patients. The incidence of hospitalization was 7% including only 6 cases (2%) of febrile neutropenia. The number of prior chemotherapy regimes was not associated with longer median duration of grade 3–4 anemia, thrombocytopenia or neutropenia, although patients who had more than two prior chemotherapies were twice as likely to develop severe thrombocytopenia. Toxicity data from patients less than 65 years of age were compared with those from patients of 65 years and older. The analysis of safety in the geriatric subset revealed no significant age-related effects in non-hematological AEs or hematological toxicity. The incidence of secondary myelodysplastic syndrome (MDS) and acute leukemia (AML) was 2.5% in a retrospective analysis of 746 patients with NHL treated with ⁹⁰Y-IT between 1996 and 2002. Patients had been treated with a median of 3 previous treatment lines (≥ 4 in 42% of patients) before receiving ⁹⁰Y-IT. MDS or AML were diagnosed at a median of 1.9 years (range 0.4 to 6.3 years) after

RIT. This incidence is comparable with the incidence in a similar patient population having been treated with alkylating agents and other chemotherapy regimens, suggesting that there is not a significant additional risk following ^{90}Y -IT treatment.²²

With the use of murine and chimeric antibodies there is a risk of immunogenicity that could potentially hamper effectiveness of repeated monoclonal antibody administration.²³ However less than 2% of all patients developed human anti-mouse antibodies (HAMA) or human anti-chimeric antibodies (HACA) and almost no patient with HAMA or HACA experienced unusual AEs, despite a case report of anaphylaxis after ^{90}Y -IT application with high HAMA blood levels recently published by Jankowitz et al.²⁴

Relapsed/refractory follicular lymphoma

Long-term efficacy data of an early phase I/II trial have been reported.²⁵ Sixty-five % ($n = 33$) of patients had FL and overall response rate (ORR) was 85% in this subgroup (CR/CRu [unconfirmed CR] 57%, PR 27%). Median time to progression (TTP) was 9.3 months for all patients (including 24% of patients with diffuse-large B-cell lymphoma and 11% of patients with nonfollicular low grade lymphoma and mantle cell lymphoma). Patients achieving CR/CRu with the 0.4 mCi/kg dose ($n = 13$) had a median TTP of 28.3 months, patients achieving a CR ($n = 8$) a median TTP of 45.0 months, underscoring the potential of ^{90}Y -IT to achieve long-term remissions even in heavily pretreated patients (median 2 prior regimens, range 1 to 7). Duration of response over 3 years was observed in 24% of responders and response duration >5 years was noted in 14%.

A randomized phase III trial including 143 rituximab-naïve patients with relapsed or refractory low grade, follicular, or transformed lymphoma then compared ^{90}Y -IT (0.4 mCi/kg, single dose) with rituximab (375 mg/m² once weekly for 4 weeks). Seventy-nine % of enrolled patients had FL, 12% other types of low-grade lymphoma and 9% transformed lymphoma. The response rates favored ^{90}Y -IT (ORR 80% vs 56%, $P = 0.002$; CR rate 30% vs 16%, $P = 0.04$).¹³ The time to progression (TTP) and the duration of response were not significantly different, although patients with FL treated with ^{90}Y -IT showed a trend towards longer TTP (12.6 months vs 10.2 months, $P = 0.062$) and achieved more often responses lasting longer than 6 months (74% vs 52%, $P = 0.019$) compared to patients in the rituximab control group. Quality of life analysis showed a significant improvement of physical, social, emotional and functional well-being in the RIT arm.

In another trial, ^{90}Y -IT was evaluated as treatment for patients with rituximab-refractory FL. Rituximab-refractory disease was defined as either failure of treatment with the unlabeled antibody or progression ≤ 6 months after rituximab treatment. Fifty-four patients with FL after a median of 4 prior treatments were enrolled. Bulky disease was present in 74% of patients. An ORR of 74% and a CR rate of 15% were observed and median TTP was 6.8 months for all patients and 8.7 months for responders.¹¹

In two reports,^{26,27} data from the 4 registration trials^{11,13,15,25} of ^{90}Y -IT were analyzed retrospectively. Long-term responses (TTP ≥ 12 months) were noted in 37% of 211 patients treated in these trials. The achievement of CR/CRu seemed to be the best predictor for achievement of long-term response. Other predictors for durable remissions in a stepwise multivariate logistic regression analysis were nonbulky disease (<5 cm) and stage I or II disease at the time of RIT. At a median follow-up of 53.5 months the median duration of response was 28.1 months and the median TTP was 29.3 months for long-term responders. The estimated OS at 5 years was 53% for all patients treated with ^{90}Y -IT and 81% for long-term responders.²⁶

63 patients were treated with ^{90}Y -IT after their first relapse and 148 patients after 2 or more therapies. Patients receiving ^{90}Y -IT after first relapse had a greater ORR (86% vs 72%, $P = 0.05$).²⁷ Also, the CR/CRu rate was significantly higher (49% vs 28%, $P = 0.004$) and the median TTP was longer (12.6 vs 7.9 months, $P = 0.025$) in the group that received ^{90}Y -IT as second-line therapy. In patients with FL, the difference was even more pronounced with a trend towards greater efficacy than in the overall patient population (Cr/CRu: 51% vs 28% $P = 0.009$; TTP: 15.4 vs 9.2 months, $P = 0.026$).

The results of the pivotal studies evaluating ^{90}Y -IT in relapsed/refractory FL are summarized in Table 1.

Consolidation treatment

In a phase II study, the efficacy of a short course of chemoimmunotherapy (3 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) followed by ^{90}Y -IT and “extended” rituximab (a single additional 4-week course of rituximab at 375 mg/m², day 1, 8, 15, 22) as first-line treatment for FL was investigated.²⁸ Of the 60 patients entering this trial, 55 patients completed therapy according to protocol. Patients with FL stage III–IV, grade 1–3 were included. Bulky disease was present in 50% of patients and 75% of patients were FLIPI high-risk. RIT induced grade 3–4 neutropenia occurred in 51% of patients and grade 3–4 thrombocytopenia in 44%. Only a single

Table 1 ⁹⁰Y-IT in relapsed or refractory non-Hodgkin lymphoma

Reference	N	Patients	Response	TTP	Response duration
Witzig et al ¹²	51	Relapsed/refractory CD20 + B-cell low and intermediate grade NHL/MCL	ORR 67% CR 26%	12.9 + months	10.8–14.4 months
Witzig et al ¹³	143	Relapsed/refractory low grade FL or transformed NHL	ORR 80% CR 30% Cru 4%	15 months (only FL)	14.2–16.7 months (only FL)
Wiseman et al ¹⁵	30	Relapsed/refractory low grade FL or transformed NHL (mild thrombocytopenia)	ORR 83% CR 37% CRu 6%	9.4 (all)–12.6 (FL) months	11.7 months
Witzig, et al ¹¹	54	Rituximab refractory FL	ORR 44% CR 27%	6.8–8.7 (responder) months	11.5 months

Abbreviations: CR, complete response; CRu, unconfirmed CR; NHL, non-Hodgkin's lymphoma; MCL, mantle cell lymphoma; FL, follicular lymphoma; ORR, overall response rate; TTP, time to progression.

patient required hospitalization because of neutropenia. For the 55 patients who completed therapy according to protocol (R-CHOP → ⁹⁰Y-IT → “extended” rituximab), the CR assessed by computed tomography (CT) was 44%, and 67% assessed by positron emission tomography (PET) after R-CHOP and increased to 89% (CT) and 96% (PET) after RIT, respectively. PET-scan after 3 cycles of R-CHOP was demonstrated to harbor the potential for early prediction of treatment failure. A correlation of early PET results with treatment outcome has so far only been reported for diffuse-large B-cell lymphoma and Hodgkin lymphoma. In this study, 7 of 18 patients who were PET positive after R-CHOP progressed, compared to 3 of 37 patients who were PET negative after R-CHOP ($P > 0.01$). On an intent-to-treat basis, the PFS and OS at 24 months were 73% and 94.8%, for patients completing therapy according to protocol the values are 78.4% and 100%.

Similarly, Shipley et al²⁹ observed an improvement of CR rates from 28% after a short course of R-CHOP to 67% following RIT consolidation. Forty-two untreated patients with grade 1–3 FL were included in this study. The PFS was 77% at 2 years.

The prospective multicenter phase II FLUMIZ-trial aimed to assess the efficacy and safety of fludarabine and mitoxantrone plus ⁹⁰Y-IT in untreated patients with follicular NHL.³⁰ 61 patients with stage III or IV, grade 1–2 untreated follicular NHL were enrolled and treated with oral fludarabine and mitoxantrone for six cycles. Patients with at least a partial response (PR), platelet counts $>100,000/\mu\text{L}$, neutrophil counts $>1500/\mu\text{L}$ and less than 25% infiltration of bone marrow were deemed eligible for consolidation therapy with single dose ⁹⁰Y-IT, according to usual

application recommendations. Treatment was administered on an outpatient-basis 6 to 10 weeks after the last cycle of chemotherapy. After 6 cycles of chemotherapy the ORR was 98% (43 of 61 patients had CR and 17 of 61 patients had PR). 57 of 61 patients went on to receive RIT. Of the 14 patient in this cohort who had PR after initial chemotherapy, 12 obtained CR after ⁹⁰Y-IT. By the end of entire treatment 55 of 57 patients achieved CR. ⁹⁰Y-IT also seemed capable of improving the rate of molecular complete remissions, as determined by monitoring the Bcl2-IgH rearrangement. With a median follow up of 30 months estimated 3-year PFS is 76% and estimated 3-year OS is 100%. The chemotherapy regime was well tolerated and reversible hematological toxicity was the most common AE. AEs after ⁹⁰Y-IT were also mainly hematological and transient. 21 of 57 patient required transfusion of either red blood cell or platelets or both. Patients with relapsed disease underwent second-line treatment (R-CHOP) with good hematological tolerance. All these patients completed 6 cycles of second-line therapy.

An international, randomized controlled phase III trial (First-Line Indolent Trial, FIT) evaluated the safety and efficacy of consolidation therapy with a single dose of ⁹⁰Y-IT in patients who achieved a PR or better with first-line induction therapy. A total of 414 patients with FL stage III or IV, grade 1–2 were enrolled³¹ and primary endpoint was PFS. Patients who achieved CR, CRu or PR after first-line induction with variable regimens were randomly assigned to receive either ⁹⁰Y-IT (208 patients) or no further therapy (control, 206 patients). The most common AEs with ⁹⁰Y-IT were hematological toxicities, which were predictable and manageable. Although infectious events were more common in the ⁹⁰Y-IT group, grade 4 infections were rare and only

7.4% of patients required hospitalization for infections in the RIT arm. After a median observation period of 3.5 years the median PFS time was significantly higher in the ^{90}Y -IT arm with 36.5 months vs 13.3 months in the control arm ($P < 0.0001$). A benefit was seen both for patients in PR after induction treatment as well as for patients in CR after induction treatment. The final CR/CRu rate was 87.4% after consolidation with ^{90}Y -IT compared with 53.3% in the control arm. After consolidation with ^{90}Y -IT, 78 of 101 patients (77%) with a PR after induction therapy converted to CR/CRu. A higher PR-CR conversion rate was noted with ^{90}Y -IT consolidation as compared to the control arm in nearly all subgroups categorized by type of induction treatment. Only for the small subgroup of patients receiving rituximab-containing induction regimens (15% of the total study population) this difference was not statistically significant. This might be due to the low number of patients in this subgroup and the even lower number of patients only achieving PR after rituximab-containing induction treatment. Also PFS was not significantly different between the treatment arms in this subgroup, and median PFS times have not been reached in either arm at the time of analysis. Thus, while providing clear evidence for a beneficial effect of ^{90}Y -IT consolidation after chemotherapy-only induction treatment, this study leaves the question unanswered if a similar benefit is achieved with RIT after a full course of R-chemotherapy induction.

The results of studies using ^{90}Y -IT as consolidation treatment for FL are summarized in Table 2.

First-line treatment

^{90}Y -IT was also studied as first-line monotherapy for patients with low-grade FL. In a pilot study including 10 patients an ORR of 100% was observed, with a CR rate of 62%³². In this study, maintenance rituximab was scheduled at 6-months intervals over 2 years. More recently, Carella et al³³ reported an ORR of 93% and a CR rate of 73% using upfront ^{90}Y -IT in a treatment-naïve cohort of

patients with FL grade 1–2. Fifteen patients were evaluable at the time of reporting.

Myeloablative allogeneic stem cell transplantation

In Phase I/II trials, ^{90}Y -IT has been incorporated in the conditioning regimen before autologous stem cell transplantation (see Table 3). Most of these trials included mainly patients with aggressive B-cell NHL, except a GELA study, which included 77 patients with CD20+ low-grade B-cell lymphoma (90% of those FL).³⁴ ^{90}Y -IT was given at the standard dose of 15 MBq/kg at day –14 combined with carmustine, etoposide, cytarabine, and melphalan (BEAM) chemotherapy starting at day –7. Median time to neutrophil reconstitution was 12 days, as was time to platelet reconstitution. Adverse events were not different from those expected with a standard conditioning regimen.

Similar results were observed in smaller trials exploring ^{90}Y -IT in combination with chemotherapy conditioning in the transplant setting^{35–37} (see Table 3). In one of these trials, escalated doses of ^{90}Y -IT were applied,³⁷ with doses of the radioimmunoconjugate calculated to deliver cohort-defined radiation-absorbed doses (RADs) to critical organs, ranging from 1 to 17 Gy. Escalated doses of ^{90}Y -IT (applied on day –14) calculated to achieve a maximum RAD of 15 Gy to the critical normal organ could be safely combined with high-dose BEAM and autologous stem-cell transplantation, with similar toxicity profile as compared to BEAM alone. Severe hepatotoxicity occurred in only one patient case, although the liver was the critical dose-limiting organ in the majority of patients. Dose-limiting toxicities were observed at the 17 Gy dose level, including pneumonia with sepsis and subsequent organ failure in one patient, and septic pulmonary emboli related to an infected intravenous catheter in a second patient.

In other trials, high-dose RIT was applied without chemotherapy before stem-cell infusion (Table 3). In one of these studies,³⁸ 30 patients with poor-risk, relapsed or

Table 2 First-line consolidation treatment with ^{90}Y -IT

Reference	Treatment	Patient number	CR after induction	CR after ^{90}Y -IT	PFS
Jacobs et al ²⁸	3x R-CHOP → ^{90}Y -IT → 4x R	55	44%	89%	78% at 2 years
Shiple et al ²⁹	4x R → 3x R-CHOP or R-CVP → ^{90}Y -IT	42	28%	67%	77% at 2 years
Zinzani et al ³⁰	6x FM → ^{90}Y -IT	61	70%	96%	76% at 3 years
Morschhauser et al ³¹	various → ^{90}Y -IT	208	Not reported	87%	Median 36.5 months
McLaughlin et al ⁴⁶	4x R-FND → ^{90}Y -IT → R-maintenance	35	Not reported	83%	74% at 3 years

Abbreviations: CR, complete response; PFS, progression-free survival.

chemotherapy-refractory B-cell NHL (including 12 patients with FL) were treated with ⁹⁰Y-IT at 2 dose levels (0.8 mCi/kg, 1.2 mCi/kg). Stem-cells were given 7 days and 14 days after RIT. Only 47% of patients developed neutropenia with absolute neutrophil count (ANC) <500/μL (grade 4) and the median duration of grade 4 neutropenia was 5 days (range 1 to 14) in this subset of patients. The platelet count fell to <25,000/μL (grade 4 thrombocytopenia) in 63% of patients, and median duration of this complication was 4 days (range 1 to 14). Infections were registered in 27% of patients, with hospitalization required in 10%.

In another trial³⁹ using escalating doses of ⁹⁰Y-IT (0.8, 1.2, 1.5 mCi/kg) before stem cell support, severe infectious complications and hepatotoxicity were noted. One patient developed bacterial pneumonia 2 months and herpes zoster infection 5 months after ⁹⁰Y-IT, and another patient experienced hepatitis C virus reactivation. Also, one patient developed a myelodysplastic syndrome (refractory anemia with excess of blasts) 2 years after treatment.

RIT has also been used as part of a reduced intensity conditioning regimen for allogeneic stem cell transplantation (⁹⁰Y-IT application on day -14). Thirty-six patients with indolent lymphoma (refractory or relapsed; age 34 to 68 years), including 15 patients with FL, have so far been treated in a phase II study. No additional toxicity was observed due to RIT in comparison with previous experience with allogeneic transplantation, and stable engraftment has been achieved in all patients.⁴⁰ Shimoni et al⁴¹ treated 12 patients with advanced chemorefractory NHL at median age 54 years using ⁹⁰Y-IT in the allogeneic transplant setting. Notably, a non-relapse mortality of 42% was observed, mainly due to acute graft-versus-host disease.

Integration of ⁹⁰Y-IT in the treatment algorithm for FL

Currently, there is a strong rationale for using ⁹⁰Y-IT either as consolidation treatment for patients achieving a PR or CR after first-line therapy for FL or for relapsed

disease. This has recently also been pointed out by Otte et al.⁴² The benefit of ⁹⁰Y-IT as consolidation treatment has been shown in a phase III trial for patients receiving chemotherapy as first line treatment.³¹ The subset of patients receiving rituximab + chemotherapy induction first-line was too small to demonstrate a beneficial effect of ⁹⁰Y-IT consolidation unequivocally, but this issue is being addressed in another trial (R-CVP + ⁹⁰Y-IT vs R-CVP alone; trial NCT00384111). Rituximab maintenance after successful first-line induction therapy is another emerging treatment approach for FL. This strategy was shown to prolong PFS after induction therapy with chemotherapy-only in the first line setting.⁴³ With R-maintenance (375 mg/m², once per week for 4 weeks, every 6 months for 4 courses) a prolongation of PFS from 15.6 months in the observation arm to 51.6 months in the rituximab arm was reported, results comparable to ⁹⁰Y-IT consolidation. In the relapsed setting, a benefit for rituximab maintenance therapy was also noted for patients receiving rituximab as part of their induction regimen.^{44,45} The issue of rituximab maintenance therapy after R-chemotherapy has also been addressed for the first line setting (MAXIMA trial NCT00430352); however, results of this trial are not available yet. Nevertheless, due to the positive results in the relapsed setting, rituximab maintenance therapy is often used after R-chemo first-line therapy (in the regimen used by Hochster et al, or 375 mg/m² every 3 months over 2 years). The question whether a rituximab maintenance strategy or a RIT consolidation after R-chemotherapy induction first-line should be used or which of these approaches is more effective is currently unanswered. It should be noted that a combined approach (R-chemotherapy induction followed by ⁹⁰Y-IT consolidation followed by rituximab maintenance therapy) has been used successfully in a small study⁴⁶ in a high-risk population of newly diagnosed patients with FL, at least demonstrating the feasibility of such approach.

Several studies have now reported that high-dose therapy with autologous transplantation can be performed safely in

Table 3 ⁹⁰Y-IT in the autologous transplant setting

Reference	No. patients FL	⁹⁰ Y-IT dose	Conditioning chemotherapy
Gisselbrecht et al ³⁴	70	15 MBq/kg	BEAM
Nademanee et al ³⁵	12	RAD 1 Gy	VPI6/Cyclophosphamide
Krishnan et al ³⁶	4	0.4 mCi/kg	BEAM
Winter et al ³⁷	4	RAD 1–17 Gy	BEAM
Devizzi et al ³⁸	12	0.8 + 1.2 mCi/kg	None
Ferrucci et al ³⁹	1	0.8–1.5 mCi/kg	None

Abbreviations: RAD, radiation-absorbed doses (RADs) to critical organs; FL, follicular lymphoma; BEAM, carmustine, etoposide, cytarabine, and melphalan.

patients relapsing after ^{90}Y -IT treatment.^{47,48} Thus it seems feasible to withhold high-dose therapy until relapse for patients treated with ^{90}Y -IT consolidation. To date, 4 trials on autologous transplantation first-line for patients with FL have been reported.^{8,49–51} None of these trials demonstrated an improvement of overall survival with the high-dose approach (not even with an extended follow-up of median 9 years in the French trial), although in 3 out of these 4 trials a benefit in terms of response rates and PFS was seen. It was concluded that high-dose therapy with autologous transplantation should preferably be applied in the relapsed setting. An upfront high-dose strategy is less attractive due to a high rate of secondary malignancies as well as the safety and efficacy of autologous transplantation performed at the time of relapse. However, when using ^{90}Y -IT consolidation therapy, caution should be taken to collect autologous stem-cells for patients suitable for high-dose therapy before ^{90}Y -IT application, as RIT might compromise stem-cell yield.

^{90}Y -IT was also shown to be effective as sole first-line therapy for FL in 2 small trials (without preceding induction chemotherapy). Currently, however, data are limited on the durability of responses. As ^{90}Y -IT is similarly safe and effective in older as in younger patients,⁵² such approach could be valuable in the older age group, where poor tolerability of chemotherapy is of concern. Notably, also retreatment with ^{90}Y -IT (ie, 2 courses of RIT) seemed feasible and effective in a retrospective analysis of a small cohort of patients with B-cell NHL.⁵³

In the relapsed setting, ^{90}Y -IT proved capable of achieving long-term remissions. However, in a randomized phase III trial RIT did not yield a significant improvement of TTP or duration of response as compared to a short course of rituximab treatment, despite better efficacy in terms of response rates. A high tumor burden (presence of bulky disease, Stage III or IV disease) seems to adversely affect long term outcome after ^{90}Y -IT, giving a rationale for using induction chemotherapy prior to RIT in the relapsed setting, in an approach analogous to the first line consolidation strategy. Currently several phase II trials are ongoing using chemo (immuno-) therapy followed by RIT for relapsed disease, but no results have been reported so far. Following such strategy, it could be expected that an improvement of CR/CRu rates can be achieved, which again are an important determinant of durability of response. For the same reasons it might be preferable to use ^{90}Y -IT in the first relapse rather than later. Higher response rates and better PFS can be expected if ^{90}Y -IT is used early in the course of disease. Also, there was concern to use ^{90}Y -IT in patients relapsed

after multiple treatment regimens including autologous transplantation because of potentially fatal hematological toxicity. Although recently this approach was reported to be safe,^{54,55} hematological side effects seem to be more pronounced as compared to first or second line RIT. Another report recommended a lower dose (0.2 mCi/kg) of ^{90}Y -IT for patients relapsing after autologous transplantation.⁵⁶ Thus, we currently favor using ^{90}Y -IT in the first relapse (eventually after debulking chemotherapy), withholding high-dose chemotherapy with autologous transplantation for the second relapse for eligible patients. A third option for patients with relapse of FL would be a rituximab-chemotherapy combination, followed by rituximab maintenance therapy. As these treatment strategies have not been compared in a randomized fashion, individual patient and disease characteristics are the main determinants for the choice of therapy. Specifically, the type of first-line therapy administered and the disease-free interval achieved should be considered when deciding about the optimal second-line treatment.

Another promising treatment strategy is integration of RIT in the conditioning protocol before autologous transplantation. In a phase II trial, the standard dose of ^{90}Y -IT (0.4 mCi/kg) could be added to BEAM chemotherapy before transfusion of stem cells seemingly without additional toxicity as compared to standard chemotherapy conditioning. However, currently it is unknown whether such strategy is capable of achieving an improvement of results as compared to conventional conditioning regimens. A phase III study enrolling patients in chemosensitive relapse of B-cell NHL (diffuse large cell or transformed FL) is planned to answer this question (trial NCT00463463). Escalated doses of ^{90}Y -IT without myeloablative chemotherapy have also been studied as conditioning regimen. This approach might be especially attractive for patients who are otherwise not good candidates for a standard transplantation strategy due to older age or co-morbidities. An European study suggested that a novel transplant regimen using up to 1.2 mCi/kg ^{90}Y -IT followed by a double stem-cell reinfusion can be performed safely without dosimetry. However, in two other studies on autologous transplantation a wide range of RADs to critical organs was observed when using a weight based dose selection, implying that dosimetry is important when ^{90}Y -IT doses are applied above the standard dose of 0.4 mCi/kg. Notably, in one of these studies significant toxicity was observed using escalated ^{90}Y -IT as sole conditioning regimen before autologous transplantation, especially at the highest dose level of 1.5 mCi/kg. Further data are thus necessary before such regimens can be incorporated into routine clinical transplantation practice.

In conclusion, we can expect that the role of RIT in the treatment of patients with FL will be of growing importance. Results of ongoing and future studies will help to further clarify the best strategy for incorporating RIT into the treatment algorithm of these patients.

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