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Review

Consensus conference: Implementing treatment recommendations on yttrium-90 immunotherapy in clinical practice – Report of a European workshop

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ABSTRACT

Radiolabelled immunotherapy is a significant step forward in the treatment of non-Hodgkin's lymphoma (NHL), with preliminary data suggesting long remissions in some patients. ^{90}Y-ibritumomab tiuxetan is the only therapy approved for use after rituximab failure and is currently indicated in the EU for the treatment of adults with rituximab-relapsed or refractory CD20-positive follicular B-cell NHL. However, retrospective analyses confirm better responses when ^{90}Y-ibritumomab tiuxetan is used earlier in the disease course. An expert panel of oncologists, haematologists and nuclear medicine physicians met at an European workshop to discuss proposed therapeutic algorithms for follicular lymphoma and the preliminary medical evidence supporting the incorporation of ^{90}Y-ibritumomab tiuxetan as an early therapeutic option. Phase II data indicate that ^{90}Y-ibritumomab tiuxetan either alone as primary therapy or as consolidation therapy following induction chemotherapy with or without rituximab achieves high response rates in follicular lymphoma, with complete remission rates of 62–80%. Phase III data are warranted, but based on preliminary observations the expert panel recommended incorporation of radiolabelled immunotherapy into national lymphoma treatment algorithms across Europe. This approach would maximise the therapeutic potential of this agent by encouraging its use early in the disease course of follicular lymphomas.

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1. Introduction

Non-Hodgkin's lymphomas (NHLs) are a biologically heterogeneous group of lymphoid malignancies of predominantly B-cell phenotype (90% of cases), characterised by a variable clinical course, ranging from aggressive, rapidly growing tumours needing immediate treatment to indolent cases, where watchful waiting is appropriate. Follicular lymphoma (FL) is the most common indolent B-NHL, characterised by a progressive course and multiple relapses.[1] FL is incurable with conventional chemotherapy, and remission duration becomes shorter with successive lines of treatment. The main impact on survival in the management of FL occurred with the introduction of immunotherapy in the last decade.[2] Addition of the anti-CD20 monoclonal antibody rituximab to conventional chemotherapy regimens substantially improved response rates and increased progression-free survival (PFS) and overall survival compared with chemotherapy alone.[3–6]

The combination of anti-CD20 immunotherapy with therapeutic radioisotopes, which allows targeted delivery of a therapeutic dose of radiation to tumours at multiple sites via monoclonal antibodies, should further improve survival in patients with FL. The only radiolabelled antibodies currently approved for the treatment of NHL are yttrium-90 (^{90}Y)-ibritumomab tiuxetan (Zevalin®, Bayer Schering Pharma AG, Berlin, Germany) and iodine-131 (^{131}I)-tositumomab (Bexxar®, GlaxoSmithKline, Research Triangle Park, NC, USA; not approved in EU), both of which are directed against the CD20 antigen. Radiolabelled immunotherapy is an established treatment option for second relapse or later; however, recent clinical data suggest that using targeted immunotherapy early in the disease course of FL can result in prolonged complete remissions of over 5 years.[7]

This article reviews the latest ^{90}Y-ibritumomab tiuxetan clinical trial data and summarises the outcomes of a European workshop, the main focus of which was the implementation of ^{90}Y-ibritumomab tiuxetan treatment recommendations and guidelines and their future development across Europe.

2. Current use of ^{90}Y-ibritumomab tiuxetan

^{90}Y-ibritumomab tiuxetan combines two treatment modalities: anti-CD20-targeted immunotherapy plus ^{90}Y radiation. The anti-CD20 monoclonal antibody ibritumomab is conjugated with the pure β-emitting radioisotope ^{90}Y via the chelator tiuxetan. The current indication for ^{90}Y-ibritumomab tiuxetan in the EU is the treatment of adult patients with rituximab-relapsed or refractory CD20-positive follicular B-cell NHL, and it is the only therapy approved for use after rituximab failure.

Comprehensive recommendations for the use of ^{90}Y-ibritumomab tiuxetan in NHL were recently developed by Weigert and colleagues,[8] which included practical advice on preparation, dosing and patient management. That paper, and other recent publications, reviews the mode of action of targeted radiotherapy agents, as well as the rationale for their use in NHL.[8–11] Single-agent ^{90}Y-ibritumomab tiuxetan has shown consistent efficacy in phase II–III clinical trials in relapsed/refractory FL, diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) (Table 1). ^{90}Y-ibritumomab tiuxetan and ^{131}I tositumomab show similar efficacy in clinical trials.

Durable responses can be obtained following ^{90}Y-ibritumomab tiuxetan therapy in FL. In a recent analysis of 153 FL patients enrolled in four clinical trials, 39% achieved a long-term response (time-to-progression [TTP] $\geqslant$12 months). At a median duration of follow-up of 55 months, the median TTP in these patients was 31 months and median response duration was 29 months, with some patients remaining in remission for over 5 years.[12]

In a study assessing the efficacy and safety of ^{90}Y-ibritumomab tiuxetan in 40 patients with relapsed/refractory indolent B-cell NHL, 22 of whom had previously received chemotherapy plus rituximab and 15 of whom had received rituximab monotherapy, the overall response rate (ORR) was 83% and the complete response (CR) rate was 63%. The median PFS was 10 months at a median follow-up of 7 months (range, 1–13). The CR rate was 73% in the 22 patients who had previously received chemotherapy plus rituximab.[13]

3. Clinical experience with ^{90}Y-ibritumomab tiuxetan: practical aspects

3.1. *Assessment of response*

Consistency in the timing of response assessment is important when comparing studies. Patients' disease status should be assessed 3 months after completing therapy; however, a further assessment at 6 months may show evidence of an ongoing response to ^{90}Y-ibritumomab tiuxetan.

3.2. *Safety and tolerability*

^{90}Y-ibritumomab tiuxetan is well tolerated, the major side effect being transient, reversible marrow toxicity. Safety data from phase II to phase III clinical trials with single-agent ^{90}Y-ibritumomab tiuxetan are reviewed in detail elsewhere.[8–10,14]

^{90}Y-ibritumomab tiuxetan is well tolerated in older patients. An integrated analysis of four ^{90}Y-ibritumomab tiuxetan clinical trials ($n = 211$) indicated no difference in the incidence of grade 3–4 haematological toxicities in older ($\geqslant$70 years) versus younger (<70 years) patients. Response rate and duration of response were also similar in older and younger patients.[15]

Conventional chemotherapy for NHL, particularly alkylating agents, is associated with an increased risk of myelodysplastic syndrome (MDS) and acute myelogenous leukaemia (AML), which develop within 10 years of exposure and are associated with a poor prognosis. One study estimated this risk at 10%[16]; however, with modern treatment approaches this risk is probably far lower. Seventeen of 746 patients treated with ^{90}Y-ibritumomab tiuxetan developed treatment-related MDS or AML (2.3%), with an annualised rate of 0.7% from the time of treatment, indicating that there is no increased risk of MDS or AML compared with conventional chemotherapy.[17,18] Most ^{90}Y-ibritumomab tiuxetan-treated patients had already received conventional chemotherapy prior to ^{90}Y-ibritumomab tiuxetan therapy. No cases of MDS/

Table 1 – Efficacy of single agent ^{90}Y-ibritumomab tiuxetan in non-Hodgkin's lymphoma (NHL) in key clinical trials[a]

Reference	N	Patients	Response	TTP	Response duration
Witzig et al.[40]	51	Relapsed/refractory CD20 + B-cell low and intermediate grade NHL/MCL	ORR 67% CR 26%	13 + mo	11–14 mo
Witzig et al.[41]	143	Relapsed/refractory low-grade FL or transformed NHL	ORR 80% CR 30% CRu 4%	15 mo (FL)	14–17 mo (FL)
Wiseman et al.[42]	30	Relapsed/refractory low-grade FL or transformed NHL and mild thrombocytopaenia	ORR 83% CR 37% CRu 6%	9–13 mo (FL)	12 mo
Witzig et al.[43]	54	Rituximab-refractory FL	ORR 74% CR 15%	7–9 (responders)	12 mo
Morschhauser et al.[44]	104	Relapsed/refractory DLBCL not appropriate for ASCT	ORR 44% CR 27%		
Younes et al.[45]	22	Relapsed/refractory MCL	ORR 36% CR/Cru 23%	6 mo (CR/CRu)	

[a] Reproduced with permission from John Wiley & Sons Ltd.
ASCT, autologous stem cell transplantation; CR, complete response; CRu, unconfirmed complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; ORR, overall response rate; TTP, time to progression.

AML have developed in a group of 76 patients receiving ^{131}I tositumomab as single agent first-line therapy with a median follow-up of almost 5 years.[19]

3.3. *Patient selection*

The ^{90}Y-ibritumomab tiuxetan prescribing information indicates that patients with >25% bone marrow infiltration by lymphoma cells, subtotal nodal irradiation (STNI), platelet count $<100 \times 10^9$/L or a neutrophil count $<1.5 \times 10^9$/L are unsuitable for treatment. Some patients who are ineligible for treatment because of lymphomatous bone marrow infiltration can be successfully pre-treated with chemotherapy, immunotherapy alone or chemoimmunotherapy to clear the marrow prior to ^{90}Y-ibritumomab tiuxetan. A low platelet count due to autoimmune disease or an enlarged spleen may also be reversible with appropriate pre-treatment.

3.4. *Quality of life*

^{90}Y-ibritumomab tiuxetan has significant advantages over chemotherapy in terms of patient quality of life. Treatment is complete after 1 week and involves a single dose of ^{90}Y-ibritumomab tiuxetan (14.8 MBq/kg, 0.4 mCi/kg), which, in contrast to ^{131}I tositumomab, can be given as a day patient. ^{90}Y-ibritumomab tiuxetan is a pure β-emitter, which means that >90% of the radiation is absorbed within 5 mm, so patient isolation is not required. The predictable myelotoxicity is rarely symptomatic and rarely associated with infectious complications. In contrast to aggressive chemotherapy regimens, other adverse toxicities such as alopecia are minimal or absent. Therefore, when ^{90}Y-ibritumomab tiuxetan is compared with chemotherapy, it proves to be an 'easier' option for the patient in terms of quality of life.

^{90}Y-ibritumomab tiuxetan is therefore particularly useful in patients who cannot tolerate aggressive chemotherapy regimens, for example, elderly or unfit patients, or patients receiving immunosuppressive therapy. It can be effective as palliative therapy for patients with transformed FL, who have a very poor prognosis.

4. ^{90}Y-ibritumomab tiuxetan in the FL treatment algorithm

Retrospective analysis of data from four clinical trials ($n = 211$) indicated that using ^{90}Y-ibritumomab tiuxetan earlier in the disease course of FL results in significantly better response.[20] The CR/unconfirmed CR (CRu) rate was higher (51% versus 28%; $P < 0.01$) and TTP increased (15 versus 9 months; $P < 0.05$) in patients in first relapse compared with those who had received 2 or more prior therapies.

European haematologists and oncologists accept that radiolabelled immunotherapy is a logical therapy increasingly supported by clinical evidence showing that it is an effective treatment, particularly early in the disease course. In clinical practice, however, it frequently remains a treatment of last resort, when it is less likely to be effective. Workshop attendees agreed that implementation of earlier use of ^{90}Y-ibritumomab tiuxetan in FL across Europe should be encouraged to optimise patient outcomes. This change in practice may be achievable by the inclusion of radiolabelled immunotherapy in local and national treatment guidelines developed by expert panels or national associations in each country, taking into account local prescribing issues. Because FL can have a variable clinical course, further clarity on the definition of 'second-line' therapy would be helpful, as this can vary depending on the patient, the treating physician and the locality.

There is currently only minimal clinical data to determine where radiolabelled immunotherapy should be placed in the treatment algorithm for NHL. Winter[21] proposed a treatment algorithm for FL, which recommends a 'watch-and-wait' approach for stage III–IV disease without a clear treatment indication, followed by chemotherapy plus rituximab as initial

therapy when needed, and radiolabelled immunotherapy such as ^{90}Y-ibritumomab tiuxetan as the initial second-line treatment for relapsed disease (Fig. 1). Since then, results from several large randomised trials of relapsed/refractory FL have shown that rituximab maintenance following chemotherapy ± rituximab results in significantly longer PFS and overall survival versus observation only.[22–24] Based on these data, the current treatment standard for relapsed or refractory FL is reinduction with chemotherapy plus rituximab followed by rituximab maintenance, although other options, such as radiolabelled immunotherapy, would also be appropriate. It is therefore logical that the role of radiolabelled immunotherapy in this setting is also thoroughly explored in large phase III comparative trials.

A German group recently published the results of a national consensus workshop to determine a therapeutic algorithm incorporating ^{90}Y immunotherapy for FL.[25] It is recommended as first-line treatment in patients who are unable to tolerate chemotherapy, and at first relapse in low-risk elderly patients. In elderly patients with high-risk disease, and in young patients with low- or high-risk disease, radiolabelled immunotherapy is one of the options recommended at first relapse, following chemoimmunotherapy.

The Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation jointly published comprehensive treatment guidelines for NHL in 2005.[26] For patients with early-stage localised FL (Grade I–II) with low tumour burden, these guidelines recommend externally involved field radiotherapy (dose 36–40 Gy). In patients with stage I–II disease and a high tumour burden or appropriate risks scores (e.g., International Prognostic Index >1), front-line chemotherapy and radiotherapy are recommended. These guidelines were developed in 2002 and so do not include immunotherapy; however, many Italian physicians incorporate rituximab into this algorithm so that patients with stage III–IV FL requiring therapy receive front-line chemoimmunotherapy. The most appropriate place for integrating ^{90}Y-labelled anti-CD20 immunotherapy into these guidelines might be as consolidation therapy in stage III–IV FL patients achieving a partial remission after first-line therapy (pending data from ongoing studies), and as second-line therapy, although further data are needed to support this.

Treatment guidelines are currently under development by the National Lymphoma Group in Denmark, and the European Association for Nuclear Medicine (EANM) is currently developing guidelines regarding the use of ^{90}Y immunotherapy in malignant lymphoma.

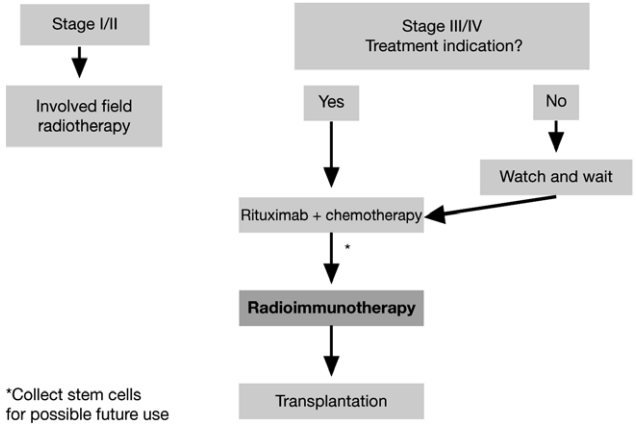

Fig. 1 – Proposed treatment algorithm for follicular lymphoma[21]. Reproduced with permission from the American Society of Hematology. Reinduction with chemotherapy-rituximab followed by rituximab maintenance should also be considered at relapse[22–24].

5. Future perspectives for ^{90}Y-ibritumomab tiuxetan in FL

Continued evaluation of the role of radiolabelled immunotherapy in FL is important, particularly as an early therapy. Many ongoing studies are assessing ^{90}Y-ibritumomab tiuxetan in refractory/relapsed lymphomas, and also as a first-line or first-line consolidation treatment in FL, DLBCL and MCL. Table 2 provides an overview of preliminary data from ongoing studies. These are mainly phase II trials and therefore only limited conclusions can be drawn from these data. Phase III studies in this setting are also underway.

5.1. *First-line therapy*

The German therapeutic algorithm suggests that radiolabelled immunotherapy may be an acceptable first-line therapy in patients with contraindications for chemotherapy.[25] First-line ^{90}Y-ibritumomab tiuxetan followed by rituximab maintenance (375 mg/m^2 × 4 every 6 months) in low-grade FL was investigated in a phase II clinical study.[27] Ten patients were enrolled, with a median age of 58 years (range 40–82), of whom 50% had stage IV disease. The ORR was 100% in the eight evaluable patients (Table 2), with grade 3 bone marrow toxicity in 3 of 8 patients.

5.2. *First-line consolidation following induction chemotherapy*

A number of trials are investigating the use of ^{90}Y-ibritumomab tiuxetan as first-line consolidation therapy in FL following short-duration chemotherapy with or without immunotherapy. The aim of consolidation therapy is to eradicate any residual disease following induction therapy and achieve a cure.

Shipley et al.[28] enrolled 42 untreated patients with grade I–III FL (median age 57 years; 60% stage IV) to short-duration cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R) induction chemotherapy followed by ^{90}Y-ibritumomab tiuxetan consolidation. The disease status after induction treatment was an ORR of 100% and CR 28%, which improved after ^{90}Y-ibritumomab tiuxetan consolidation to a CR rate of 67% with an actuarial 2-year PFS of 77% after a median follow-up of 20 months (Table 2). Toxicities were mainly haematological, as expected (grade 3).

In a second study evaluating ^{90}Y-ibritumomab tiuxetan consolidation and rituximab maintenance following short CHOP-R induction, 16 of 36 patients with grade I–III or transformed FL have completed therapy and follow-up.[29] ^{90}Y-ibrit-

Table 2 – Phase II studies investigating the use of ^{90}Y-ibritumomab tiuxetan earlier in the treatment algorithm in FL, MCL and DLBCL

Reference	N enrolled/evaluable	Patients	Response after induction chemotherapy	Response after ^{90}Y-ibritumomab tiuxetan
First-line in FL				
Sweetenham et al.[27]	10/8	Untreated low-grade FL	N/A	ORR 100% CR 62%
First-line consolidation in FL				
Shipley et al.[28]	42/42	Untreated FL	ORR 100% CR28%	ORR 100% CR 67% 2-year PFS 77% (median 20 months follow-up)
Demonaco et al.[29]	36/16	Untreated FL	PET-CT negative 53% CR 36%	PET-CT negative 100% C: 89%
Gregory et al.[30]	7/4	Untreated FL[a]	ORR 4 pts CR 0 pts	CR 1 pt PET-negative 2 pts
First-line consolidation in MCL				
Jurczak et al.[32]	20/20	MCL not suitable for SCT at first CR or PR	ORR 100% CR 20%	CR 85% 2-year EFS 78%
	10/10	MCL not suitable for SCT at relapse 1–3	ORR 100% CR 0%	CR 50% Medium TTP 8 months
Smith et al.[33]	57/44	Untreated MCL	ORR 72% CR/CRu 14%	ORR 84% CR/Cru 45%
First-line in DLBCL				
Hamlin et al.[34]	26/14	Previously untreated high-risk DLBCL	Not stated	OS 60% EFS 55% (median 14 months follow-up)

CR, complete response; CRu, unconfirmed complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FL, follicular lymphoma; MCL, mantle cell lymphoma; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PR, partial response; ORR, overall response rate; OS, overall survival; SCT, stem cell transplantation.
a Five patients with relapsed FL were also enrolled but are not reported here.

umomab tiuxetan consolidation substantially improved the quality of responses following CHOP-R (Table 2), with the CR rate increasing from 36% to 89% following consolidation.

Preliminary data from a study investigating first-line ^{90}Y-ibritumomab tiuxetan consolidation therapy and maintenance rituximab (375 mg/m^2 × 4 every 6 months) following four cycles of fludarabine plus mitoxantrone (FM) chemotherapy in newly diagnosed FL is also promising. In four evaluable patients achieving a PR after 4–6 cycles of FM, the response after ^{90}Y-ibritumomab tiuxetan included 1 CR and 2 patients with a negative positron emission tomography scan (Table 2).[30]

Phase III studies investigating ^{90}Y-ibritumomab tiuxetan consolidation following chemotherapy ± rituximab are ongoing, and these data will provide a clearer picture of where ^{90}Y immunotherapy should be integrated in the treatment algorithms of different lymphoma subtypes, as well as provide information on the contribution of single-agent immunotherapy. The first-line indolent lymphoma trial (FIT) is a phase III randomised, controlled, open-label study investigating first-line ^{90}Y-ibritumomab tiuxetan consolidation versus no further treatment following first-line chemotherapy in stage III–IV FL. The study was carried out in 76 centres in Europe and the US, and 414 patients were enrolled. Results of an interim safety analysis were presented in 2003[31] and the final results are expected at the 49th annual American Society of Hematology meeting in 2007. The Randomised Intergroup Zevalin Trial (RITZ) is a recently started phase III randomised trial evaluating ^{90}Y-ibritumomab tiuxetan consolidation followed by rituximab maintenance versus rituximab maintenance alone in relapsed/refractory FL responding to immunochemotherapy induction. Alternative ^{90}Y-ibritumomab tiuxetan treatment regimens are also being explored in clinical trials, including fractionated ^{90}Y-ibritumomab tiuxetan in untreated FL, using 2 doses of 11.1 MBq/kg ^{90}Y-ibritumomab tiuxetan up to 12 weeks apart.

5.3. *First-line consolidation in MCL*

The role of ^{90}Y-ibritumomab tiuxetan consolidation therapy in MCL, which is generally considered incurable with conventional therapy, is being investigated by the Polish Lymphoma Research Group. In this multicentre phase II study, patients who are not suitable for stem cell transplant are given ^{90}Y-ibritumomab tiuxetan consolidation following chemotherapy with fludarabine, cyclophosphamide and mitoxantrone (FCM) ± rituximab. Of 20 patients treated at diagnosis or first partial response, four were in CR after chemoimmunotherapy, and a further 13 attained CR after ^{90}Y-ibritumomab tiuxetan consolidation, resulting in a 2-year event-free survival (EFS) of 78%. The outcome was less impressive for

relapsed patients, with 5 of 10 achieving a CR after consolidation, but with a medium time to progression of 8 months (Table 2).[32]

^{90}Y-ibritumomab tiuxetan consolidation following CHOP-R therapy in previously untreated stage III–IV MCL patients also improved the quality of response to induction chemotherapy in a multicentre phase II trial of 50 evaluable patients. The ORR was 72% and the CR/CRu rate was 14% after chemotherapy, with an improved response in 15 of 37 patients after ^{90}Y-ibritumomab tiuxetan, resulting in a final ORR of 84% and a CR rate of 45% (Table 2).[33] MCL patients have such a poor prognosis that it may be reasonable to consolidate all patients not suitable for transplant with ^{90}Y-ibritumomab tiuxetan after first-line treatment, although phase III clinical studies are needed to ascertain this. Clinical study data indicate that ^{90}Y-ibritumomab tiuxetan is also a reasonable palliative approach in relapsed patients.

5.4. *First-line consolidation in aggressive lymphoma*

^{90}Y-ibritumomab tiuxetan consolidation following R-CHOP21 in previously untreated DLBCL patients >60 years old and ineligible for stem cell transplant is currently under investigation by Hamlin et al.[34] Preliminary results in 14 patients who have completed this protocol confirm an overall survival rate of 60% and EFS of 55% at a median of 14 months follow-up. Haematological toxicity was similar to that of single-agent ^{90}Y-ibritumomab tiuxetan in these high-risk elderly patients. The ongoing phase III ZEAL (ZEvalin as consolidation therapy in Aggressive Lymphoma) registration study is assessing first-line ^{90}Y-ibritumomab tiuxetan consolidation following six cycles of R-CHOP21 in DLBCL.[35]

5.5. *Subsequent treatment is feasible after ^{90}Y-ibritumomab tiuxetan*

Although recent data suggest that ^{90}Y-ibritumomab tiuxetan should not be held back for use as salvage therapy but should be given early on in the treatment algorithm, there may be some reluctance to use this treatment option early on in clinical management because of the concern that other conventional treatments may be less effective after ^{90}Y-ibritumomab tiuxetan. Clinical data show that ^{90}Y-ibritumomab tiuxetan treatment does not compromise the subsequent use of other therapy such as chemotherapy, immunotherapy or stem cell transplantation, with no difference in responses or increase in side effects.[36,37] An ongoing study evaluating stem cell collection following front-line consolidation with ^{90}Y-ibritumomab tiuxetan is expected to provide further useful data.

5.6. *Re-treatment with ^{90}Y-ibritumomab tiuxetan*

Preliminary results also suggest that ^{90}Y-ibritumomab tiuxetan re-treatment with a reduced dose is feasible and well tolerated. In a phase I study in which 15 of 18 patients received a second dose (without growth factor support), 6 patients (33%) remain in continuous remission at a median of 29 months (range, 23–41). In another group of patients who were receiving prophylactic growth factor support, 10 of 17 received a second dose of ^{90}Y-ibritumomab tiuxetan. Five of the patients receiving 2 doses remain in continuous, unmaintained remission at a median of 17 months (range, 11–27+).[38]

A retrospective analysis of 10 relapsed FL patients who received two courses of ^{90}Y-ibritumomab tiuxetan confirmed that a second treatment is effective and well tolerated, even if the other treatment is used between the two doses.[39] After the first and second doses, the ORRs were 90% and 70%, and the CR rates were 60% and 40%, respectively. Rates of grade III–IV marrow toxicity were similar after each dose.

5.7. *Other indications*

Other indications for radiolabelled immunotherapy being evaluated include primary central nervous system lymphoma, mucosa-associated lymphoid tissue (MALT), gastric NHL, non-gastric MALT and orbital lymphoma. Combination therapies are likely to be investigated in the future, such as an ongoing trial of combined ^{90}Y-ibritumomab tiuxetan and the pyrimidine analogue gemcitabine.

^{90}Y-labelled immunotherapy is likely to play a significant role as part of the conditioning treatment prior to stem cell transplant, as an alternative to total body irradiation (TBI). TBI-containing transplant regimens are intensive and poorly tolerated in older patients with NHL. The role of ^{90}Y-ibritumomab tiuxetan in transplantation is being assessed in ongoing studies.

6. Conclusions

It is now established that ^{90}Y-ibritumomab tiuxetan is effective and well tolerated in relapsed/refractory FL, achieving durable responses in approximately two-thirds of patients achieving a CR. Response rates are higher and tolerability is better in patients who have received fewer previous therapies, providing a rationale for the earlier use of ^{90}Y-ibritumomab tiuxetan. Current data indicate that other therapies can be given following ^{90}Y-ibritumomab tiuxetan without any impact on their efficacy or tolerability.

Preliminary data from ongoing phase II studies indicate that first-line ^{90}Y-ibritumomab tiuxetan therapy is effective and well tolerated, which is of particular relevance for patients who cannot tolerate chemotherapy. Preliminary data from phase II studies suggest that first-line ^{90}Y-ibritumomab tiuxetan consolidation following induction chemotherapy with or without rituximab improves the response duration in FL. It is anticipated that long-term data from ongoing phase III studies in this setting will confirm these preliminary findings. Further phase II studies are needed to clarify the potential role of ^{90}Y-ibritumomab tiuxetan in MCL and DLBCL.

The ongoing phase III trials are expected to provide sufficient data to clearly determine where ^{90}Y-ibritumomab tiuxetan should be incorporated in lymphoma treatment algorithms across Europe. This may be best achieved by the development of local algorithms in individual countries, taking into account existing local guidelines and regulations in order to provide practical and flexible treatment options. These treatment algorithms will have to evolve as new data become available that clarify the roles of chemotherapy, immunotherapy and radiolabelled immunotherapy in NHL.

Conflict of interest statement

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