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New strategies with ^{90}Y-ibritumomab tiuxetan in diffuse large B-cell lymphoma and mantle cell lymphoma

Franck Morschhauser

Service des Maladies du Sang
Hôpital Huriez,
Centre Hospitalier Universitaire,
Lille, France

Corresponding author:
Franck Morschhauser
Email: f-morschhauser@chru-lille.fr

A B S T R A C T

Both diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) remain major therapeutic challenges in spite of the recent improvements conferred by the addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy. Radioimmunotherapy (RIT) which enhances the efficacy of anti-CD20 immunotherapy by taking advantage of the high radiosensitivity of lymphoma cells is an option to improve outcome. Encouraging results with ^{90}Y-ibritumomab tiuxetan as a single agent have been reported in relapsed/refractory DLBCL and MCL. However, in light of the constantly increasing clinical experience with RIT, clinicians face the challenge of how to best integrate this promising new treatment option into existing established treatment algorithms. Preliminary results with ^{90}Y-ibritumomab tiuxetan as a consolidation treatment following first-line immunochemotherapy are promising. By incorporating the most recent data in this rapidly developing field, this review article serves to define the potential role of ^{90}Y-ibritumomab tiuxetan in the overall management of DLBCL and MCL patients not eligible for transplantation.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent non-Hodgkin's lymphoma (NHL) subtype, comprising 30% to 35% of all NHL cases, and is characterized as an aggressive lymphoma as per its typical biological behaviour of rapid growth and limited survival in the absence of effective treatment. DLBCL can be cured in a significant percentage of patients, although this is dependent on the initial characteristics of the tumour, stage of disease and the comorbidities of the host. Approximately 40% of all advanced stage DLBCL cases can be cured using cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapeutic regimens.[1,2] More recently, the addition of the anti-CD20 monoclonal antibody, rituximab, to CHOP (R-CHOP) has resulted in significantly improved complete response (CR) rates, progression-free survival (PFS), and overall survival (OS) in first-line therapy and has now become the standard of care for these patients;[3,4,5] however, the addition of rituximab only improves overall survival by 10–15%. In addition, the treatment of DLBCL remains unsatisfactory for patients with high intermediate and high International Prognostic Index (IPI) score at diagnosis[5] where the benefits of the addition of rituximab are less pronounced and new treatment strategies are therefore required. Thus, an unmet need for the treatment of DLBCL remains.

Mantle cell lymphoma (MCL) represents approximately 4% to 6% of all non-Hodgkin's

lymphomas (NHL).[6-8] In contrast to DLBCL, MCL is not always considered an aggressive NHL and is currently not curable. MCL usually presents as advanced-stage disease, often in elderly male patients, and has a tendency for extranodal involvement in the gastrointestinal tract and frequent infiltration of the bone marrow.[9,10] MCL is often responsive to a range of chemotherapy regimens, especially more aggressive approaches, with up to 97% response rates; however, no therapy is curative[11,12] and the favorable response rates seen with newer therapies have not translated into better long-term outcome.[9,10,13] These challenges underscore the need for additional, innovative approaches such as targeted therapy in the treatment of MCL.

Rationale for the use of radioimmunotherapy in patients with DLBCL or MCL

The use of radiolabeled monoclonal antibodies, or radioimmunotherapy (RIT), could further enhance the efficacy of anti-CD20 immunotherapy seen in DLBCL and MCL by taking advantage of the high radiosensitivity of lymphoma cells in both lymphoma subtypes. Conversely, since radioimmunoconjugates kill lymphoma cells predominantly by radioactive emissions after antigen binding, they can be useful even when the patient has failed treatment with unmodified monoclonal antibodies.[14,15] This review will focus on RIT with yttrium-90 (^{90}Y)-ibritumomab tiuxetan in DLBCL and MCL outside the context of transplantation.

^{90}Y-ibritumomab tiuxetan in patients with DLBCL

^{90}Y-ibritumomab tiuxetan RIT is well tolerated and effective for relapsed or refractory CD20^{+} B-cell NHL, and long-term follow-up data have been reported in responding patients based on International Workshop Response Criteria.[16] Of enrolled patients with DLBCL (n=12, 24%), the overall response rate was 58%. In addition, median duration of response for DLBCL patients was 49.8 months (range: 1.3–67.6+) and median time-to-progression was 4.6 months (range: 0.9–68.6+) [included 7 responders and 5 non-responders]. Two patients with DLBCL remain in remission beyond 5 years. Adverse events with ^{90}Y-ibritumomab tiuxetan were primarily haematologic and transient as previously described.[17]

Further to the encouraging data from Gordon et al.,[16] a Phase II trial was initiated to confirm these data in a larger study group. The most appropriate study population to be tested comprised elderly patients with histologically-confirmed first relapse or primary refractory disease who were not eligible for stem cell transplant and for whom there was no curative option.[18] Patients were divided into 2 groups: those previously treated with chemotherapy alone (Group A, n=76) and those previously treated with chemotherapy and rituximab (Group B, n=28). Patients in Group A were further divided into patients in whom induction therapy had failed (stratum AI, n=33) and patients who had relapsed after achieving CR (stratum AII, n=43). All patients received a single dose of ^{90}Y-ibritumomab tiuxetan 14.8 MBq/kg (0.4 mCi/kg) up to a maximum dose of 1184 MBq (32 mCi). The ORR was 52% and 53% in strata AI and AII and 19% in group B, with CR/CRu rates of 24%, 39.5%, and 12%, respectively. Given that group B contained more patients with a poorer overall prognosis, a high or high-intermediate risk, and/or bulky disease (lymph nodes >5 cm) than group A, the low response rates in group B suggest that the failure of R-CHOP therapy is a potential predictor of refractory disease. After a median follow-up of 21.7 months, 13

patients in group A (17%), including those who failed induction therapy, had a durable response lasting longer than 20 months, with 4 patients still in remission at 30 months. Progression-free survival curves for strata AI and AII were similar, suggesting that the differences in responsiveness to chemotherapy between the groups may not influence the durability of response to RIT in responding patients. Adverse events, with the exception of haematological adverse events, were generally mild or moderate (Grade 1/2) in severity. An earlier nadir was reported compared with follicular trials. Of note, the incidence of severe infection was low, with only 7% of patients hospitalised due to infection during the study. Similarly, Buff et al. have performed a Phase II multicentre clinical trial to examine the efficacy of ^{90}Y-ibritumomab tiuxetan induction followed by maintenance rituximab in patients with DLBCL relapsed or refractory to anthracycline-based chemotherapy or who were intolerant of anthracycline-based chemotherapy.[19] Of 16 patients enrolled in the study (40 patients planned), the median number of prior regimens was 2 (range: 1–5) and 44% of patients had a secondary IPI score 3. An overall response rate of 37.5% with 25% CR at 12 weeks has been achieved. All patients with a CR had a secondary IPI of 1. Among responding patients, the EFS has not yet been reached (median follow-up of over 11 months). Five patients (31%) continue to be in remission greater than 6 months, and 3 patients (19%) remain in remission at 1 year.

Given the encouraging data with ^{90}Y-ibritumomab tiuxetan in relapsed DLBCL patients and good data in patients without bulk, consolidation with ^{90}Y-ibritumomab tiuxetan after debulking appears to be an attractive option. Several clinical studies investigating this strategy with ^{90}Y-ibritumomab tiuxetan after CHOP or R-CHOP in patients with DLBCL are ongoing.

A prospective, single-arm, open-label, non-randomized study has evaluated the efficacy and safety of ^{90}Y-ibritumomab tiuxetan as consolidation therapy following CHOP in patients with previously untreated elderly DLBCL.[20,21] Patients were treated with standard CHOP chemotherapy every 21 days for 6 cycles and those patients who achieved at least a partial response after 6 cycles of CHOP were eligible for consolidation with a single dose of ^{90}Y-ibritumomab tiuxetan (up to a maximum dose of 1184 MBq (32 mCi). A total of 20 patients have been enrolled (median age: 68 yrs, range: 61–84), 6 of whom were stage II and 14 stage III-IV.[21] Following treatment with CHOP, 15 (75%) and 5 (25%) patients achieved a CR or PR, respectively. However, subsequent treatment with ^{90}Y-ibritumomab tiuxetan enabled 4/5 (80%) patients to improve their remission status from PR to CR. The most common grade ≥3 adverse events with ^{90}Y-ibritumomab tiuxetan were neutropenia (11 patients) and thrombocytopenia (7 patients), as expected.

Hamlin et al. investigated the efficacy and safety of R-CHOP-21 followed by ^{90}Y-ibritumomab tiuxetan RIT in untreated patients ineligible for autologous stem cell transplantation (ASCT) aged >60 years with high-intermediate or high-risk DLBCL.[22] Interim data (n=26; median age: 75 years [range: 65–85 years]) indicate that sequential R-CHOP + ^{90}Y-ibritumomab tiuxetan is feasible and associated with manageable toxicity in this study group. Median nadir counts during RIT occurred at weeks 6–7. Grade 3 or 4 absolute neutrophil count, haemoglobin or platelet count occurred in 78%, 39% and 61% of patients, respectively. Overall survival and event-free survival for all patients (ITT population) was 60% and 55%, respectively, with median follow-up of 14 months. In addition, haematological toxicity appeared similar to that reported with single-agent use of ^{90}Y-ibritumomab tiuxetan in these high-risk elderly patients.

A Phase III registration trial (randomization of ^{90}Y-ibritumomab tiuxetan versus no further treatment) known as the ZEAL (ZEvalin as consolidation therapy in aggressive lymphoma) study is assessing first-line ^{90}Y-ibritumomab tiuxetan consolidation in patients with DLBCL in CR/CRu following six or eight cycles of R-CHOP-21, while a Phase II study is examining the efficacy of ^{90}Y-ibritumomab tiuxetan in elderly (>60 years of age) patients with DLBCL in partial remission with positive PET scan after R-CHOP therapy (Hovon 77).[23] The ECOG group is investigating the efficacy and safety of ^{90}Y-ibritumomab tiuxetan following R-CHOP treatment in patients with previously untreated stage I (plus at least one risk factor) or II DLBCL (ECOG-E3402).[24] The aim of the ECOG study is to investigate the efficacy of ^{90}Y-ibritumomab tiuxetan in preventing outfield relapse in patients who would normally be treated with R-CHOP followed by involved-field radiotherapy. Finally, a phase I/II study is currently investigating the efficacy and safety of integrating two doses of ^{90}Y-ibritumomab tiuxetan with 4 cycles of R-CHOP-21 chemotherapy in treatment of newly diagnosed DLBCL in patients >60 years of age. ^{90}Y-ibritumomab tiuxetan will be given in weeks 6 and 15 in a dose-escalated fashion (8 and 11 MBq/kg). The purpose of the study is to investigate achieving a better early disease control with minimal side effects while reducing the total number of cycles of chemotherapy, which would prove helpful in elderly patients.

^{90}Y-ibritumomab tiuxetan in patients with MCL

MCL represents a clinical challenge in need of novel therapeutic approaches. Though MCL is extremely radiosensitive,[25] the use of external beam radiation therapy is limited by the systemic nature of the disease. As with DLBCL, RIT can address this limitation by targeting radionuclides to the tumour. However, as a consequence of overlapping toxicity between RIT and chemotherapy, these treatments need to be administered sequentially if not administered with stem cell support.

Wang et al. have recently reported data from a completed Phase II clinical trial of ^{90}Y-ibritumomab tiuxetan in patients with relapsed and refractory MCL.[26] Thirty-five patients (median age: 68 years, range: 52–79) had previously been treated with rituximab with or without other chemotherapy (median number of prior regimens was 3) and 12 patients had not responded to their last regimen. Objective responses were observed in 13/31 patients for an ORR of 42% including 8 CR/CRu (26%) and 5 PR (16%). Of note, two patients who achieved CR had previously received four lines of therapy. Median PFS for responding patients was 6 months after a median follow-up time of 16 months. In addition, treatment with ^{90}Y-ibritumomab tiuxetan was generally well tolerated, with the most common toxicity being haematological in nature, as expected. Conversely, another group of patients with relapsed or refractory MCL (n=14; median age: 68 years, range: 56–71) who were not eligible for ASCT and had previously been treated with regimens containing rituximab (median number of prior regimens: 4) had a less promising response to ^{90}Y-ibritumomab tiuxetan therapy.[27] A partial response was seen in 33.3% of evaluable patients (2 of 6), while an additional patient had stable disease; median PFS for these patients was 3.9 months.

The Polish Lymphoma Research Group is currently investigating consolidation treatment with ^{90}Y-ibritumomab tiuxetan following the standard chemotherapy regimen of fludarabine, cyclophosphamide and mitoxantrone with/without rituximab in MCL

patients deemed unsuitable for stem cell transplantation. In this multicentre Phase II trial, of 20 patients treated at diagnosis or first partial response, 4 were in CR after chemoimmunotherapy, and a further 13 were in CR after ^{90}Y-ibritumomab tiuxetan consolidation (2 year EFS: 78%). The results were less spectacular in relapsed patients: as although 5 (50%) achieved a CR after consolidation, the response was short lasting, with a medium time to progression of 8 months.[28] Of particular note was the toxicity of ^{90}Y-ibritumomab tiuxetan following treatment with the fludarabine-based combination (up to 6 cycles), which highlights the need to determine the optimal number of cycles of fludarabine-based chemotherapy prior to ^{90}Y-ibritumomab tiuxetan in an attempt to minimize potential toxicity.

The efficacy and safety of ^{90}Y-ibritumomab tiuxetan following R-CHOP induction in patients with MCL has recently been reported.[29] After receiving 4 cycles of R-CHOP over a 4–8 week period, patients received 0.4 mCi/kg ^{90}Y-ibritumomab tiuxetan. Of 56 eligible patients, 50 were evaluable for response after R-CHOP and 44 after ^{90}Y-ibritumomab tiuxetan. Following R-CHOP, 7 patients (14%) achieved CR/CRu, 29 (58%) had a PR, 13 (26%) had stable disease, and 1 (2%) had progressive disease. The use of ^{90}Y-ibritumomab tiuxetan improved treatment response in 15/37 patients who had failed to achieve CR/CRu (CR/CRu, n=13; PR, n=2). Thus, the use of ^{90}Y-ibritumomab tiuxetan improved the number and quality of responses after the use of R-CHOP in untreated MCL, and these results coupled with those discussed above suggest that ^{90}Y-ibritumomab tiuxetan should be used as part of a first-line treatment strategy to achieve better response in these high-risk patients.

Conclusions

The use of RIT in the treatment of DLBCL and MCL appears promising, with demonstrated efficacy in patients who have failed treatment with unmodified monoclonal antibodies or commonly used chemotherapy regimens. First-line consolidation with ^{90}Y-ibritumomab tiuxetan following induction chemotherapy or chemoimmunotherapy can improve quality of response and appears promising in MCL and DLBCL. In addition, haematological toxicities seen with this consolidation regimen appear similar to that with single agent ^{90}Y-ibritumomab tiuxetan alone, supporting a favourable tolerability profile. Ongoing studies, including one Phase III randomized trial in elderly patients with DLBCL, aim to demonstrate the benefit of ^{90}Y-ibritumomab tiuxetan as part of first line therapy and to determine the optimal number of prior chemotherapy cycles in this setting.

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