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Radioimmunotherapy in Mantle Cell Lymphoma

Alan P. Skarbnik, MD¹ and Mitchell R. Smith, MD, Ph.D^{2,*}

¹Post-Doctoral Fellow, Fox Chase Cancer Center and Temple University Hospital.

Alan.Skarbnik@fccc.edu . Address: 333 Cottman Avenue, Philadelphia, PA 19111. Phone: 215-728-6900. Fax: 215-728-3639

²Professor, Director Lymphoma Service, Fox Chase Cancer Center. Mitchell.Smith@fccc.edu.

Address: 333 Cottman Avenue, Philadelphia, PA 19111. Phone: 215-728-2674. Fax: 215-728-3639

Abstract

Mantle cell lymphoma (MCL), though characterized by the chromosomal translocation t(11; 14) (q13; q32), is a heterogeneous disease. Often termed an aggressive lymphoma in the U.S., but included in indolent lymphoma trials in Europe, MCL is not curable with standard immuno-chemotherapy. There is no single standard initial therapy for this disease. Although standard lymphoma therapies yield high response rates, relapse is inevitable. Unmet needs in MCL include better induction therapy, consolidation treatments to prolong first remission and better therapeutic options for relapsed disease. In this review, we evaluate the role of radioimmunotherapy (RIT) in MCL, a novel strategy combining monoclonal antibodies with radioisotopes to deliver radiation directly to tumour tissue, both in the frontline and relapsed setting.

Keywords

Mantle Cell Lymphoma; Non-Hodgkin's Lymphoma; Radioimmunotherapy; tositumomab; ibritumomab tiuxetan

Mantle cell lymphomas (MCL) represent about 6% of all non-Hodgkin lymphomas (NHL) and are characterized by the chromosomal translocation, t(11;14)(q13;q32), placing the *bcl-1* gene locus on chromosome 11 adjacent to the immunoglobulin heavy chain gene on chromosome 14, deregulating expression of cyclin D1 [1, 2]. MCL presents in patients at a median age of ~65 years, with a 3-4:1 male predominance. The majority of patients present with stage III/IV disease. About 65% have bone marrow involvement and extranodal sites, particularly the gastrointestinal system, are often involved. Overall survival (OS) is increasing [3] though still requires significant improvement.

There is no single standard initial therapy for MCL [4]. Standard lymphoma therapies such as rituximab (R)-CHOP [5] or R-bendamustine [6] yield high response rates, but responses are not durable. Even young, fit patients treated with intensive regimens such as R-

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*Corresponding author: Mitchell.Smith@fccc.edu.

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HyperCVAD/R-MA[7] or high dose chemotherapy with stem cell support after R-CHOP, R-CHOP alternating with R-DHAP, or more intense regimens [8, 9], eventually relapse. At relapse, additional chemotherapy may again yield responses, but at lower rates and of shorter duration[10, 11]. Bortezomib is approved in the U.S. for relapsed MCL[12]. Standard second-line combinations such as DHAP and ICE have activity. Novel targeted agents such as immunomodulatory agents[13, 14], mTOR inhibitors[15] and histone deacetylase (HDAC) inhibitors[16] also have activity. With any of these, however, relapse is inevitable. Thus, unmet needs in MCL include better induction therapy, consolidation treatments to prolong first remission and better therapeutic options for relapsed disease.

For several decades, there have been attempts to treat B-cell lymphomas with immunotherapy using monoclonal antibodies targeted against B-cell specific antigens[17, 18]. Early studies used murine antibodies with disappointing results, due to poor recruitment of human immune effector mechanisms, development of human anti-murine antibody (HAMA) and down-regulation and/or circulating soluble target antigen[19, 20]. The development of genetically modified chimeric antibodies containing murine variable-region genes and human constant-region genes, and more recently humanized and human antibodies, and the identification of specific B-cell antigens that minimally shed or modulate, has led to significant progress in immunotherapeutic strategies for B-cell lymphomas.[21] Nonetheless, unlabeled monoclonal antibodies are not curative for indolent lymphoma or MCL. Ultimately, B cell lymphomas become resistant to such antibody therapy even though usually still expressing the target antigen. Approaches to enhance antibody efficacy include antibody engineering for improved binding to the target or enhanced effector functions such as complement activation and antigen-dependent cell cytotoxicity (ADCC). Other approaches use antibodies that are internalized to carry drugs (antibody-drug conjugates) or toxins (immunotoxins) into cells. All of these, however, require antibody to reach every tumour cell in order to eradicate them. An alternative approach is to use antibody to target radiation (radioimmunotherapy (RIT)) to the vicinity of the lymphoma.

RIT should ideally target tumour specific antigens, sparing normal cells when possible. Thus, as for rituximab, CD20, a transmembrane phosphoprotein expressed in more than 90% of B-cell NHL, as well as in mature B-cells and pre-B cells, but not in plasma cells or stem cells, presents an attractive target in lymphoma.[22] Since MCL is radiosensitive and expresses surface CD20, there is rationale to target radiation directly to MCL cells via CD20.

Potential advantages of RIT in lymphoma include: 1) lymphoma cells are inherently radiosensitive; 2) when bound to tumour cells, RIT can kill surrounding tumour cells within the path length of the isotope by a crossfire effect, important in bulky or poorly vascularized tumours or if some cells express low or absent levels of CD20; 3) due to the limited path length of particle emissions and selectivity of the associated antibody, surrounding normal tissue is exposed to less radiation than tumour cells; 4) RIT delivers continuous radiation directly to tumour tissue systemically with a lower peak dose than conventional radiation; 5) with continuous exposure to radiation, tumour cells are usually unable to perform DNA damage repair. [23, 24].

RADIOISOTOPES CURRENTLY USED IN RIT

Currently, there are two approved RIT agents for use in B cell lymphoma. ¹³¹I-tositumomab (Bexxar®; GSK) and ⁹⁰Y-ibritumomab tiuxetan (Zevalin®; Spectrum pharmaceuticals), both target CD20. Table 1 depicts the main characteristics and differences between the two compounds. One key difference involves beta versus gamma radiation. Beta emissions are

electrons that penetrate only short distances through tissue, while gamma emissions or “rays” penetrate through tissue and beyond. Gamma emitters can be used for imaging because these emissions can be detected outside the body. Internal beta emissions are not detectable outside the body and can be blocked by plexiglas[25], making radiation safety easier .

Iodine -131 (^{131}I) has been used in RIT for many years, but has limitations. ^{131}I gamma emission may irradiate distant organs and imposes restrictions on the patient to prevent radiation exposure to healthcare personnel, family members and the public. The half-life of ^{131}I is 8 days. Its elimination is controlled by dehalogenation, both in blood and at tumour sites. Since rates of dehalogenation are extremely variable, whole body clearance-based dosing calculation (dosimetry) is necessary to compensate for these variations.[26, 27]

Novel methods for attaching metal chelating groups to proteins permit study of alternate radioisotopes in RIT. Yttrium-90 (^{90}Y) differs from ^{131}I , delivering higher beta energy (2.3 MeV vs. 0.61 MeV) with longer path length (5-10 mm vs. 1 mm), which in theory may improve its ability to kill both targeted and surrounding tumour cells, but also potentially add more toxicity to normal cells . ^{90}Y is excreted in the urine at a weekly rate of about 7% of delivered dose, with minimal variability amongst patients, eliminating the need for dosimetry. ^{90}Y is a pure beta-emitting isotope, thus patients may be treated as outpatients, [28] but it cannot be used for imaging. To circumvent that, indium-111 (^{111}In), a gamma-emitting isotope serves as a surrogate imaging agent when conjugated to the same monoclonal antibody.[26] There have been no studies directly comparing efficacy between these two RIT agents.

TREATMENT SCHEMA

Careful selection with strict criteria for patients appropriate to receive RIT with the currently approved agents is important. Patients must possess adequate marrow reserve, with both adequate normal cellularity and less than 25% of the bone marrow space involved by lymphoma, preferably on bilateral core biopsies. A platelet count of $150,000/\text{mm}^3$ is required for full dose treatment, while patients with platelet counts between $100,000\text{--}149,000/\text{mm}^3$ are eligible for a reduced dose.

Radioimmunotherapy is delivered in two sets of infusions, usually 7 days apart. Both infusions are preceded by a dose of unlabeled antibody, murine tositumumab (for ^{131}I -tositumomab) and chimeric rituximab for ^{90}Y -ibritumomab tiuxetan . Because of the larger dose of murine antibody, the development of HAMA is higher for tositumomab. The first “cold” dose of antibody, given before the dosimetry (for ^{131}I -tositumomab) or biodistribution (for ^{90}Y -ibritumomab tiuxetan) imaging dose of the selected RIT agent, aims to clear soluble CD20, circulating normal or malignant B-cells that express CD20, and to block CD20 sites in the spleen. The second “cold” dose of anti-CD20 is given prior to the therapeutic dose of the selected RIT agent and should bind peripheral sites of tumour masses, facilitating the penetration of radiolabeled antibody.[25] While it is clear that bio-distribution is improved by these “cold” doses, surprisingly little data exist on the optimal doses. As the unlabeled antibody for ^{90}Y -ibritumomab tiuxetan is rituximab, some component of tumour cell elimination via the effector mechanisms of antibody targeting - ADCC, complement-dependent cytotoxicity (CDC) and apoptosis - may also be active. Both approved RIT agents use a murine antibody for radio-isotope delivery to shorten the circulation time of non-lymphoma bound radiolabelled antibody.

Following the first unlabeled antibody dose, a trace amount of the radioactive agent is given, enabling the evaluation of body radiation clearance with gamma camera scans, ensuring that abnormal or altered distribution to normal organs is not present and that it is safe to proceed

with the larger therapeutic dose. In the case of ^{131}I -tositumomab, the scan also allows for dosimetry calculations. In Europe, and more recently in the U.S., imaging for ^{90}Y -ibritumomab tiuxetan is no longer required as the incidence of abnormal biodistribution is < 1%.

The therapeutic dose is delivered about 1 week after the initial imaging/biodistribution dose. In the case of ^{131}I -tositumomab therapy, several factors affect clearance of the antibody, including tumour size, splenomegaly and bone marrow involvement leading to a wide variation in effective half-life of the radioactive product.[26] Thus, the dosimetry scans are used to determine the appropriate dose of ^{131}I to be bound with 35mg of tositumomab, specifically calculated to deliver a target dose of 75 cGy total body exposure (65 cGy if the platelets are between 100,000 and 149,000/ mm^3) to the individual patient. For therapy with ^{90}Y -ibritumomab tiuxetan, a weight-based fixed dose of 0.4 mCi/kg, to a maximum of 32 mCi, is delivered to the patient (0.3 mCi/kg if platelets are between 100,000 and 149,000/ mm^3).

Given the potential for thyroid toxicity when using ^{131}I -tositumomab, the thyroid protective agent saturated solution of potassium iodide (SSKI) should be administered, beginning at least 24 hours prior to administration of the dosimetry dose and continued until 2 weeks after administration of the therapeutic dose.

The most common toxicity for both radioisotopes is myelosuppression, somewhat delayed, with thrombocytopenia and neutropenia usually beginning two to three weeks following the therapeutic dose, remaining low for several weeks and baseline levels being recovered after two to three months.[29] Pre-treatment bone marrow involvement with lymphoma is a good predictor of advanced grade haematological toxicity. Non-haematological toxicities are fairly uncommon and usually minor.

USE OF RADIOIMMUNOTHERAPY IN LYMPHOMA

I. Background

Both ^{131}I -tositumomab and ^{90}Y -ibritumomab tiuxetan were initially studied in Phase I/II trials in the setting of relapsed or refractory low-grade NHL, followed by Phase III trials in the same setting, with additional studies as frontline therapy and as consolidation of first remission for low-grade NHL. The initial Phase I/II trial of ^{131}I -tositumomab in relapsed/refractory low-grade NHL[30, 31] defined its maximum tolerated dose (MTD) at 75 Gy for pre-stem cell transplant patients and 45 Gy for post-stem cell transplant patients. The pivotal trial [33] reported a 65% response rate for ^{131}I -tositumomab in patients with chemotherapy-refractory low-grade or transformed NHL with median duration of response of 6.5 months. In patients with indolent or transformed B-cell lymphoma who had progressive disease after rituximab [34], ^{131}I -tositumomab yielded a response rate (RR) of 65% and median progression-free survival (PFS) of 10.4 months. The MTD for ^{90}Y -ibritumomab tiuxetan in patients with relapsed/refractory lymphoma was 0.4mCi/kg (maximum 32 mCi) for patients with a platelet count of $\geq 150,000/\text{mm}^3$ and 0.3 mCi/kg for patients with platelet counts 100,000 - 149,999/ mm^3 . [35, 36] Response rates were 67%, though none of the three patients with mantle-cell lymphoma responded. The phase III pivotal trial [37] randomized rituximab-naïve patients with relapsed or refractory low-grade, follicular or transformed NHL to receive either four weekly doses of rituximab or ^{90}Y -ibritumomab tiuxetan. Overall response rate and CR rate were higher for the ^{90}Y -ibritumomab tiuxetan group. A retrospective analysis of four trials revealed that earlier use of ^{90}Y -ibritumomab tiuxetan was more effective. [38].

RIT as frontline therapy for indolent NHL has yielded promising results in selected patient populations [39,40] [41]. An alternative strategy is to use RIT to consolidate first remission. In follicular lymphoma, Phase 2 data of CHOP followed by ^{131}I -tositumomab was promising [42]. The randomized trial of R-CHOP compared to CHOP followed by ^{131}I -tositumomab demonstrated similar excellent results for both arms [43]. Consolidation with ^{90}Y -ibritumomab tiuxetan after various first line therapies in advanced stage follicular lymphoma prolonged PFS compared to no further treatment [44].

Thus, RIT is active against relapsed or refractory indolent or transformed lymphoma, in consolidating first remission of follicular lymphoma, and as initial therapy alone in selected patients with indolent lymphoma. MCL is a heterogeneous disease, often termed an aggressive lymphoma in the U.S., but included in indolent lymphoma trials in Europe. Given its incurability with standard immuno-chemotherapy, and its radiation sensitivity, it is reasonable to assess efficacy of RIT in MCL.

II. Radioimmunotherapy for Mantle Cell Lymphoma

Efficacy data for RIT in MCL are limited. Wang *et al* reported a phase II trial [45] of the safety and efficacy of ^{90}Y -ibritumomab tiuxetan in patients with refractory or relapsed MCL who met standard criteria for RIT, including platelets $\geq 100,000/\text{mm}^3$. The thirty-five enrolled patients, thirty-four of whom received ^{90}Y -ibritumomab tiuxetan, had a median of three (range one to six) prior chemotherapy regimens, with 22 having had previously received HyperCVAD/MA and thirty-two prior rituximab. ORR was 67%. Bulky disease (≥ 5 cm), more than 2 prior therapies and previous Hyper-CVAD were all negative predictors of response. With median follow-up of 22 months, median OS was 21 months and median event-free survival (EFS) was 6 months. EFS duration was longer for responders (28 *vs.* 3 months; $p < 0.0001$), for those with a tumour measuring less than 5cm (9 *vs.* 3 months; $p = 0.015$), and for those who had relapsed from prior CR as opposed to those not achieving CR after their last regimen (11 *vs.* 3 months; $p = 0.0005$).

In this trial, as for ^{90}Y -ibritumomab tiuxetan in other settings, toxicity was primarily haematologic, transient, and reversible. Grade 3/4 thrombocytopenia in 24% of the patients and grade 3/4 neutropenia in 32. One patient developed neutropenic fever. Two patients developed myelodysplastic syndrome (MDS) 20 and 48 months after receiving therapy and remained alive 33 and 72 months, respectively, after study entry.

This study demonstrated that ^{90}Y -ibritumomab tiuxetan has clinical activity in heavily pretreated patients with relapsed or refractory MCL, with a favorable safety profile, although remission durations were disappointing. This study raised the possibility of novel strategies for incorporating RIT into treatment regimens for MCL. Potential approaches to combining RIT with systemic chemotherapy are summarized in Table 2.

Zelenetz *et al* [46] tested the use of sequential RIT with ^{131}I -tositumomab followed by CHOP chemotherapy for patients with newly diagnosed advanced stage (III/IV) MCL with $< 25\%$ bone marrow involvement by lymphoma who were not eligible for, or were unwilling to undergo, high-dose chemotherapy with stem cell support. Twenty-five patients were enrolled and twenty-four were treated with the therapeutic dose of RIT. The ORR to RIT was 83% (CR/CRu 46%; PR 38%). Twenty-one patients continued to consolidation with CHOP and after completion of therapy the ORR was 86% (CR/CRu 67%, PR 19%). With a median follow-up of 2.1 years, median EFS was 1.4 years. Median OS was not reached, and OS at 2.1 years was 92%. These data indicate a much higher response rate when RIT is used as initial therapy then in the heavily pre-treated relapsed setting.

Patients were evaluated for minimal residual disease (MRD) following RIT and following consolidation with CHOP by a clonotypic PCR method. Of the 17 patients with informative results, 6 patients were molecularly negative in both bone marrow and peripheral blood following RIT. Despite the increase in clinical CR following consolidation with CHOP, there was no increase in the number of molecular responses in this small group. Again, in this trial the most common toxicities were haematologic with typical time course for cytopenias. At least 35% of treated patients developed HAMA, most before initiating consolidation chemotherapy..

These data are encouraging in the high response rate to RIT as initial therapy for MCL. Unfortunately, even followed by chemotherapy, this did not translate into durable remissions. Further, CHOP did not reduce MRD in patients initially treated with RIT, and RIT prior to chemotherapy induced development of HAMA in a significant percentage of patients. Given that frontline RIT use [46] yields higher response rates, including CR, than in relapsed disease[45], and the data that earlier use of RIT results in higher response rates [38], it is logical to consider RIT consolidation of first remission of MCL.

The ECOG trial E1499 tested the hypothesis that R-CHOP for four cycles would cytoreduce MCL disease burden in a high percentage of patients who could then receive RIT to consolidate the remission, and that this brief treatment would be effective and well-tolerated even in the typical older patient with MCL.[47] In this trial, patients with newly diagnosed stage II-IV MCL (CD20+; cyclin D1+) received only 4 cycles of R-CHOP chemotherapy followed by consolidation with the standard therapeutic regimen of ⁹⁰Y-ibritumomab tiuxetan. The primary endpoint of this study was a 50% increase in the 1.5 year time-to-treatment-failure (TTF) rate, when compared to historical controls receiving R-CHOP for 6 cycles. Data from this study reveal that four cycles of R-CHOP led to high overall response rates, though only 37% CR, in previously untreated patients with MCL. Consolidation with ⁹⁰Y-ibritumomab tiuxetan improved both overall and complete response rates, converting some partial responses into complete responses. No unexpected toxicity was observed with ⁹⁰Y-ibritumomab tiuxetan administered shortly after 4 cycles of R-CHOP. There were theoretic concerns that circulating rituximab might lead to prolonged RIT exposure and excess toxicity, as well as compromising efficacy by blocking radiolabelled antibody access to CD20 on lymphoma cells. Such blocking effect has been demonstrated in mouse models [48], but not in clinical situations. RIT consolidation did improve response rates, though perhaps we cannot be sure that effects would have been better in the absence of circulating rituximab. The study met its primary endpoint of improved 18 month TTF, and updated data[49] shows a 2.5 year median PFS among all patients in this study using this 5 month well-tolerated regimen.

III – RIT-based stem cell transplant regimens for MCL

High-dose chemotherapy (HDC), either alone or combined with total body irradiation therapy (TBI), followed by stem cell/bone marrow support (SCT) is curative in 10-50% of relapsed NHL, but there is a 40-80% rate of post-transplant relapse and 5-20% of patients, depending on stem cell source, die from transplant-related complications.[50, 51]. As lymphomas are radiosensitive, an effective component of several transplant conditioning regimens for patients with NHL is external beam TBI. However, standard TBI delivers as much radiation to normal organs as it does to tumour sites, limiting safely administered TBI doses to 12-15.75 Gy. Escalating the dose of radiation therapy becomes prohibitive due to unacceptable morbidity and mortality.[52] The concept of using high dose targeted radiation in the form of RIT, whose dose-limiting toxicity is myelosuppression, to replace the non-specificity and normal organ toxicity of TBI becomes an attractive transplant conditioning strategy. Delivering large doses of radiation therapy directly to tumour sites with high-dose RIT might avoid prohibitive side effects to normal tissues and improve the therapeutic

window. Phase I/II trials of high-dose RIT, with or without chemotherapy, as a conditioning regimen for B-cell NHL prior to autologous stem cell transplant estimated that critical normal organs can receive up to 27 Gy radiation using single agent ^{131}I -tositumomab, with minimal non-hematological toxicity.[53, 54]. When combined with chemotherapy (etoposide 60mg/kg and cyclophosphamide 100 mg/kg) the MTD of radiation delivered to normal organs with ^{131}I -tositumomab is 25Gy.[55]

Based on these results, Gopal *et al* [56] have reported on the use of high-dose chemo-RIT with autologous stem cell support. They have retrospectively analyzed their data for patients with relapsed mantle cell lymphoma treated in these dose-escalation studies. Eligible patients were adults younger than 60 years of age, with CD20+ relapsed or refractory B-cell NHL, preserved bone marrow function (<25% involvement) and absence of HAMA. Patients could not have splenomegaly or a calculated total tumour burden > 500 cm³ as assessed by CT scan as the experience of these investigators was that such patients do not respond well to RIT. Patients initially received a biodistribution dose of tositumomab 1.7 mg/kg trace labeled with ^{131}I (5-10 mCi [185-370 MBq]) and then had serial gamma camera imaging to calculate the absorbed radiation dose to normal organs and whole body. A therapeutic dose of ^{131}I -tositumomab calculated to achieve a target dose of 25 Gy to the normal organ receiving the highest dose of radiation, as defined by the biodistribution studies, was administered 14 days after the dosimetry dose. After a median of 10 days of radiation isolation (range 8-13 days) patients received high-dose etoposide, followed two days later by high-dose cyclophosphamide. When radiation exposure was less than 0.02 mSv/hour (2 mR/hour) at 1 meter, autologous blood stem cells were infused.

Their patient cohort included sixteen patients with MCL, all had stage IV disease and median age was 54 years. Eight had high or high-intermediate age-adjusted IPI. Of these sixteen MCL patients, two received a lower dose of radiation (23 Gy and 20 Gy) and four received a lower dose of chemotherapy (etoposide 30 mg/kg; cyclophosphamide 60 mg/kg). There were no unexpected grade III/IV toxicities and no study related mortality. After the conditioning regimen, 11 patients had disease evaluable for radiographic response, while 5 had only minimal radiographic disease or molecular evidence of disease. All patients with MRD after conditioning remained progression-free at a median follow-up of 19 months. Of the 11 patients that had radiographic evidence of disease following conditioning, 8 (73%) achieved a CR, 1 (9%) had a PR and 2 did not respond to transplant, but remained progression-free at the 1-month post ASCT evaluation. Both patients who did not respond initially eventually did achieve CR, at 3 months and 1 year following ASCT respectively. The estimated 3-year OS, with 19 month median follow-up since transplantation (range 6-57 months), was 93% and the estimated 3-year PFS was 61%.

The same group reported outcomes in MCL patients older than 60 years for high-dose RIT with ^{131}I -tositumomab alone, without chemotherapy, followed by autologous SCT. Because of excessive treatment related toxicity, older patients are often felt not to be candidates for HDC/ASCT. High-dose RIT alone followed by ASCT appears to be better tolerated than standard chemoradiation conditioning regimens with TBI. Gopal *et al* studied the safety and efficacy of high-dose RIT and ASCT in patients aged 60-80 years with CD20+ MCL.[57] Again, in this trial, patients had low tumour burden (<500 cm³, no splenomegaly) and good bone marrow function (<25% lymphoma involvement). Eight patients with relapsed/refractory MCL received a calculated therapeutic dose of ^{131}I -tositumomab of up to 27 Gy of radiation to the most adsorbent critical normal organ. Fourteen days after the therapeutic dose of ^{131}I -tositumomab, patients received autologous blood stem cell support. Of the eight patients, all had stage III/IV disease and 7 (88%) were resistant to previous chemotherapy. Patients had a median of 4 previous treatment regimens (range 3-5). After a median follow-

up of 1.2 years, there were no treatment-related deaths and no unexpected grade IV toxicity. Six of the eight(75%) were alive and 3 (38%) were alive and progression free.

For ^{90}Y -ibritumomab tiuxetan, a Phase I trial [58] of escalated dose RIT followed by high dose chemotherapy with carmustine, etoposide, cytarabine and melphalan (BEAM) and autologous blood stem-cell support determined the maximum-tolerated radiation-absorbed dose (RAD) to critical organs as 15 Gy. Of forty-four patients with refractory or relapsed CD 20+ NHL, 7 (16%) had MCL. Of the entire cohort, 75% had previously received rituximab and 16% prior radiation. Patients not responding to salvage therapy were eligible, with 30% achieving less than a PR to the most recent treatment. Patients received ^{90}Y -ibritumomab tiuxetan calculated by dosimetry to deliver a cohort-defined RAD to critical organs (range 1-17 Gy), rather than a fixed weight-based approach, given substantial patient to patient variability of antibody biodistribution. RIT was followed by high-dose BEAM chemotherapy and autologous blood stem cell support. Among the 29 (66%) patients with active disease at study entry, 11 achieved CR and 6 achieved PR after protocol treatment. With a median follow-up of 33 months, the estimated 3-year PFS and OS were 43% and 60% respectively. Median TTP was 20 months. Patients in CR at study entry presented a favorable trend (3-year PFS, 53% vs. 38% $p=0.41$; 3-year OS, 79% vs. 50% $p=0.09$). There were no significant differences in PFS or OS when outcomes were analyzed according to histologic subtype.

The current data for RIT with autologous stem cell support in MCL are encouraging. There is a rationale for developing non-myeloablative treatments with RIT followed by allogeneic stem cell transplant, given that the presence of the allograft might sustain longer remissions due to a graft-versus-lymphoma (GVL) effect. Further studies with adequate doses of radiation and long term outcomes with both autologous and allogeneic stem cell transplantation are warranted.

SUMMARY AND RECOMMENDATIONS

Mantle cell lymphoma continues to be a therapeutic challenge. While there are several new and exciting molecularly targeted therapeutic interventions being studied in this disease, MCL is quite radiosensitive and this modality can be integrated with other novel therapeutics. RIT allows targeting this effective modality with ease of administration and predictable and manageable haematologic toxicity and minimal non-haematologic toxicity. RIT has provided encouraging response rates as a single agent in both upfront[46, 47, 49] and relapsed/refractory[45, 56] settings. The evidence that RIT might improve responses and treat MRD when used as consolidation after first-line chemotherapy in MCL, as in indolent lymphoma[43], is encouraging. Further studies are warranted to better establish its efficacy, compared either against or in addition to standard of care therapies such as maintenance rituximab. In the stem cell transplant realm, it has been shown that RIT can be administered safely as an effective single agent (including patients ≥ 60 years)[57] and in combination with high-dose chemotherapy (for patients < 60 years)[56] as conditioning regimen for autologous SCT, with evidence suggesting ability to overcome chemotherapy resistance. Further studies with RIT followed by allogeneic SCT are reasonable to explore the possibility of RIT reducing the burden of MRD to a point where GVL effect could be curative.

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Practice Points

Standard radio-immunotherapy (RIT) is active in MCL as a single agent, though not approved specifically for this indication.

Optimal incorporation of RIT into MCL therapy remains to be determined, but use to consolidate remission and as part of a conditioning regimen for stem cell transplant are active areas of investigation.

Research Agenda

As rituximab maintenance therapy becomes more widely used, investigation of radio-immunotherapy (RIT) consolidation of remission instead of, or in addition to, rituximab.

As bendamustine-rituximab (BR) becomes a more common induction regimen for MCL, to document safety of RIT after BR as has been done for R-CHOP.

Investigation of RIT as a replacement for total body irradiation in stem cell transplant regimens.

Table 1

Comparison of Yttrium-90-ibritumomab tiuxetan to Iodine-131-tositumomab

US Trade Name	⁹⁰ Y-ibritumomab tiuxetan	¹³¹ I-tositumomab
Parent Antibody (murine)	IDEC-2B8/ibritumomab	Anti-B1/tositumomab
Radionuclide	Yttrium-90	Iodine-131
Antibody (unlabeled)	Rituximab (chimeric)	Anti-B1 (murine)
Antibody (dosimetry)	Not necessary, weight based fixed dosing	¹³¹ I-anti B1
Antibody (imaging/biodistribution)	¹¹¹ In-ibritumomab No longer required in U.S.	¹³¹ I-anti B1
Emission	Pure β -emitter	β - and γ - emitter
Radiation Penetration	5-10 mm	1-3 mm
Half-life	2.7 days	8.1 days
Dosimetry required	No	Yes
Imaging required	No, including U.S.	Yes
Urinary excretion	7.2% / 7days	67% / 5 days (variable)

Table 2

Pros and Cons of potential strategies to combine RIT with chemotherapy

Strategy	Pros	Cons
Chemotherapy followed by RIT	- RIT may be used for minimal residual disease (MRD)	- Poor tumour vasculature following chemotherapy might limit the access of RIT to lymphoma cells
RIT followed by Chemotherapy	-Enhanced crossfire RIT activity - Intact tumour vasculature for potentially better tumour penetration by RIT.	- Patients more likely to develop HAMA (especially with tositumomab) - Bone marrow involvement by lymphoma limits patient eligibility for RIT
Concurrent RIT and Chemotherapy	- Possible synergistic activity	-Possible synergistic toxicities; might require stem cell support