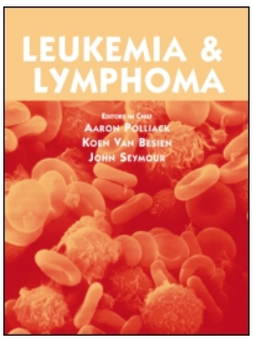

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Consolidation with ^{90}Y ibritumomab tiuxetan radioimmunotherapy in mantle cell lymphoma patients ineligible for high dose therapy: results of the phase II multicentre Polish Lymphoma Research Group trial, after 8-year long follow-up

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Consolidation with ^{90}Y ibritumomab tiuxetan radioimmunotherapy in mantle cell lymphoma patients ineligible for high dose therapy: results of the phase II multicentre Polish Lymphoma Research Group trial, after 8-year long follow-up

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ABSTRACT

Polish Lymphoma Research Group performed a phase-II trial to test whether ^{90}Y ibritumomab tiuxetan radioimmunotherapy (Y90) may constitute an alternative consolidation for mantle cell lymphoma patients unfit for high-dose therapy. Forty-six patients were consolidated with Y90 following response to the 1st ($n = 34$) or 2nd line ($n = 12$) (immuno)chemotherapy. Majority of the patients had advanced disease (stage IV and presence of B-symptoms in 85% and 70%, respectively) and high MIPI (5.8, range 4–7). Consolidation with Y90 increased the complete remission (CR) rate obtained by the 1st line therapy from 41% to 91% and allowed for median PFS of 3.3 and OS of 6.5 years. In the first relapse, CR rate increased from 16% to 75%, while median PFS and OS totaled 2.2 and 6.5 years, respectively. At 8 years, 30% of patients, consolidated in the 1st line CR were alive, without relapse. Toxicity associated with Y90 is manageable, more severe after fludarabine-based regimens.

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Mantle cell lymphoma; radioimmunotherapy; ibritumomab tiuxetan

Introduction

Mantle cell lymphoma (MCL) is a relatively common (4–7%) non-Hodgkin lymphoma (NHL) subtype that has distinct clinical and diagnostic features [1,2]. The majority of patients are elderly males, over 60 years of age, with a generalized disease involving lymph nodes, spleen, bone marrow, and peripheral blood. MCL prognosis is uncertain with a limited number of patients surviving >5 years [3]. Induction immunochemotherapy followed – wherever feasible – by autologous stem cell (ASCT) consolidation and/or Rituximab maintenance is the current standard of care [4–6]. At relapse, targeted therapy agents interacting with intracellular pathways (ibrutinib, bortezomib, temsirolimus) or immunomodulatory drugs (lenalidomide) have been approved. Allogeneic stem cell transplantation may also be considered in younger patients.

Achieving a complete response (CR) and long progression-free survival (PFS) is the target of the first line therapy, as relapsed MCL often becomes refractory to cytostatics. Advanced age and comorbidities limit the use of intensive treatment regimens; for some of MCL patients, even 6-8 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine) or R-B (rituximab, bendamustine) may not be feasible [7,8]. Therefore, Polish Lymphoma Research Group (PLRG) completed a phase-II trial investigating the efficacy of induction followed by radioimmunotherapy (RIT) consolidation in responding patients.

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Methods

Trial protocol

In 2005, PLRG initiated a phase-II multicentre prospective study in patients with advanced (clinical stage III–IV) MCL, chemo-sensitive to 1st or 2nd line therapy, not eligible for ASCT or not willing to be subjected to it. Patients responding to induction were consolidated with Ibritumomab tiuxetan (Zevalin – a ^{90}Y labeled anti-CD20 monoclonal antibody). Recruitment was completed in 2009 ($n = 46$), with median observation time of 4.6 years (range 0.4–12 years). Feasibility of the regimen (adverse events analysis) and complete response rate analysis after RIT were the primary targets of the study, while progression-free and overall survival (PFS & OS) constituted the secondary targets. The study was approved by the local Ethics Committees of all of the participating centers. A written informed consent was obtained from patients enrolled onto the trial.

We postulated that RIT consolidation would be feasible in patients without intensive bone marrow infiltration and efficient in those with an adequate tumor burden reduction. The protocol allowed for the shortening of chemotherapy in responding patients, but excluded cases refractory to initial treatment (Figure 1). Response to the induction therapy was assessed after 3rd and every successive cycle. RIT consolidation was performed in all patients with a confirmed reduction of the maximal lymph node diameter to <3 cm, the longest spleen measurement to <15 cm and bone marrow infiltration to $<20\%$.

The details of chemotherapy induction regimens were as follows: CVP (Cyclophosphamide–750 mg/m^2, Vincristine 1.4 mg/m^2–max 2 mg, Prednisone 60–100 mg in day 1–5), CHOP (Cyclophosphamide–750 mg/m^2, Doxorubicin–50 mg/m^2, Vincristine1.4 mg/m^2–max 2 mg, Prednisone 60–100 mg on day 1–5), FC (Fludarabine 25 mg/m^2 on day 1–3, Cyclophosphamide –250 mg/m^2 on day 1–3), FCM (Fludarabine 25 mg/m^2 on day 1–3, Cyclophosphamide–250 mg/m^2 on day 1–3, Mithoxanthrone–12.5 mg/m^2 – day 1). Rituximab (R) was not regarded a standard of care at the time, so it was given based on availability basis, on day 1 of every cycle at the dose of 375 mg/m^2 in 27/46 (58.5%) of the cases. None of the patients were subjected to R maintenance.

RIT consolidation was scheduled 3–5 weeks after the preceding chemotherapy cycle, with the possibility of a further 3-week delay, delivering a "bridging" dose of rituximab (375 mg/m^2) to cytopaenic patients. The RIT procedure consisted of two doses of rituximab at 250 mg/m^2, administered 7 days and 24 h prior to intravenous injection of ^{90}Y-labeled Ibritumomab tiuxetan (Y90). The actual dose was of 0.4 mCi/kg (14.8 MBq per kg) for patients with normal platelet count and 0.3 mCi/kg (11.1 MBq per kg) for those with platelet count between 100,000 and 150,000 cells/mm^3. The maximum dose of Y90 was that of 32.0 mCi (1184 MBq).

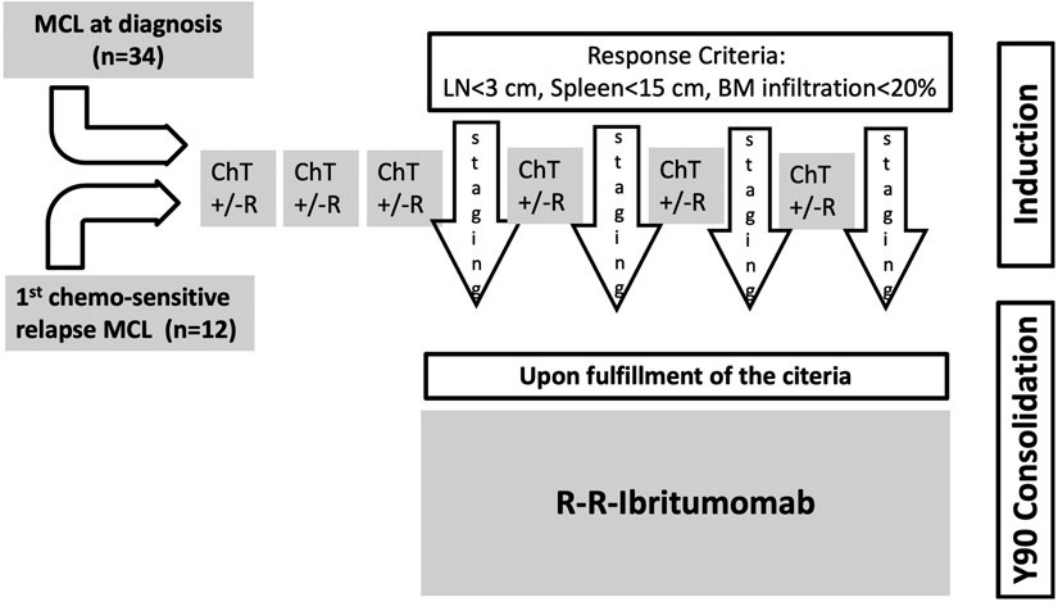

Figure 1. Study protocol.

Patient assessment (medical history, physical examination, CT scans, bone marrow aspirates, trephine biopsy and blood tests) were performed at the study entry, after the 3rd cycle, before RIT procedure and 6 weeks after its completion. During cytopenias after RIT, full blood count analysis was performed twice a week, until recovery. Adverse events were reported according to CTCAE version 3.0. We used International Working Group response criteria [9] to assess response to therapy. The follow-up was based medical history, physical examination and CT scans performed at 3 months intervals for the consecutive 2 years, and once a year thereafter.

Patients

Forty-six patients completed the entire protocol: 34 were consolidated upon completion of the 1st line therapy, whist 12 were subjected to RIT in the first relapse. The study was not planned as an intend to treat analysis – 5 additional patients, not subjected to radio-immunotherapy were not analyzed further. One of them remained thrombocytopenic after the 1st line FCM regimen, 4 others did not achieve required response to the 2nd line therapy.

Patients' demographics and clinical characteristics at diagnosis are shown in Table 1. The median age was 60 (range 30–78). Out of three younger patients enrolled, two had severe cardiovascular disorders (one myocardial infarction and one unstable angina requiring cardiovascular surgery) and one did not agree to ASCT due to religious beliefs. Majority of patients had classical features of advanced disease in clinical stage III/IV – they presented with intermediate or high risk according to MIPI (32.6 and 28.4% respectively), extra-nodal disease (87%), general symptoms (70%) and elevated LDH. Per protocol, patients with central nervous system involvement, other neoplastic disorders, active infections and previous radiotherapy were excluded.

Table 1. Patients' characteristics.

Characteristic	Number of cases ($n = 46$)
Median age	60 years (range 30–78)
Male gender	32 (70%)
MIPI	5.8 (range 4–7)
Low risk	18 (39%)
Intermediate risk	15 (32.6%)
High risk	13 (28.4%)
Clinical stage IV	39 (85%)
Maximum nodal mass >10 cm	3 (6.5%)
Extra-nodal disease	40 (87%)
Bone marrow involvement	19 (41%)
Splenomegaly	7 (15%)
B-symptoms	32 (70%)
LDH – elevated	33 (71%)

Statistical analysis

Statistical analysis was performed using the Statistica software (version 8.0). In order to compare the response before and after RIT, Chi-square test with Fisher's amendment was used. Adverse events (AE) were assessed using descriptive statistic methods. Survival analysis was evaluated by the Kaplan–Meier method, using log-rank test for comparison. Both overall survival (OS) and progression free survival (PFS) were calculated from the date of RIT procedure until death of any cause and death of any cause or disease progression/relapse respectively.

Results

The 1st line induction treatment with fludarabine-based regimens (FCM/FC ± R) were administered to 20 individuals, while CHOP/CVP ± R to 14 patients. Response rates were comparable for both regimens: 14 patients (41%) achieved CR and 20 (59%) partial remission (PR). In a relapsed cohort, CHOP/CVP ± R combination was used in 11/12 cases, as all 12 patients received FC or FMC as 1st line treatment. Only 2 patients (17%) achieved CR and 10 patients (83%) – PR (Figure 2). Table 2 shows details of treatment received, and responses obtained by the patients prior to RIT consolidation.

Response to consolidation RIT of chemo-sensitive patients was the study primary endpoint. In the 1st line induction RIT consolidation improved the CR rate from 41% (14/34) to 91% (31/34) (Figure 2). CRs were obtained in 13/14 (93%) of patients treated with CHOP/CVP and in 18/20 (90%) of those who received a fludarabine-based chemotherapy. In the relapsed setting, the relatively low CR rate of 16% (2/12) after initial (immuno)-chemotherapy was increased to 75% (9/12) after RIT (Figure 2). Neither the choice of chemotherapy regimen nor the administration of Rituximab had an impact on the CR rates achieved after radio-immunotherapy consolidation.

Median PFS of all patients consolidated after 1st line of therapy was 3.3 years, compared to 1.8 years ($p < .05$) after chemo-sensitive relapse. The corresponding median OS times were found to be 6.5 years and 2.2 years, respectively ($p < .05$) (Figure 3). Encouraging results were obtained in patients achieving CR after the 1st line therapy – RIT consolidation allowed for median PFS of 5.8 years. Survival analysis demonstrated that the specific chemotherapy regimen used, as well as the addition of rituximab to it prior to RIT consolidation did not influence the outcomes in terms of both PFS and OS. Twenty-six patients died in

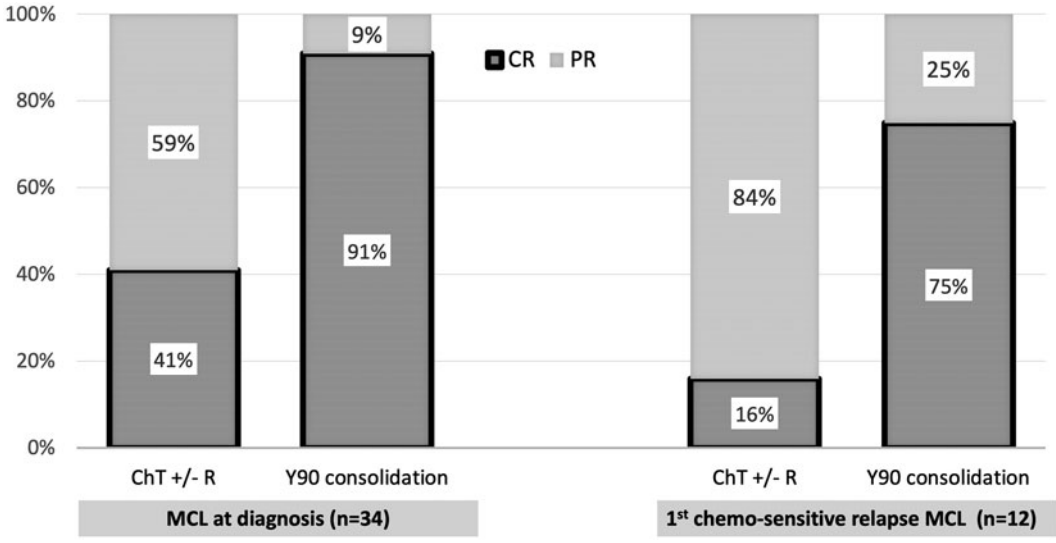

Figure 2. Response rates obtained after 1st line or post-relapse induction and Y90 consolidation.

Table 2. Treatment regimens and response to 1st and 2nd line treatment.

Chemotherapy	Number of patients (Chemo + R)	Median number of cycles (range)	PR (Chemo + R)	% PR	CR (Chemo + R)	% CR
1st line treatment						
FC/FMC	20 (12)	4 (3–9)	12 (8)	60%	8 (4)	40%
CHOP/CVP	14 (9)	6 (3–7)	8 (5)	57%	6 (4)	43%
Total	34 (21)	5 (3–9)	20 (13)	59%	14 (8)	41%
2nd line treatment in chemo-sensitive relapse patients						
FC/FMC	1 (1)	4	1 (1)	100%	0	0%
CHOP/CVP	11 (6)	6 (5–10)	9 (5)	82%	2 (1)	18%
Total	12 (7)	6 (4–10)	10 (6)	83%	2 (1)	17%
All consolidated patients						
FC/FMC	21 (13)	4 (3–9)	13 (9)	62%	8 (4)	38%
CHOP/CVP	25 (15)	6 (3–10)	17 (10)	68%	8 (5)	32%
Total	46 (28)	6 (3–10)	30 (19)	65%	16 (9)	35%

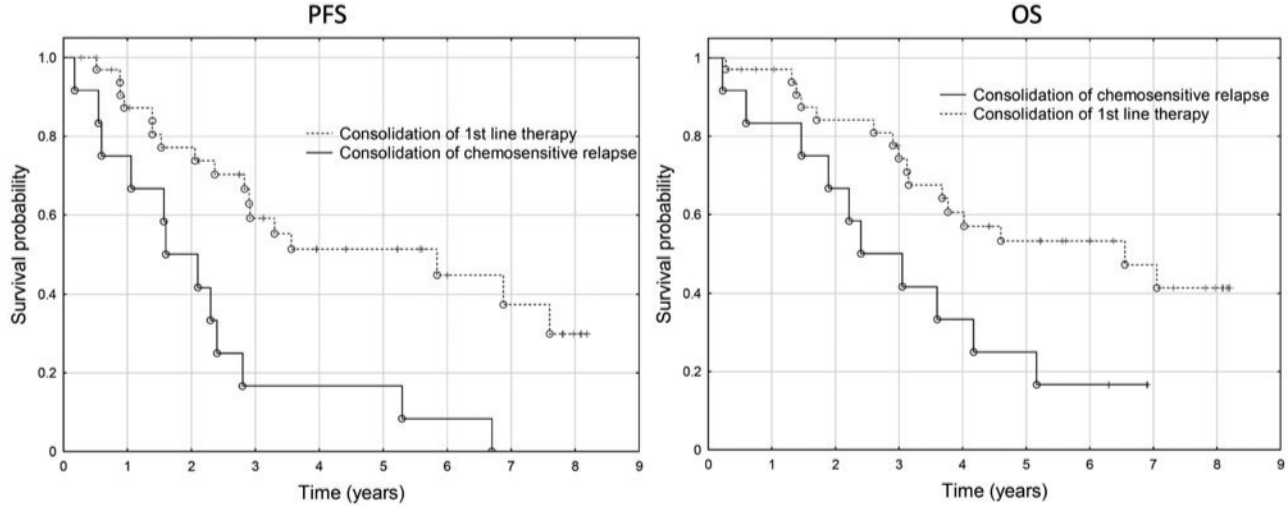

Figure 3. PFS and OS Kaplan-Meier survival curves.

Table 3. Toxicity of Y90 consolidation.

	Grade 3-4 adverse events				Lethal adverse events			
	FC/FCM ($n = 19$)		CHOP/CVP ($n = 25$)		FC/FCM ($n = 19$)		CHOP/CVP ($n = 25$)	
Adverse effect	N	%	N	%	N	%	N	%
Hematological								
Leukopenia	12	63.2	3	12.0	–	–	–	–
Neutropenia	12	63.2	3	12.0	–	–	–	–
Thrombocytopenia	10	52.6	2	8.0	2	10.5	–	–
Anemia	7	36.8	0	0.0	–	–	–	–
Infective								
Upper airways/lung infections	1	5.3	1	4.0	–	–	–	–
Fever	2	10.5	1	4.0	–	–	–	–
Secondary neoplasia								
Myelodysplasia	–	–	–	–	4	21.1	1 (*)	4.0

*Patient previously consolidated with ASCT.

the course of the study: 2 (4.3%) of early complications, 5 (10.8%) after developing myelodysplastic syndrome and 16 (38%) due to MCL relapse/progression.

The entire protocol was well tolerated. We have encountered no unknown adverse effects (AE) during and after the treatment with ^{90}Y (Table 3). As largely expected, most patients experienced bone marrow toxicity in the form of cytopaenias: 19 (43%) of grade 1–2 and 15 (34%) of grade 3–4. The onset of thrombocytopenia and neutropenia was delayed compared to chemotherapy, it usually begun 3–4 weeks after administration of ibritumomab tiuxetan, lasting 3.7 (range 0–12) and 2.9 (range 0–15) weeks, respectively. Their severity was proportional to BM infiltration with CD20 positive cells, and chemotherapy regimen proceeding RIT. Grade 3–4 thrombocytopenia and leukopenia were more frequent in patients treated with fludarabine based regimens (63.2 vs 12% and 63.2 vs 12% respectively, $p < .05$). Thrombocytopaenia after FCM/FC lasted longer (median time – 7.2 vs 1.0 weeks, $p < .05$) and required more platelet transfusions (50 vs 15% respectively, $p < .05$). In two patients consolidated with RIT after FCM regimen induction, prolonged thrombocytopaenia was the cause of death (due to hemorrhagic strokes at day +80 and +62). Twenty-two (48%) patients developed infections following treatment with ^{90}Y, none of them were life threatening, however, 5/22, all treated with fludarabine-based regimens, required hospital admittance. Five patients developed MDS in the course of the disease with the median onset time of 26 (10–38) months. The diagnosis of MDS was confirmed by histopathological analysis and complex karyotypes abnormalities in 4/5 cases. None of the patients, who developed MDS, was treated with CHOP/CVP chemotherapy plus ^{90}Y only. Indeed, four received FCM regimens, while the remaining one was subjected to a prior ASCT procedure.

Discussion

Historically, MCL is regarded as a malignancy with poor overall prognosis. High response rates achieved with standard lymphoma immuno-chemotherapy are rarely durable [3]. Intensification of therapy with ASCT consolidation, feasible in younger patients without disabling comorbidities, has clearly improved PFS, but is far from constituting a cure for MCL. For the majority of MCL patients, eight cycles of R-CHOP or six cycles of BR induction immunochemotherapy followed by Rituximab maintenance are regarded the standard of care [8]. Here, we report the results of a phase-II multicentre study in which MCL patients responding to induction regimens were consolidated with Y90 that improved response rates, OS and PFS. Although RIT consolidation was not offered to refractory cases, the same principle is true in the transplant setting. Moreover, median age and other risk factor distribution in the cohort enrolled onto PLRG trial mirrored a typical elderly MCL population and were worse than usually found in ASCT consolidated cases. The same regimen was also tested in the cohort of relapsing patients responding to the 2nd line therapy.

We have previously demonstrated the importance of post-induction treatment in 279 MCL patients included in a retrospective study conducted by the PLRG [10]. The Kaplan–Meier survival curves of all three patient cohorts that underwent post-induction therapy (rituximab maintenance, ASCT or Y90 consolidation) clustered together and were clearly better than observed in patients who received only induction therapy. At 5 years, projected OS and PFS were 65 and 40% versus 20% and 0% respectively ($p = .0003$).

The intensive cytarabine-based (immuno)-chemotherapy followed by ASCT consolidation can be offered to 16–20% of all MCL patients [11], usually those with lesser risk according to MCL international

prognostic index (MIPI) compared to scores frequently encountered in the elderly population. Neither Y90 nor ASCT consolidation has ever been challenged against R-CHOP with R maintenance in the randomized trial, were patients were stratified according to MIPI – the only randomized data in favor of the transplant strategy derive from the results obtained with the since abandoned interferon maintenance [12]. RIT is a safe and effective therapeutic option for patients with indolent B-cell Non-Hodgkin lymphoma, in both *de novo* and relapsed/refractory setting [13]. It combines the specificity of a monoclonal antibody directed against CD20 B-cell surface marker with pure β-radiation of ^{90}Y. RIT has been applied in cases of follicular lymphoma (FL) (reviewed in [14]), diffuse large cell B-cell lymphoma (DLCBCL) [15–18], mantle cell lymphoma (reviewed in [19]) and even in Burkitt's lymphoma [20].

Recently, the Eastern Cooperative Oncology Group published the results of the E1499 phase-II study that assessed the efficacy of a consolidation strategy with Y90 after an initial therapy of four cycles of CHOP-R and compared the results with historical CHOP-R data [21]. Fifty-six patients were analyzed and the ORR was 82% (55% of CR and CR-unconfirmed), median time to treatment failure was 2.85 years and the estimated median 5 year-OS reached 79%. The results obtained with Y90 compared favorably with historical CHOP-R data. While, our data reported here, comprise a significantly longer follow-up, there are only 34 patients consolidated after the 1st line therapy. The better response rates (ORR–100%, CR–91%) and longer median PFS/OS (3.3 years and 6.5 years respectively) than in the E1499 study may be due to low patient numbers. In PLRG trial, there were no refractory patients in the cohort while only one patient was not subjected to RIT (therefore, per protocol not included in analysis) due to low blood platelet count after FCM regimen. Importantly, both trials constitute phase II multicentre studies and demonstrated efficacy of RIT used as a consolidation strategy.

Clearly, the results obtained in a cohort of patients ineligible for aggressive treatment have to be compared to the results of other therapeutic schemes used in such a scenario, such as R-CHOP or R-bendamustine with/out R maintenance in the responding patients. Kluin-Nelemans et al found that R-CHOP induction followed by maintenance therapy with rituximab is effective for older patients (median age 70 years) with mantle-cell lymphoma [22]. R-CHOP-responders, subjected to maintenance therapy with R obtained 4-year survival rate of 87%. Patients randomized to R-FC responded worse and their OS was significantly shorter than of those treated with R-CHOP (4-year survival rate, 47% vs. 62%; $p = .005$). Incidentally, also in this study the toxicity of fludarabine was noted [22]. Recently, a prospective, multicentre, phase II study evaluating rituximab, bendamustine, bortezomib and dexamethasone as first-line treatment for patients with mantle cell lymphoma aged 65 years or older was performed. A total of 74 patients were enrolled with a median age of 73 years. After a median follow-up of 52 months, the 2-year PSF rate was 70% [23]. In the PLSG study, the 2-year PFS for the patients consolidated in 1st line was comparable and equaled 75%.

The results of our study underline the significance of the time of RIT and the response obtained after debulking treatment. Consequently, patients that underwent RIT in CR of 1st line treatment fared better than the PR counterparts (median PFS 5.8 vs 2.8 years respectively). It was previously reported, that RIT in follicular lymphoma is effective if the maximum diameter of the enlarged lymph nodes is less than 5 cm [24]. As MCL is a clinically more aggressive lymphoma subtype, we took it even further – our protocol allowed for ibritumomab tiuxetan infusion only if the maximum diameter of the lymph nodes was less than 3 cm. However, patients with only a PR to proceeding chemotherapy had a shorter median PFS, advocating against the concept of shortening the induction regimen, unless CR could be obtained. Our results argue the case for the application of Y90 consolidation as soon as newly diagnosed patients enter into CR. Similarly, in ASCT consolidation, long-term outcomes depend on the response to preceding therapy, it being best in patients achieving minimum residual disease level after 1st line therapy [25].

Responses to (immuno)-chemotherapy in the cohort treated in the 1st relapse were worse: four patients were refractory (therefore not consolidated with RIT), majority achieved PR. CR rate increased from 2/12 to 9/12. The rationale for such a scenario is further corroborated by the reports on the use of Y90 in relapsing/refractory MCL cases. Weigert et al observed partial responses in two of six evaluable patients (33.3%), whilst in another patient the disease remained stable. Median PFS was 3.9 months in this high-risk group. It was concluded that patients with bulky disease did not respond to RIT [26]. In a phase-II study from the MD Anderson Centre the safety and efficacy of Y90 was tested in a group of 34 MCL patients with relapsed/refractory disease. Ten out of 34 (10%) patients achieved CR or PR, the median event-free

survival (EFS) of 6 months and OS duration of 21 months. Patients who responded displayed the median EFS of 28 months, whereas non-responders only 3 months [27]. In our group median PFS (1.8 years), very close to median OS (2.2. years), reflects both the efficacy of the protocol and bad prognosis once lymphoma relapses for the second time and becomes refractory. At the time the patients were treated Bruton kinase inhibitors, the current standard in R/R MCL, were not available.

The issue of haematological toxicity of RIT procedure after the shortened induction regimen was one of the primary targets of the study. Toxicities appeared manageable albeit worse in patients who received fludarabine-based regimen directly proceeding 90Y: two died as the effect of prolonged thrombocytopaenia and further four after they developed MDS. Indeed, fludarabine-based protocols are being progressively abandoned and this study provides a further evidence for the notion that they should be avoided. CHOP/CVP ± R treatments, instead, should clearly be recommended as induction regimens: none of the patients had grade 5 toxicity, whereas only one – relapsing after prior ASCT – developed MDS. The choice of chemotherapy regimen proved to be more important than the number of cycles (on the average patients received 4 FC/FCM and 6 CVP/CHOP cycles), therefore, the concept of shortened induction regiment is hard to defend. Given the net advantage observed in patients with better responses, we believe that the initial debulking is utmost important. The doses of RIT can hardly be modulated, thus, ideally, a patient that is to be subjected to RIT consolidation should have an adequate bone marrow reserve to limit the toxicity of the treatment.

In conclusion, RIT consolidation with Y90 in MCL following abbreviated (immuno)-chemotherapy appears to confer good response rates and PFS. It is feasible in elderly or unfit patients with comorbidities, ineligible for high-dose chemotherapy-ASCT. The achieved responses are durable. Although, several novel agents and targeted therapies alone or in combination are currently being studied and developed in both the upfront and relapsed settings, RIT constitutes a valid and underused option especially in the first line setting.

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Authors' contributions

Conception and design: WJ, PLZ; Provision of study materials or patients: WJ, DZC, AG, KK, MS, TW, WKP, EK; Acquisition, analysis, or interpretation of data for the work: All authors.

Data analysis and interpretation: WJ, AMG, ABS, AHD, PLZ; Manuscript writing: WJ, AMG with the help of all authors; Final approval of manuscript: All authors.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at https://doi.org/10.1080/10428194.2019.1602261.

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