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The necessity of post-induction therapy in mantle cell lymphoma patients: A multicenter retrospective real-world analysis by Polish Lymphoma Research Group (PLRG)

Potrzeba leczenia poindukcyjnego u pacjentów z chłoniakiem z komórek płaszcza – wieloośrodkowa, retrospektywna analiza danych z rejestru Polskiej Grupy Badawczej Chłoniaków (PLRG)

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Summary

Aim: Mantle cell lymphoma (MCL) patients have poor prognosis, due to development of chemo-resistance in relapsing patients. Therefore, despite the features of indolent lymphoma at presentation, consolidation and/or maintenance strategies to achieve minimal tumor burden and postpone subsequent relapses remain the standard of care.

Material/Methods: In the retrospective analysis of Polish Lymphoma Research Group (PLRG), post-induction strategies were assessed in 355 MCL patients. Those in complete or partial remission (CR or PR) after induction regimen (n = 263, 74.08%) were consolidated with autologous stem cell transplantation (ASCT) (n = 71, 20%) or radioimmunotherapy (RIT, n = 37, 10.42%), subjected to rituximab maintenance (MR, n = 17, 4.79%) or had none post-induction treatment (NPI, n = 138, 38.87%). Responses to therapy, progression and overall survival (PFS and OS) were compared.

Results: CR after induction was significantly increased by consolidation strategies, from 68% to 95% in ASCT and from 43% to 90% in RIT cohort. Median PFS in patients subjected to ASCT and RIT was significantly higher compared to NPI group (2.3, 3.8 and 1.8 years respectively, $p < 0.05$). Consolidation strategies also prolonged median OS (not reached in ASCT, 7.3 in RIT and 4 years in NPI cohort, $p < 0.005$).

Conclusions: Our data confirms the efficacy of ASCT consolidation in selected patients and demonstrates that RIT may be regarded as an alternative consolidation strategy for patients not eligible for ASCT. At the time the study was performed, there were few possibilities to retreat elderly and comorbid patients; therefore, despite PFS benefit of RIT, younger, transplanted patients experienced a longer median OS.

Keywords: **mantle cell lymphoma • consolidation therapy • ASCT • radioimmunotherapy**

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Abbreviations: **ASCT** – autologous stem cell transplantation, **BEAM** – carmustine, etoposide, cytarabine and melphalan regimen, **BR** – rituximab plus bendamustine, **BTK** – Bruton tyrosine kinase, **CR** – complete remission, **CVP** – cyclophosphamide, vincristine and prednisone, **GELTAMO** – Grupo Español de Linfomas y Transplante Autólogo de Médula Ósea, **HCVAD/MA** – hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methothrexat/cytarabine, **HDAC** – high-dose cytarabine, **LDH** – lactate dehydrogenase, **MCL** – mantle cell lymphoma, **MDACC** – MD Anderson Cancer Center, **MIPI** – Mantle Cell Lymphoma International Prognostic Index, **MRD** – minimal residual disease, **NPI** – none post-induction treatment, **OS** – overall survival, **PFS** – progression free survival, **PLRG** – Polish Lymphoma Research Group, **PR** – partial remission, **R-CHOP** – rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, **R-DHAP** – rituximab, dexamethasone, cytarabine and a platinum derivative, **R-FC** – rituximab, fludarabine and cyclophosphamide, **R-maxiCHOP** – dose-intensified **R-CHOP, RIT** – radioimmunotherapy, **RM** – rituximab maintenance, **TBI** – total body irradiation, **WBC** – white blood cell count.

INTRODUCTION

Mantle cell lymphoma (MCL) is a subtype of the mature B cell neoplasm with annual incidence approximately 1–2 cases/100 000/year. It has an aggressive clinical course due to high relapse rate and early development of chemoresistance [16]. The initial treatment depends on disease related risk factors, patient performance status and comorbidities [4, 5]. Most centers use the Mantle Cell Lymphoma International Prognostic Index (MIPI) incorporating patient's age, lactate dehydrogenase (LDH), performance status and white blood cell count (WBC) [9]. In one of the studies, overall survival (OS) varied depending on the MIPI score with 5-year OS of 60% for low-risk patients, and median OS of 51 and 29 months for the intermediate and high-risk patients respectively [23].

The adequate choice of the first-line therapy depends on patient age, performance status and comorbidities. In younger, fit patients an intensive frontline immunochemotherapy in corporating cycles with high-dose cytarabine (HDAC), followed by ASCT consolidation, increases response rates and prolongs the time to treatment failure and overall survival [6, 8, 12]. The three most commonly used regimens include rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), which were amended with rituximab, dexamethasone, cytarabine and a platinum derivative (R-DHAP), based on European Mantle Cell Lymphoma Network (EMCLN) experience [8], dose-intensified R-CHOP (R maxi-CHOP) altering with R-HDAC, described by Nordic Lymphoma Group [7, 12] and intensive high-dose therapy as hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with a high-dose methothrexat/cytarabine (HCVAD/MA), developed at the MD Anderson Cancer Center (MDACC) [1, 19]. The less intense the induction regimen, the greater the role of ASCT consolidation; therefore, it should be considered in all patients treated with R-CHOP as well [10, 18]. There are no differences between the efficacy of different transplant conditioning regimens, in particular between high dose chemotherapy and TBI (total body irradiation) [17, 22]. Rituximab maintenance following high-dose regimens and ASCT has been recently recommended after the results of LyMA trial were published [14].

Older patients, i.e. after the median age of 65 years, are commonly treated with R-CHOPor purine analoque-based regimen [13, 15, 20]. Rituximab maintenance proved to increase both PFS and OS, especially in R-CHOP treated patients. It seemed to be less effective due to adverse reactions, after induction therapy based on purine analoques [19].

Radioimmunotherapy with ibritumomabtiuxetan (a monoclonal antibody directed against the CD20 combined with tiuxetan chelating radioactive Yttrium-90, RIT) may be an alternative consolidation approach for elderly patients with comorbidities, not eligible for a transplant. In a retrospective analysis of PLRG the outcome and results of initial treatment followed or not by post-induction consolidation (ASCT, RIT or MR) was compared in responding MCL patients.

MATERIALS AND METHODS

Study cohort, oncological status and treatment

355 MCL, treatment-naive patients were diagnosed, treated and retrospectively evaluated in 12 PLRG centers between 1997 and 2014. Diagnosis of MCL was confirmed by histopathology with adequate cytochemical stains, including the presence of cyclin D1 over expression. Data on Ki-67 expression was not available. MIPI was calculated at the time of diagnosis based on age, performance status (Eastern Cooperative Oncology Group – ECOG), LDH activity, and WBC [9]. Staging was assessed according to Ann Arbor classification. The disease response was determined according to Cheson criteria revised in Lugano [3]. The complete assessment was performed after completing induction therapy, and later repeated every 6 months during the follow-up period. After a 5-year follow-up, patients were still under control annually, during which they were given physical examinations and blood tests. The median follow-up period was 5.4 years (range 0–11 years).

Patients were classified into 5 subgroups according to the response to induction therapy and the type of post-induction treatment. The first four cohorts consisted of patients achieving CR or PR after induction regimen (n = 263, 74.08%) with post-induction ap•proaches as follow:

- consolidation with ASCT (n = 71, 20%),
- consolidation with RIT (n = 37, 10.42%),
- rituximab maintenance (n = 17, 4.79%),
- no post-induction treatment (NPI, n = 138, 38.87%).

The fifth subgroup consists of primary refractory patients, where no consolidation or maintenance could have been implemented. The retrospective design of the study did not allow for an intention to treat analysis (IIT), so those patients were not evaluated any further.

Table 1. Characteristics of patients divided in 5 subgroups

Parameter	1	2	3	4	5	1-5	p value	p value
	ASCT n (%)	RIT n (%)	MR n (%)	≥PR, NPI n (%)	<PR n (%)	All n (%)	between 1st and 4th subgroup	between 2nd and 4th subgroup
n	71	37	17	138	92	355		
Age - median (range)	53 (31–78)	61 (38–78)	58 (37–77)	62 (32–79)	67 (37–84)	60 (31–84)	<0.05	NS
Sex (male)	53 (75)	29 (78)	10 (59)	92 (67)	61 (66)	245 (69)	NS	NS
ECOG >1	4 (6)	6 (16)	0 (0)	22 (16)	29 (32)	61 (17)	NS	NS
Clinical stage III-IV	69 (97)	35 (95)	17 (100)	133 (96)	91 (99)	345 (97)	NS	NS
B symptoms	41 (58)	18 (49)	5 (29)	73 (53)	65 (71)	202 (57)	NS	NS
WBC [G/l] - median (range)	10 (2–13.6)	7,3 (3.1–34)	7 (4–41)	8 (1.5–96)	10,8 (1.2–28)	8,7 (1.2–96)	NS	NS
LDH activity (increased)	34 (48)	15 (41)	3 (18)	59 (43)	57 (62)	168 (47)	NS	NS
MIPI - low ris	40 (56)	14 (38)	8 (47)	40 (29)	15 (16)	117 (33)	<0.05	NS
MIPI - intermediate risk	15 (21)	12 (32)	7 (41)	46 (33)	21 (23)	101 (28)	<0.05	NS
MIPI - high risk	10 (14)	11 (30)	1 (6)	38 (28)	51 (55)	111 (31)	<0.05	NS
MIPI - missing data	6 (8)	0	1 (6)	14 (10)	5 (5)	26 (7)	<0.05	NS

Statistical analysis

Clinical characteristics were compared between treatment subgroups using the $\chi 2$ test for categoric variables and the *t* test for continuous variables. The main analyzed endpoints included PFS and OS. PFS was defined as the time from the date of diagnosis to disease progression, relapse, or the date the patient was last known to be alive. OS was measured from the date of diagnosis until death from any cause or the date of the last follow-up. PFS and OS were evaluated using the Kaplan-Meier method powered by log-rank statistics. A *p* value of less than 0.05 was considered significant. Statistical analyses were performed using the Statistica software version 10 (Stat Soft, Kraków, Poland).

RESULTS

Patient characteristics

Patient characteristics and demographics comparing the five subgroups are shown in Table 1. The median age at diagnosis was 60 (range 31–84) with male/female ratio of 2.23. Patients subjected to ASCT were younger than patients in subgroups 2–4. The vast majority (97%) of patients presented the advanced stage of disease (III–IV). There were no significant differences in the characteristics between patients with radioimmunotherapy consolidation, rituximab maintenance and those with with no post-induction therapy. The transplanted patients have lower median age and lower MIPI score ($p < 0.05$). Patients who were refractory to first line treatment had the most negative predictive factors and unfavorable prognosis with median survival of approximately 7 months. They were the oldest subgroup with the worst ECOG status and MIPI index, the highest rate of B symptoms and most increased LDH activity.

The data on response rates after specific induction therapies and median follow-up time is presented in Table 2. The most common regimen was CHOP (n = 157, 44.23%), followed by purine – analoque based (n = 44, 12.39%), maxi-CHOP/HDAC (n = 40, 11.27%), CVP(n = 33, 9.29%), HCVAD/MA (n = 14, 3.94%). The median number of administered cycles was 6 (range 1–10). Analysis focused on subgroups 1–2 and 4 comparing patients responding to induction therapy and excluded from subsequent survival analysis subgroup 3 (rituximab maintenance), because of relatively low number of patients.

Table 2. Induction first-line treatment of patients with mantle cell lymphoma divided in 5 subgroups

	1	2	3	4	5	1-5	p value	p value
	ASCT	RIT	MR	≥PR, NPI	SD and PD	all	between 1st and 4th cohort	between 2nd and 4th cohort
n	71	37	17	138	92	355		
Immunochemotherapy (with Rituximab)	61 (86)	22 (59)	16 (94)	82 (59)	28 (30)	209 (59)	<0.05	NS
CHOP-like	23 (32)	27 (73)	5 (29)	70 (51)	32 (35)	157 (44)		
Purine analogue-based	1 (1)	7 (19)	0	23 (17)	13 (14)	44 (12)		
maxiCHOP/HDAC	23 (32)	0	3 (18)	11 (8)	3 (3)	40 (11)	<0.05	NS
HCVAD/MA	5 (7)	2 (5)	0	5 (4)	2 (2)	14 (4)		
CVP	3 (4)	1 (3)	0	9 (7)	20 (22)	33 (9)		
Chl or GKS	0	0	0	1 (1)	12 (13)	13 (4)		
Missing data	16 (23)	0	9 (53)	19 (14)	10 (11)	54 (15)		
N of cycles Median (range)	6 (1–8)	5 (1–6)	6 (3–18)	6 (0–9)	3 (0–10)	6 (0–10)	NS	NS
CR after induction	48 (68)	16 (43)	10 (59)	71 (51)	NA	145 (41)	<0.05	NS
CR after consolidation	95%	90%	N/A	N/A	N/A	N/A		
Follow-up (years) Median (range)	6.1(0.3–10.7)	6.2 (0.8–9)	5.5(1.1–10.6)	5.1 (0–10.6)	0.9 (0–6.7)	5.4 (0–11)		
Median OS (years)	Not reached	7.3	4	4	0.83		<0.05	<0.05
Median PFS (years)	2.25	3.75	1.83	1.83	0.5		<0.05	<0.05

Chl or GKS - chlorambucil or glicocorticoids

Rituximab was administered in 59% patients (n = 209). It was least frequently used in refractory patients (n = 28, 30% of the cases), most commonly in ASCT and Rituximab maintenance cohort (86% and 94% respectively). Forty-six patients (12.96%) received suboptimal induction consisting of cyclophosphamide, vincristine andprednison (CVP), chlorambucil, or glicocorticosteroids. Anthracycline and/or intermediate dose cytarabine containing regimens clearly increased the number of responding patients and CRs (Table 2). In ASCT cohort, 67% of patients underwent carmustine, etoposide, cytarabine and melphalan regimen (BEAM) and 33% received total body irradiation (TBI) with high-dose cyclophosphamide.

Two hundred sixty-three patients (74.08%) responded to the induction treatment, 145 (40.8%) with CR. Ninety-two patients (25.9%) did not respond to initial therapy and were analyzed as a separate cohort to allow for a fair assessment of the role of post-induction strategies, possible only in responding patients. We did not draw any conclusions from rituximab maintenance cohort, as there were only 17 patients treated this way. CR after induction was significantly increased by consolidation strategies, from 68% to 95% in ASCT and from 43% to 90% in RIT cohort. Kaplan Meier analysis is presented on Figure 1 and 2. Median PFSin patients subjected to ASCT and RIT was significantly higher compared to NPI cohort (2.3, 3.8 and 1.8 years respectively, p <0.05). Consolidation strategies also prolonged median overall survival (not reached in ASCT, 7.3 years in RIT and 4 years in cohort with no post induction therapy, p <0.005).

During the study, 148 patients (41.7%) died: 119 (33.52%) due to relapsing/refractory MCL, 29 (8.17%) secondary to non-relapse events (infections 8–2, 25%, cardiotoxicity 8-2.25%, myelodysplastic syndrome/acute myeloid leukemia 4–1.13%, multi-organ failure 2–0.56%, suicide 1–0, 28%, unknown reason 4–1, 13%).

DISCUSSION

Consolidation of frontline therapy MCL patients with ASCT became an undisputable standard of care after EMCLN trial performed in pre-rituximab era [6]. High dose therapy prolonged median PFS (3.7 years vs 1.6 years in patients treated with interferon) without significant differences in 3-year OS (83 vs 77%). Since most of the clinical trials and retrospective analyses focused on the choice of the best induction regimen, European "second generation" EMCLN randomized comparison between R-CHOP and R-CHOP/R-DHAP, both consolidated by ASCT in 497 newly diagnosed MCL patients, was the first trial proving the efficacy of cytarabine-based induction regimen. It significantly prolonged time to treatment failure (median TTF 9.1 years vs 3.9 years in control group) and without evident overall survival benefit at the time of analysis (projected OS at 5 years 76 vs 69% respectively) [8]. In most publications, 5-year overall and progression-free survival rates were reported as 60–80% and 35–70%, respectively [6, 7, 8, 12, 23]. In this perspective, transplant results of MCL patients described in PLRG comparison do not look satisfactory, even considering the difference between the real-life experience and clinical trials. Although median OS was not reached after observation time exceeded 6 years, median PFS was only 2.25 years, which was at most comparable to I generation EMCLN trial. The MIPI score and risk factor distribution was typical for transplanted patients. The majority of the patients (86%) were treated with rituximab containing induction regimens, but only 39% received intermediate dose cytarabine. Further 31 patients received rituximab maintenance at the time of molecular relapse, which had a major impact on PFS analysis. Considering only clinical relapses, median PFS in the whole group increased from 2.25 to 4.1 years.

Only 20% of MCL patients described in our analysis were consolidated with ASCT after first-line treatment. This confirms the limited accessibility of this procedure for selected patients (younger, with lower MIPI). The major-

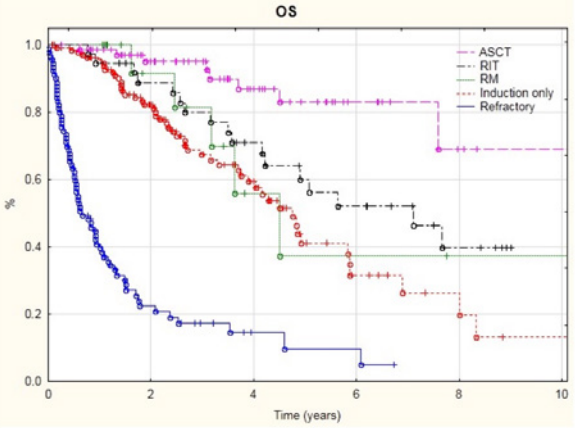

Fig. 1. Kaplan Mayer analysis – OS in subsequent cohorts

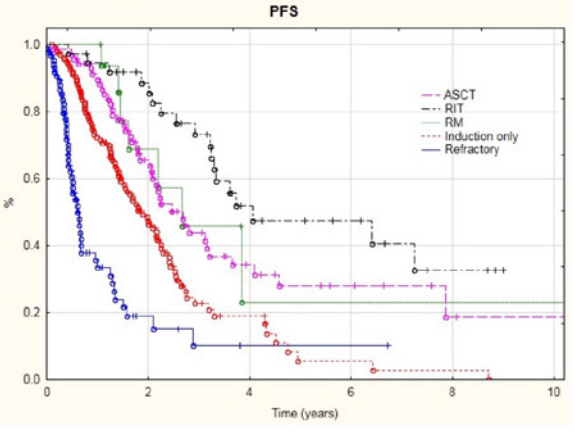

Fig. 2. Kaplan Mayer analysis – PFS in subsequent cohorts

ity of patients are transplant-ineligible, due to advanced age, poor performance status or comorbidities. Minimal residual disease (MRD) status is predictive of clinical progression [18]; thus, alternative post-induction approaches should be recommended.

Radioimmunotherapy as an alternative method of consolidation, which can be relatively safe in patients who are transplant-ineligible, with increased risk of toxicity due to age or comorbidities. Complications after radioimmunotherapy are relatively delayed and are mainly related to prolonged cytopenias. They are feasible in most patients with response to first line treatment, with bone marrow infiltration of less than 10% and lymph node size less than 2–3 cm. The efficacy of radioimmunotherapy with ibritumomabtiuxetan as a consolidation in first line treatment was demonstrated in 3 multicenter clinical trials, performed by: ECOG [21], Grupo Español de Linfomas y Transplante Autólogo de Médula Ósea (GELTAMO) [2], and PLRG [11]. In ECOG trial the intent-to-treat five-year OS was 73%. In GELTAMO four-year OS was 87% and failure free-survival 55%. In PLRG trial, 40% of patients consolidated in CR did not progress within 8 years of observation. In our analysis, most of the patients subjected to radioimmunotherapy either participated in the PLRG MCL 04 clinical trial or were treated by the centers participating in this trial; therefore, they do not present genuine real-life data. The patients' demographic MIPI and risk factors distribution were fully comparable to elderly MCL cohort, which were not submitted to any post-induction therapy (Table 1). Our data demonstrated the superiority of ibritumomabtiuxetan consolidation. It increased the CR rate from 43% to 90%. Both median PFS and median OS of patients subjected to RIT was significantly prolonged, compared to the cohort with no post induction therapy (3.75 vs 1.83 years and 7.3 vs 4.0 years respectively, $p < 0.05$). One third of the patients consolidated with radioimmunotherapy are in continuous remission, 8 years after the procedure.

Rituximab maintenance is at present the standard of care in both elderly and transplanted patients. It significantly improves PFS and OS after R-CHOP immunochemiotherapy [13]. The R-CHOP with subsequent maintenance therapy with rituximab has shown the OS rates (4-year survival rate, 87%). At the time of analysis, it was not the standard of care in Poland; RM cohort was too small to draw any meaningful conclusions.

While in young patients consolidation with ASCT is an indisputable standard of care, in older patients ineligible for ASCT the choice of optimal therapy is still disputable. Furthermore, this may be changed in nearby future by Bruton tyrosine kinase (BTK) inhibitors. Both (ibrutinib, acalabrutinib) are registered for relapsed/refractory MCL [24, 25] and their potential role in the frontline therapy is being evaluated. Two randomized clinical trials comparing efficacy of rituximab plus bendamustine (BR) followed by Rituximab maintenance with or without BTK inhibitors are ongoing (SHINE, ACE-LY-308), the preliminary results of Ibrutinib trial should be announced in 2019. Interpretation of results may be difficult, as purine analoque-based immunochemotherapy with rituximab maintenance is not regarded as a standard of care, and rituximab, fludarabine and cyclophosphamide (R-FC) was inferior to R-CHOP in a randomized in EMCLN trial [13]. Although both trials have PFS as a primary target, with an already established role of BTK inhibitors in relapsed MCL, only OS benefit could change the clinical practice in the I line therapy.

In conclusion, taking into account the lower level of evidence of retrospective studies, our findings confirm that in younger, selected patients with MCL the ASCT consolidation in first CR or PR provides satisfactory OS and PFS rates. In transplant-ineligible MCL patients in first CR or PR radioimmunotherapy as consolidation may be alternative to rituximab maintenance. Our results emphasize the necessity of post-induction approaches in all MCL patients, responding to the first line therapy.

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