

Mantle cell lymphoma has been recognized as a distinct entity from the other non-Hodgkin lymphomas in middle 1990's. It carries a worst prognosis among all mature B-cell malignancies. Cyclin D1 and recently SOX11 are the hallmarks for this disease. Even if it is highly responsive to induction treatment, it remains incurable, since it inevitably relapses. Highly aggressive approaches with stem cell transplantation can shift the survival curve for a bit, but even so the overall survival is not significantly improved in most of the cases. Small portion of patients with this heterogeneous disease have an indolent course with long-term survival. Conventional immunochemotherapy has reached its maximal possibilities, so novel target agents are absolutely warranted. The large number of ongoing early phase trials demonstrated promising results, especially emphasizing agents that target B-cell receptor. They are mostly investigated in relapsed/refractory disease, while front-line approaches with those agents need to be explored in future times.

Key words: mantle cell lymphoma, targeted agents, immunochemotherapy, stem cell transplantation.

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Are we a step forward with targeted agents in resolving the enigma of mantle cell lymphoma?

Ivan Petković¹, Ivica Pejčić^{1,2}, Svetislav Vrbić^{1,2}

¹Oncology Clinic Clinical Center Niš, Serbia

²Medical Faculty University of Niš, Serbia

Introduction

Mantle cell lymphoma (MCL) is a subtype of B-cell lymphomas first defined as a clinical entity distinct from the other non-Hodgkin lymphomas (NHL) in 1994 [1]. It accounts for 2–10% of all NHL, with male predominance (about 2.3–2.5 : 1) and a median age at presentation close to 70 years [2]. The stage usually is advanced, adenopathy typically is non-bulky, but extranodal involvement is frequent, such as bone marrow, liver, spleen, or Waldeyer ring. Gastrointestinal tract involvement, especially in a form of multiple lymphomatous polyposis (MLP) is the common presentation [3, 4]. A leukemic phase is not uncommon, but CNS involvement is unusual at presentation, yet can be seen upon relapse or when histology is blastic. Although morphologically similar, MCL is significantly more aggressive than other small cell lymphomas and therefore must be differentiated from them.

Mantle cell lymphoma is characterized by the chromosomal translocation t(11;14)(q13;q32), resulting in constitutional overexpression of cyclin D1 and cell cycle dysregulation in virtually all cases [5]. Cyclin D1 is detected by immunohistochemistry in 98% of MCL, although in remaining cases it may lack [6]. Those cyclin D1 negative cases often show expression of cyclin D2 and cyclin D3 [7]. The SOX11 (neuronal transcriptional factor) is highly expressed in both cyclin D1 negative and positive MCL, suggesting that in addition to its value as a diagnostic biomarker, it may be an important factor in the pathogenesis of MCL [8].

The MCL International Prognostic Index (MIPI) is the prognostic model most often used as a predictive tool for overall survival (OS) rates. It incorporates: ECOG performance status, age, leukocyte count, and lactic dehydrogenase level. MIPI classifies patients in 3 risk subgroups (low, intermediate and high risk) with the portion of patients (44%, 35% and 21%), respectively. The median OS for the low risk group was not reached (5-year OS of 60%), for the intermediate risk group was 51 months and 29 months for the high risk group [6]. Adding cell proliferation Ki67 index to MIPI (MIPI biological index-MIPI-B) is an important biological marker that showed strong additional prognostic relevance [9].

Conventional chemotherapy is only palliative and the median duration of remission (DOR) is only 1–2 years. With the exception of allogeneic stem cell transplantation (allo-SCT), current treatment approaches are non-curative and corresponding survival curves are characterized by a delayed, but continuous decline and a median survival of 3 to 7 years [5]. Mantle cell lymphoma has the worst prognosis among all adult B-cell malignancies.

Novel agents targeting various molecular pathways are now in the focus of investigation mostly as phase II studies in relapsed/refractory disease. Awaiting phase III studies will show their accurate clinical benefit.

Current overview of the induction approach to MCL patients

“Gold standard” CHOP/CHOP-like protocols (cyclophosphamide, doxorubicin, vincristine, prednisone) have been the main induction approach to MCL, for long period of time. After the introduction of rituximab (R) and its adjuvant to CHOP chemotherapy, in the study of Lenz *et al.*, it was demonstrated an increased overall response rate (ORR) from (76% to 94%, $p = 0.0054$), and the complete remission rate (CR) from (7% to 34%, $p = 0.00024$), respectively [10]. Interestingly, this improvement does not translate into prolonged OS and even significantly better progression free survival (PFS). The results of a meta-analysis of randomized controlled trials in ($n = 260$) MCL patients allegedly demonstrated survival benefit in patients treated with immunochemotherapy compared to those treated with chemotherapy alone [11]. Nevertheless, the number of patients included express doubts of the validity and the sufficient statistical power to confirm such findings. Elderly patients seem to have benefit of R-CHOP induction followed by rituximab maintenance therapy. This is not only in PFS but also in a significant survival advantage [12].

Treatment of MCL in younger patients is the most challenging, since the primary goal is to develop long-term remissions with prolongation of survival or to cure a patient, if possible. For transplant-eligible patients the standard of care is up-front induction therapy followed by autologous (auto-SCT) consolidation in first remission, especially in the intermediate risk group, whereas in the high risk group such an approach remains suboptimal. Randomized studies are needed to clarify the significance of allo-SCT in first remission, which seems to be the best known option to this time point [13].

There are many published trials which used R-HCVAD/AM (hyperfractionated cyclophosphamide, high dose dexamethasone, vincristine, doxorubicin/high dose methotrexate and cytarabine) as an induction treatment followed by consolidation with auto-SCT. The Italian group published results for patients aged ≤ 70 years who received 4 alternating cycles each of R-HCVAD/AM. Patients who obtained a partial response proceeded to auto-SCT. ORR and CR rates were 83% and 72%, respectively. After a median follow-up of 46 months (range 1–72) the estimated 5-year OS and PFS rates were 73% and 61%, respectively. MIPI maintained the prognostic value with an estimated 5-year OS of 89%, 80% and 24% for low, intermediate, and high risk groups, respectively ($p < 0.001$). This multicentre study confirmed that R-HCVAD-AM is an active regimen for the initial treatment of patients with MCL, but is associated with significant toxicity [14]. The authors of the SWOG 0213 trial had the same conclusions in patients aged < 65 years, with median OS of 6.8 years [15]. The results of the GELTAMO group showed that induction with R-HCVAD-AM and consolidation with ^{90}Y -ibritumumab tiuxetan is effective, although less feasible than expected. The substantial toxicity advised against the use of this strategy [16].

Polish single center experience study in patients was conducted. The median age of patients was 59 years (range 41–68) with 90% of stage 3/4 MCL. As an induction regi-

men R-CHOP was used in all patients except 1 who received R-CVAD. All patients responded ($n = 13$ first CR, $n = 4$ second CR and $n = 3$ PR). The conditioning regimen was CBV (high dose cyclophosphamide, BCNU, etoposide) in ($n = 18$) and BEAM (BCNU, etoposide, cytarabine and melphalan) in ($n = 2$) patients, respectively. Median OS and PFS were 48 and 29.8 months, respectively. The estimated 5-year OS and PFS were found to be 52% and 35%, respectively. After median follow-up after auto-SCT of 36 months 10 patients were alive (8 remaining in CR, and 2 relapsed). Other 10 patients died from disease recurrence and subsequent chemoresistance. Authors concluded that auto-SCT consolidation for MCL patients is safe and effective procedure [17]. A French group of authors published their results of phase II study with CHOP and DHAP (high dose dexamethasone, etoposide, cytarabine, cisplatin) + rituximab followed by auto-SCT in MCL [18]. Included were patients aged < 66 years with stage 3/4 MCL. As an induction treatment 3 cycles of CHOP (the third one was with the addition of rituximab) and 3 cycles of R-DHAP sequentially, were used. Responding patients were eligible for auto-SCT with conditional regimens (TAM6 or BEAM). The ORR was 93% after (R)-CHOP and 95% after R-DHAP. With a median follow-up of 67 months, the median EFS were 83 months, and the median OS had not been reached. Five-year OS was 75%. This study confirmed that induction with rituximab and cytarabine-based regimen is safe and effective in MCL patients. In an updated review of the Nordic MCL2 trial, median observation (6.5 years), the authors reported median OS and response duration longer than 10 years, and median EFS of 7.4 years. The MIPI and Ki-67 expression were the only independent prognostic factors for EFS and OS. Subdivided by the MIPI-B, more than 70% of the patients with low-intermediate MIPI-B were alive at 10 years, in contrast to 23% of the patients with high MIPI-B. The conclusion was that risk-adapted treatment strategy is required [19]. The study of Eastern German Study Group Hematology/Oncology (OSHO) conducted in ($n = 39$), where ($n = 33$) responding patients proceeded allo-SCT after induction with R-CHOP/R-DHAP for *de novo* MCL, or R-DHAP for relapsed/refractory MCL demonstrated 5-year PFS of 67% and OS of 73%. Enrolled were patients aged (18–65). Most of the patients received reduced intensity conditioning (RIC) ($n = 26$) with TreoFlu (treosulfan, fludarabine) protocol-age > 55 years and ($n = 7$) received myeloablative regimen BuCy (busulfan, cyclophosphamide) aged < 55 years. The overall mortality after the procedure was 24% ($n = 8$) with ($n = 5$) patients who relapsed after the procedure. The results were comparable between *de novo* MCL and relapsed/refractory MCL patients. The authors concluded that allo-SCT is a feasible and promising consolidation therapy for relapsed and refractory disease and an attractive option for young patients with *de novo* MCL of high risk and that significantly better outcome was in younger patients [20]. Summarized results of up-front use of SCT are presented in (Table 1).

Nevertheless, in younger transplant-eligible patients first line induction with R-HCVAD/AM followed by auto-SCT consolidation remains the standard of care with documented survival benefit, at this time point. The problem with this regimen is connected with the frequent stem cell mobilization failure and high toxicity rate. This implies the

need for new front-line treatment strategy (Polish, French, Nordic MCL trials and OSHO) or consideration of an early stem cell collection, when R-HCVAD/ AM induction regimen is to be used. One is clear that high doses cytarabine containing regimens should be used before proceeding SCT in transplant-eligible MCL patients.

Some very new statements [21] are questioning the role of SCT consolidation approach in first remission, especially in the era of an improved survival and higher response rates with immunochemotherapy. This might be due to the heterogeneity of some clinical factors that have to be considered (patient age, MIPI or comorbidity index scores) before making a decision on SCT. The most current trial (the comparison of R-CHOP+R-DHAP sequential induction followed by consolidation with auto-SCT and ibrutinib maintenance arm vs. the same combination but without auto-SCT, followed only with ibrutinib maintenance therapy arm) will try to define the role of SCT consolidation in first remission. This was orally presented by Prof. Dreyling at European Hematology Association (EHA 19) Congress 2014 in Milan.

Targeted agents in mantle cell lymphoma

As above mentioned, optimal treatment approach to MCL is undefined. This disease still remains incurable with almost inevitable relapse over time period of remission, whatever approach is used. Novel targeted agents are infallible needed. Many of them are included in various numbers of studies, mostly phase II with more than promising results, among some of them. However, larger phase III studies are required to determine real clinical benefit of those novel therapies. The aim of this review article will be to summarize an updated treatment approaches and recent study results through consideration of different mo-

lecular target pathways. Summarized results of efficacy of targeted agents in MCL are presented in (Table 2).

Inhibitors of mammalian target of rapamycin

The mammalian target of rapamycin (mTOR) is an intracellular kinase that controls the mRNA translation of many proteins (eg, cyclin D1 in MCL) that can act as oncogenes and contribute to lymphomagenesis [22]. Temsirolimus as the first generation mTOR inhibitor agent was investigated in phase II and III trials in MCL. In two phase II studies, first conducted in ($n = 35$) patients, the ORR for the single-agent temsirolimus 250 mg was 38% and the DOR for responders was 6.9 months [23], and in the second one single-agent temsirolimus 25 mg dose, 3 years later, in ($n = 29$) patients the ORR was 41%, with median DOR in responders of 6 months [24]. In pivotal phase III study in ($n = 162$) patients who were randomized as 1 : 1 : 1-(175 mg weekly for 3 weeks followed by either 75 mg (175/75 mg), 25 mg (175/25 mg) weekly, or investigator's choice therapy from prospectively approved options). It was found that 175/75 mg dose schedule significantly improved PFS and objective ORR of 22% compared with investigator's choice therapy (ORR of 2%) in patients with relapsed/refractory MCL [25]. The safety profile of temsirolimus is mostly acceptable and manageable with dose modifications or medical interventions [26]. In multicenter phase II study with single-agent everolimus with ($n = 35$) patients enrolled, the ORR was 20%, median PFS was 5.5 months and 17 months for responders (those who received 6 or more cycles of therapy) [27].

Proteasome inhibitors

The proteasome inhibitors are agents that block the action of proteasomes, cellular cylindrical complexes that

Table 1. Summarized review of the outcome in patients who proceeded SCT (auto or allo)

Reference	Number of patients enrolled	Induction protocol + type of SCT	ORR	Median follow-up in the study [months]	PFS	Median OS [months]
[14]	($n = 63$) 60 eligible	R-HCVAD alternating AM + auto-SCT	83%, 73% CR	46 months	estimated median 5-years PFS 61%	estimated median 5-year OS 73%
[15]	49	R-HCVAD alternating AM + auto-SCT	86%, 47% CR	4.8 years (58 months)	median PFS 4.8 years estimated 5-year PFS 49%	median OS 6.8 years estimated median 5-years 63%
[17]	20	R-CHOP/ R-CVAD in 1 patient + auto-SCT	100%, 85% CR	36 months	48 months estimated 5-year PFS 35%	29.8 months estimated 5-year OS 52%
[18]	60	(R)-CHOPx3/ R-DHAPx3 + auto-SCT	93–95%, 57% CR	67 months	84 months	not reached, 5-year OS 75%
[19]	($n = 160$) 145 proceeded SCT	maxiCHOP alternating with HD cytarabine + auto-SCT	96%, 54% CR	6.5 years (112 months)	at 10-years not reached EFS 7.4 years as intent to treat	at 10-years not reached
[20]	33	R-CHOP/R-DHAP for <i>de novo</i> MCL, or R-DHAP × 4 for R/R MCL + allo-SCT	60%	2.8 years (32 months)	5-year PFS was 67%	5-year OS was 73%

R/R MCL – relapsed/ refractory MCL

Table 2. Summarized review of targeted agents efficacy in relapsed/refractory MCL

Reference	Phase of the study	Number of patients enrolled	Agent investigated	ORR	PFS [months]	Median OS [months]
[23]	II	35	temsirolimus 250 mg – single agent	38%	6.5	12
[24]	II	29	temsirolimus 25 mg – single agent	41%	6 median DOR, PFS not evaluated	14
[25]	III	162	temsirolimus 175/75 mg – single agent	22%	4.8	12.8
[27]	II	35	everolimus – single agent	20%	5.5 and 17 for responders	not evaluated
[28]	II	155/assessable <i>n</i> = 141	bortezomib – single agent	33%	9.2 median DOR, PFS not evaluated	not reached after 13.4 months of follow-up
[29]	II	141	bortezomib – single agent	32%	4.1–4.5, refractory vs. patients with prior HD therapy	23.5 and 35.4 for responders
Up-dates of the same study in [27]						
[30]	II	40	bortezomib – single agent	47%	5.6–3.9 relapsed vs. refractory, responders: 7.8–8.4 relapsed vs. refractory	not evaluated
[31]	II	<i>n</i> = 25 both FL/MCL patients	rituximab + bortezomib	29%	estimated PFS 24%, and 60% in responders	not evaluated
[32]	II	16	rituximab + bortezomib + dexamethasone	81.3%	12.1 and 38.7 if CR was obtained	38.6 and not reached for patients who achieved CR
[32]	II	16	thalidomide + rituximab	81%	20.4	estimated for 36 months – 75%
[33]	II	134	lenalidomide – single agent	28%	4	19
[23]	II	5 only MCL patients	lenalidomide + low dose-dexamethasone + rituximab	58%	no evidence for MCL	no evidence for MCL
[35]	I	10 only MCL patients	flavopiridol + rituximab + fludarabine	80%	21.9 and 35.9 for non-blastoid MCL	not evaluated
[38]	II	111	ibrutinib – single agent	68%	estimated 13.9	not reached, estimated 58% for 18 months
[41]	I	40	idelalisib – single agent	40%	3.7 with 1-year PFS of 22%	not evaluated

HD therapy – high dose therapy; FL – follicular lymphoma

break down proteins which are damaged or unneeded in cell. By blocking those systems cells are collecting warped proteins and dies. The PINNACLE study of Fisher RI *et al.*, led to the acceptance of bortezomib in relapsed/refractory MCL. The study enrolled (*n* = 155) patients, previously treated (1–3 prior therapies) with median follow-up of 13.4 months. Results showed that in (*n* = 141) assessable patients, ORR was 33% with 8% of CR, median DOR was 9.2 months and median OS was not reached. The administration schedule, as well the adverse effects of bortezomib

was the same as in multiple myeloma treatment [28]. Updated time-to-event evaluation of this study showed that median OS was 23.5 months. Responders had expectable better results with the median OS of 35.4 months. Patients achieved CR had heterogeneous disease characteristics of MCL [29]. O' Connor OA *et al.*, conducted multicenter phase II PINNACLE study (*n* = 40) with heavily pretreated MCL patients. The ORR was 47% with 5% CR and 14% PR. The relapsed and primary refractory patients achieved ORR of 50% and 43%, respectively, while PFS was almost

similar. The collected data suggest that MCL patients with refractory or poorly responsive disease may still derive meaningful clinical benefit from the treatment with bortezomib [30]. In early clinical model of the phase II study that included rituximab to bortezomib, which enrolled ($n = 25$) patients with MCL and follicular lymphoma (FL), the ORR was 40% for both arms, while MCL patients had ORR of 29%. The estimated PFS was 24% in all and 60% in responding patients. Although significant activity of this combination, the safety profile found to be of limiting clinical applicability (grade 3 neurotoxicity was delivered in 52% of patients) [31]. The phase II study ($n = 16$) patients enrolled of triple combination bortezomib, rituximab and dexamethasone gave ORR of over 81% with 43.8% patient achieved CR. The median PFS and OS were 12.1 and 38.6 months, respectively. In responding patients median PFS and OS have not yet been reached. This combination has promising activity with manageable toxicity in heavily pretreated patients with MCL [32]. In responding patients bortezomib as a single-agent is associated with lengthy responses and notable survival in patients with relapse/refractory MCL, suggesting substantial clinical benefit [29], although the addition of rituximab or dexamethasone significantly increases ORR, those combinations are decreasing their safety profiles.

Immunomodulatory agents or drugs

Immunomodulatory drugs (IMiDs) target microenvironment and neoangiogenesis of the tumor and have immunomodulatory activity. We found only one published trial with thalidomide and rituximab in relapsed/refractory MCL. It included ($n = 16$) patients. Objective response was achieved in 81% of patients, with 5 CR (31%). Median PFS was 20.4 months and estimated 3-year survival was 75%. In responders PFS was expectably longer. The study suggested that rituximab plus thalidomide has marked activity in relapsed/refractory MCL with low toxicity profile [33]. In phase II MCL-001 (EMERGE) trial single-agent lenalidomide was investigated in relapsed/refractory or patients who progressed after bortezomib. Study included ($n = 134$) patients, median age of 67 with a median prior therapies (range 2–10). The achieved ORR was 28% with 7.5% CR, median DOR was 16.6 months, median PFS 4 months and median OS 19 months. This study showed durable efficacy of lenalidomide after the progression on bortezomib [34]. The combination of lenalidomide, low-dose dexamethasone, and rituximab achieved high response rates with durable responses in patients with rituximab-resistant, indolent B-cell lymphomas and MCL ($n = 5$) in this phase II study. ORR increased from 29% after two 28-day cycles of lenalidomide and low-dose dexamethasone to 58% after the addition of rituximab, suggesting that lenalidomide can overcome resistance to rituximab [35].

Cyclin-dependent kinase inhibitors

Cyclin-dependent kinases (CDK) are a family of protein kinases which have the role in cell cycle regulation. They are coded by CDK genes. This small molecules binds with regulatory proteins called cyclines and become full active

and than phosphorylate their substrates. CDK inhibitors (CDKi) target cyclin-dependent kinases and are involved in cell cycle arrest at G1 phase. The phase I study of Lin TS *et al.*, with flavopiridol (NSC-649890) added to rituximab and fludarabine (FFR) regimen was investigated in indolent lymphomas of which one group included MCL ($n = 10$). The MCL patients (median age 68, of whom 6 were untreated and 4 relapsed patients who had each received two prior therapies), received a median of 3.5 cycles. Eight patients responded (7 had CR, 1 PR). Median PFS was 21.9 months, ranging from 1.1 months when a patient withdrew to receive another regimen to at least 68.2 months. Two patients with blastoid variant MCL responded but relapsed within 1 year of study entry. Median PFS of the eight patients with non-blastoid MCL was 35.9 months. This regimen appeared to be most promising in older MCL patients with acceptable toxicity. However, results indicate a larger phase II study in previously untreated or relapsed disease to define regimen's activity across the MIPI risk group [36]. Furthermore, findings from this study suggest that FFR may be active in a particular histology of MCL even if flavopiridol demonstrates limited clinical activity as monotherapy for that particular lymphoma [37]. The single-agent activity of this first-generation CDKi suggests that other agents in this class merit further study in lymphoid malignancies, both alone and in combination [38].

Bruton's tyrosine kinase inhibitors

The Bruton's tyrosine kinase (BTK) is a mediator of the B-cell receptor signaling pathway. Its gene is located on X chromosome and it plays a crucial role in B cell maturation, but exact mechanism of action remains unknown at this moment. The potent inhibitor of this pathway-ibrutinib (PCI-32765), have demonstrated the power to induce impressive responses in B-cell malignancies through irreversible bond with cysteine-481 in the active site of BTK (TH/SH1 domain) and inhibits BTK phosphorylation on Tyr 223 [39]. Phase I studies have pointed to its antitumor activity in MCL. Afterword, pivotal phase II study, conducted on ($n = 111$) patients with relapsed/refractory MCL, at daily doses of 560 mg (patients previously received at least 2 cycles of bortezomib or less, or who had no received bortezomib), with median age of 68 years and 86% of patients had intermediate or high risk disease, showed ORR of 68% with 21% CR rate and PR of 47%. The estimated median follow up was 15.3 months, with the estimated DOR of 17.5 months, median PFS 13.9 months and median OS not reached (estimated OS rate was 58% at 18 months). This study concluded durable single agent efficacy of ibrutinib in relapsed/refractory MCL [40]. Axelrod *et al.*, have performed a preclinical combinatorial screen of ibrutinib and carfilzomib as a targeted agents that could provide improved clinical response. All 4 cell lines responded to the combination of proteasome and BTK inhibition, including Jeko-1, a leukemic, classically indolent form of MCL, and Z138, a blastic, characteristically aggressive form of MCL, suggesting that the carfilzomib and ibrutinib combination may prove efficacious regardless of variations in specific patient MCL tumor biology. The study suggested

that combination of agents not targeting BTK with ibrutinib provides higher benefit, over combination with two BTK inhibitors [41]. Awaiting phase III trials with ibrutinib will show its real clinical benefit.

Phosphatidylinositol 3-kinase δ inhibitors

Idelalisib (CAL-101, GS-1101) is a phosphatidylinositol 3-kinase inhibitor (PI3K δ) which specifically blocks the delta isoform of the enzyme p110 δ . This isoform plays a critical role in B-cell homeostasis and function. It was evaluated in phase I study in ($n = 40$) patients with relapsed/refractory MCL. Patients who entered the study had median age of 69 years and received 4 prior therapies and were refractory to their most recent treatment. ORR was 40%, with CR in 5% of patients. Median DOR was 2.7 months, median PFS was 3.7 months, and 1-year PFS was 22%. These data provide proof of concept that targeting PI3K δ is a viable strategy and worthy of additional study in MCL [42]. Safety profile of idelalisib in this study showed moderate adverse events.

Other agents in most current trials

In phase II study the addition of bevacizumab (monoclonal antibody that blocks VEGF) to the standard R-CHOP regimen in ($n = 11$) MCL patients as induction approach did not appear to significantly improve efficacy beyond that observed from previous studies using R-CHOP alone [43]. The phase II study investigated histone deacetylase (HDAC) inhibitor-vorinostat in patients with relapsed/refractory indolent B-cell lymphomas and MCL ($n = 4$) patients. First results showed moderate ORR, but results are mostly based for FL. Those results warrant further investigations of this agent for MCL [44]. The second HDAC inhibitor-panobinostat was investigated in phase I study but with small number of relapsed/refractory MCL patients concomitant with everolimus, this combination found to be active especially in Hodgkin lymphoma but is associated with severe thrombocytopenia [45]. There are many pre-clinical investigations of MCL cell lines with very promising results which awaits clinic introduction in future times.

Today, we know that MCL is very heterogeneous disease with approximately 15% of patients with an indolent course, slow in progress which could be hold only with "watch and wait" strategy. However, in remaining percentage it behaves aggressively or it inevitably relapses after induction treatment, so new agents are ultimately required or rather we need to change the current treatment paradigm by introducing new agents. Furthermore, risk stratification by using MIPI, MIPI-B as predictive tools should be incorporated in treatment decisions. The possibilities of conventional immunochemotherapy in MCL without SCT are well established. SCT is the only measure that can shift the survival curve, but it still remains unclear if long-remissions are possible. Auto-SCT gives the opportunity of durable remissions in younger fit patient, but late relapses still occur. Allo-SCT has curative potential, however with poor applicability, due to its toxic potential and high procedure-related mortality rates, especially in pretreated patients and the median age when MCL mostly occur. Large

number of patients is not feasible for such radical options, so the procedure has to be limited only for those patients who will have the optimal benefit. Nevertheless, by using RIC regimens it might become more widely applicable, but still in highly selected group of patients (younger, fit, and with high risk who does not have any choice for longer survival with other approaches). Mantle cell lymphoma is still considered as incurable disease, but something is definitely changing. The recent period of investigations has demonstrated some progress which could be found to be encouraging. As from that point of view, ibrutinib even as a single agent has demonstrated long time expected promising results like no other agent did in past history of MCL treatment. This agent is now included in large number of trial combinations and the results are still expected. Did we make a step forward with targeted agents? We can conclude that slight approach to the target has been made, but still need a time to see are we really close enough to solve the enigma of MCL.

The authors declare no conflict of interest.

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Address for correspondence

Ivan Petković
 Oncology Clinic
 Clinical Center Niš
 Bulevar Dr Zorana Djindjica 48
 18000 Nis, Serbia
 e-mail: ivan76.unsu@yahoo.com

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