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## The role of targeted treatment in mantle cell lymphoma: is transplant dead or alive?

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### ABSTRACT

Based on the profound biological insights of the last years into the molecular pathogenesis of mantle cell lymphoma and the clinical introduction of new targeted drugs, with high efficacy and a good safety profile, the therapeutic scenario for this tumor has been shown to be thoroughly favourable. No longer characterized by a uniformly dismal prognosis, mantle cell lymphoma has been revealed as a spectrum of different diseases, ranging from very indolent cases to highly aggressive and refractory ones. Thus, there is an urgent need to adapt therapy to accommodate the diverse presentations of the disease. High-dose chemotherapy, followed by autologous stem cell transplantation is the current standard of care for younger patients, generally providing high responses and long survival rates, but hampered by acute and long-term toxicity. In addition, some patients may be overtreated, while others could benefit from targeted approaches, based on the new, molecular-directed compounds. Such a personalized treatment based on the specific characteristics of individual patients may be guided by validated prognostic tools, such as the Mantle Cell Lymphoma International Prognostic Index and the Ki-67 Proliferative Index, as well as by early predictors of treatment response, like minimal residual disease analysis. Moreover, mutation screening of distinctive genomic alterations may provide new, predictive biomarkers, with an additional impact on clinical practice. Only after tailoring treatment according to the clinical and biological heterogeneity of the disease the role of transplantation and modern therapeutic options will be redefined in mantle cell lymphoma.

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### Introduction

Mantle cell lymphoma (MCL) is a relatively rare lymphoma subtype, constituting nearly 6-8% of all non-Hodgkin Lymphomas (NHL) in Europe and North America. MCL is typically diagnosed in elderly males, with a median age at diagnosis of 65 years and a male preponderance of 3 to 1.<sup>1</sup> Since its worldwide recognition in 1994, it has been known to have a dismal prognosis (“the worst lymphoma to have”), with a median overall survival (OS) rate of 3 years only. Unfortunately, no curative therapy has been established so far.<sup>2,3</sup>

After many years without significant advance in the management of patients with MCL, recently the prognosis for younger patients has improved significantly due to the introduction of dose-intensified regimens containing cytarabine, some incorporating autologous stem cell transplantation (ASCT), and the introduction of anti-CD20 monoclonal antibody rituximab. However, these intensive regimens raise some concern regarding acute and late toxicities and are not suitable for elderly patients, who represent the majority of MCL patients.<sup>4</sup> The superiority of sequential regimens with ASCT consolidation after high-dose cytarabine schemes *versus* some intensive schedules like Hyper-CVAD/MA are debated, especially between European and American clinical groups.<sup>5</sup> More importantly, even among younger patients, a minority presents with clinically indolent features (“indolent MCL”) or with classical MCL but characterized by low tumor mass and low-risk

according to the MIPI (MCL International Prognostic Index) and/or the Ki-67 Proliferative Index. These patients also represent a dilemma for the clinician as to whether to offer them a high-dose therapy or not, as intensive treatments, with or without ASCT, are hampered by short- and long-term toxicities, including secondary malignancies.<sup>6,7</sup>

Moreover, recently the scientific and therapeutic scenario for MCL patients has rapidly changed: new biological insights into the molecular pathogenesis of MCL have highlighted some crucial oncogenic signaling pathways, underlying the aggressiveness and chemorefractoriness of the disease. Such discoveries have paved the way for the concept of personalized medicine in MCL. On one hand, the availability of these new diagnostic tests offers a better and more rational biology-based prognostic stratification of patients at baseline, suggesting different treatment strategies for patients with various risk profiles. On the other hand, a deeper unveiling of the underlying mechanisms has led to the clinical development of many new small molecules acting towards specific molecular targets, with high anti-lymphoma activity in some cases.<sup>8,9</sup> The current availability of effective, targeted drugs and the increasing clinical application of robust and predictive diagnostic tools have already started to change the therapeutic algorithms of MCL and will challenge the established role of ASCT.

Therefore, our review will draw on the current landscape of evidence supporting ASCT in MCL, subsequently describing the most important new drugs available in clinical practice for this lymphoma and will finally debate the role of ASCT in the near future, proposing a new therapeutic algorithm for MCL in the era of personalized medicine.

### The role of high-dose therapy and autologous transplantation

Soon after the recognition of MCL as a distinct entity in the REAL (Revised European-American Lymphoma) Classification back in 1994, it became obvious that this lymphoma subtype has a more aggressive clinical course with rapid relapses and subsequent chemorefractoriness, as compared to indolent lymphoma. Initially, MCL typically showed slightly lower response rates to polychemotherapy and a short event-free survival (EFS) and OS of 8 and 28 months, respectively, in a German series of 45 patients.<sup>2,3</sup> The combination of rituximab with fludarabine or CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), though improving the response rate and the time to treatment failure (TTF), did not impact on OS, resulting in a median progression-free survival (PFS) of only slightly more than one year, with virtually unchanged long-term perspectives.<sup>10,11</sup>

On the contrary, more promising results were obtained in phase II studies implementing high-dose cytarabine, with or without ASCT. A sequential CHOP-DHAP (dexamethasone, high-dose cytarabine and cisplatin) regimen led to a CR rate of >80% in a series of 28 patients. Responding patients underwent intensified consolidation with total body irradiation (TBI), high-dose Ara-C, melphalan and ASCT, resulting in an impressive 3-year EFS rate of 83% and 3-year OS rate of 90%.<sup>12</sup>

Similarly, high response rates of more than 90% were demonstrated by the MD Anderson Cancer Center with a

dose-intensified approach. Twenty-five patients received an alternating regimen of hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) with high-dose cytarabine and methotrexate (MA). However, in this elderly patient population the median TTF was only 15 months, and hematologic toxicity was significant.<sup>13</sup>

The role of consolidation by dose intensification and ASCT was supported by encouraging results obtained by different phase II studies, aiming at the elimination of residual lymphoma cells after conventional chemotherapy.<sup>14-16</sup> In addition, the benefit of TBI as part of the conditioning regimen in MCL was suggested by a retrospective analysis (PFS after 4 years: 71% vs. 0%,  $P<0.0001$ ; OS 89% vs. 60%,  $P=0.07$ ).<sup>17</sup>

Thus, in 1996, the European MCL Network embarked on a randomized comparison of CHOP followed by myeloablative radiochemotherapy (high-dose cyclophosphamide + 12 Gy TBI) followed by ASCT versus IFN $\alpha$  maintenance in patients under 65 years of age in order to assess more precisely the impact of ASCT. Patients in the ASCT arm experienced a significantly longer PFS, even though the 3-year OS was not significantly superior (Table 1).<sup>18</sup> However, in a subsequent analysis the median OS was also superior in the ASCT arm after extended median follow-up (63 months) (90 months versus 54 months,  $P=0.034$ ).<sup>19</sup> Therefore, chemotherapy dose intensification and ASCT support became the standard of care for younger MCL patients. However, the non-curative potential of this intensive approach was witnessed by the continuous relapsing pattern and lack of molecular remissions (MR) (determined by Bcl-1 or immunoglobulin rearrangement nested-PCR approach).<sup>20,21</sup>

Nonetheless, the subsequent integration of rituximab and high-dose cytarabine into ASCT programs led to unprecedented levels of cytoreduction, making MR an attainable target in MCL patients. In 2003 Massimo Gianni *et al.* reported MR in 19 out of 20 patients receiving a rituximab-supplemented high-dose sequence (R-HDS), along with very favorable 4-year EFS and OS rates (79% and 89%, respectively).<sup>22</sup> Comparable results were reported for a multicenter phase II trial by the Nordic Lymphoma Group. One hundred and sixty MCL patients received an induction with R-maxi-CHOP alternating with R-high dose cytarabine, followed by a high-dose consolidation (BEAM) with ASCT. MR was achieved in 92% of the 79 evaluable patients, while overall and complete response was achieved in 96% and 54%, respectively. The 6-year EFS, PFS and OS were 56%, 66%, and 70%, respectively, with no relapses observed after 5 years.<sup>23</sup> Moreover, achievement of MR, irrespective of high-dose therapy with ASCT or less intensive immuno-chemotherapy regimens, was an independent predictor of clinical outcome.<sup>24,25</sup>

Additional phase II studies, as well as a large retrospective population-based analysis showed similar favorable clinical results of high-dose cytarabine-containing schedules followed by ASCT, with overall response rates (ORR) ranging from 70% to 100% (CR: 64-96%), 5-year OS ranging from 64% to 75% and acceptable toxicity profiles (treatment-related mortality  $\leq 5\%$ ), but a significant dropout rate (13%-30%).<sup>26-29</sup>

Similarly, the MD Anderson Hyper-CVAD/MA regimen with rituximab resulted in excellent results in a monocen-

**Table 1.** Published clinical studies investigating first-line dose-intensified therapy in MCL.

Author	Study Features	Evaluable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (years)	Median OS (years)	Dropout rate	TRM	Secondary tumors rate	
Dreyling <i>et al.</i> , 2005 [18]	Phase III, randomized	122	R-CHOP + TBI + ASCT	98 (81)	3,3	NR (83% 3-y OS)	13%	5%	5%	
			<i>vs.</i> R-CHOP + TBI + interferon- $\alpha$	<i>vs.</i> 99 (37)	<i>vs.</i> 1,4	<i>vs.</i> NR (77% 3-y OS)	<i>vs.</i> na	<i>vs.</i> 0%	<i>vs.</i> 0%	
Hermine <i>et al.</i> , 2012 [34]	Phase III, randomized	455	R-CHOP + TBI + ASCT	98 (63)	3,8	6,8	na	4%	na	
			<i>vs.</i> R-CHOP/R-DHAP + HD-araC + ASCT	<i>vs.</i> 99 (61)	<i>vs.</i> 7,3	<i>vs.</i> NR	<i>vs.</i> na	<i>vs.</i> 2,5%	<i>vs.</i> 6%	
Damon <i>et al.</i> , 2009 [26]	Phase II	77	R-CHOP + methotrexate + HD-araC/etoposide + ASCT	88 (69)	NR (56% 5-y PFS)	NR (64% 5-y OS)	13%	3%	na	
Van't Veer <i>et al.</i> , 2009 [27]	Phase II	87	R-CHOP + HD-araC + ASCT	70 (64)	NR (36% 4-y PFS)	NR (66% 4-y OS)	30%	5%	na	
Geisler <i>et al.</i> , 2012 [39]	Phase II	160	R-Maxi-CHOP + HD-araC + ASCT	96 (54)	7,4	NR (64% 10-y OS)	9%	5%	4%	
Delarue <i>et al.</i> , 2013 [28]	Phase II	60	R-CHOP/R-DHAP + HD-araC + ASCT	100 (96)	6,9	NR (75% 5-y OS)	18%	1,5%	18%	
Touzeau <i>et al.</i> , 2013 [29]	Retrospective	396	Different ASCT-based schedules	83 (77)	NR (67% 3-y PFS)	NR (83% 3-y OS)	na	2,5%	6%	
Kolstad <i>et al.</i> , 2014 [40]	Phase II	160	R-Maxi-CHOP + HD-araC +/- Zevalin + ASCT	94 (82)	NR (71% 4-y PFS)	NR (78% 4-y OS)	9%	6%	3%	
Le Gouill <i>et al.</i> , 2014 [42]	Phase III, randomized	299	R-DHAP + ASCT +/- rituximab maintenance	na (92)	NR (74% 3-y PFS)	NR (83% 3-y OS)	14%	na	na	
Cortelazzo <i>et al.</i> , 2015* [99]	Phase III, randomized	260*	R-CHOP+R-CTX+HD-araC+ASCT +/- lenalidomide maintenance	86 (78)	NR (78% 2-y PFS)	NR (89% 2-y OS)	22%*	2%	na	
Non-ASCT based regimens	Romaguera <i>et al.</i> , 2010 [6]	Phase II, monocentric	97	R-Hyper-CVAD	97 (87)	4,6	NR (64% 10-y OS)	29%	8%	5%
	Merli <i>et al.</i> , 2012 [31]	Phase II, multicentric	60	R-Hyper-CVAD	83 (72)	NR (73% 5-y PFS)	NR (61% 5-y OS)	63%	6,5%	1,5%
	Bernstein <i>et al.</i> , 2013 [32]	Phase II, multicentric	49	R-Hyper-CVAD	86 (55)	4,8	6,8	39%	2%	4%

\* the accrual is not yet completed. MCL: mantle cell lymphoma; ORR: overall response rate; CR: complete response; PFS: progression-free survival; OS: overall survival; R: rituximab; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; TBI: total body irradiation; ASCT: autologous stem cell transplantation; DHAP: dexamethasone, cytarabine and cisplatin; HD-araC: high dose cytarabine; R-CTX: rituximab-high dose cyclophosphamide; Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone + methotrexate-cytarabine; NR: not reached; na: not available; ne: not evaluable; y: years; vs.: versus.

tric series of 97 patients. Nonetheless, this dose-intensive regimen was not devoid of TRM and high dropout rates (8% and 29%, respectively)<sup>30</sup> and its application in multicentric trials revealed a limited feasibility.<sup>31,32</sup> Finally, a recent “real-life”, population-based observational study by the Nordic Lymphoma Group, demonstrated that rituximab (n=766; HR=0.66;  $P<0.001$ ) and ASCT (n=273; HR=0.55;  $P<0.004$ ) were independently associated with improved OS among patients receiving systemic treatment.<sup>33</sup>

Based on these promising data, in 2004 the European MCL Network launched the “MCL Younger” phase III trial, comparing a conventional R-CHOP induction to the “experimental” French one (alternating induction of 3 courses of R-CHOP and R-DHAP), both followed by myeloablative consolidation, TBI and ASCT. Preliminary results confirmed that the R-CHOP/R-DHAP arm achieved a significantly improved median TTF and OS (Table 1), with a comparable number of treatment-related deaths in both groups.<sup>34</sup> The impact of cytarabine on the

TTF rate was closely linked to MR in the bone marrow, which was much more frequent in the R-CHOP/R-DHAP arm (68% vs. 24%,  $P<0.001$ ).<sup>35</sup>

Therefore, ASCT is currently considered the standard first-line consolidation therapy for younger MCL patients (including “low-risk” cases), as stated by international guidelines,<sup>36,37</sup> as well as a recent consensus of the European MCL Network and the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (EBMT).<sup>38</sup>

However, although the overall results of all these high-dose cytarabine-containing regimens are excellent, with a median OS of more than 10 years in the updated Nordic Lymphoma Group experience, late relapses continue to occur, highlighting that even ASCT-based programs alone are not able to eradicate MCL.<sup>39</sup> A recent trial by the Nordic Lymphoma Group failed to demonstrate an improved outcome after <sup>90</sup>Yttrium-ibritumomab tiuxetan-BEAM conditioning before ASCT.<sup>40</sup> On the other hand, more promising maintenance strategies are being implemented after ASCT,

**Table 2.** Recent published clinical studies investigating targeted approaches in MCL (with more than 10 evaluable MCL patients).

Author	Study Features	Evaluable Patients	Therapeutic regimen	ORR% (CR%)	Median PFS (months)	Median OS (months)
Goy <i>et al.</i> , 2009 [46]	Phase II, relapse	141	bortezomib	33 (8)	6,7 (TTP)	23,5
Ruan <i>et al.</i> , 2011 [50]	Phase II, upfront	36	R-CHOP + bortezomib	91 (72)	44% (2-y PFS)	86% (2-y OS)
Robak <i>et al.</i> , 2015 [51]	Phase III, randomized, upfront	244	R-CHOP <i>vs.</i> VR-CAP	89 (42) <i>vs.</i> 92 (53)	14,4 <i>vs.</i> 24,7	54% <i>vs.</i> 64% (4-y OS)
Hess <i>et al.</i> , 2009 [52]	Phase III, randomized, relapse	54	temsirolimus 75mg/75mg	22 (2)	4,8	12,8
		54	temsirolimus 75mg/25mg	6 (0)	3,4	10
		53	investigator's choice	2 (2)	1,9	9,7
Ansell <i>et al.</i> , 2011 [53]	Phase II, relapse	69	temsirolimus + rituximab	59 (19)	9,7	29,5
Witzig <i>et al.</i> , 2011 [56]	Phase II, relapse	57	lenalidomide	35 (12)	8,8	NR
Eve <i>et al.</i> , 2012 [57]	Phase II, relapse	26	lenalidomide	31 (8)	3,9	10
Goy <i>et al.</i> , 2013 [59]	Phase II, relapse	134	lenalidomide	28 (8)	4	19
Wang <i>et al.</i> , 2012 [60]	Phase II, relapse	44	lenalidomide + rituximab	57 (36)	11,1	24,3
Zaja <i>et al.</i> , 2012 [58]	Phase II, relapse	33	lenalidomide + dexamethasone	52 (24)	12	20
Albertsson-Lindblad <i>et al.</i> , 2015 [62]	Phase II, upfront	51	lenalidomide + rituximab + bendamustine	91 (78)	42	53
Zaja <i>et al.</i> , 2015 [61]	Phase II, relapse	52	lenalidomide + rituximab + bendamustine	79 (55)	51% (2-y PFS)	66% (2-y OS)
Wang <i>et al.</i> , 2013 [63]	Phase II, relapse	111	ibrutinib	68 (21)	13,9	NR (1,5-y OS 58%)
Kahl <i>et al.</i> , 2014 [64]	Phase I, relapse	40	Cal-101	40 (5)	3,7	na
Morschhauser <i>et al.</i> , 2013 [67]	Phase II, relapse	40 (15 MCL)	GA-101	27 (13)	2,7*	na
Lin <i>et al.</i> , 2010 [71]	Phase I**	10	flavopiridol + fludarabine + rituximab	80 (70)	21,9	na
Evens <i>et al.</i> , 2012 [75]	Phase II	11	abexinostat	27 (na)	4	na

\*Data derived from the overall population of the study, not exclusively from patients with MCL. \*\*6 patients received the schema as first-line therapy, 4 patients after relapse. MCL: mantle cell lymphoma; ORR: overall response rate; CR: complete response; PFS: progression-free survival; OS: overall survival; TTP: time to progression; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone; NR: not reached; na: not available; y: years; vs.: versus.

based on the results of rituximab maintenance in elderly MCL patients.<sup>41</sup> The ongoing phase III *Lyra* trial (NCT00921414) investigated the role of rituximab maintenance after four courses of R-DHAP and ASCT. Besides confirming very favorable CR, PFS and OS rates (Table 1), the data from the interim analysis show a promising 2-year EFS of 93% in the rituximab maintenance arm *versus* 82% in the control arm (hazard ratio, HR = 2.1), suggesting that rituximab maintenance after ASCT may become a new standard of care in MCL.<sup>42</sup> Currently, the randomized phase III trial *FIL-MCLO208* (EudraCT Number 2009-012807-25) is exploring lenalidomide maintenance in young MCL patients after ASCT, and results are eagerly awaited.<sup>99</sup>

Despite high response rates and long-term survival advantages after the described high-dose schedules, the non-negligible toxicity profile of such an approach has to be disclosed. Dropout rates generally range between 10%-30% in all the studies (Table 1), with the major adverse events being infectious (neutropenic fever, pneumonia) and gastrointestinal (10%-15% of patients), besides the need for red cell and platelet transfusions (10%-30% of cycles). TRM generally ranges between 2%-8%, mainly due to infectious and cardiac complications. Moreover, costs of hospitalization for high-dose therapy and ASCT have to be considered. Finally, all the reported intensive regimens displayed a significant rate of second tumor development, ranging from 4% up to 18% (Table 1). These results are in line with the long-term secondary neoplasia rates of a large retrospective study on more than 1000 lymphoma patients treated with high-dose therapy,

rituximab and ASCT (10-year rates of myelodysplasia/acute leukemia, 4.5% and solid tumors, 6.8%).<sup>7</sup>

Table 1 describes the most important published clinical studies investigating first-line high-dose therapy in MCL.

### The emerging role of new drugs

During the last years, growing insights into the molecular biology of MCL have led to the systematic exploration of targeted approaches.<sup>8</sup> Many new compounds are currently being tested within clinical trials, and some of them have already received approval both in the USA and Europe (Table 2), based on impressive activity in relapsed/refractory patients. Current trials are investigating the combinations with immunochemotherapy in earlier treatment lines, with the aim of enhanced efficacy, without adding further toxicity.

In the USA the first new agent registered in relapsed MCL was bortezomib, a selective and reversible proteasome 26S inhibitor. Some phase II, single-agent data showed significant responses and favorable PFS and OS rates, with predictable toxic effects.<sup>43-46</sup> Since then, many combinations with rituximab and chemotherapy were tested, mainly in a limited series of relapsed/refractory patients.<sup>47-50</sup> More recently, the phase III trial LYM-3002 showed that the substitution of vincristine by bortezomib in front-line R-CHOP ("VR-CAP" regimen) improved outcomes in elderly patients with MCL (Table 2); however, an increased hematologic toxicity was observed.<sup>51</sup>



Temsirolimus, an intravenous mammalian target of rapamycin (mTOR) inhibitor, received the European Medicines Agency (EMA) approval in 2009, due to its single-agent activity. This approval was based on a randomized phase III trial, showing superiority to mono-chemotherapy (Table 2).<sup>52</sup> The addition of rituximab showed even higher response rates in a phase II study.<sup>53</sup> To further improve its efficacy, temsirolimus is currently being investigated in combination with BR: of note, all evaluable patients of the phase I part responded to this combination.<sup>54</sup>

The immunomodulatory compound lenalidomide showed high activity in relapsed/refractory MCL patients in many phase II trials, either as a single-agent or combined with dexamethasone.<sup>55-59</sup> Subsequently, a chemofree lenalidomide-rituximab combination resulted in even higher response rates (Table 2) and impressive response duration of up to 19 months.<sup>60</sup> Finally, preliminary results of a phase II trial in first relapse showed activity and the feasibility of a dose reduced rituximab, lenalidomide plus bendamustine combination, followed by lenalidomide maintenance.<sup>61</sup> Nevertheless, a full dose combination in a front-line setting showed an excess of toxicity and secondary malignancies.<sup>62</sup>

Recently, highly promising data were reported for inhibitors of the B-cell receptor pathway. The covalent oral inhibitor of Bruton's tyrosine kinase (BTK) ibrutinib showed durable single-agent efficacy in relapsed or refractory MCL.<sup>63</sup> Based on an international phase II trial in heavily pre-treated MCL patients responses were achieved in the majority of patients paired with excellent tolerability (Table 2). Prior treatment with bortezomib had no effect on the response rate. The most common adverse events were mild or moderate diarrhoea, fatigue, and nausea. Grade 3 or higher hematologic events were infrequent and included neutropenia (16%), thrombocytopenia (11%), and anemia (10%). One phase III trial comparing ibrutinib *versus* temsirolimus monotherapies in relapsed patients (NCT0164021) has confirmed the superiority of the BTK inhibitor, and another trial assessing a BR schedule plus/minus ibrutinib in first-line therapy (NCT01776840) has completed accrual.

Another antagonist of the BCR signal cascade, idelalisib, a specific inhibitor of phosphatidylinositol 3-kinase delta isoform, also achieved high response rates in MCL, but

had a disappointing median duration of response of only 2.7 months.<sup>64</sup>

Finally, many other promising targeted drugs are also currently being tested in MCL. New anti-CD20 monoclonal antibodies (mAB), such as obinutuzumab and ofatumumab,<sup>65-67</sup> bispecific anti-CD19/anti-CD3 mAB blinatumumab,<sup>68,69</sup> the toxin-immunoconjugated mAB anti-CD79b DCDS4501A,<sup>70</sup> direct inhibitors of cyclin-dependent kinase 4 and 6 (flavopiridol and PD0332991),<sup>71-73</sup> oral second generation BCL-2 inhibitors (venetoclax)<sup>74</sup> and novel oral pan-histone deacetylase inhibitors (abexinostat).<sup>75</sup> Overall, the above mentioned compounds showed activity in MCL. Nevertheless, additional studies on larger MCL patient cohorts are warranted to assess their specific role in this lymphoma subtype.

A summary of the recently published clinical trials of targeted approaches in MCL is presented in Table 2.

### Looking for a tailored treatment in MCL

The well known biological and clinical heterogeneity of MCL, as well as the recent availability of highly active, but also expensive new compounds, urges the introduction of the concept of "personalized medicine" into the clinical practice of MCL. However, to effectively tailor the therapeutic approach according to the individual patient's risk profile reliable prognostic tools applicable in clinical routine are mandatory. The ideal prognosticator should integrate clinical and biological features, taking into account the recent knowledge of molecular pathogenesis.

Currently, the most widely applied tool is the prognostic MIPI score, encompassing simple clinical parameters such as age, performance status, LDH and the leukocyte count.<sup>76</sup> Based on easy calculations available via internet, and validation in a "simplified" version<sup>76,77</sup> (Table 3), the MIPI is able to stratify newly diagnosed patients into three risk classes with different 5-year OS rates: 83%, 63%, and 34% in MIPI low, intermediate, and high-risk groups, respectively.<sup>78</sup> However, there are some important limitations: first of all, as the "age" is one of the most important variables, MIPI fails to correctly classify some younger "high-risk" patients; moreover, it is not able to precisely stratify the outcomes of "low" and "intermediate" risk groups among elderly patients.<sup>78</sup> Therefore, the integration of a validated biomarker, such as the Ki-67 proliferative index, has been proposed ("biological-MIPI", MIPI-b).<sup>76</sup> A Ki-67 index  $\geq 30\%$  was associated with poor outcome in different patients series, after conventional or intensified chemotherapy plus rituximab.<sup>25,79,80</sup> The Ki-67 integration into the MIPI-b was validated in a large series of patients from randomized trials carried out by the European MCL Network, identifying patients at higher relapse risk in both the younger and older age categories, but again not reliably stratifying between "low" and "intermediate" risk groups.<sup>78</sup> This limitation has been overcome by a recently improved version of "combined" MIPI, MIPI-c, identifying four risk classes based on a 30% Ki-67 cut-off value (5-year OS rates, 85%, 72%, 43% and 17%, respectively,  $P < 0.0001$ )<sup>81</sup> (Figure 1). However, an important limitation is the reproducibility of the Ki-67 evaluation in pathology labs, where the published guidelines may not be routinely followed.<sup>82</sup> Moreover, a representative lymph node biopsy is required: thus, cases diagnosed only on BM histology are often not sufficiently evaluable.

**Table 3. Simplified MIPI calculation.**

Points	Age (years)	ECOG Performance Status	LDH/ULN	Leukocytes ( $\times 10^9/L$ )
0	<50	0-1	<0.670	6700
1	50-59	-	0.670-0.999	6700-9999
2	60-69	2-4	1.000-1.499	10000-14999
3	>69	-	>1.499	>14999

For each prognostic factor, 0 to 3 points are given to each patient and points are summed up to define a category of risk

#### Risk stratification

0-3 points	low-risk
4-5 points	intermediate-risk
6-11 points	high-risk

MIPI: Mantle cell lymphoma International Prognostic Index; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ULN: upper limit of normal; L: liter.

More recently, the integration of new biomarkers in the MIPI has been proposed. A study by the Nordic Lymphoma Group reported that microRNA (miR)-18b overexpression identifies MCL patients with poor outcome.<sup>85</sup> Despite the intriguing biological rationale of this work, the wide application of this tool appears to be hampered by the missing availability of miR analysis in clinical routine.

The only other validated prognosticator in MCL is the post-treatment evaluation of MRD by allele-specific oligonucleotide (ASO)-PCR. MRD analysis is able to detect very low levels (up to 1.00E-05) of residual lymphoma cells in patients achieving complete clinical response (CR) after treatment. This tool, currently applicable in 90% of MCL patients (with an available diagnostic specimen and BM or peripheral blood follow-up samples) is an effective early predictor of outcome, with an independent prognostic value in a large series of patients, which is even superior to CR achievement in multivariate analysis.<sup>25</sup> Its value has been confirmed in various patients series through different treatments (both standard and high-dose chemotherapy, as well as maintenance therapy) in both young and elderly patients.<sup>24,25,35,39,84</sup> Moreover, MRD prospective assessment is able to identify early those high-risk patients with molecular relapse only and thus prone to clinical relapse within the subsequent two years.<sup>84</sup> This setting allows preemptive trials investigating non toxic treatments at MRD reappearances.<sup>85,86</sup> The major limitations of this approach is the technical complexity of the MRD analysis with patient-specific primers, currently reliable only in specialized labs, applying standardized guidelines and performing regular quality control rounds (“EuroMRD group”).<sup>87</sup>

However, although such predictive tools effectively stratify patients into different risk classes, solid data on their application into personalized treatments are still lacking. To our knowledge, thus far only two trials designed by the Nordic Lymphoma Group have investigated tai-

lored therapy in MCL. The “MCL2” trial proposed a “pre-emptive” rituximab strategy for 26 patients experiencing MRD recurrence after ASCT:<sup>85</sup> even though molecular reconversion rates and preliminary data on survival are promising, the limited patient number does not yet justify therapeutic approaches in clinical routine.<sup>39</sup> Moreover, the attempt to improve the prognosis of “high-risk” MCL (according to MIPI and MIPI-b) by offering increased doses of cytarabine did not yield satisfying results (“MCL5”).<sup>88</sup> Therefore, although broadly validated, neither MIPI nor Ki-67 nor MRD are currently routinely applied to guide treatment decisions in MCL.<sup>36</sup> Thus, a practical application of these predictors in the next clinical trials is eagerly awaited, to finally investigate tailored therapies in MCL.

In addition, in the last years, many new molecular pathways involved in tumor survival, aggressiveness and treatment refractoriness have been identified.<sup>8,89</sup> Thus, numerous molecular markers (including *SOX11* expression, *p53* alterations and *Notch-1* mutations)<sup>90-94</sup> have been linked with outcome. However, a reliable translation of biological data into the context of clinical patient care is currently lacking, not yet allowing for a personalized strategy in the majority of MCL cases.

**MCL: is transplant dead or alive?**

Given that a high-dose schedule containing cytarabine and rituximab, followed by an ASCT, is nowadays widely recognized as the standard of care for younger patients affected by MCL, some important considerations should be made that might change the therapeutic scenario in the upcoming years.

First of all, the valuable results in terms of improved survival rates after high-dose therapy and ASCT consolidation are counterweighted by non-negligible toxicities, as previously described.<sup>7</sup> Given that some patients do not

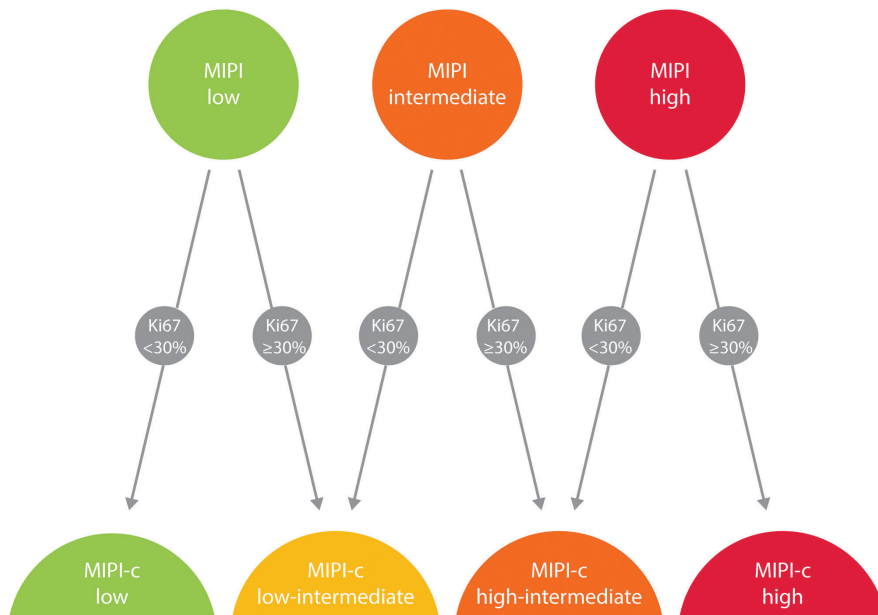
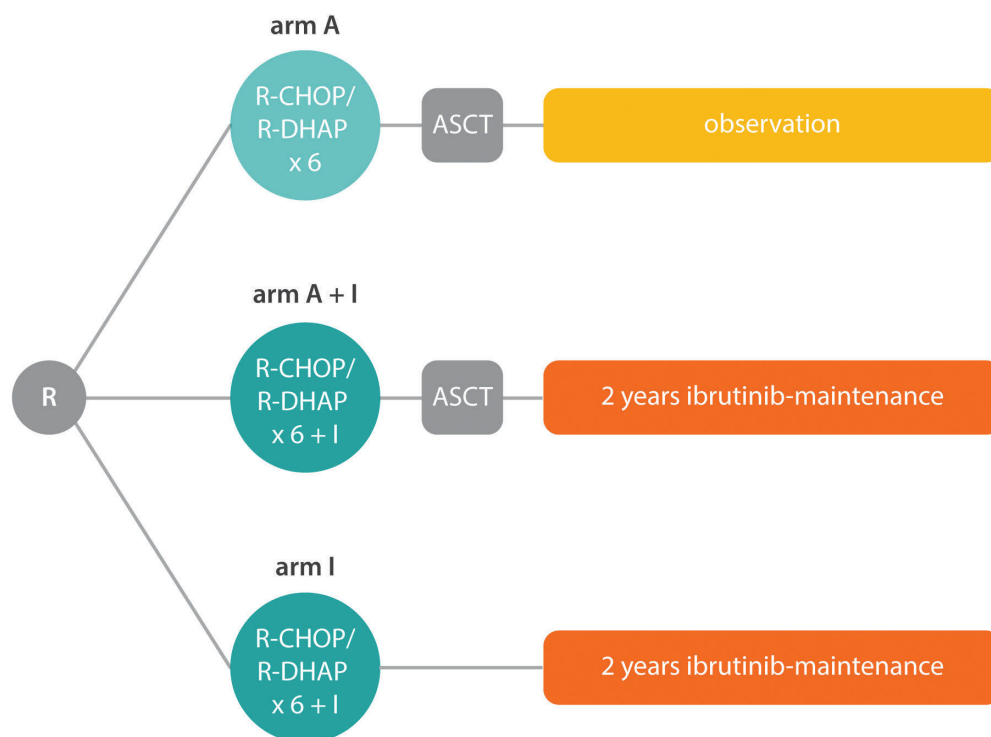


Figure 1. Alternative combination of Ki-67 index and MIPI: MIPIc. MIPI-c: combined mantle cell lymphoma international prognostic index.



**Figure 2.** Schematic representation of the “Triangle” trial by the European MCL Network. MCL: mantle cell lymphoma; R: randomization; ASCT: autologous stem cell transplantation; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAP: rituximab, dexamethasone, cytarabine and cisplatin.

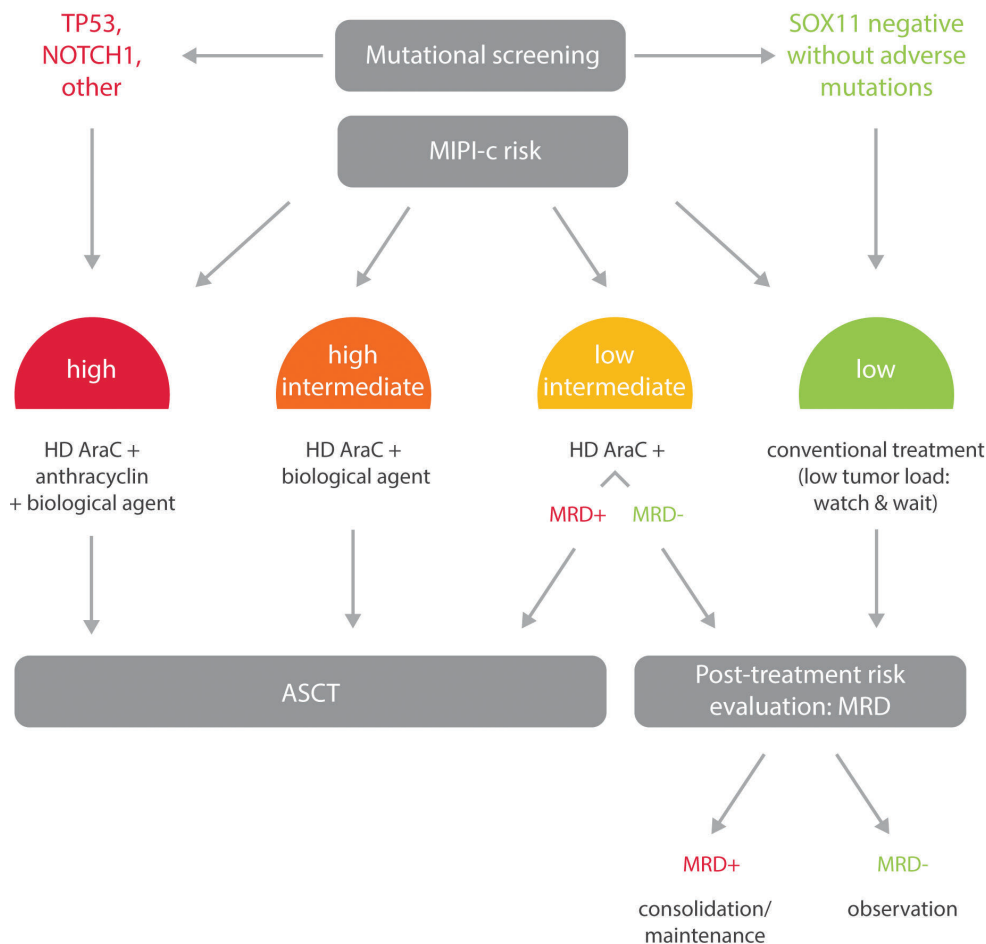
need immediate treatment (the clinically defined “indolent MCL”, potentially identified by the lack of *SOX11* expression),<sup>95-97</sup> and others benefit from very long remissions after ASCT, it is reasonable to challenge the value of intensified treatment in these patients in order to avoid unnecessary toxicities. In this context, the recent improvements in induction schemes,<sup>34,98</sup> as well as the very promising data on rituximab maintenance,<sup>41</sup> even after ASCT,<sup>42</sup> strongly suggest a more sustained PFS, especially in younger patients.

Moreover, the high activity of the targeted drugs as a single-agent in relapsed patients has prompted their investigation in combination with immunochemotherapy in first-line trials.<sup>51,62</sup> Their impact on long-term survival will potentially result in new options for first-line treatment, and might challenge the current role of ASCT consolidation. This is precisely the concept of the upcoming phase III trial “Triangle” by the European MCL Network (EudraCT Number 2014-001363-12), assessing whether the implementation of a BTK-inhibitor in first-line treatment could eliminate the need for an ASCT consolidation in younger patients. In detail this trial offers a randomization between conventional induction R-CHOP/R-DHAP + ASCT, *versus* the identical scheme with the addition of ibrutinib, *versus* R-CHOP/R-DHAP + ibrutinib without ASCT (Figure 2). However, this trial does not implement personalized treatment according to the discussed prognosticators.

Interestingly, some important data on the value of ASCT are emerging from MRD studies, supporting the concept of “dispensable therapy”. High-dose consolidation followed by ASCT demonstrated a high impact on tumor reduction in the pooled treatment arms (R-CHOP vs. R-CHOP/R-DHAP) of the European MCL Network

“Younger” trial, increasing the MR rate from 50% to 75% ( $P=0.0001$ ). However, this improvement was prominent only in the R-CHOP arm (29% to 65%;  $P=0.0023$ ), while detectable but not statistically significant after the more effective R-CHOP/R-DHAP arm (76% to 88%;  $P=0.18$ ). Remarkably, MR after induction was associated with a significantly improved remission duration (89% vs. 74% at 24 months,  $P=0.002$ ), and sustained MR during the first year after ASCT was also predictive for outcome.<sup>35</sup> This observation underlines the important role of cytarabine in inducing sustained MR in MCL. Thus, it may be speculated that patients already achieving MR after high-dose cytarabine plus rituximab induction might do well without ASCT consolidation. Conversely, patients with persistent MRD positivity after a highly effective cytarabine induction might not benefit from ASCT, and thus may be potential candidates for experimental strategies. In accordance, such molecular results have been recently presented for the Italian “MCL0208” trial: preliminary MRD data demonstrate only a marginal improvement of the MR rate (from 67% to 73%) after ASCT.<sup>99</sup> Of course, these MRD results have to be confirmed by subsequent PFS results: however, in our opinion, they should prompt the investigation of MRD-guided personalized treatment strategies.

Finally, despite their high efficacy, ASCT based regimens do not lead to complete eradication of the disease. Actually, even among long-term responders, late relapses still continue to occur up to 10 years after the transplantation.<sup>39</sup> In addition, MRD reappearance has shown to herald full-blown relapse (with a median time to clinical relapse of 18 months).<sup>84</sup> Thus, even after ASCT, effective maintenance therapies have to be considered<sup>42</sup> and MRD-driven pre-emptive treatments may be investigated in the context of maintenance trials. Finally, a problem which



**Figure 3. Suggested personalized treatment strategy according to risk stratification in mantle cell lymphoma (MCL).** MIPI-c: combined MCL International Prognostic Index; MRD: minimal residual disease; ASCT: autologous stem cell transplantation; HD AraC: high-dose cytarabine-based regimen.

remains unresolved are the “very high-risk” patients, in whom the standard high-dose + ASCT approach does not result in long-term disease control.<sup>88</sup> There is an urgent need to identify those patients at baseline, in order to investigate new front-line approaches, tailored on the high risk of early disease progression. Currently, some genomic alterations have been described, predicting high risk of treatment failure: in particular *p53* and *CDK2N* mutations, as well as complex karyotype mutations.<sup>94,100</sup> Those patients who are refractory to intensified therapies and ASCT are appropriate candidates to explore new, targeted approaches or to undergo immunological approaches, such as allogeneic transplantation or the recently described chimeric antigen receptor T cells.<sup>101</sup> However, all of these therapeutic approaches have to be further investigated in the context of well-designed clinical trials, carefully weighing the pros and cons. In this regard, concerns are actually rising about the unsustainable costs of the unselected use of targeted drugs, as well as their long-term toxicity; very little is known about their role in inducing subsequent aggressive transformations of the disease.<sup>102</sup>

On the basis of all these considerations we propose a rational strategy of “personalized first-line treatment” for younger MCL patients, to be investigated in a clinical trial (Figure 3). In our model risk stratification is based on MIPI-c and mutational analysis at baseline, and MRD evaluation during therapy: low-risk and MRD negative low-intermediate risk patients may not proceed to ASCT consolida-

tion, while high-intermediate and high-risk patients should receive a combined chemotherapy induction with biological agents; finally, consolidation and maintenance strategies may be carried out in all patients based on the post-treatment MRD result.

## Conclusions

The clinical scenario of MCL has completely changed during the last years due to the availability of highly effective targeted drugs, as well as reliable predictive tools determining the prognostic heterogeneity of such patients. Currently, a high-dose immunochemotherapeutic regimen based on cytarabine and rituximab, supported by ASCT, is the standard of care for younger patients, in spite of its non negligible toxicity. However, recent biological insights on MCL molecular pathogenesis are paving the way for both the development of new drugs and refined prognostication. Therefore, it is likely that in the near future the therapeutic approach in this disease will become more and more personalized, based on the individualized risk of relapse, and potentially ASCT will be reserved only for those cases who will really benefit from this effective, but toxic procedure.

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