

New Paradigms in Mantle Cell Lymphoma: Is It Time to Risk-Stratify Treatment Based on the Proliferative Signature?

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Abstract

The elucidation of crucial biologic pathways of cell survival and proliferation has led to the development of highly effective drugs, some of which have markedly improved mantle cell lymphoma (MCL) therapeutic opportunities in the past 10 years. Moreover, an undeniable clinical heterogeneity in treatment response and disease behavior has become apparent in this neoplasm. Thus, the need for biologic markers stratifying patients with MCL in risk classes deserving different treatment approaches has recently been fervently expressed. Among several newly discovered biomarkers, the dismal predictive value of a high proliferative signature has been broadly recognized in large studies of patients with MCL. Different techniques have been used to assess tumor cell proliferation, including mitotic index, immunostaining with Ki-67 antibody, and gene expression profiling. Ki-67 proliferative index, in particular, has been extensively investigated, and its negative impact on relapse incidence and overall survival has been validated in large prospective clinical trials. However, one important pitfall limiting its widespread use in clinical practice is the reported interobserver variability, due to the previous lack of a standardized approach for quantification among different laboratories. In the present review, we describe some of the major techniques to assess cell proliferation in MCL, focusing in particular on the Ki-67 index and its need for a standardized approach to be used in multicenter clinical trials. The value of MCL biologic prognostic scores (as MIPI-b) is discussed, along with our proposal on how to integrate these scores in the planning of future trials investigating a tailored therapeutic approach for patients with MCL.

See all articles in this CCR Focus section, "Paradigm Shifts in Lymphoma."

Clin Cancer Res; 20(20); 5194–206. ©2014 AACR.

Introduction

The articles in this edition of *CCR Focus* deal with some current and intriguing issues on lymphomas, particularly about pathogenesis and new "smart" treatment approaches, targeting some peculiar genetic alterations or personalizing therapies on the basis of specific biomarkers (1–5). Accordingly, this review focuses on new treatment strategies for mantle cell lymphoma (MCL), describing the current evidence supporting the need for a therapeutic modulation based on its proliferation signature.

MCL is a rare entity, accounting for 6% to 8% of all lymphomas, formerly characterized by poor responses to conventional combination chemotherapy and dismal prognosis (6). However, in the past decade, the clinical scenario for patients with MCL has significantly improved (7). The addition of the anti-CD20 monoclonal antibody rituximab to the classic treatment backbone has increased clinical responses and prolonged time to treatment failure (TTF) and overall survival (OS; refs. 8, 9). In addition, the introduction of intensified schedules, based on high-dose cytarabine and autologous stem cell transplantation (ASCT), achieves durable clinical remissions (up to 8–10 years) in younger patients at the price of a generally manageable toxicity (10–14). Finally, the rediscovered efficacy and tolerability of bendamustine and the application of rituximab maintenance achieved longer progression-free survival (PFS) in elderly patients as well (15, 16). Recently, discoveries concerning the molecular pathogenesis of MCL have led to the introduction of innovative compounds (such as bortezomib, temsirolimus, lenalidomide, and ibrutinib), which are now also being tested in a variety of combinatorial approaches (17–20).

However, from a clinical point of view, MCL is still a heterogeneous neoplasm, ranging from indolent cases not requiring treatment for years to aggressive, rapidly progressing disease (21). Thus, diagnostic tools that can stratify

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doi: 10.1158/1078-0432.CCR-14-0836

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patients with MCL in different risk classes are urgently warranted, to allow tailored strategies with treatment intensification only in high-risk cases, sparing toxicities in more indolent diseases. Minimal residual disease (MRD) analysis has been demonstrated to be a reliable posttreatment predictor, allowing for the identification of patients with high risk of relapse (22). On the other hand, among all prognosticators evaluated so far, only the proliferative activity of lymphoma cells has been confirmed to identify high-risk cases with poor PFS and OS (23–25). Other biomarkers have been investigated as well, but they are mostly related to proliferation and lose their independent significance in multivariate analysis, or have not yet been properly evaluated in comparison with proliferation (26–28).

In the present review, we offer the pathologist's point of view on cell proliferation, describe current investigational techniques, and introduce the published standardized guidelines for assessing this feature of the disease. We also present the clinical impact of cell proliferation in MCL, report the results from the most relevant series of patients so far, and discuss the value of the current available biologic prognostic scores. Finally, we comment on the practical application of these scores to investigate a personalized treatment for patients with MCL and propose a combined risk-adapted strategy, based on proliferation and MRD, deserving to be explored in future trials.

MCL as a Paradigm of Cell-Cycle Dysregulation

MCL is a B-cell neoplasm characterized by the translocation $t(11;14)(q13;q32)$ in the majority of patients (6). This translocation juxtaposes the cyclin D1 (*CCND1*) gene at chromosome 11q13 to the immunoglobulin heavy chain gene (*IGH*) at chromosome 14q32. Under the influence of the *IGH* enhancer, *CCND1* is constitutively overexpressed. Thus *CCND1* protein, not detectable in physiologic lymphoid tissue, is a useful marker for the diagnosis of MCL (6, 29). *CCND1* promotes the transition from the G_1 to the S phase of the cell cycle. Therefore, MCL is regarded as the paradigm of a lymphoma with increased proliferation due to impaired cell-cycle regulation.

A proliferation signature obtained by gene expression profiling (GEP) correlates with *CCND1* mRNA expression (27). Correspondingly, *CCND1* mRNA levels are higher in

MCL with Ki-67 > 30% (30). Moreover, the relative abundance of *CCND1* mRNA truncated variant is associated with higher proliferation and poor outcome (27, 31). However, the causal relationship between *CCND1* and proliferation rate is not fully understood, because no direct association between Ki-67 index and *CCND1* expression has been observed (32, 33). Accordingly, *CCND1* downregulation in MCL cell lines leads to variable results with regard to cell-cycle control, proliferation, and cell viability (34–36).

Features of MCL Correlating with Cell Proliferation

In addition to *CCND1*, several other features correlate with cell proliferation. MCL blastoid variant is characterized by higher Ki-67 and mitotic index (MI), dismal prognosis, and abundant genetic alterations, such as chromosome 17p losses or *TP53* mutations (6, 23, 33, 37–41). Thus, overexpression of p53 reflecting *TP53* mutations is associated with a higher proliferation rate (33, 38). Conversely BIK, a BCL2-interacting proapoptotic protein, was shown to be downregulated in highly proliferative MCL (42). A 32-gene expression signature was identified comparing MCL with low and high proliferation rate. These genes are involved in mitotic spindle formation, gene transcription, and cell-cycle regulation, but many might be a consequence of rather than the cause of cell proliferation (30). Moreover, MCL proliferation rate has a tendency to increase over time, as shown in comparative analyses of sequential biopsies (41, 43). However, the molecular features that functionally determine the lymphoma proliferation rate have not yet been defined.

Current Technologies to Assess Proliferation

The methods to assess proliferation in MCL are similar to those for other tumors (like breast cancer) and include MI, Ki-67 index, other IHC proliferation markers, and various GEP methods. However, the technical prerequisites and the level of evidence for these methods differ significantly (Table 1).

Mitotic index

The MI is assessed by counting mitotic events per high-power field (HPF). Thus, the number of mitoses identified is

Table 1. Overview of current techniques to assess cell proliferation in MCL

Technique	Technical requirements	Availability	Level of evidence ^a
Mitotic count	Low	Widespread	Moderate
IHC for Ki-67	Low	Restricted	High
IHC for topoisomerase 2 α	Low	Restricted	Moderate
IHC for MDM2	Low	Restricted	Moderate
IHC for pH3	Low	Restricted	Low
Gene expression analysis	High	Highly restricted	Moderate

^aHigh, validated in prospective randomized trials with immunochemotherapy; moderate, validated in heterogeneously treated or small cohorts only; low, not validated in MCL.

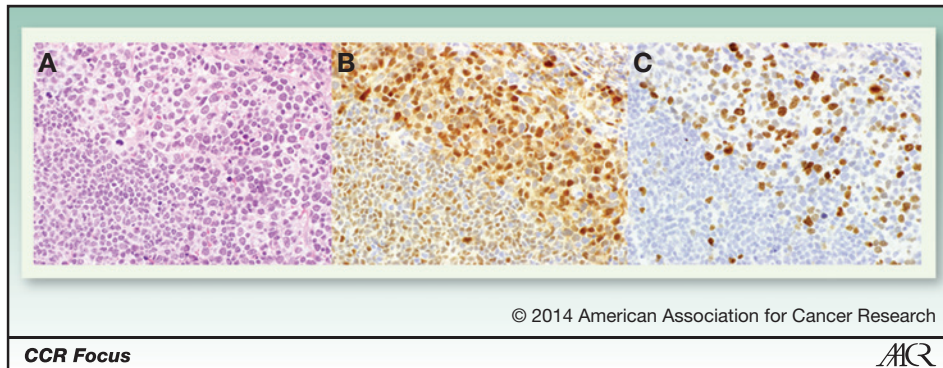


Figure 1. Ki-67 immunostaining. A relatively rare situation of a MCL with two differentiated populations of lymphoma cells. A classic cytology with low proliferation is shown in the left lower corner and a blastoid cytology with high proliferation in the right upper corner (A, H&E; B, cyclin D1; C, Ki-67).

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not related to cell numbers but to areas of lymphoma tissue. This technique is well established for grading of solid neoplasms. Available studies of MCL assessed MI in five or ten selected HPF (representing a 1–2 mm² area, respectively; ref. 23). Two large retrospective analyses assessed MI in 272 (23) and 121 patients (44), respectively. Both studies showed a strong correlation between MI, Ki67-index, and OS (23, 44). The MI is assessed in conventional hematoxylin and eosin (H&E)-stained slides of formalin-fixed paraffin-embedded (FFPE) tissue and is thus widely applicable without technical obstacles.

Ki-67 index and other immunohistochemically assessed proliferation markers

Using IHC, cell proliferation can be assessed by detecting the expression of several proteins. Although FFPE tissue can be easily used, technical requirements are higher than for an H&E. However, the more widespread use of automated antigen retrieval and staining devices, as well as quality assessment by interlaboratory tests, improved its reliability. Despite being widely used in scientific studies, biomarkers based on standard IHC techniques suffer from poor reproducibility, challenging the use of these techniques for clinical decision making (45). Most of the interobserver variability might be due to the varying procedure of analysis ("eye balling"; refs. 45, 46).

Proliferation markers studied in MCL include Ki-67, topoisomerase II α , MDM2, repp86, and survivin (47–51). However, except for Ki-67, none of these biomarkers have to date been validated in larger cohorts (Table 1). MDM2 is expressed in G₁, S, G₂, and M; Ki-67 and topoisomerase II α in late G₁, S, G₂, and M; survivin and repp86 only in G₂ and M phase. Thus, the major difference between these markers is their differential expression pattern throughout the phases of the cell cycle. Therefore, selection of one marker for clinical decision making should be primarily based on widespread availability. Conversely, the phosphorylated histone H3, which detects only cells in M-phase, may become a more specific tool but has not been studied in MCL so far (52).

The most commonly used proliferation marker is Ki-67, which is expressed in late G₁, S, G₂, and M-phase. The Ki-67 index is defined as the percentage of lymphoma cells positive for Ki-67; thus, the interobserver variability can be

reduced by counting a defined number of cells (53, 54). On the basis of our previous analyses, we recommend counting in two fields of view with 100 cells each.

The prognostic significance of Ki-67 at diagnosis was demonstrated in large patient cohorts, with survival differing up to 3 years (23, 44, 55). One study confirmed the Ki-67 index also in relapsed MCL (41). In contrast with other techniques (including MI and GEP), the Ki-67 index was proven to predict outcome also in randomized trials of rituximab-containing regimens (24). Moreover, as a unique feature, the Ki-67 index remains an independent prognostic factor even if incorporated into the MCL International Prognostic Index (MIPI; refs. 25, 56). The variability of Ki-67 immunostaining is shown in Fig. 1.

Gene expression profiling

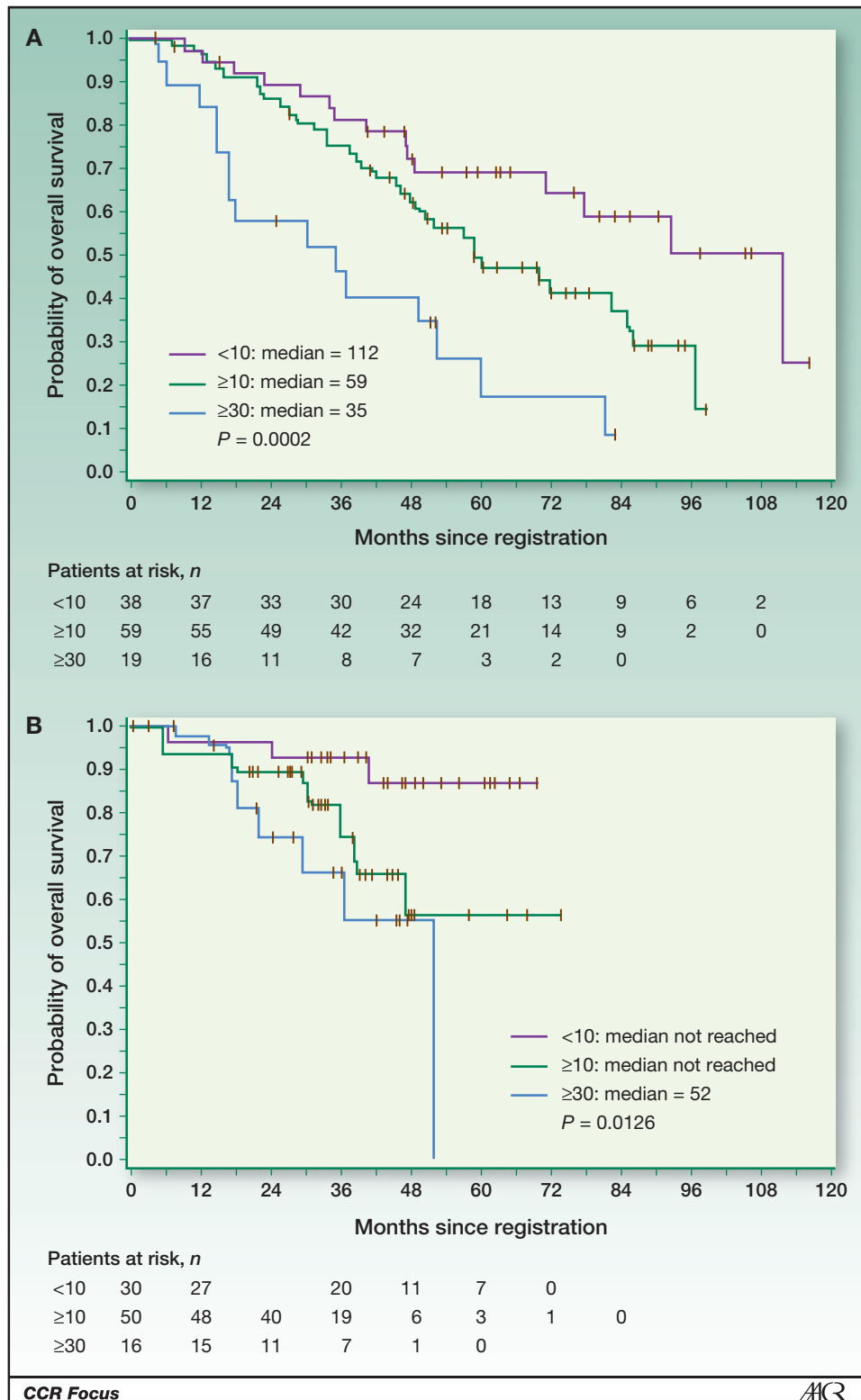
GEP assesses mRNA extracted from bulk tissue and thus can only indirectly be related to a cell-based assay such as the Ki-67 index. The majority of genes associated with outcome in MCL are expressed in a proliferation-dependent manner (27). This proliferation signature was later used as a basis for the development of a quantitative PCR assay successfully applied to FFPE tissue (57). Another 26-gene expression signature also showed prognostic significance, but, similar to the PCR-based assay, incorporated additional proliferation-independent genes (42). The great advantage of GEP is its quantitative nature. However, GEP still suffers from some limits, hampering its use in clinical trials. First, interlaboratory tests have not yet been published to the best of our knowledge. Second, the bioinformatic analyses of published GEP data are not easily transferable because they are not yet based on standardized commercially available assays (27, 42). Third, although new technologies such as digital multiplexed GEP (58, 59) might overcome many technical limitations, the RNA extraction from FFPE tissue still remains a challenging task.

ESMO Recommendations to Assess Proliferation in MCL

The Ki-67 proliferative antigen is the most applicable and discriminative method to evaluate proliferation in MCL, so far (54). However, its major limitation for clinical practice is the lack of reproducibility among different pathologists (45). In clinical studies, the Ki-67 index should be evaluated consistently by the same observer, following established

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Figure 2. Impact of Ki-67 proliferative index on survival. Kaplan–Meier plot for OS of patients treated with CHOP (A) and R-CHOP (B) stratified in three groups according to the Ki-67 index of less than 10%, 10% to less than 30%, and 30% or more Ki-67-positive cells. Republished with permission of the American Society of Hematology from ref. 24: Determann O, Hoster E, Ott G, Wolfram Bernd H, Lodenkemper C, Leo Hansmann M, et al. Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group. *Blood* 2008;111:2385–7. Permission conveyed through Copyright Clearance Center, Inc.



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guidelines (54). Thus, Ki-67 staining is recommended in routine practice as a prognostic indicator, but the results should be evaluated with caution, particularly when com-

paring studies from different institutions (ESMO consensus conference 2013, MCL; Level of evidence: I; Grade of recommendation: A; ref. 60).

Prognostic Impact of Ki-67 Proliferation Rate

When the world-wide distinction of MCL was established in the Revised European–American Classification of Lymphoid Neoplasms (REAL) classification in 1994 (61), a low proliferative index was associated with a better outcome. In 1996, Velders and colleagues described the clinical impact of Ki-67 immunostaining on a small series of 29 patients with MCL (62). Similar results had also been reported by Leith and colleagues (63) in 33 cases of diffuse small cleaved-cell lymphoma, a pre-REAL denomination most likely including cases of MCL. Another report from the University of British Columbia (Vancouver, Canada) subsequently confirmed the dismal prognostic value of high MI in 80 patients with MCL (64). In 2002, a larger series of 127 Finnish cases confirmed that high Ki-67 was associated with shortened survival in multivariate analysis (44).

In 2005, the European MCL Network performed a large clinicopathologic study on 304 patients with MCL heterogeneously treated in the context of different prospective trials (23). A high proliferation rate was again associated with shorter OS. Two hundred and seventy-two cases were assessed by MI and 187 by Ki-67; as expected, a strong correlation between the two indexes was found ($P < 0.0001$). Moreover, the prognostic role of cell proliferation and its superiority to all other histomorphologic and clinical criteria were confirmed in multivariate analyses.

A subsequent study by the European MCL Network confirmed the Ki-67 predictive value in 249 advanced-stage MCL patients, treated at diagnosis with CHOP \pm rituximab in a prospective, randomized trial (Fig. 2; ref. 24). As a continuous parameter, Ki-67 showed strong prognostic relevance for OS with a relative risk (RR) of 1.27 for 10% higher Ki-67 [95% confidence intervals (CI), 1.15–1.39, $P < 0.001$] independently from the MIPI prognostic score (adjusted RR 1.20; 95% CI, 1.09–1.33, $P < 0.001$) and treatment arm. Thus, the authors concluded that Ki-67 index might be the first biologic parameter for risk stratification of MCL in the rituximab era.

In a multivariate analysis, the Nordic Lymphoma Group confirmed Ki-67 as the sole independent predictor of EFS in a series of 160 younger patients treated with high-dose cytarabine and ASCT (13). Moreover, in an

updated report, a Ki-67 $>33\%$ remained predictive for shorter OS (65).

More recently, Hoster and colleagues described the clinical impact of Ki-67 staining in the largest MCL series available so far (66). A total of 543 patients receiving current standard of care (chemo-immunotherapy \pm high-dose consolidation) were included in the study. Patients with Ki-67 $\geq 30\%$ had median TTF and OS of 19 and 45 months compared with 64 months and not reached with Ki-67 $< 30\%$ ($P < 0.0001$ each). The separation of a high-risk group as defined by Ki-67 $\geq 30\%$ was consistently seen within both trials, as well as the different treatment arms (Table 2). The authors concluded that Ki-67 evaluation should be integrated in clinical routine to potentially allow a more individualized therapeutic approach in MCL.

Is There a Role for a Biologic MIPI?

When the MIPI prognostic index was established, the proliferation marker Ki-67 was also considered in the analysis, in an attempt to develop a combined biologic index (MIPI-b). MIPI-b was calculated as $[0.03535 \times \text{age (years)}] + 0.6978$ (if ECOG > 1) $+ [1.367 \times \log_{10}(\text{LDH/ULN})] + [0.9393 \times \log_{10}(\text{white blood cell count})] + [0.02142 \times \text{Ki-67 (\%)}]$; low risk was defined when a score is < 5.70 , intermediate when it is 5.70–6.49, and high risk when it is ≥ 6.50 (56). However, the authors concluded that a combined MIPI-b was not yet applicable outside of clinical studies.

In a study by Geisler and colleagues of 119 uniformly treated evaluable patients, MIPI-b was an independent prognostic marker and divided patients into two groups, low/intermediate and high risk (65). Of note, in the MIPI-b low-risk group, no relapse was reported later than 4 years after end of treatment. Moreover, the feasibility of a simplified version of MIPI-b was described (Table 3; refs. 65, 67). Similar observations have been reported from another recently published trial (68).

Finally, in the MIPI validation study of an independent cohort of 958 patients with MCL, the high-risk group according to MIPI-b revealed a substantially worse outcome both in younger and elderly patients, as shown in Fig. 3 and Table 4 (25).

Table 3. Simplified MIPI-b calculation

Points	Age, y	ECOG performance status	LDH/ULN	Leukocytes ($\times 10^9/L$)	Ki-67 (%)
0	<50	0–1	<0.670	<6,700	<30
1	50–59	—	0.670–0.999	6,700–9,999	≥ 30
2	60–69	2–4	1.000–1.499	10,000–14,999	—
3	>69	—	>1.499	>14,999	—

NOTE: For each prognostic factor, 0 to 3 points are given to each patient and points are summed up to define a category of risk: 0–3 points, low risk; 4–5 points, intermediate risk; 6–11 points, high risk.

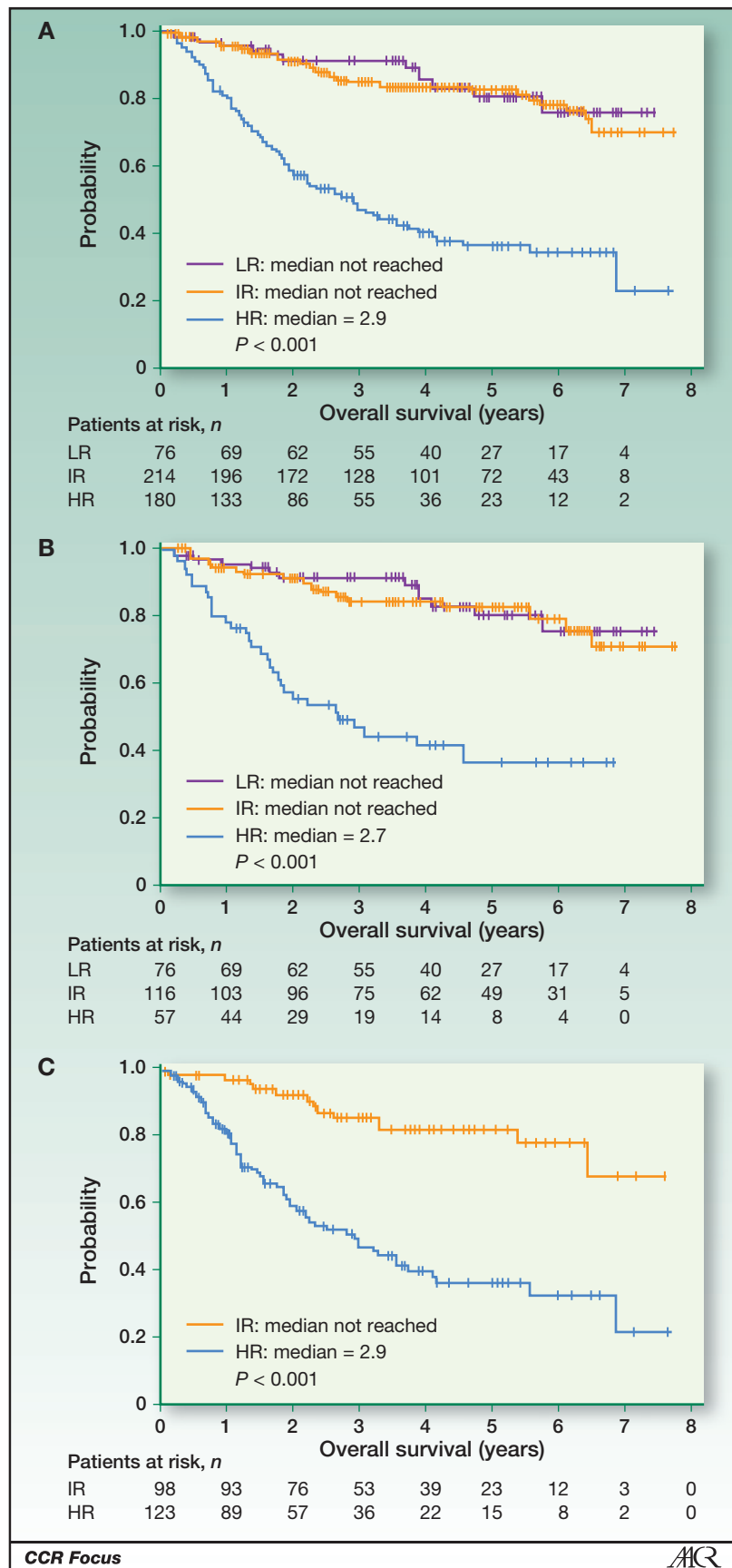
Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 4. Published studies investigating the predictive value of MIPI-b in patients with MCL

Studies	Involved clinical trials	Therapeutic regimen	Evaluable patients	5-y OS (%)	P	HR for OS ^a	95% CI	P
Hoster et al. (56)	GLSG1996/GLSG2000	Conventional chemotherapy ± rituximab ± ASCT consolidation ± IFN α maintenance	236	LR 76; IR 48; HR 17	<0.001	NA	NA	NA
Geisler et al. (67) & 2012 (65)	ISRCTN 87866680	High-dose Ara-C-containing chemotherapy + rituximab + ASCT	119	LR 93; IR 84; HR 47	<0.001 ^b	2.64	1.61–4.32	0.001
Kolstad et al. (68)	NCT00514475	High-dose Ara-C + rituximab + ASCT ± ibitrimumab tiuxetan	142	NA	NA	3.52	1.69–7.31	0.001
Hoster et al. (25)	Elderly: NCT00209209/ Younger: NCT00209222	Elderly: conventional chemotherapy + rituximab + maintenance (rituximab vs. IFN α)/ Younger: chemotherapy ± high-dose Ara-C + rituximab + ASCT	958	LR 81; IR 83; HR 37	<0.001	2.38	1.89–3.01	<0.001
Husby et al. (69) ^c	ISRCTN 87866680/ NCT00514475	High-dose Ara-C-containing chemotherapy + rituximab + ASCT ± ibitrimumab tiuxetan	172	LR 94; IR 63; HR 21 ^c	<0.001	NA	NA	NA

NOTE: The table describes the main clinical results of the studies reported in the text.
 Abbreviations: Ara-C, cytarabine; GLSG, German Low-grade Lymphomas Study Group; LR/IR/HR, low/intermediate/high risk, according to MIPI-b; NA, not available; ISRCTN, International Standard Randomised Controlled Trial Number; NCT, National Clinical Trial; y, years.
^aHR in multivariate analysis.
^bOnly LR vs. HR and IR vs. HR.
^cThis study proposes a new biologic MIPI, integrating the classic MIPI-b with miRNA profiling (MIPI-b-miR).

Figure 3. Impact of MIPI-b on survival. Kaplan–Meier plot for OS of patients according to MIPI-b in pooled trials (A), MCL Younger trial (B), and MCL Elderly trial (C). Patients with MIPI-b score below 5.70 were classified as low risk (LR), patients with MIPI-b score ≥ 5.70 but ≤ 6.50 as intermediate risk (IR), and patients with an MIPI score of 6.50 or higher as high risk (HR). Reprinted with permission from Hoster et al. (25). © 2014 American Society of Clinical Oncology. All rights reserved. Hoster E, Klapper W, Hermine O, Kluin-Nelemans HC, Walewski J, van Hoof A, et al. Confirmation of the mantle-cell lymphoma international prognostic index in randomized trials of the European Mantle-cell Lymphoma Network. *J Clin Oncol* 2014;32:1338–46.



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Because classic MIPI is suboptimal in identifying high-risk cases among younger patients, an integration of Ki-67 index has been recommended to improve MIPI stratification power. Recently, the clinical-biologic risk score MIPI-b has been combined with microRNA profiling (MIPI-b-miR), which seems to further segregate patients between low- and intermediate-risk groups, as well as identifying very high-risk patients (69). Although not yet

validated and not easily applicable in clinical practice, this new prognostic score highlights the need for a biologic MIPI to improve the predictive value of clinical parameters alone.

Looking for a Tailored Therapy in MCL

Due to the heterogeneity of MCL, there is no uniform treatment that fits all cases. Thus, conventional

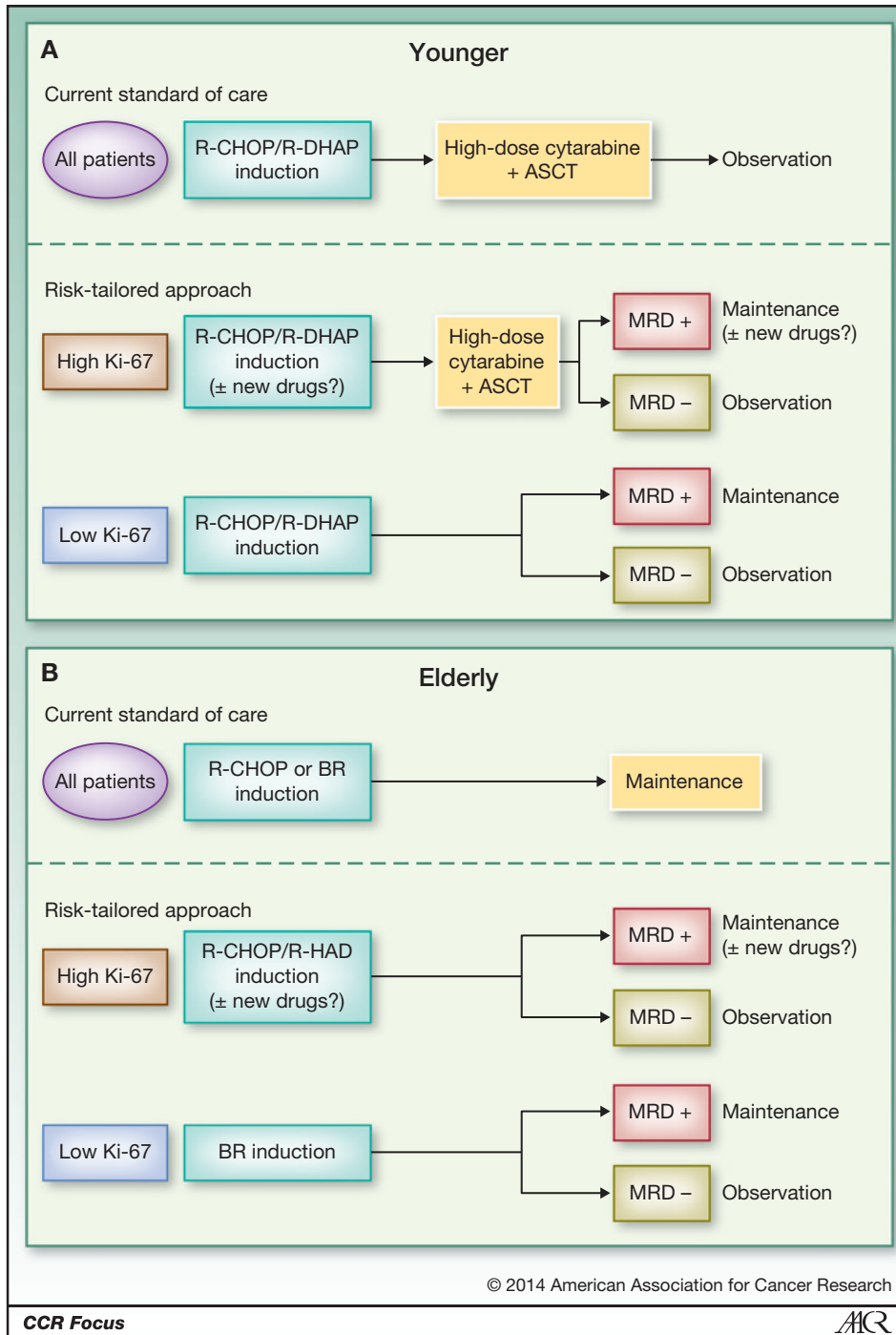


Figure 4. Proposal for a tailored therapeutic approach in MCL. Standard and hypothesized tailored therapeutic approach, based on Ki-67 index and MRD, for first-line younger (A) and elderly (B) MCL patients. R, rituximab; CHOP, cyclophosphamide–doxorubicin–vincristine–prednisone; DHAP, dexamethasone–cytarabine–cisplatin; BR, bendamustine–rituximab; HAD, cytarabine–dexamethasone.

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therapeutic decision making, based on age and comorbidities, is no longer appropriate for such a complex lymphoma subtype. As of today, younger and fit patients with MCL receive, as a standard-of-care, R-CHOP/R-DHAP induction (or other cytarabine-based intensified immunotherapy), followed in responding cases by ASCT (Fig. 4A; ref. 21), independent of high- or low-risk disease at diagnosis. Similarly, elderly or young unfit patients undergo upfront R-CHOP (or bendamustine-rituximab; BR) immunotherapy followed by rituximab maintenance, again irrespective of their particular risk profile. (Fig. 4B; ref. 21). It is likely that some patients are overtreated, whereas others are potentially undertreated, with this approach. In fact, an objective tool to reliably identify indolent MCL is still lacking, with the most applicable method relying on clinical parameters and close patient observation (60, 70–73). For patients requiring treatment, MIPI is the most important prognostic tool, as well as Ki-67 proliferative index and MIPI-b (13, 65–68). Nevertheless, to the best of our knowledge, only one clinical trial ("MCL5," from the Nordic Lymphoma Group, EudraCT 2011-001557-85) offering tailored therapies has been performed to date (74). MCL5 was launched in 2011, aimed at improving the outcome of younger patients with MCL with high-risk MIPI or MIPI-b. On the basis of the expected pharmacologic efficacy of the cell cycle active drug cytarabine in highly replicating cells (75) and on the promising results in recent MCL clinical trials (13, 14, 76), this protocol consisted of a high-dose cytarabine-containing induction followed by ASCT. Unfortunately, MCL5 was closed very early due to the limited efficacy of the treatment in the initially enrolled patients. Thus, higher doses of cytarabine alone are most likely not sufficient to overcome the dismal role of proliferation, supporting the hypothesis that anthracycline combinations are still worthwhile (74).

These results highlight the urgent need for tailored approaches in MCL and the current lack of long-lasting effective drugs for this small, but not negligible subgroup of high-risk patients. Recently, several targeted drugs have raised the interest of clinicians due to their reported unprecedented efficacy and tolerability in heavily pretreated patients (17–20). Unfortunately, none of these agents has been demonstrated to be more active in highly proliferating MCL, simply because the Ki-67 value was not determined in these clinical studies. However, as the Bruton tyrosine kinase inhibitor (77) ibrutinib directly blocks the survival signal of the B-cell receptor pathway, it is tempting to speculate that this compound in combination with cytarabine may especially benefit the high-risk patients.

Thus, such tailored approaches and new drug combinations need to be investigated in future trials. It is evident that every study moving forward in MCL should quantify the proliferative index in every patient. It is clear that failure to incorporate this important biologic feature of the disease will preempt our ability to interpret the

impact of one agent over another, and to understand the implications of proliferative index on response. A study design offering patients therapeutic options of increasing intensity, based on their MIPI-b score, represents an intriguing option; a subsequent consolidation, maintenance, or preemptive therapy might be given only in those cases with an increased relapse risk due to the persistence or reappearance of MRD (22,78–80). A preliminary proposal for such a personalized therapeutic approach in MCL, based on upfront Ki-67 evaluation and posttreatment MRD stratification, is presented in Fig. 4.

Finally, a refined version of the MIPI-b that integrates other biomarkers may further improve the reliability of a risk-adapted therapeutic approach (69, 81, 82).

Conclusions

Reliable prognostic tools are urgently needed in MCL to offer personalized therapy in clinical routine (21). The proliferation signature has been generally accepted as the most important biologic prognostic factor with a strong impact on both EFS and OS (24). Accordingly, the most broadly applied Ki-67 index has been validated in several prospective clinical trials (13, 25, 56). However, the recent validation of MIPI-b, including clinical parameters and Ki-67, is only the first step to investigate risk-adapted tailored therapies in the context of future trials (25, 56).

Disclosure of Potential Conflicts of Interest

M. Dreyling reports receiving speakers bureau honoraria from Celgene, Gilead, Janssen, Mundipharma, and Roche, and is a consultant/advisory board member for Bayer, Celgene, Janssen, and Pfizer. S. Ferrero reports receiving speakers bureau honoraria from Mundipharma. W. Klapper reports receiving a commercial research grant from Roche and speakers bureau honoraria from Takeda/Millennium. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

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Acknowledgments

The authors thank Antonella Fiorillo for excellent secretarial support.

Grant Support

S. Ferrero was supported by Progetti di Ricerca Finalizzata 2008, head unit: IRCCS Centro di Riferimento Oncologico della Basilicata (CROB), Rionero in Vulture (Potenza), Italy (code: 7.07.08.60 P49); Progetto di Ricerca Sanitaria Finalizzata 2008, head unit: Divisione di Ematologia S. Cortelazzo, A. O. S. Maurizio, Bolzano/Bozen, Italy, (code: 7.07.08.60 P51); Progetto di Ricerca Sanitaria Finalizzata 2009, head unit: Divisione di Ematologia S. Cortelazzo, A. O. S. Maurizio, Bolzano/Bozen, Italy (code: RF-2009-1469205); Progetto di Ricerca Sanitaria Finalizzata 2010, head unit: Divisione di Ematologia, A. O. S. Maurizio, Bolzano/Bozen, Italy, (code: RF-2010-2307262); and Progetti di Ateneo 2012—Finanziatore Compagnia di San Paolo (code: TO_call03_2012_0055).

Received June 26, 2014; revised August 5, 2014; accepted August 20, 2014; published online October 15, 2014.

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