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Mantle Cell Lymphoma: Contemporary Diagnostic and Treatment Perspectives in the Age of Personalized Medicine

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Received 6 October 2015; accepted 20 February 2017
Available online 6 April 2017

KEYWORDS Mantle cell lymphoma; Prognosis; Treatment

Abstract Mantle cell lymphoma is a clinically heterogeneous disease occurring within a heterogeneous patient population, highlighting a need for personalized therapy to ensure optimal outcomes. It is therefore critical to understand the benefits and risks associated with both intensive and deintensified approaches. In the following review we provide a therapeutic roadmap to strategically guide treatment for newly diagnosed and relapsed/refractory patients highlighting pivotal and recently published results involving known and novel therapies.

Introduction Mantle cell lymphoma (MCL) is an uncommon B-cell malignancy subtype that was officially classified as a distinct class of non-Hodgkin lymphoma (NHL) by the revised European-American classification (REAL) in 1994 [1] and characterized as a mature B cell neoplasm with morphological variants of diverse clinical behavior by the 2008 World Health Organization classification [2]. It usually accounts for 6% of all NHL in United States, and 7–9% in Europe [3,4]. New cases of MCL have increased with a recently reported incidence of 0.64 per 100,000 person years in the US population [5,6]. The disease is more commonly diagnosed in older men with a median age at diagnosis of 68 years, and a male/female ratio of 2.6:1 [5,6]. Epidemiological risk factors are incompletely defined, with data to suggest both inherited and exogenous triggers related to the development of this malignancy [7–11].
Histologically, MCL is composed of mature monomorphic small to medium size B cells with indented nuclei frequently lacking visible nucleoli [2,12]. The 2008 World Health Organization classification described four different morphological variants of MCL: small cell variant that morphologically mimics small lymphocytic lymphoma; marginal zone-like variant that may resemble marginal zone lymphoma and clinically presents with massive splenomegaly in >80% of patients [13]; and pleomorphic variant and blastoid variant with lymphoblast-like cells that have a high mitotic rate [2]. In the spectrum of MCL morphological variants, the blastoid and pleomorphic types have clinical prognostic significance [2,14,15]. The classic immunophenotype of MCL includes an intense surface immunoglobulin (IgM/IgD more commonly associated with lambda restriction, positivity for CD5, CD19, CD20 (bright), CD22, weakly positive or negative CD23, and negative expression of CD10 [2]. Even though the above immunophenotypic presentation is the most typical, up to 26% of MCL are positive for CD23 at diagnosis [16]. It is also clinically relevant to acknowledge the higher prevalence of aberrant CD10 expression and/or CD5 loss among the blastoid and pleomorphic MCL variants [13,17,18]. Finally, all MCL cases are BCL2 positive and almost all express cyclin D1 [2,19–21]. The identifying cytogenetic alteration of MCL is the translocation t(11;14) (q13;32), which is found in the majority of cases [2,22]. This genetic event juxtaposes the protooncogene to the Ig heavy chain locus resulting in cyclin D1 overexpression [2,11]. Notably, fluorescence in situ hybridization (FISH) is more sensitive and specific for the detection of cyclin D1 and other variants, rather than conventional cytogenetic analysis [23–26]. Cytogenetic and FISH evaluation are of importance when evaluating for blastoid/pleomorphic subtypes with aberrant antigen expression, as bcl1 and bcl2 overexpression can also be seen in some cases of diffuse large B-cell lymphoma. Certain rare MCL variants lacking cyclin D1 have been described, and may be identified by overexpression of the nuclear transcription factor SOX11 [27,28]. Cyclin-D1-negative MCL may show cyclin D2 and possibly cyclin D3 overexpression and/or translation instead, with small case series suggesting inferior prognosis [29].

Disease presentation and initial work-up
The initial presentation of MCL can be variable. Patients can present in a leukemic phase with marked leukocytosis, with pancytopenia, or even with localized involvement of unusual extranodal areas such as skin, central nervous system, or lacrimal glands [12,30]. However, the disease more commonly presents in advanced stages (III/IV) with disseminated lymphadenopathy, splenomegaly, and bone marrow infiltration. Remarkably, the gastrointestinal (GI) tract is one of the preferred extranodal homing sites of MCL and many will show involvement on endoscopy/colonoscopy, particularly if random biopsies are obtained in the absence of visible abnormalities [4,31,32]. Other potentially involved sites at presentation are the liver and Waldeyer’s ring [28].

Retrospective studies suggest that up to 30% of newly diagnosed MCL patients may have an indolent presentation and do not require immediate treatment [11,33,34]. Clinically, such patients usually debut with modest lymphocytosis, nonbulky lymphadenopathy, splenomegaly, bone marrow infiltration and/or GI involvement [33–36]. The cellular proliferation marker Ki-67 is usually low (<30%) in these patients, consistent with an indolent course [37,38]. Serial biopsies of both indolent and classic tumors with evidence of morphological and proliferation changes suggest that the indolent MCL variant has a different natural history, and could be part of an initial low-grade disease spectrum with steady progression towards a more aggressive tumor [33–35,39]. Retrospective evaluations suggest that those with slow progression to symptomatic disease (i.e., >12 months before treatment is indicated) may have overall better prognosis [31,33,35]. It is critical to distinguish indolent tumors from in situ MCL [35]. The natural history of in situ MCL is not well characterized and in most series, the diagnosis of in situ cases is only appreciated retrospectively from biopsies obtained prior to the clinical manifestation of MCL [35,40–43]. Nonetheless, in situ MCL usually has a very long latency period and close follow-up without active treatment is indicated [35].

To obtain accurate staging and useful prognostic information, initial workup for MCL needs to include a thorough history and physical examination with detailed documentation of baseline performance status (i.e., Eastern Cooperative Oncology Group score) [44], constitutional symptoms, lymphadenopathy, hepatosplenomegaly, and/or other possible areas of extranodal involvement [4]. A complete blood count, peripheral blood flow cytometry, metabolic profile, j2 microglobulin, and lactate dehydrogenase (LDH) level should be part of the initial evaluation, as well as HIV, hepatitis B and C serology since almost all current systemic therapies include anti-CD20 monoclonal antibodies with the potential for virus-mediated complications [4]. As with other NHLs, initial staging should include a bone marrow biopsy with immunophenotyping by flow cytometry, cytogenetics with FISH evaluation, as well as a computed tomography (CT) with contrast of the neck, chest, abdomen, and pelvis [4]. When available, fluorodeoxyglucose positron emission tomography (PET)/CT should also be considered to guide nodal biopsy (to the site with highest uptake) and to improve detection of extranodal disease manifestations. Despite the high frequency of GI tract involvement, with some reports describing incidences as high as 88–92% [31,32], routine use of upper endoscopy and colonoscopy usually does not influence initial treatment approach. In accordance with current guidelines [4,13], we recommend the use of endoscopy/colonoscopy as part of the initial workup in patients that have symptoms or signs of GI involvement or to confirm Stage I/II disease that would otherwise be treated with localized therapeutic modalities. Finally, a lumbar puncture to evaluate central nervous system involvement is warranted in patients with neurological symptoms, blastoid variant MCL and/or high Ki-67 (>50%) [4,45].
Prognosis

Baseline prognostic characterization was initially established using risk scores validated for low-grade B-cell lymphomas (follicular lymphoma prognostic index; FLIPI) and/or aggressive lymphomas (International Prognosis Index; IPI). However, both failed to adequately stratify patients in different risk subgroups, especially low-risk patients [13,35,46,47]. In 2008 the European MCL Network developed a tailored prognostic score for MCL: the Mantle Cell Lymphoma International Prognostic Index (MIPI) [48]. Using data from >450 patients, four variables emerged as independent prognostic factors for shorter overall survival (OS): older age, advanced performance status, elevated LDH, and high white blood cell count, which effectively stratified patients into three different risk groups: low, intermediate, and high. After a median follow-up of 32 months, the low-risk group had not reached a median OS (5-year OS, 60%), while patients in the intermediate- and high-risk groups had a median OS of 51 months and 29 months, respectively. Addition of the Ki-67 proliferation index at diagnosis to the MIPI score may increase the discriminatory power [49,50]. Research is currently ongoing to improve interobserver reproducibility of Ki-67, which may further increase its prognostic utility [51,52]. The MIPI score has been validated by different groups, however; prognostic estimations using the MIPI have only been validated prior to first therapy, and the score is not predictive of response to any particular chemoimmunotherapeutic regimen [35]. Other disease features, including gender, the presence of B symptoms, and j2 microglobulin may add further to differentiate low- and intermediate-risk groups [53,54]. Anecdotally, the presence of B symptoms appears to improve the discrimination of the indolent MCL variant, which may frequently present with modest leukocytosis in older patients. Finally, there is emerging evidence that loss and/or mutation of specific genes, including TP53 and CDKN2A, may also inform prognosis, and are associated with poor outcomes in spite of aggressive therapy [55].

Outside clinical trials we do not recommend to use MIPI as a tool to guide therapeutic decisions in patients with newly diagnosed MCL. Alternatively, those with higher proliferative rates as defined by Ki-67 immunostaining, may benefit from more intensive treatment approaches, although the optimal approach is not yet defined.

Risk-directed treatment: a glimpse of personalized therapy in MCL

Therapies in MCL have classically been envisioned around the goal of obtaining longer remission by the way of deeper initial responses using intensive induction regimens. The exquisite chemosensitivity of MCL to a variety of front-line agents encourages this hypothesis, especially in the young and/or healthy population, where Phase II studies with multiagent regimens and dose escalation of cytotoxic compounds seem to prolong progression-free survival (PFS), and potentially extend patient survival [35,56–60]. Regardless of the potency of the initial regimen, MCL remains an incurable disease with a median duration of remission of around 5 years and OS of 3–10 years across most clinical trials [13]. More recently, alternative cytotoxic agents and newer targeted molecules have proven to be effective in clinical trials directed to patients with relapsed/refractory (R/R) disease and/or elderly individuals [61–66]. Precision agents might set the stage for a shift in the treatment of MCL in which less toxic therapies with high response rates are taken to the front-line setting in all patients regardless of their chronological and/or functional age.

Treatment of indolent MCL

Given that MCL is an incurable hematological malignancy destined to relapse, monitoring asymptomatic patients with favorable biological features (e.g., nonblastoid histology, low Ki-67 proliferation rate, and low MIPI) under a watchful waiting approach is an emerging therapeutic strategy [33,34]. Although we acknowledge there is an absence of randomized prospective data, we believe this approach is reasonable, regardless of age at diagnosis or disease stage, given our own institutional experience, as well as that gleaned from other published retrospective data sets [33,67]. We suggest that asymptomatic patients with favorable clinical and biological characteristics can be followed every 3–6 months with a complete history and physical exam, complete blood count, complete metabolic panel, and LDH. Albeit there is lack of data to support the use of contrasted CT scans and/or PET/CT imaging in this population, these images can potentially be done under the same proposed surveillance schedule, and may be tailored according to the clinical evolution of individual patients. As in chronic lymphocytic leukemia, systemic treatments should be started once patients develop constitutional symptoms, rapidly growing or symptomatic lymphadenopathy and/or splenomegaly, or disease-related cytopenias [13,35]. It also has been suggested that oncologists and patients who do not feel comfortable with only vigilant disease surveillance can consider monotherapy with weekly rituximab for 4 weeks, followed by maintenance every 2 months [35,68]. Importantly, this recommendation has not been systematically studied in the indolent MCL population in contrast to indolent follicular lymphoma [69,70]. Accordingly, several questions remain unanswered, including the duration of rituximab therapy (lifelong vs. 2 years), appropriate rituximab treatment strategy (rituximab retreatment at time of asymptomatic progression vs. rituximab maintenance), safety of rituximab maintenance (RM), and the cost-effectiveness of this approach [69,70]. In patients with symptomatic splenomegaly characterized by left upper quadrant pain, early satiety and cytopenias related to hypersplenism, palliative splenectomy has been shown to delay the initiation of chemotherapy by several years [71,72]. This surgical intervention can be an especially attractive option for patients who otherwise have limited systemic evidence of MCL, akin to splenic marginal zone lymphoma.

An important clinical caveat is to distinguish indolent MCL with leukocytosis from the aggressive leukemic phase of MCL most commonly characterized by hyperleukocytosis (often >50,000/mL), constitutional symptoms, elevated LDH, progressive splenomegaly and symptomatic cytopenias.
[73–75]. These patients will often present with rapid doubling time of the white blood cell count, in addition to mutation or loss of p53 [75, 76]. Aggressive chemotherapy is frequently used, although there is emerging data for the use of lenalidomide and rituximab in this context [77]. However, if patients have deteriorated at diagnosis and are not candidates for any available therapies, palliative splenectomy can be a therapeutic alternative for symptomatic control [35, 78].

**Treatment of limited stage MCL (Stage I and nonbulky Stage II)**

Limited presentation of symptomatic MCL is rare (6–17% of newly diagnosed patients) with available treatment information based on retrospective series and expert opinions [4, 79, 80]. It is our recommendation that, before engaging in active therapy of these patients, extensive disease involvement (Stage III/IV) needs to be ruled out by a thorough staging strategy including imaging (PET/CT scan), bone marrow biopsy with a sensitive flow cytometry technique, and GI diagnostic studies (endoscopy and colonoscopy) [4, 35]. A retrospective analysis by Leitch et al. [81] involved 26 symptomatic MCL patients with Stage I and nonbulky Stage IIA disease treated with chemotherapy and with or without involved field radiotherapy (IFRT). Patients receiving IFRT with or without chemotherapy (n = 17) had a 5-year PFS of 68%, compared with 11% for those not receiving radiation therapy (n = 9, ρ = 0.002) with no disease progression after 6 years of follow-up. Also, the 6-year OS after IFRT plus chemotherapy was 71%, compared to 25% in patients treated only with chemotherapy (ρ = 0.13) [81]. A more contemporary retrospective series from Princess Margaret Hospital in Toronto, Canada described 21 patients with limited stage MCL that were treated with curative intent [79]. Of note, this population was less homogeneous, including five patients with blastoid MCL. Fifteen patients received concurrent cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-like chemotherapy with IFRT (35 Gy), two were treated with just IFRT and two were treated with chemotherapy followed by autologous stem cell transplantation (ASCT). Median PFS and OS were 3.2 years and 6.4 years, respectively, with Stage II and blastoid variant being negative prognostic factors for systemic relapses in univariate analysis [79]. Remarkably, all of the available series suggest that OS is not affected in patients treated initially with locally directed therapy, underscoring that salvage chemotherapy at the time of disease progression retains efficacy. In short, for patients with confirmed Stage I/ nonbulky Stage II symptomatic disease, we recommend treatment with IFRT (30–36 Gy) with or without chemotherapy, in accordance with recently published guidelines [4]. Our own approach is to favor concurrent chemoimmunotherapy (CIT) in patients with pronounced B symptoms, as well as with bulky lymphadenopathy at presentation. Finally, patients achieving complete remission (CR) should be followed every 3–6 months for the first 5 years and yearly (or as clinically indicated) thereafter. Patients with R/R disease should ideally be treated with systemic CIT regimens commonly used in those with advanced disease stages (bulky Stage II and Stage III/IV) [4].

**First-line treatment of advanced stage MCL in elderly and unfit patients: precision above intensity**

The design of treatment approaches in newly diagnosed older and/or infirm patients has focused on the deintensification of induction therapy, with the goal of minimizing toxicity, coupled with extended maintenance approaches to maximize duration of response (Table 1). The advent of targeted agents with activity in MCL has provided the necessary ammunition to achieve these objectives such that we can now treat this population with the realistic opportunity to improve disease related symptoms and survival.

Rituximab was one of first rationally designed therapies that showed promising single-agent activity in MCL. In Phase II clinical trials, single-agent rituximab showed an overall response rate (ORR) of 22–38% with CR of 2–15% across all studies [68, 82–85]. Based on positive preclinical synergetic experiments, rituximab was added to the CHOP chemotherapy backbone and tested in a single-arm Phase II clinical trial of 40 newly diagnosed MCL patients [86]. In spite of high ORR/CR (96% and 48%, respectively) as well as a complete molecular response (negative PCR-detectable BCL-1/IgH or clonal products in peripheral blood or bone marrow) of 36%, median PFS was short, at 16.6 months with no discernable benefit for those with molecular CR (16.5 vs. 18.8 months) [86]. These results led to a pivotal randomized Phase II trial by the German Low Grade Lymphoma Study Group that compared R-CHOP to CHOP in 122 previously untreated patients [87]. A significant improvement in ORR (92% vs. 75%, ρ = 0.0139), CR (33% vs. 8%, ρ = 0.0008) and median time to treatment failure (TTF) (21 months vs. 14 months, ρ = 0.0131) was observed with the R-CHOP regimen; no differences were seen in PFS and OS between the two groups. It is notable that TTF was measured from the time of first treatment, while the PFS calculation was done from the time of treatment completion only in patients with partial response (PR) and/or CR; hence, PFS in this study was equivalent to duration of response [87]. Based on this information, we might infer that the most valuable role of rituximab is to sensitize patients with refractory tumors to the chemotherapy backbone [35]. Further studies have confirmed the high ORR when rituximab is added to CHOP, in turn reflected by prolonged disease control. In fact, both a meta-analysis of seven randomized controlled trials and a robust retrospective analysis of >600 patients with a mean age of 75 years have suggested that front-line CIT containing rituximab might improve OS of newly diagnosed MCL patients [88, 89].

Fludarabine, a purine analog with established clinical effectiveness in chronic lymphocytic leukemia/small lymphocytic lymphoma [90, 91], has also been used in elderly MCL patients [92, 93]. The combination of fludarabine with cyclophosphamide and rituximab (FCR) resulted in CR of 65% along with prolonged PFS and OS (31 months and 46 months, respectively) [94]. Nonetheless, mortality related to other causes (i.e., infections and secondary malignancies) was high in patients treated with the combination (29%). More recently, a Phase III randomized study in elderly patients (median age = 70 years) done by the European MCL group compared FCR to R-CHOP in treatment-naïve patients.
Although CR rates were similar between the two groups (40% and 34%, respectively; \( p = 0.10 \)), the 4-year OS was superior in the R-CHOP group (62% vs. 47%; \( p = 0.005 \)), related to a higher rate of deaths associated with lymphoma relapse (20% vs. 26%), as well as infectious complications and secondary cancers in the FCR arm. This study also included a second randomization of maintenance with rituximab versus interferon \( \alpha \) in patients who responded to induction therapy [95]. The best response was seen in the group allocated to RM following R-CHOP induction (4-year PFS and OS 57% and 87%, respectively). This landmark trial provided strong evidence for prolonged PFS in MCL with RM, and delineated a paradigm shift in the care of elderly patients, highlighting that lower-intensity maintenance strategies could yield outcomes comparable to those seen in younger patients treated more intensively [15,58–60].

Driven by the idea of prolonging disease remission, the proteasome inhibitor bortezomib was recently introduced to the first-line setting of MCL treatment. Based upon encouraging clinical outcomes of bortezomib in the relapsed setting [62,96–98], investigators of the recently reported Phase III LYM-302 study substituted vincristine for bortezomib in the classic R-CHOP regimen (VR-CAP) and compared it in a randomized fashion to R-CHOP [99]. Although response rates were similar between the study groups, CR rates were significantly higher in the VR-CAP group compared to patients treated with R-CHOP (53% vs. 42%, respectively), which reflected in a significant longer PFS (24.7 months vs. 14.4 months, respectively) with a hazard ratio (HR) favoring the bortezomib-based study arm (0.63, \( p < 0.001 \)). Importantly, duration of response (DOR) was maintained across all MIPI categories and Ki-67 values. Also, while patients treated in the R-CHOP group achieved a median OS of 56.3% after a median follow-up of 40 months, the median OS for the VR-CAP group has not been reached (HR = 0.80; \( p = 0.17 \)). Notably, a high proportion of Asian Americans were treated on this study (32%), which suggests a unique advantage to proteasome-based approaches in this population [99]. Finally, although peripheral neuropathy was comparable among groups, VR-CAP patients required more frequent platelet transfusions due to higher grade 3/4 thrombocytopenia (57% vs. 6%), more frequent use of growth factors and antibiotics due to higher rates of severe neutropenia (85% vs. 67%) and infectious episodes (21% vs. 14%), but without differences in febrile neutropenia. This trial, as well as other MCL studies [100], illustrates the high clinical activity of bortezomib-based therapies in newly diagnosed MCL, although combination with new synergistic agents warrants further exploration.

Another agent that has shown significant clinical activity and favorable toxicity profile in MCL is bendamustine, a unique nitrogen mustard-derivative alkylating agent with a purine-like benzimidazole ring [35,101]. This compound was initially tested in relapsed MCL through several Phase II studies showing encouraging ORR (>75%) and CR rates (38–58%), translating in PFS as high as 1.5 years, even in elderly patients that had undergone multiple lines of therapy [61,102,103]. These data pre-empted a randomized Phase III European study (StiL trial) in which bendamustine plus rituximab (BR) was compared against R-CHOP in newly diagnosed indolent NHL lymphomas and MCL [104]. Of the
study population, 94 patients (median age = 70 years) had MCL. The study showed similar ORR (>90%) for both treatment arms, although higher CR rates and longer PFS were seen in the BR group (PFS = NR vs. 42.3 months, \( p = 0.0072 \)). No differences in OS were found between treatments, which might have been confounded by patient crossing over to the BR arm after disease progression on R-CHOP. Notably, a follow-up study of RM × 2 years after BR was recently presented, and suggests that RM may be of less benefit after BR. However, a higher rate of progressive disease (and lymphoma associated death) in the BR/RM arm, as well as a rapid drop-off in event-free survival (EFS) and DOR at 36 months merits further exploration before any definitive conclusions can be drawn [105]. A valuable outcome seen in the elderly patients treated within this trial was the remarkably low rate of side effects in the BR group, including lower rates of neutropenia, paresthesia, stomatitis, and mucositis [104]. Flinn et al. [106] performed a large international noninferiority trial to confirm these data in a broader population. In this study, treatment-naive patients with low-grade NHL or MCL were equally randomized to BR versus a rituximab-containing regimen (R-CHOP/R-CVP (rituximab, cyclophosphamide, vincristine and prednisone)) based on the treating physician criteria [106]. Of note, in this study there were fewer MCL patients (n = 74) and they were younger (median age = 63 years). The ORR was similar between the two study groups; however, CR rates among MCL patients treated with BR were higher (50% vs. 27%; \( p = 0.018 \)). At the time of publication, time-to-event results were not mature to evaluate PFS and OS, although no differences were seen at this early time point due to unexpected deaths among those treated with BR. Similarly, while neurological and hematological toxicities were higher in the R-CHOP/R-CVP patients, the incidence of nausea/vomiting, poor appetite, fevers, and chills was higher in the BR-treated group [104,106].

Given the widely recognized benefit of cytarabine (Ara-C) in the induction regimens of younger MCL patients [15,107,108], incorporation of this pyrimidine analog at intermediate doses to the BR combination in the front-line therapy of elderly patients (R-BAC) has also been explored. This combination demonstrated impressive results in a small Phase I/II trial including both untreated and relapsed MCL with a median age of 70 years. Specifically, among untreated patients, 100% ORR (CR 95%) was observed, while among those with relapsed disease the ORR was 80% (70% CR). This translated into a 2-year PFS of 95% and 70% among untreated and relapsed patients, respectively [109]. A follow-up Phase II trial with further attenuation of Ara-C demonstrated improvement in hematological toxicity and preserved CR rate (91%). However, outcomes remained inferior in those with proliferative MCL (Ki-67 > 30%), for whom 2-year EFS was ~44% (vs. 100% in remainder) [110]. An alternative approach adding subcutaneous bortezomib and dexamethasone to the BR backbone (RiBVD) was recently explored. In this study, 74 newly diagnosed MCL patients with a median age of 73 years were treated with six cycles of RiBVD, and subsequently followed without maintenance. After all cycles were completed, this regimen demonstrated a CR/CR unconfirmed of 74% (74% molecular response in the bone marrow), which translated into a 2-year PFS and OS of 69% and 80%, respectively [111].

Striving for biological-based therapies, or chemotherapy-free regimens, different types of NHL have been treated with the combination of rituximab plus the immunomodulatory drug (IMID) lenalidomide. With previous positive experiences using lenalidomide in R/R MCL that will be further discussed [112], and encouraging data of rituximab/lenalidomide combination (R²) in the front-line treatment of indolent NHL [113], this nonchemotherapy doublet was tested in a previously untreated MCL population. Ruan et al. [114] recently reported the results of a Phase II multicenter study of 38 newly diagnosed symptomatic MCL patients treated with R². The patient’s median age was 65 years and baseline clinical characteristics were similar. Treatment consisted of 12 cycles of induction therapy with lenalidomide (20 mg/day × 21 days) plus rituximab (4 weekly doses, followed by 1 dose every other cycle), followed by a maintenance phase (lenalidomide 15 mg/day × 21 days plus rituximab every 2 months). After a median follow-up of 30 months, patients achieved an impressive ORR of 92% (CR 64%), along with high 2-year PFS and OS (85% and 97%, respectively). These outcomes demonstrated the feasibility of a low-intensity biological regimen in MCL, coupled with high responses and durable disease control.

Successful outcomes seen in the elderly and unfit population with first-line deintensified regimens coupled with maintenance strategies, may equate to the benefits of prolonged disease remission obtained with intensified chemotherapy with or without ASCT. While it remains unclear whether prospective evidence with RM will demonstrate a clinical benefit independent of chemotherapy choice, a recent meta-analysis of >430 MCL patients treated in randomized trials demonstrated an improvement in PFS [HR 0.60, 95% confidence interval (CI) 0.44–0.82] and an apparent lower mortality (HR 0.67, 95% CI: 0.37–1.69), although the combined trials were heterogeneous with regard to OS (\( I^2 = 54\% \) [115]). This evidence reinforces our recommendation of using a lower-intensity CIT regimen, such R-CHOP, BR, R², or VR-CAP followed by RM in responding patients that achieve at least a PR. Due to the positive strides made in B-cell tumor biology, leading to the generation of active antilymphoma agents, efforts are underway to evaluate the effect of novel therapies both in combination with front-line therapy and as maintenance for elderly and unfit MCL patients. This is exemplified by the ongoing US intergroup E1411 study of BR ± bortezomib followed by rituximab ± lenalidomide (ClinicalTrials.gov-NCT01415752).

**First-line treatment for advanced-stage MCL in young and fit patient: high intensity for all?**

While no regimen has proven to yield an OS benefit for patients with advanced MCL, upfront therapy of young (<65 years) and fit (Eastern Cooperative Oncology Group performance status ≤1 with preserved end-organ function) patients have centered on the premise of achieving deep responses with higher-intensity treatments (Table 2). After demonstrating synergistic activity with Ara-C and cisplatin for the treatment of refractory NHL [116], French researchers were the first to showcase the notion that aggressive therapies may specifically benefit young patients with
Mantle cell lymphoma

Clinical outcomes of selected first-line regimens for young (<65 years) or fit MCL patients.

<table>
<thead>
<tr>
<th>Clinical trial/phase</th>
<th>Regimen</th>
<th>No. of patients</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>Efficacy outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romaguera et al./II [56,107]</td>
<td>R-HyperCVAD w/o ASCT</td>
<td>97</td>
<td>97</td>
<td>87</td>
<td>46% 8-y TTF 68% 8-y OS</td>
</tr>
<tr>
<td>Bernstein et al./II [58]</td>
<td>R-HyperCVAD w/o ASCT</td>
<td>49</td>
<td>86</td>
<td>55</td>
<td>53% 5-y PFS 69% 5-y OS</td>
</tr>
<tr>
<td>Merli et al./II [118]</td>
<td>R-HyperCVAD w/o ASCT</td>
<td>60</td>
<td>83</td>
<td>72</td>
<td>61% 5-y PFS 71% 5-y OS</td>
</tr>
<tr>
<td>Damon et al./II [120]</td>
<td>R-CHOP + MTX/R + HDAraC + VP-16</td>
<td>77</td>
<td>88</td>
<td>69</td>
<td>54 3.8-y PFS vs. 7.3-y PFS 64% 5-y OS</td>
</tr>
<tr>
<td>Geisler et al./II [57]</td>
<td>R-Maxi-CHOP + HD AraC</td>
<td>160</td>
<td>96</td>
<td>54</td>
<td>66% 6-y PFS 70% 6-y OS</td>
</tr>
<tr>
<td>Hermine et al./III [121]</td>
<td>R-CHOP</td>
<td>455</td>
<td>98 vs. 99</td>
<td>63 vs. 61</td>
<td>78% vs. 61, 86% vs. 64, 6-y OS</td>
</tr>
<tr>
<td>Le Gouill et al./III [123]</td>
<td>R-DHAP</td>
<td>RM vs. placebo</td>
<td>299</td>
<td>89.3 vs. 77.3</td>
<td>78.9% vs. 61.4% 4-y EFS 82.2% vs. 78.4% 4-y OS</td>
</tr>
</tbody>
</table>

Note. ASCT = autologous stem cell transplantation; CR = complete remission; HDAraC = high-dose cytarabine; MTX = methotrexate; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAP = rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-HyperCVAD = rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, cytarabine; RM = rituximab maintenance; TTF = time to treatment failure; VcR-CVAD = bortezomib, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; VP-16 = etoposide.

MCL. They treated 25 MCL patients who failed to achieve a CR after four cycles of CHOP with two or three cycles of dexamethasone, high-dose Ara-C and cisplatin (DHAP), achieving a CR conversion of 84% [117]. DHAP chemotherapy also served as a bridge to ASCT in 23 of these patients, culminating in a favorable disease control (3-year OS 90.4%). Similar data was generated by the MD Anderson Cancer Center, who introduced the R-HyperCVAD/M-AraC regimen for the treatment of MCL. In this Phase II trial they demonstrated an ORR of 97%, with an accompanying CR rate of 87% [56,107]. Among younger patients, these high response rates were accompanied by prolonged remissions (TTF = 4.6 years) and an 8-year OS of 68%. Notably among older patients (>65 years), necessary decreases in relative dose intensity were accompanied by shorter remissions and survival (8-year OS 33%), reinforcing the benefit of intensified therapy in younger/fit patients [107]. At least two other Phase II multicenter clinical trials have confirmed the high activity and, in particular, the hematological toxicity of R-HyperCVAD/MA [58,118].

In an effort to improve the duration of remissions and survival, further studies were developed in which intensive induction was followed in turn by myeloablative consolidation chemotherapy and autologous stem cell transplantation. In the landmark Phase II clinical trial by the Nordic group, 160 newly diagnosed young patients with MCL were treated with six alternating cycles of Maxi-CHOP (cyclophosphamide 1200 mg/m² and doxorubicin 75 mg/m²) and rituximab with high dose Ara-C [15]. Responders received high-dose chemotherapy with ASCT. This regimen yielded a 96% ORR with a 54% CR rate. After a median follow-up of 11.4 years the Nordic protocol achieved a median PFS of 8.5 years and a median OS of 12.7 years [119]. Unfortunately, as had been observed with HyperCVAD, no plateau in the PFS or OS was observed [57]. CALGB 59909 used an abbreviated CIT combination consisting of two cycles of R-CHOP (cyclophosphamide 2 g/m²) with methotrexate (300 mg/m²) followed by rituximab, high-dose Ara-C and etoposide, and ASCT consolidation with post-transplant rituximab x 2 doses [120]. This approach yielded a 5-year PFS and OS of 56% and 64%, respectively, comparable in terms of both efficacy and toxicity with HyperCVAD/MA and Maxi-CHOP [35]. Given the success previously observed with R-CHOP/R-DHAP, a large prospective randomized study was conducted comparing this induction regimen to R-CHOP, followed in turn by ASCT. Preliminary analysis of the results showed that both groups had a similar ORR after induction (90% vs. 94%; p = 0.14), but with significantly higher CR/CR unconfirmed (39% vs. 55%; p = 0.0005) and molecular remission rates (47% vs. 79%; p < 0.0001) in the R-CHOP/R-DHAP arm. The R-CHOP/R-DHAP arm similarly demonstrated a longer TTF (9.1 years vs. 3.9 years; p = 0.038), but similar OS (5-year OS 76% vs. 69%; p = 0.12). It is important to note that differences in conditioning therapy between the two groups could have likewise influenced these endpoints [35,121,122].

Finally, it is worth mentioning emerging data that suggests a possible benefit of RM (given every 2 months for 3 years) following autologous transplantation. At the 2016 ASH annual meeting, data from a randomized trial was presented in this regard, which demonstrated a benefit in EFS (HR = 0.46, p = 0.0016), PFS (HR = 0.4, p = 0.0007), and OS.
(HR = 0.5, p = 0.045) in favor of RM [123]. Also presented at this meeting were data using a pre-emptive, rather than prophylactic, approach to RM in MCL following autologous transplantation. In this study, patients were followed for molecular relapse, at which time they could receive ≥1 cycles of rituximab (given as 4-weekly doses). Remission was similarly prolonged, with patients showing a median of 55 months from first molecular relapse to frank clinical relapse [124]. These data suggest a reappraisal of RM after autologous transplantation, and furthermore, lay the groundwork for a pending cooperative group trial comparing RM with autologous transplantation.

Based on the perceived benefits of deep responses and prolonged disease control, most front-line therapeutic strategies in young healthy MCL patients have tried to bundle ASCT after the first complete remission (CR1). Since patients failing to achieve major disease remission are usually not considered for ASCT and experience faster relapses, this suggests that the best induction chemotheraphy is one that achieves the deepest disease control. As an example, some groups have suggested that, obtaining molecular remission (negative minimal residual disease) after induction with CIT correlates with prolonged disease control, and is a more powerful predictor for disease relapse than other baseline risk factors (i.e., MIPI) [125,126]. However, neither the role of front-line stem cell rescue, nor the most appropriate pretransplant induction regimen has been appropriately tested in a randomized fashion, leaving us with management uncertainties. For example, a retrospective analysis of the NCCN NHL database published in 2012, which included 167 MCL patients under the age of 65 years, implied that ASCT improved clinical outcome only in patients previously treated with less-intense induction regimens [127]. After a median follow-up of ~3 years, no significant differences were seen between HyperCVAD/MA and HyperCVAD/MA followed by ASCT and R-CHOP followed by ASCT in terms of 3-year PFS (58%, 55%, and 56%, respectively). In contrast, patients treated only with R-CHOP had a significantly lower PFS compared to individuals treated with R-HyperCVAD with/without ASCT (p = 0.04 and p = 0.01, respectively). Nonetheless, ASCT-backed regimens did not show any OS advantage over R-CHOP. The above clinical outcomes do not take into account rituximab maintenance strategies that, although not directly comparable, have yielded similar disease control rates with lower side effect rates [95].

R/R MCL: making a difference through biological innovation

Endeavors to improve the outlook of patients with MCL are undeniable and have proven to be successful. Nonetheless, a high proportion of patients will eventually relapse or present with refractory disease, despite intensive and/or prolonged CIT. R/R MCL is challenging, as current chemotherapy regimens yield low response rates (CR < 30%) with short remission duration [4]. By the end of 2016, there were only three agents approved for treatment of R/R MCL in the US and a clear standard of care for these patients has not been established [4,13,128,129]. We should acknowledge that there are some patients in whom relapsed disease is initially asymptomatic and can potentially be closely followed without treatment; this is especially applicable in the elderly and/or unfit population [13]. However, these asymptomatic presentations have not been well characterized by any studies and a active surveillance approach should be adopted on a case-by-case basis with caution. Regarding CIT approaches, second-line regimens utilizing a different combination of agents from the ones used in the front-line setting, can be considered. We have already alluded to the efficacy of the BR combination, which can induce response rates in more than three-quarters of R/R MCL patients with low proliferative rate, accompanied by durable remissions in excess of 50% in selected trials [61,102]. In the original 2005 trial by Rummel et al. [61], BR yielded an ORR of 92% (CR of 60%) in 63 R/R MCL patients. In another Phase II study, BR showed an ORR of 92% (CR 42%) in a similar, although smaller (n = 12), MCL population [102]. The StIL trial reinforced the positive results of this CIT combination in a larger randomized setting. In this clinical trial, >200 patients with R/R indolent NHL and MCL were treated with either BR or fludarabine/rituximab [130]. Among these patients, 20% (n = 44) had MCL. After a median follow-up of 8 years, BR demonstrated superior CR and PFS compared to fludarabine/rituximab (38.5% vs. 16.2%, p = 0.0004 and 34 months vs. 12 months; p < 0.0001, respectively) with an associated better OS (9 years vs. 4 years; p < 0.01, respectively) [130]. After acknowledging these enthusiastic responses obtained with this doublet, we also need to recognize that BR has long-term toxicities with almost 15% of patients developing secondary malignancies (5 patients with secondary hematological neoplasia), possibly related to alkylator-driven myelotoxic effects in conjunction with lingering suboptimal cellular immunosurveillance. As previously described, the incorporation of Ara-C onto a BR backbone (R-BAC) was accompanied by high response rates with manageable toxicity and largely preserved dose intensity [109].

The last decade of research has yielded targeted and effective therapies for MCL. The proteasome inhibitor bortezomib reflects the first approved drug in the evolution of therapy for this NHL. Its role in chemotherapy combinations has already been briefly summarized, and other novel combinations are anticipated. The activity of bortezomib as a single agent for R/R MCL was defined by the Phase II PINNACLE study wherein 155 patients with R/R disease were treated with intravenous bortezomib until progression. The ORR with single agent bortezomib was 33%, with 8% showing a CR [62]. More importantly, remission was accompanied by nearly a 16-month improvement in OS at 2 years [96]. The second generation proteasome inhibitors, such as carfilzomib, may provide novel means to circumvent anticipated treatment associated neuropathy, while maintaining similar therapeutic benefits.

The impact of IMIDs in MCL was first appreciated in a small Phase II study of thalidomide given with rituximab. In this study of 16 patients, the researchers observed an ORR of 81% (CR 31%) and accompanying median PFS of 20.4 months [131,132]. While highly active, thalidomide was commonly complicated by fatigue, neuropathy, and thrombotic events, prompting further larger studies with the second-generation IMID lenalidomide [35]. The anti-MCL activity of lenalidomide monotherapy was initially seen
among R/R MCL patients treated in the Phase II NHL-002 and NHL-003 trials, where an ORR of 35–53% (CR 12–20%) and an accompanying DOR of 13.7–16.3 months were observed [133–135]. The MCL-001 study focused on 134 more heavily pretreated MCL (median prior therapies = 4; 60% bortezomib refractory), and provided the foundation of its US Food and Drug Administration approval in 2013 [112]. Specifically, the authors observed a 28% ORR (7.5% CR) with corresponding DOR of 16.6 months. These responses were consistent across subgroups according to baseline characteristics, with the exception of patients with high baseline LDH in whom responses were less frequent. An exploratory analysis of patients with available Ki-67 treated in the MCL-001 trial suggested that lenalidomide was active in patients with both high and low baseline Ki-67, although a lower baseline proliferation index (<30%) was associated with better DOR and OS [64]. As with bortezomib, the success of single-agent therapy has prompted to study lenalidomide in combination with other therapies. The combination of lenalidomide and rituximab has shown considerable promise in both the front-line and the R/R setting [13,112,114]. Among R/R patients the combination improved the ORR (57% with a CR of 36%), culminating in a median DOR of 18.9 months [136].

Preclinical studies using MCL cell lines and patient-derived tumor cells from treatment-naïve patients have suggested that activation of the PI3K/ATK/mTOR pathway may play a fundamental role in disease pathogenesis [137]. Accordingly, mTOR inhibitors have been tested in the R/R MCL setting with modest single-agent activity, particularly when compared with gemcitabine- or fludarabine-based therapies [35,138–140]. As has been observed with other agents, responses may be further improved when given together with other compounds as recently observed from the combination with bendamustine and rituximab [141].

A strategy with well-documented durable clinical activity and favorable toxicity profile in follicular lymphomas is anti-CD20 radioimmunotherapy (RIT) [142]. This approach was initially tested by the MD Anderson group in a small pilot study of 34 heavily pretreated older patients (median age = 68 years) with R/R MCL [143]. After a single dose of yttrium-90 ((90Y)-ibritumomab, 31% achieved a CR, with an EFS of 6 months and a OS of 21 months. Patients with bulky disease and RIT resistant disease (<PR post-RIT) had inferior survival outcomes. The European MCL network also investigated the role of RIT in a similar population through a Phase II clinical trial using this molecule, escalating ibrutinib doses were tested in 56 patients with a myriad of R/R NHL (9% had MCL) [153]. The MTD was established at 560 mg/day with a toxicity profile characterized mostly by manageable grade 3/4 hematological toxicities. The ORR was encouraging (54%) for this heavily pretreated population, and it was even more striking in MCL (77%). The safety and biological activity inspired the Phase II clinical trial carried out by Wang et al. in older (mean age 68 years) older patients with R/R MCL. In this study, single-agent ibrutinib (560 mg/day) was given to 111 patients until progression or until unacceptable adverse events occurred. Ibrutinib achieved an ORR of 68%, mostly driven by PR (47%), and a median DOR of 17.5 months [66]. After a median follow-up of 26.7 months, the 2-year median PFS and OS were 31% and 47%, respectively. The most common adverse events were diarrhea (50%), fatigue (50%), nausea (33%), and dyspnea (32%), and the most prevalent grade ≥3 adverse events were hematological [66,154]. Two categories of clinically relevant adverse events emerged during the trial: bleeding episodes and atrial fibrillation. Overall, half of the patients experienced at least one bleeding event during the study period; however, most of them were grade 1/2 contusions, epistaxis, and petechias, with only 2% of grade ≥3 episodes (subdural hematoma and hematuria), without any fatal events [66,155]. Regarding atrial fibrillation, there were 12 new episodes recorded (11%), seven of which were grade 3, and mostly occurred in patients with previous cardiovascular risk factors. Among the patients who experienced these adverse events, only one needed ibrutinib dose reduction and two required treatment discontinuation due to subdural bleeding [155]. Based on these data, ibrutinib was granted accelerated US Food and Drug Administration approval for the treatment of R/R MCL patients who have received at least one prior line of therapy. With longer follow-up it is apparent, however, that most patients will ultimately relapse following ibrutinib, some with more aggressive and highly chemotherapy refractory disease [154,156]. At present, an elevated Ki-67 (>50%) appears to be the primary feature associated with a reduced likelihood of response.
Attempts to circumvent resistance by coupling ibrutinib with rituximab have shown higher response rates with overall good tolerability; however, there is insufficient follow-up to gauge duration of response. Similarly, a large randomized study of bendamustine and rituximab given with or without ibrutinib has recently been completed, and these data are highly anticipated. Finally, second generation BTK inhibitors, including ACP-196, are now under active study in the clinic, with the potential to improve the adverse event profile while capitalizing on a similarly pronounced response rate.

**Role of hematopoietic stem cell transplantation in R/R MCL: old habits die hard**

Despite intensive and/or prolonged CIT approaches with or without the inclusion of novel agents, we have yet to achieve a permanent cure for patients with MCL, more concretely in R/R disease, for which tumoral progression is certain and often fatal. Although the addition of rituximab improves the clinical outcomes of front-line regimens in MCL [13,35,89,127], before the advent of targeted therapies, patients with R/R MCL after high-dose CIT and ASCT had limited options for prolonged disease control, paired with high toxicity of salvage therapy strategies [13,157]. Initial results of small retrospective series using high-dose chemotherapy and ASCT in the R/R setting were disappointing. For instance, the MD Anderson group reported the single-institution outcomes of 121 MCL patients who underwent hematopoietic stem cell transplantation (HSCT), and found that the 6-year PFS and OS for patients treated with ASCT in the R/R setting were significantly inferior compared to HSCT in first remission [158]. Nonetheless, in the largest analysis of transplanted chemotherapy sensitive MCL patients (n = 519) done through the Center for International Blood & Marrow Transplant Research (CIBMTR), the 132 patients who received ASCT for R/R disease had a 5-year OS of 44% with a 1 year nonrelapse mortality (NRM) of 9% [159]. Although ASCT in chemosensitive MCL could offer some clinical benefit in the R/R setting, recent expert guidelines fail to give concise recommendations regarding the role of ASCT in R/R disease [160].

Even with the risk of short-term severe complications (i.e., NRM) and chronic toxicity (chronic graft vs. host disease), allogeneic HSCT (allo-HSCT) is recognized as a possible curative intervention for both R/R indolent and high-grade NHL due to the putative beneficial role of a tumor-free graft, and the well described graft versus lymphoma effect [161–164]. Importantly, the use of nonmyeloablative (NST)/reduced intensity conditioning (RIC) regimens has broadened the applicability of allo-HSCT due to its lower toxicity while maintaining the graft versus lymphoma effect [164,165]. The use of allo-HSCT in R/R MCL was originally...
described in a retrospective study of 33 patients treated with NST allo-HSCT whom achieved a 2-year PFS and OS of 60% and 65%, respectively, along with an NRM of 24% [157]. Tam et al. [158] reported encouraging outcomes of 35 patients with R/R MCL treated with NST allo-HSCT with a striking 6-year PFS and OS of 46% and 53%, paired with a 1-year NRM of 9%. Most importantly, plateaus in both PFS and OS were witnessed in nine patients whom had >5 years of follow-up (63–110 months). The large CIBMTR series by Fenske et al. [159] also analyzed the outcomes of RIC allo-HSCT in chemotherapy sensitive R/R MCL and noticed a 5-year OS and PFS of 31% and 24%, respectively, which were not significantly different from the outcomes in patients with R/R disease treated with ASCT. These results are probably explained by higher early NRM (17%) with lower rates of relapse/progression (5-year rates 38%) in allo-HSCT patients [159]. Last but not least, Hamadani et al. [164] assessed the role of allo-HSCT in 202 patients with exclusively chemorefractory R/R MCL. Despite the fact that almost 60% of patients received NST/RIC, there were no significant differences noted in 3-year rates of NRM, PFS, and OS between the above patients and the ones conditioned with myeloablative regimens (43% vs. 47%, p = 0.68; 25% vs. 20%, p = 0.53; 30% vs. 25%, p = 0.45; respectively) [164]. This study demonstrated that in patients eligible for aggressive salvage regimens, allo-HSCT can provide long-term disease control in approximately one-third of heavily pretreated chemorefractory R/R MCL. In the R/R MCL setting, we concur with recent consensus guidelines that proposed using RIC allo-HSCT in eligible patients with a suitable donor after achieving at least a second PR with reinduction CIT, particularly in those with features that predict for longer disease control (e.g., disease recurrence >1 year after ASCT) [160].

Recent innovative cellular therapeutic approaches, such as chimeric antigen receptor (CAR) T cells may also prove to be effective and safe in the R/R MCL population [166]. CAR T cells are genetically modified autologous T cells designed (at present) to target and proliferate upon engagement of CD19. Early data suggest high remission rates, which may serve as a quintessential bridge for transplantation [167–169]. Nonetheless, CAR-T therapy in R/R MCL is still experimental and has not demonstrated prolonged disease remissions leading to potential cures, which can be occasionally obtained with allo-HSCT [161–164].

Conclusions

Patients with MCL have a heterogeneous clinical evolution that can present as slow progressors with an indolent tumor, or as aggressive debutantes with a florid disease in need of prompt treatment. For many years, advances in MCL lagged behind those for other NHLs; however, the past decade has given us improved tools for prognostication and novel therapeutics that are facilitating meaningful improvements in the life expectancy of patients. Our proposed therapeutic approach for patients with both newly diagnosed and R/R MCL is illustrated in Fig. 1. Treatment selection should not only be based on age cutoffs or clinical presentations, but on the evaluation of biological factors, such as the Ki-67 proliferative index, so that the intensity of therapy is rationally coupled to both the aggressiveness of the underlying MCL and the capacity for the patient to safely receive such therapy. The advent of novel therapies has already yielded considerable benefit for those with relapsed and refractory MCL, and their utility in frontline combinations is becoming increasingly apparent. In this context, it is important to recognize that these novel agents are for the first time facilitating a deintensification of care for those with newly diagnosed disease, allowing for both extended disease control and an improvement in toxicity. Treatments such as BR, R², VR-CAP, and ibritunib-based regimens exemplify these approaches. Integration of rituximab maintenance following chemotherapy, and possibly autologous transplantation, has been shown across studies to prolong remission duration, and serves perhaps as the first standard of care for MCL patients.

Unfortunately, relapse is an inevitable outcome in MCL, and may be accompanied by more aggressive and chemotherapy refractory disease. However, we can now appreciate that our armamentarium is improving. Noteworthy in this regard are phosphatidylinositol 3-kinase/DNA protein kinase inhibitors, selective histone deacetylase inhibitors, next-generation IMIDs (pleotropic protein modifiers), oral and irreversible proteasome inhibitors, and novel immunotherapeutic approaches, such as CAR-T cells, checkpoint inhibitors, and haploididentical allogeneic transplantation. The future of MCL is a bright one, and one in which we may realistically reappraise this disease as a truly indolent lymphoma.

Conflicts of interest

Celgene, Pharmacyclics, Acetylon, Spectrum.

Shah: Celgene, Acetylon, Spectrum, Pharmacyclics.

Sotomayor: no relevant conflicts.

Sandoval: no relevant conflicts.

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Mantle cell lymphoma


