Refining the Mantle Cell Lymphoma Paradigm: Impact of Novel Therapies on Current Practice

Irit Avivi¹ and Andre Goy²

¹Tel Aviv Medical Center, Tel Aviv, Israel, and ²John Theurer Cancer Center at HUMC, Hackensack, New Jersey.

Corresponding Author: Irit Avivi, Department of Hematology & Bone Marrow Transplantation, Tel Aviv Sourasky Medical Center, 6 Weitzman Street, Tel Aviv, Israel 64239. Phone: +972 3-697-3782; Fax: +972 3-554-1530; E-mail: irit_avivi@hotmail.com

Note: I. Avivi and A. Goy share senior authorship.

Running Title: Clinical Perspectives in MCL

Disclosure of Potential Conflicts of Interest

A. Goy reports receiving speakers bureau honoraria from and is a consultant/advisory board member for Celgene Corporation, Johnson & Johnson/Pharmacyclics, and Takeda. No potential conflicts of interest were disclosed by the other author.
Abstract

Although mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma, proactive research efforts fueled by challenges in the management of MCL have led to an increase in median overall survival (OS) of 2.5 years in the mid 1990s to beyond 5 years nowadays. This improvement is due mostly to the use of dose-intensive strategies, particularly cytarabine-containing regimens (with or without high-dose therapy [HDT] followed by autologous stem cell transplantation [ASCT] consolidation), which are associated with deeper remission (and higher molecular complete response rate), as well as better salvage therapies. Along this line, MCL became the first lymphoma for which 4 novel agents have been approved in the relapsed/refractory setting: temsirolimus, lenalidomide, ibrutinib, and bortezomib (the last agent approved both in relapsed/refractory disease and firstline combination therapy). In addition, the use of rituximab maintenance has helped reduce relapse rates and improve outcome. However, in routine practice (i.e., outside clinical trials), the outcome of MCL remains overall unchanged with standard immunochemotherapy, and even after HDT-ASCT, most patients still relapse and frequently develop chemoresistance. The persistent lack of consensus for the treatment of MCL explains the rather impressive variability in management of these patients. The integration of newer therapies, either in combination with immunochemotherapy or as consolidation/maintenance post-induction, offers new opportunities for MCL patients. This review highlights how such developments can help refine the current MCL paradigm.
Introduction

Mantle cell lymphoma (MCL) accounts for about 6% of all non-Hodgkin lymphomas (NHL), though recent reports suggest an increase in incidence (1). Median age at diagnosis is mid-60s, with a 3:1 male:female ratio and frequent extranodal involvement (bone marrow, blood, and gastrointestinal tract particularly) (2,3). Since WHO first recognized MCL as a separate entity in 1994, the median overall survival (OS) has improved from <2.5 years to >5 years, although recent reports suggest that for the overall population (i.e., outside clinical trials), median OS remains <3 years (4).

Derived from mostly antigen-naïve cells, MCL cells proliferate in the mantle zone around germinal centers (2), with morphological (diffuse, nodular, mantle zone), as well as cytological variants (small cells, pleomorphic, blastoid). Diagnosis suspected on immunophenotype (CD20+, CD5+, CD23−, and FMC7+) requires confirmation by CYCLIN D1 overexpression due to t(11;14) translocation, which is generally identified by FISH rather than cytogenetics (2,3,5). Rare cases of CYCLIN D1-negative–MCL show CYCLIN D2 or D3 overexpression (through rearrangements with IGH or IGL loci) and share similar clinical behavior and outcome with CYCLIN D1-positive cases (6).

Prognostic Factors in MCL

Outcome in MCL may be predicted by the MCL International Prognostic Index (MIPI) based on age, ECOG performance status, lactate dehydrogenase (LDH) levels, and white blood cell counts (7-10). MIPI stratifies patients into 3 risk groups, low, intermediate, and high, with median OS not reached, 51 months, and 29 months, respectively (7). Gene expression profiling (GEP) revealed a proliferation signature with dramatic impact on outcome (median OS ranging from <1-7+ years) (6). Ki-67 (or MIB1) has been used as a surrogate marker of proliferation (<\text{\geq} 30\%),
showing value independently of MIPI (11). However, KI-67 evaluation by immunohistochemistry remains by nature semiquantitative and is found in most cases at baseline in the <10% to <30% range. Rare cases presenting with high KI-67 at baseline, often carrying DEL17P/P53 mutation; both features are consistent with blastoid variant and/or are more commonly seen with successive relapses (i.e., clonal evolution). Other prognostic variables have been reported in MCL including $\beta_2M$, miRNAs, and complex karyotype; while overall P53 abnormalities are likely underestimated (2,12). SOX11 expression can help diagnose CYCLIN D1-negative cases and seems to correlate with outcome (13), though consensus on a validated analysis tool for SOX11 remains to be determined (14). Comprehensive genomic studies have confirmed the complex mutational landscape of MCL, which contributes to pathogenesis and disease progression, including mutations in ATM, P53, BIRC3, WHSC1 and NOTCH1 (15).

Indolent MCL

About 10%-15% of MCL patients presenting with high leukemic phase, minimal or no lymphadenopathy, and/or large splenomegaly, are SOX11 negative and show distinct GEP, carry a more indolent course, and should be managed conservatively (1,6,16-18). Genetically, these patients with “truly indolent MCL” typically show somatic mutations, which like in chronic lymphocytic leukemia correlates with higher genetic instability (fewer secondary genetic abnormalities over time than classic MCL), although some cases may acquire DEL17P/P53 mutation (1,2,19). In situ MCL lesions have been reported (usually an incidental finding) with a very indolent behavior, distinguishable from mantle zone variant or overt MCL and should be monitored (20). More challenging are low-risk MCL patients (low tumor burden, low KI-67) who can also be monitored (16), as illustrated in the watch-and-wait group from the recent Nordic Lymphoma Group observational report for $\geq$2 years of untreated patients who had a 3-year OS.
of 79% (9). Putting aside the caveats related to these retrospective series, up to one-third of MCL at diagnosis can be monitored with a time to therapy of 1 year, though there are no clear criteria to identify such cases.

**Induction for Younger/Fit, Dose-Intensive/High-Dose Therapy–Eligible Patients**

Most patients present with “classic” MCL and are considered for treatment at diagnosis (21,22). Selection of induction therapy is usually based on patient’s ability to tolerate intensive therapy, thereby involving age (<65 years) and comorbidities. If feasible, there is clear consensus that intensive strategies lead to significant improvement in progression-free survival (PFS; >5 years) over standard immunochemotherapy such as R-CHOP, which has been proven both in clinical trials (23) and routine practice (24). In the MCL NCCN database, 3-year PFS for R-CHOP was 18% (3 times lower than with dose-intensive strategies: 55%-58%), and no OS benefit was shown for pooled dose-intense combinations versus R-CHOP (24). The benefit of cytarabine-containing induction was suggested in several phase II studies; R-CHOP/R-DHAP (3 cycles of each) in a series of 60 patients (aged ≤66 years) followed by ASCT led to significant improvement in complete responses (CR) (57% vs. 15%) over historical R-CHOP alone, translating into an impressive median event-free survival (EFS) of 83.9 months, median PFS of 84 months, and 5-year OS of 75% (median not reached) (25). Several other regimens corroborated those findings, including R-hyper-CVAD (26,27), NORDIC MCL2 (28,29), CALGB regimens (30), among others (Table 1) (25-31). The benefit of regimens containing HD-AraC was confirmed in a large (>200 patients/arm) randomized European MCL Network trial comparing arm A (R-CHOP→myeloablative radiochemotherapy [TBI, cyclophosphamide] and ASCT) vs. arm B (alternating R-CHOP/R-DHAP→HD-Ara-C-containing myeloablative regimen [TBI, Ara-C, melphalan] and ASCT) (abstract-only references (32,33)). At a median follow-up of 51 months,
results showed superiority for the HD-AraC arm for time to treatment failure (primary endpoint: 46 vs. 88 months, \(P=0.038\)), remission duration (49 vs. 84 months, \(P=0.0001\)), and OS (82 months vs. NR, \(P=0.045\)). Though the proportion of patients receiving ASCT was similar (72% vs 73%), benefit in the HD-AraC arm was attributed to higher and earlier CR rate paralleled by increased molecular CR, translating into fewer relapses in responders (n=81 vs. n=40) (34).

In summary, MCL in young and/or fit patients should be managed using a cytarabine-containing intensive approach with or without ASCT (27,35), which translate into PFS in excess of 5 years. However, late relapses still do occur (28,29), supporting emerging strategies of maintenance and/or consolidation particularly with biological agents (including rituximab), as shown recently after R-DHAP-ACST, where maintenance post-ASCT showed significantly improved EFS and PFS (36). Ongoing trials evaluating the role of other biologicals, particularly ibrutinib, after induction therapy will help refine the best approach to prevent recurrence, and will likely be based on minimal residual disease (MRD) status.

**Induction Regimens for Older, Non-Transplant–Eligible Patients**

*R-CHOP-like induction*

For older patients or those deemed ineligible for dose-intensive therapy, R-CHOP has been the default backbone. With an ~80% overall response rate (ORR), CR remains low (30%-40%) and most patients relapse as shown by the 18%-25% 2-year PFS (Table 1) (37-39). Building upon R-CHOP, several regimens have explored strategies incorporating newer therapies such as fludarabine (40) or HD-cytarabine (ongoing elderly trial in EU), replacement of cisplatinum compounds with other derivatives (e.g., oxaliplatinum), and addition of novel biologicals such as bortezomib - promising in early phase II study (41) - leading to establishment of a new
standard in frontline MCL as part of the LYM-3002 trial (42). The pivotal LYM-3002 study comparing VcR-CAP with R-CHOP showed significantly higher CR rate and improved median PFS in the bortezomib-containing arm (24.7 vs. 14.4 months, \( P<0.001 \), respectively) (42), leading to extended FDA approval for bortezomib in previously untreated MCL in October 2014 (43). Because of HyperCVAD-related toxicity (44), a modified combination (no cytarabine or methotrexate) was developed with results intermediate between R-CHOP and standard HyperCVAD, but better tolerated, also offering a platform for bortezomib combinations (45). This benefit was confirmed in the multicenter setting by the ECOG E1405 study, in which VcR-CVAD followed by maintenance rituximab in newly diagnosed MCL showed an ORR of 95%, with a 68% CR/CR unconfirmed (CRu), and 3-year PFS of 72% (46).

**Bendamustine-based induction**

The bendamustine + rituximab (BR) regimen was established by the StiL trial, comparing BR \((n=261)\) versus R-CHOP \((n=253)\) in indolent NHL (iNHL, >50% follicular lymphoma) (47). BR showed superior CR (40% vs. 30% R-CHOP, \( P=0.021 \)) and median PFS (69.5 vs. 31.2 months, \( P<0.0001 \)) for all patients while in the subset of MCL patients \((n=46 BR \text{ and } n=48 R-CHOP)\), PFS was 35.4 for the BR arm versus 22.1 months for R-CHOP \((P=0.0044, \text{ Table 1})\). In an effort to replicate these data, the US-based BRIGHT trial in iNHL and MCL compared BR \((n=213 \text{ [n=36 MCL]})\) with R-CHOP/R-CVP \((n=206 \text{ [n=38 MCL]})\) suggesting a higher CR in favor of BR (31% vs. 25%), although some patients received only R-CVP (48). BR toxicity was less favorable than in the StiL trial, and PFS was not clearly different (47,48). Despite of the lack of difference in OS, the overall favorable short-term toxicity profile, particularly in the StiL trial, established a new standard in MCL, offering a new backbone for combinations such as BR + bortezomib, which showed very promising results in phase II studies in relapsed/refractory MCL (83% ORR, 52%).
The LYSA group recently presented impressive results with frontline RiBVD (rituximab, bendamustine, bortezomib and dexamethasone) in 74 MCL patients (no maintenance) with a 74% CR/CRu alongside measurable molecular remission in blood (83%) and bone marrow (74%), translating into an estimated 24-month PFS and OS of 69% and 80%, respectively (50). Other studies combining BR with ibrutinib (SHINE trial) or lenalidomide are ongoing. The addition of cytarabine to BR (R-BAC) was reported in MCL patients aged ≥65 years; in this small series, results were impressive, with 100% ORR (95% CR) and 95% 2-year PFS for previously untreated MCL (n=20), and 80% ORR (74% CR) with a 70% 2-year PFS for relapsed/refractory MCL (n=20) (51).

Integrating New Agents into the First-Line Setting

Bortezomib was the first novel agent integrated into upfront MCL strategies, either with standard therapy as seen above with R-CHOP (SWOG-S0601 study abstract) (52,53), or after HDT and ASCT (54). Lenalidomide, with durable responses in the relapsed/refractory setting (55), was combined with rituximab in relapsed/refractory patients with promising results (56). A similar combination in the frontline setting (12 cycles R² induction followed by R² maintenance until progression) showed rapid responses (median time to response 2.8 months), leading to an ORR of 84%, including 53% CR/CRu and an 84% estimated 2-year PFS (57). A number of ongoing studies are looking at other biological combinations, e.g., BR ± ibrutinib (NCT01776840) or BR ± bortezomib followed by rituximab ± lenalidomide maintenance in elderly patients (ECOG1411, NCT01415752). Both lenalidomide and ibrutinib are also being evaluated as part of HDT-ASCT approaches in combination or sequentially as maintenance.

Consolidation and Maintenance Strategies
The European MCL Network Clinical Intergroup phase III study in patients aged ≥60 years (median, 70 years) evaluated R-CHOP21 (8 cycles) versus R-FC (6 cycles) followed by a second randomization in responders for maintenance with rituximab versus interferon alfa (IFN-α) (39). Although similar ORR and CR were seen with R-CHOP or R-FC induction, the 4-year OS differed significantly (62% vs. 47%, \( P = 0.0005 \)), and patients experienced higher mortality and toxicity with R-FC induction. In addition in the R-CHOP arm, rituximab maintenance significantly reduced relapse, and improved OS at 4 years (87% vs. 63%, \( P = 0.0005 \)). Of notice, by design, patients remained on rituximab maintenance until progression (some still on study beyond 5 years). As expected, hematologic toxicity was more common with R-FC than R-CHOP; in the maintenance arms, toxicity from IFN-α (vs. rituximab) led to lower compliance.

In the NORDIC MCL2 trial, rituximab was added as "preemptive maintenance" based on MRD monitoring with PCR conversion taken as an indicator of molecular relapse (i.e., not considered failures), leading most patients to convert again to PCR negativity after additional rituximab (29). Several ongoing trials are investigating the potential advantage of lenalidomide ± rituximab maintenance following R-chemotherapy (NCT01035463, NCT01865110) or lenalidomide/rituximab (NCT01996865). Bortezomib has also been tested as an optional agent for maintenance in 65 patients receiving bortezomib maintenance after R-CHOP SWOG-S0601), leading to an estimated doubled 2-year PFS (62% bortezomib vs. 30% historical R-CHOP alone) (52). Given the radiosensitivity of iNHL and MCL, radioimmunotherapy was tested as consolidation after 4 cycles of R-CHOP (n=56) showing promising results, with an ORR of 82% (55% CR/CRu), including a tripling of CR rate post-RIT (from 18% to 55%), as well as favorable PFS compared to historical controls (58). On the other hand, in the NORDIC MCL3 trial, the addition of RIT consolidation (ibritumomab tiuxetan [0.4 mCi/kg] pre-HDT (if in CRu/PR),
showed no clear benefit (59). While still being evaluated in numerous ongoing trials, the use of post-induction strategies as maintenance/consolidation, even following HDT-ASCT, is now supported by randomized trials showing the benefit of rituximab in both younger (36) and elderly (39) MCL patients. The next step will be to build on maintenance rituximab by using biological combinations, although such strategies should be targeted to patients at higher risk of recurrence because of added potential toxicities and cost issues.

**Assessment of Quality of Response to Predict Outcomes: MRD and PET in MCL**

Though high CR rates can be obtained with either dose-intensive strategies or combinations of biologicals with standard therapy, a significant proportion of patients still relapse. Two strategies have been evaluated to appreciate the quality of response in MCL: functional imaging (positron emission tomography [PET]) and MRD assessment. Retrospective studies of PET following R-hyper-CVAD induction showed a significant association between post-treatment PET-positivity and outcome, while interim PET was not predictive (60). PET-negativity before upfront ASCT was associated with superior PFS and OS in MCL (61), but not if induction was R-CHOP only (62) (likely because response was not deep enough with R-CHOP). No correlation was found between KI-67 or MRD measurements by PCR and PET, although patients with PR but negative MRD status seem to do as well as CR patients (34). As in other subtypes of NHL, issues with residual activity and interpretation of SUV values changes (and often-small patient series) limit definite conclusions and recommendations for use in practice, until results of larger prospective studies become available.

The role of MRD status in MCL, although not yet used in routine practice, is gaining interest. Several studies have confirmed, not surprisingly, that the achievement of molecular remission (MR; i.e., molecular CR) in peripheral blood and/or bone marrow following induction
immunochemotherapy is significantly associated with a better outcome, independently of other prognostic variables in both elderly and younger patients (34,63), and should become the goal in upcoming or ongoing immunochemotherapy trials (64).

**Treatment in the Relapsed/Refractory Setting**

Multiple chemotherapy- and molecular-based treatments have been used in relapsed/refractory MCL, with no clear standard of care established to date (21,22). Induction strategies may be carried over into the relapsed setting in an attempt to achieve better response with a different treatment than was initially received. For example, BR showed 75% ORR (50% CR) and median PFS of 18 months in 16 MCL patients (1-3 prior therapies) and may be considered second-line after non-BR regimens (65). As noted above, R-BAC showed promising results following ≥1 prior treatment (80% ORR, 70% CR), with a 2-year PFS of 70% (51). The most common grade 3/4-toxicity associated with R-BAC was transient and reversible myelosuppression (83% grade 3/4 thrombocytopenia).

Until 2013, bortezomib was the only FDA-approved agent for relapsed/refractory MCL in the US (66,67), as was temsirolimus in the EU (68). Two additional newer agents, lenalidomide and ibrutinib, were recently approved in the US for relapsed/refractory MCL (55,69). Multiple phase II studies of lenalidomide, an immunomodulator also with direct antineoplastic effects, have provided consistent ORR (28%-53%) with durable activity (median duration of response [DOR], 13.7-16.6 months) in heavily pretreated patients, including those failing bortezomib (NHL-002, NHL-003, and MCL-001 studies) (55,70,71). Recently reported results from MCL-002, a randomized phase II study of relapsed/refractory MCL patients, demonstrated superior median PFS following lenalidomide (8.7 months) versus investigator’s choice monotherapy (5.2 months; \( P=0.004 \)) (72). Also approved in 2013 was ibrutinib, a small-molecule inhibitor of
Bruton’s tyrosine kinase, based on its phase II activity (68% ORR and median DOR 17.5 months) and favorable safety profile (69). Table 2 summarizes key clinical study findings for all 4 approved agents in relapsed/refractory MCL, with lenalidomide and ibrutinib showing durable responses, including following multiple prior therapies (55,66-71).

Although overall studies do not support the use of ASCT in the relapsed/refractory setting (73,74), allogeneic transplantation can be potentially curative (75,76), though associated with a >50% risk of chronic graft-versus-host disease (GVHD). Approaches using haplotransplantation or TH2 amplification (to reduce GVH) or autologous chimeric antigen receptor (CAR) T cells might help implement cell therapy in an often elderly population with chemoresistant disease (77).

**Upcoming Novel Strategies**

The availability of newer agents with efficacy in disease refractory to standard therapies offers new opportunities for risk-adapted and molecular-based targeted therapy, appealing options in an older population. Based on early activity of rituximab combined with thalidomide in relapsed/refractory MCL and the improved safety profile with lenalidomide over thalidomide (78), studies combining rituximab with lenalidomide (i.e., R²) show impressive activity compared with either agent alone in the relapsed/refractory (57% ORR, 36% CR and median DOR of 18.9 months (56)) and first-line (84% ORR, 53% CR, estimated 2-year PFS 84%) (56,57) settings.

Preclinical data suggest superiority of second-generation monoclonal antibodies versus rituximab, including GA-101 (obinutuzumab (79)) and ofatumumab (80). Although ofatumumab showed modest activity in a recent phase II study (81), a dramatic response was reported in a patient with refractory, high leukemic phase MCL (82). ORR in the GAUGUIN phase II study (2
doses of obinutuzumab) in 21 heavily pretreated diffuse large B-cell lymphoma (DLBCL) and MCL patients was 24%-37%, with median DOR of 9.8 months (83). Additional ongoing studies are looking at second-generation monoclonal antibodies for newer immunochemotherapy regimens in MCL.

Several novel agents including BH3 mimetic-type BCL2 inhibitors such as navitoclax (ABT-263) (84) and obatoclax mesylate (85) showed modest activity; more recently, venetoclax (ABT-199; abstract results (86)) showed very impressive phase I activity in MCL and is being tested in combination. PI3Kδ inhibitors (e.g., idelalisib) or other small molecules including second-generation BTK inhibitors are being developed (87). Adoptive transfer of autologous CAR T-cells, genetically engineered to express anti-CD19 specificity demonstrated impressive results in NHL, including DLBCL and MCL; supporting planned studies focusing on MCL (77,88). Other strategies to induce T-cell responses through checkpoint inhibitors (e.g., anti–PD-1 antibodies) show extremely promising results in a number of tumors and are currently being explored in different lymphomas subtypes (89,90).

Conclusions and Author Perspectives

Based on evolving clinical options, our recommendations for sequencing therapies in MCL are outlined in Fig. 1. First-line treatment should be based on “functional general condition” (not just a “cut-off” of age 60 or 65 years), as well as a patient's ability to tolerate intensive therapy. Achieving an early CR in MCL very clearly impacts OS, and by extension, depth of CR. Molecular CR should be our goal moving forward and may also serve as an "endpoint" for treatment adjustment according to the interim molecular response. Dose-intense therapy with high-dose Ara-C–containing induction, with or without HDT-ASCT, translates into higher CR and molecular
CR rates, with extended PFS (>5 years). The need to maintain HDT-ASCT after induction in patients with CR/molecular CR is currently debatable and is being evaluated in ongoing trials.

In non–HDT-eligible patients, induction with R-chemotherapy and other biologicals such as VcR-CAP offers a new backbone for frontline FDA approval while BR is being tested as another platform for combinations. The use of maintenance is now supported in both younger and older patients, though the role and duration of maintenance beyond MRD-negative status is unclear, requiring further study.

In the relapsed/refractory setting, standard chemotherapy should not be the only option, considering its limited benefit and frequent chemoresistance. Novel therapies often provide durable responses but are not curative—only non-myeloablative transplantation may provide a cure. The development of novel combinations both in frontline and relapsed/refractory settings will likely expand and provide opportunities for non-chemotherapy options and/or chemotherapy combinations either sequentially or as maintenance/consolidation post-induction. Clinical trials should be the default in managing MCL patients given the rapid changes in the field. Finally, efforts are needed to help translate the impressive biological diversity of MCL into relevant clinical markers to better stratify patients and further improve the MCL treatment paradigm overall. MCL is changing, so let us continue to embrace those changes.

Acknowledgments

The authors received editorial support in the preparation of this manuscript from Julie Kern, PhD, CMPP, of Bio Connections LLC, which was funded by Celgene Corporation.
References


54th ASH Annual Meeting and Exposition; 2012 Dec 9-11; Atlanta, GA. Washington (DC):
American Society of Hematology; 2012. Abstract nr 151.


57. Ruan J, Martin P, Shah BD, Schuster SJ, Smith SM, Furman RR, et al. Sustained remission with the combination biologic doublet of lenalidomide plus rituximab as initial treatment for


Abstract nr 1665.

Table 1. Clinical efficacy of select induction regimens in previously untreated MCL

<table>
<thead>
<tr>
<th>Treatment/study</th>
<th>ORR</th>
<th>CR</th>
<th>Efficacy endpoints</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aggressive treatment: younger and transplant-eligible patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-hyperCVAD/R-MA (N = 97) (26,27)</td>
<td>97%</td>
<td>87%</td>
<td>Median 10-year TTF = 4.6 years (5.9 years for ≤ 65 years)</td>
<td>3-year OS = 82% (74% for ≥ 65 years)</td>
</tr>
<tr>
<td>NORDIC MCL2: maxi-CHOP alternating with rituximab + HD-AraC (N = 160) (28)</td>
<td>96%</td>
<td>54%</td>
<td>6-year EFS* = 56% 6-year PFS = 66%</td>
<td>6-year OS = 70%</td>
</tr>
<tr>
<td>Sequential R-CHOP/R-DHAP (N = 60) (25)</td>
<td>87%</td>
<td>57%</td>
<td>Median DFS = 78 mo Median EFS† = 83.9 mo 5-year EFS = 64%</td>
<td>Median OS = NR 5-year OS = 75%</td>
</tr>
<tr>
<td>CALGB immunochemo therapy regimen (N = 78) (30)</td>
<td>88%</td>
<td>69%</td>
<td>2-year PFS = 76% 5-year PFS = 56%</td>
<td>2-year OS = 87% 5-year OS = 64%</td>
</tr>
<tr>
<td><strong>Less aggressive: older (aged &gt; 65 years) and/or transplant-ineligible patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CHOP (n = 239) vs. R-FC (n = 246) (39)</td>
<td>86% vs. 78%</td>
<td>34% vs. 40%</td>
<td>Median TTF = 28 vs. 26 mo Median DOR = 36 vs. 37 mo</td>
<td>4-year OS = 62% vs. 47% R-CHOP+R = 87% R-CHOP+IFN-α = 63%</td>
</tr>
<tr>
<td>R-CHOP (n = 62) vs. CHOP (n = 59) (38)</td>
<td>94% vs. 75% (P = 0.0054)</td>
<td>34% vs. 7% (P = 0.00024)</td>
<td>Median TTF = 21 vs. 14 mo (P = 0.0131) No difference in PFS or OS</td>
<td>2-year survival: 77% for both arms</td>
</tr>
<tr>
<td>R-CHOP/R-AraC + R-F/AraC + CHOP + R maintenance in responders (N = 60) (40)</td>
<td>95%</td>
<td>87%</td>
<td>4-year PFS = 70% 4-year EFS* = 66%</td>
<td>4-year OS = 72%</td>
</tr>
<tr>
<td>ECOG E1405: VcR-CVAD + R maintenance or ASCT (N = 75) (46)</td>
<td>95%</td>
<td>68%</td>
<td>3-year PFS = 72%</td>
<td>3-year OS = 88%</td>
</tr>
<tr>
<td>Treatment/study</td>
<td>ORR</td>
<td>CR</td>
<td>Efficacy endpoints</td>
<td>OS</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>-------------</td>
<td>--------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>BR (n = 261) vs. R-CHOP (n = 253) (47)</td>
<td>93% vs. 91%</td>
<td>40% vs. 30% (P = 0.021)</td>
<td>Median PFS = 69.5 vs. 31.2 mo (P &lt; 0.0001)</td>
<td>No difference in OS</td>
</tr>
<tr>
<td>BR (n = 213 [n=36 MCL]) vs. R-CHOP/R-CVP (n = 206 [n=38 MCL]; BRIGHT) (48)</td>
<td>94% vs. 84%</td>
<td>51% vs. 24% (P = 0.0180)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>R-BAC (n=20 first-line; n=20 R/R) (51)</td>
<td>100% first-line 80% R/R</td>
<td>95% first-line 74% R/R</td>
<td>2-year PFS = 95% first-line 2-year PFS = 70% R/R</td>
<td>—</td>
</tr>
</tbody>
</table>

*EFS was calculated from study entry to treatment failure due to progression, toxicity, or death from any cause.

†EFS was defined as relapse after CR/CRu.

Abbreviations: BAC, bendamustine, cytarabine; BR, bendamustine, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CALGB, Cancer and Leukemia Group B; CR, complete response; CRu, CR unconfirmed; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; CVP, cyclophosphamide, vincristine, prednisolone; DHAP, dexamethasone, AraC, cisplatin; DOR, duration of response; EFS, event-free survival; FC, fludarabine, cyclophosphamide; FFS, failure-free survival; HD, high dose; MA, methotrexate, cytarabine; mo, months; MR, maintenance rituximab; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; R/R, relapsed/refractory; TTF, time to treatment failure; VcR-CVAD, bortezomib, rituximab, modified hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone without alternating cycles of cytarabine [AraC] and methotrexate).
Table 2. Clinical efficacy for approved treatments with relapsed/refractory MCL

<table>
<thead>
<tr>
<th>Patients</th>
<th>ORR</th>
<th>CR</th>
<th>Median DOR, months</th>
<th>Median PFS, months</th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (PINNACLE; N = 155) (66,67)</td>
<td>32%</td>
<td>8%</td>
<td>9.2</td>
<td>6.5</td>
<td>23.5</td>
</tr>
<tr>
<td>Temsirolimus (175/75 mg; n = 54) vs. Temsirolimus (175/25 mg; n = 54) vs. Investigator’s choice (n = 54) (68)</td>
<td>22% vs. 6% vs. 2%</td>
<td>2% vs. 0% vs. 2%</td>
<td>7.1 vs. 3.6 vs. N/A</td>
<td>4.8 vs. 3.4 vs. 1.9</td>
<td>12.8 vs. 10.0 vs. 9.7</td>
</tr>
<tr>
<td><strong>Lenalidomide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL-002 (N = 15) (70)</td>
<td>53%</td>
<td>20%</td>
<td>13.7</td>
<td>5.6</td>
<td>NR</td>
</tr>
<tr>
<td>NHL-003 (N = 57) (71)</td>
<td>35%</td>
<td>12%</td>
<td>16.3</td>
<td>8.8</td>
<td>NR</td>
</tr>
<tr>
<td>MCL-001 (EMERGE; N = 134) (55)</td>
<td>28%</td>
<td>8%</td>
<td>16.6</td>
<td>4.0</td>
<td>19.0</td>
</tr>
<tr>
<td>MCL-002: Lenalidomide (n = 170) vs Investigator’s Choice (n = 84) (72)</td>
<td>40%</td>
<td>5%</td>
<td>16.1</td>
<td>8.7</td>
<td>27.9</td>
</tr>
<tr>
<td>Ibrutinib (N = 111) (69)</td>
<td>68%</td>
<td>21%</td>
<td>17.5</td>
<td>13.9</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; DOR, duration of response; N/A, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
Figure 1. Sequential treatment algorithm in MCL patients: first-line treatment for younger, fit versus older and/or frail patients, consolidation or maintenance, and treatment for relapsed/refractory disease. First-line treatment is commonly selected based on patient age and condition, gauging a patient's tolerability to aggressive versus less aggressive induction immunochemotherapy. Patients eligible for high-dose therapy are typically considered for cytarabine-containing induction regimen, such as R-CHOP/R-DHAP followed by autologous SCT or R-hyper-CVAD if tolerated. Older, transplant-ineligible or unfit patients mainly receive BR, R-CHOP, or R-CHOP-bortezomib induction followed by rituximab maintenance. Non-myeloablative allogeneic transplant is a potential approach for special cases of fit patients who failed several lines of therapy; its use reflects a physician preference rather than significant clinical evidence. FDA-approved therapies for relapsed/refractory MCL include bortezomib, lenalidomide, and ibrutinib, while temsirolimus is approved in the EU.

CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; EU, European Union; HD, high dose; PD, progressive disease; R, rituximab; R-CHOP, rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; SCT, stem cell transplantation.
Figure 1:

- **MCL diagnosis**
  - **Younger, fit patients**
    - **First-line induction**
      - **R-chemotherapy**
        - R-CHOP- and HD cytarabine-based combination regimens
  - **Nonintensive therapy**
    - **R-chemotherapy**
      - BR, R-CHOP, or R-CHOP-bortezomib (intensity based on patient’s condition and disease characteristics)
    - **Watch and wait/observation**
      - Reassess regularly for symptoms or other treatment indications

- **Relapsed/refractory disease**
  - **Second line**
    - Responders
      - R-chemotherapy (different than first line)
        - Bortezomib
        - Temsirolimus
        - Lenalidomide
        - Ibrutinib
  - **Nonresponders**
    - **Third line**
      - Treatment based on patient and prior therapies
      - Eligible, fit patients: allogeneic SCT

- **First-line consolidation or maintenance**
  - **Transplant eligible**
    - Autologous SCT consolidation
  - **Transplant ineligible**
    - Rituximab maintenance

- **Relapse/PD**
  - **Second line**
    - Eligible, fit patients: allogeneic SCT

Author Manuscript Published OnlineFirst on June 9, 2015; DOI: 10.1158/1078-0432.CCR-15-0488
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.
Clinical Cancer Research

Refining the Mantle Cell Lymphoma Paradigm: Impact of Novel Therapies on Current Practice

Irit Avivi and Andre Goy

Clin Cancer Res Published OnlineFirst June 9, 2015.

Updated version
Access the most recent version of this article at:

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/early/2015/06/09/1078-0432.CCR-15-0488. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.