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

Irit Avivi and Andre Goy

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 cytoreductive-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 four 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 in first-line 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 immunohematotherapy, and even after HDT-ASCT, most patients still relapse and frequently develop chemo-resistant. 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 immunohematotherapy or as consolidationmaintenance postinduction, offers new opportunities for patients with MCL. This review highlights how such developments can help refine the current MCL paradigm.

Review

Introduction

Mantle cell lymphoma (MCL) accounts for about 6% of all non–Hodgkin lymphomas (NHL), although 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; refs. 2, 3). As WHO first recognized MCL as a separate entity in 1994, the median overall survival (OS) has improved from <2.5 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 morphologic (diffuse, nodular, mantle zone) as well as cytologic variants (small cells, pleomorphic, blastoid). Diagnosis suspected on immunophenotype (CD20<sup>+</sup>, CD5<sup>+</sup>, CD23<sup>+</sup>, and FMC7<sup>+</sup>) 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, Eastern Cooperative Oncology Group (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 to 7+ years; ref. 6). Ki-67 (or MIB1) has been used as a surrogate marker of proliferation (<≤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 <M2M, miRNAs, and complex karyotype, whereas overall P53 abnormalities are likely underestimated (2, 12). SOX11 expression can help diagnose CYCLIN D1-negative cases and seems to correlate with outcome (13), although 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% to 15% of patients with MCL 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 correlate with higher genetic instability (fewer secondary genetic abnormalities over time than classic MCL), although some cases may acquire DEL17P/PS3 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 patients with MCL (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 ≥2 years of untreated patients who had a 3-year OS rate 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, although 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, 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-intensive combinations versus R-CHOP (24). The benefit of cytotoxic-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 autologous stem cell transplantation (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 rate of 75% (median not reached; ref. 25). Several other regimens corroborated those findings, including R-hyper-CVAD (26, 27), NORDIC MCL2 (28, 29), CALGB regimens (30), among others (Table 1; refs. 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] versus 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. not reached, \( P = 0.045 \)). Although 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; ref. 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 biologic agents (including rituximab), as shown recently after R-DHAP-ASCT, where maintenance post-ASCT showed significantly improved EFS and PFS (36). Ongoing trials evaluating the role of other biologicals, particularly bortezomib, 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, Nontransplant-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 about 80% overall response rate (ORR), CR remains low (30%–40%) and most patients relapse as shown by the 18% to 25% 2-year PFS (Table 1; refs. 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; ref. 42), leading to extended FDA approval for bortezomib in previously untreated MCL in October 2014 (43). Because of hyper-CVAD–related toxicity (44), a modified combination (no cytarabine or methotrexate) was developed with results intermediate between R-CHOP and standard hyper-CVAD, 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; ref. 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, whereas in the subset of patients with MCL (n = 46 BR and n = 48 R-CHOP), PFS was 35.4 for the BR arm versus 22.1 months for R-CHOP (\( P = 0.0044 \), Table 1). In an effort to replicate these data, the U.S.-based BRIGHT trial in iNHL and MCL compared BR (n = 213 [n = 36 MCL]) with R-CHOP/R-CVP (n = 206 [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 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% CR; ref. 49). The LYSa group recently presented impressive results with frontline RiiBVD (rituximab, bendamustine, bortezomib, and dexamethasone) in 74 patients with MCL (no maintenance) with a 74% CR/CRu along with measurable molecular remission in blood (83%) and bone marrow (74%), translating into an estimated 24-month PFS and OS rates 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 patients with MCL aged ≥65 years; in this small series, results were impressive, with 100% ORR (95% CR) and 95% 2-year PFS rate for previously untreated MCL (n = 20), and 80% ORR (74% CR) with a 70% 2-year PFS rate for relapsed/refractory MCL (n = 20; ref. 51).

### 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>
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<tbody>
<tr>
<td>Aggressive treatment: younger and transplant-eligible patients</td>
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<tr>
<td>R-hyper-CVAD/R-MA (n = 97; refs. 26, 27)</td>
<td>97%</td>
<td>87%</td>
<td>Median 10-year TTF = 4.6 years</td>
<td>3-year OS rate = 82%</td>
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<tr>
<td>NORDIC MCL2: maxi-CHOP alternating with rituximab + HD-AraC (n = 160; ref. 28)</td>
<td>96%</td>
<td>54%</td>
<td>6-year EFS* rate = 56%</td>
<td>6-year OS rate = 70%</td>
</tr>
<tr>
<td>Sequential R-CHOP/R-DHAP (n = 60; ref. 25)</td>
<td>87%</td>
<td>57%</td>
<td>Median DFS = 78 mo</td>
<td>Median OS = NR</td>
</tr>
<tr>
<td>CALGB immunochemotherapy regimen (n = 78; ref. 30)</td>
<td>88%</td>
<td>69%</td>
<td>2-year PFS rate = 76%</td>
<td>2-year OS rate = 87%</td>
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| Less aggressive: older (aged ≥65 years) and/or transplant-eligible patients | | | | |
| R-CHOP (n = 239) vs. R-FC (n = 246; ref. 39) | 86% vs. 78% | 34% vs. 40% | Median TTF = 28 vs. 26 mo | 4-year OS rate = 62% vs. 47% |
| R-CHOP (n = 62) vs. CHOP (n = 59; ref. 38) (P = 0.0054) | 94% vs. 75% (P = 0.00024) | 34% vs. 7% | Median TTF = 21 vs. 14 mo (P = 0.0131) | No difference in PFS or OS |
| R-CHOP/R-AraC + R-F/AraC + CHOP + R maintenance in responders (n = 60; ref. 40) | 95% | 87% | 4-year PFS rate = 70% | 4-year OS rate = 72% |
| ECOG E1405: VCR-CVAD + R maintenance or ASCT (n = 75; ref. 46) | 95% | 68% | 3-year PFS rate = 72% | 3-year OS rate = 88% |
| BR (n = 261) vs. R-CHOP (n = 253; ref. 47) | 93% vs. 91% | 40% vs. 30% (P = 0.021) | Median PFS rate = 69.5 vs. 31.2 mo (P < 0.0001) | No difference in OS |
| BR (n = 213) vs. R-CHOP/R-CVP (n = 206) (n = 38 MCL; BRIGHT; ref. 48) | 94% vs. 84% (P = 0.0180) | 51% vs. 24% | — | — |
| R-BAC (n = 20 first-line; n = 20 R/R; ref. 53) | 100% first-line | 95% first-line | 2-year PFS rate = 95% first-line | — |

Abbreviations: BAC, bendamustine, cytarabine; CALGB, Cancer and Leukemia Group B; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVAD, cyclophosphamide, vincristine, doxorubicin, cyclophosphamide; CV; BAC, bendamustine, cytarabine, dexamethasone; CVP, cyclophosphamide, vincristine, prednisone; DHAP, dexamethasone, AraC, cisplatin; FC, fludarabine, cyclophosphamide; MA, methotrexate, cytarabine; MR, maintenance rituximab; NR, not reached; 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].

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

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-0601 study abstract; refs. 52, 53) or after high-dose therapy (HD) 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
biologic combinations, for example, 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 (6 cycles) versus R-FC (6 cycles) followed by a second randomization in responders for maintenance with rituximab versus IFNα (39). Although similar ORR and CR were seen with R-CHOP or R-FC induction, the 4-year OS rates 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 IFNα (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; ref. 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 with historical controls (58). On the other hand, in the NORDIC MCL3 trial, the addition of RIT consolidation [ibrutinumab 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 postinduction 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) patients with MCL. The next step will be to build on maintenance rituximab by using biologic 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

Although high CR rates can be obtained with either dose-intensive strategies or combinations of biologics 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 posttreatment PET positivity and outcome, whereas 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 (ref. 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 immunotherapy 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 immunotherapy 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 patients with MCL (1–3 prior therapies) and may be considered second-line after non-BR regimes (65). As noted above, R-BAC showed promising results following ≥1 prior treatment (80% ORR, 70% CR), with a 2-year PFS rate 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 United States (66, 67), as was temsirolimus in the European Union (68). Two additional newer agents, lenalidomide and ibrutinib, were recently approved in the United States 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; refs. 55, 70, 71). Recently reported results from MCL-002, a randomized phase II study of relapsed/refractory patients with MCL demonstrated superior median PFS following lenalidomide (8.7 months) versus investigator’s choice monotherapy (5.2 months; P = 0.004; ref. 72). Also approved in 2013 was ibrutinib, a small-molecule inhibitor of Bruton tyrosine kinase, based on its phase II activity (68% ORR and median DOR 17.5 months) and favorable safety.
including second-generation BTK inhibitors, are being developed chemotherapy regimens in MCL.

second-generation monoclonal antibodies for newer immunotherapy options in an older population. On the basis of 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 "cutoff" 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-intensive therapy with high-dose Ara-C containing, or without HDT-ASCT, transplants 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 whereas BR is being tested as another platform for combinations. The use of maintenance is now supported in both younger and older patients, although 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 postinduction. Clinical trials should be the default in managing patients with MCL given the rapid changes in the field. Finally, efforts are needed to help translate the impressive biologic diversity of MCL into relevant clinical markers to better stratify patients and further improve the 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), although associated with a >50% risk of chronic 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 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. On the basis of 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; ref. 56) and first-line (84% ORR, 53% CR, estimated 2-year PFS rate, 84%; refs. 56, 57) settings.

Preclinical data suggest superiority of second-generation monoclonal antibodies versus rituximab, including GA-101 (obinutuzumab; ref. 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 GAU-GUIN phase II study (2 doses of obinutuzumab) in 21 heavily pretreated patients with diffuse large B-cell lymphoma (DLBCL) and MCL was 24% to 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; ref. 84) and obatoclax mesylate (85), showed modest activity; more recently, venetoclax (ABT-199; abstract results; ref. 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

On the basis of 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 "cutoff" 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-intensive therapy with high-dose Ara-C–containing induction, with or without HDT-ASCT, transplants 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 whereas BR is being tested as another platform for combinations. The use of maintenance is now supported in both younger and older patients, although 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 postinduction. Clinical trials should be the default in managing patients with MCL given the rapid changes in the field. Finally, efforts are needed to help translate the impressive biologic 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.

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.

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