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

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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 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 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 postinduction, offers new opportunities for patients with MCL. 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), 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+, 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, 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 82M, 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 CEP, 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/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
diagnosis can be monitored with a time to therapy of 1 year,
although there are no clear criteria to identify such cases.

Induction Regimens 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 comorbid-
ities. If feasible, there is clear consensus that intensive strategies
lead to significant improvement in progression-free survival
(PFS; >5 years) over standard immunotherapy 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
rate 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 autolog-
ous stem cell transplantation (ASCT) led to significant
improvement in complete responses (CR; 57% vs. 15%) over
historical R-CHOP alone, translating into an impressive medi-
an 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 Net-
work trial comparing arm A [R-CHOP—myeloablative radio-
chemotherapy (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: 48 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 cytotoxic-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 partic-
ularly with biologic 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.

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 LYSMA group recently presented impressive results with frontline RibVD (rituximab, bendamustine, bortezomib, and dexamethasone) in 74 patients with MCL (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 rates of 69% and 80%, respectively (50). Other studies combining BR with ibrutinib (SHINE trial) or lenalidomide are ongoing. The addition of cytarnbine 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).

### 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; refs. 52, 53) or after high-dose therapy (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
such strategies should be targeted to patients at higher risk of
maintenance rituximab by using biologic combinations, although
patients with MCL. The next step will be to build on mainte-
nance strategies as maintenance/consolidation, even following 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 “pre-
emptive 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 lenali-
domide ± 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 borte-
zomib 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 consoli-
dation 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
crystalization [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 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 mainte-
nance 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 tomog-
raphy (PET)] and MRD assessment. Retrospective studies of PET
following R-hyper-CVAD induction showed a significant associ-
ation between posttreatment PET positivity and outcome, where-
as 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 SIUV values changes (and
often-small patient series) limit definite conclusions and recom-
endations 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;
more common with R-FC than R-CHOP; in the maintenance arms, toxicity from IFNα (vs. rituximab) led to
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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 strat-
egies 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 regimens (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 trans-
ient 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
tensirolimus 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 immu-
nomodulator also with direct antineoplastic effects, have pro-
vided 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 inves-
tigator’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

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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 GA-101 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-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 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/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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References


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