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Understanding Health-Related Quality of Life in Patients with Mantle Cell Lymphoma

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Introduction

Mantle cell lymphoma (MCL) is a unique non-Hodgkin lymphoma (NHL) subtype characterized by heterogeneous clinical behavior with features of both aggressive and indolent disease. Historically felt to be incurable, treatment of MCL is directed at inducing prolonged remission and/or achieving optimal disease and symptom control. Numerous controversies exist with no firmly established standards for treatment in the frontline or relapsed/refractory setting, underscoring the relevance of accounting for health-related quality of life (HRQOL) in treatment decision making. In the frontline setting, for young, fit patients, it remains to be established if the most aggressive induction approaches (such as R-HyperCVAD or Nordic MCL2 regimen) are superior to less aggressive chemotherapy (such as bendamustine and rituximab (BR)) with or without consolidative autologous stem cell transplant (ASCT) and/or maintenance anti-CD20 antibody therapy. In this population, where superiority of survival outcomes in one approach has not been clearly established, illuminating HRQOL among disparate treatment approaches would be beneficial, though data are lacking. In the relapsed or refractory disease setting, exciting scientific progress in therapeutic options, including the development of 1st and 2nd generation Bruton tyrosine kinase (BTK) inhibitors, immunomodulators, proteasome inhibitors, B-cell lymphoma 2 (BCL2) inhibitors, has led to improved outcomes and a variety of potential management

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strategies for patients on and off study. Patients with mantle cell lymphoma are now living longer with their disease, many on chronically administered treatments in various stages of remission or stable disease. In this population, treatment tolerability including the impact of adverse events over months to years of continuous treatment on a patients' HRQOL, is relevant, though once again, bears limited existing data.

The purpose of this review is to highlight why HRQOL in patients with MCL matters, to revisit what is known about HRQOL and other patient-centered outcomes in this disease, and to explore the numerous unanswered questions that remain. We will first discuss these issues as applied to frontline therapy for newly diagnosed disease, then in the relapsed/refractory setting, drawing knowledge from other types of NHL where relevant. We will conclude by exploring challenges and future directions in understanding the patient experience through better evaluation of the patient perspective and HRQOL in MCL.

Why is understanding HRQOL particularly relevant in patients with mantle cell lymphoma?

Before exploring the particular importance of HRQOL in patients with MCL, it is valuable to clarify terminology. Patient-reported outcomes (PRO) are evaluations that come directly from a patient about the status of their health without amendment or interpretation of their response by a clinician or anyone else¹. PROs are an assessment method, designed to provide the patient's perspective on functional outcomes, adverse events, and symptoms over time, treatment preferences, and other aspects. Meanwhile, the terms quality of life (QOL) and health-related quality of life (HRQOL) are specific clinical outcomes assessed using one (or several) PRO measures. QOL is a broad multidimensional concept which covers all aspects of life even beyond health (but is sometimes used interchangeably with HRQOL), complicating its measurement. HRQOL maintains a narrower focus on the effects of illness and treatment, and has been defined as the subjective perception of the effect of health (including disease and treatment) on domains including physical, psychological, and social functioning and overall wellbeing.² The goal of evaluating HRQOL in cancer clinical trials is to evaluate the effects of cancer and its treatment together on the patient's subjective perception of his or her wellbeing; these data are intended to complement the usual primary outcomes (response rate, survival).³

It is possible to assess HRQOL generally and by domain with a variety of validated instruments, such as the Functional Assessment of Chronic Illness/ Cancer Therapy (FACIT/ FACT) scales^{4,5} (including the lymphoma-specific scale FACT-Lym)⁶, European Organization for Research and Treatment of Cancer (EORTC) questionnaires⁷, EuroQOL EQ-5D instruments⁸, among others⁹. For the purposes of this article, we will focus not on detailed data from specific instruments, but rather on trends in HRQOL data evaluating mantle cell lymphoma patients' perspectives on their disease and treatment experience.

HRQOL assessment is relevant in newly diagnosed as well as in relapsed or refractory MCL patients. In frontline therapy, when there is no clearly defined approach that offers a superior overall survival based on current randomized clinical trial data, HRQOL data can help guide the best choice of regimen for a given patient. Evaluation of HRQOL and AEs from the

patient perspective is also crucial in patients with MCL in the relapsed and refractory setting. As opposed to frontline treatment which typically involves finite-duration cytotoxic approaches (with or without maintenance anti-CD20 antibody therapy), treatments for relapsed and refractory MCL in the modern era include the use of several chronic or continuously administered oral therapies. The toxicity profile of these novel agents is starkly different from that of shorter duration conventional cytotoxic therapy, and when treatment is prolonged, in addition to treatment safety, evaluation of both tolerability and toxicity over time from the patient's perspective becomes even more important.

HRQOL in Patients with Newly Diagnosed MCL

With an understanding of the relevance of HRQOL assessment in MCL patients, we will now explore what is known about HRQOL in newly diagnosed MCL patients based on existing studies. MCL is a heterogeneous disease where some patients presenting with asymptomatic, low burden, often incidentally identified, leukemic-phase MCL can defer therapy at diagnosis¹⁰. Data from trials in follicular lymphoma patients suggest that observation (versus treatment with rituximab) may have a negative impact on HRQOL, related to coping with the illness¹¹. However, no HRQOL data for “watchful waiting” in MCL are available.

For patients who require treatment at diagnosis, multiple therapy options bear similar efficacy (primary outcomes) and a different toxicity profile. Therefore, evaluation of HRQOL and the patient perspective becomes crucial. Attempts to elucidate HRQOL differences between intensive treatment regimens for young, fit patients newly diagnosed with MCL have been made but are limited in the ability to provide clinically meaningful evidence. Widmer et al. reported a single center retrospective study comparing the outcome and therapy tolerance of 43 young, fit MCL patients treated with R-CHOP/ASCT vs R-HyperCVAD/MTX-AraC without ASCT. They found no difference in progression free survival (PFS) or overall survival (OS) between the two groups. However, the hospitalization rate, hematologic toxicity and economic burden were significantly higher in the R-HyperCVAD group. HRQOL was measured using EORTC QLQ-C30, a standardized questionnaire that incorporates global health status, functional assessment and symptom assessment. In this study, EORTC QLQ-C30 data were evaluable in 24 patients and reportedly better in the R-HyperCVAD group, though these results are indeterminate as only 5 patients with QLQ-C30 data received R-HyperCVAD. The authors recommend R-CHOP/ASCT over R-HyperCVAD given the significant toxicity and attribute the contradictory HRQOL data to discrepancy in physician-observed AEs and patient experience. The major limitation of the study design was that the HRQOL surveys were administered retrospectively and likely subject to recall bias¹².

For patients who are not candidates for intensive frontline therapy, the results from two phase 3 randomized trials of first line therapy for indolent NHL and MCL, established the non-inferiority of BR to R-CHOP/R-CVP in terms of response rates and PFS^{13,14}. In one of these studies, the BRIGHT trial, HRQOL was a secondary endpoint systematically collected using the EORTC QLQ-C30¹⁵. The study included 74 patients with MCL (17% of total study participants), 36 in the BR arm and 38 in the R-CHOP/R-CVP arm. By conventional

clinician-based common terminology criteria for AE (CTCAE)¹⁶ assessment, BR had different AEs with little alopecia and neuropathy, but more nausea (potentially due to differences in prophylactic antiemetic regimens between arms) and hypersensitivity reactions. This study also identified that from the patient perspective, fatigue was improved at several time points in the BR group compared with standard therapy. In contrast, physician CTCAE reporting reported rates of fatigue as similar between arms, a difference which underscores the value of including PROs for AE assessment in trials and confirms a large body of research affirming systematic underreporting of clinician-rated AEs as compared to patient reports^{17–19}. Like the primary analysis, HRQOL was not evaluated by tumor type (MCL) specifically, but among all patients, treatment with BR was associated with improved scores for cognitive, physical, social and emotional functioning for at least one time point, and with improved physical functioning throughout therapy. The BRIGHT study provides valuable PRO and HRQOL data on regimens that can assist patients and their physicians with decision-making. Although in the current era most patients not fit enough for an aggressive frontline approach undergo BR (rather than R-CHOP or R-CVP), the principle remains that in this malignancy, HRQOL assessment and measurement of other PROs can offer valuable patient-centered perspectives on the treatment experience to assist patients and their clinicians in an individualized treatment choice when multiple approaches are possible.

HRQOL data specifically for autologous stem cell transplantation (ASCT) in first remission for MCL is lacking. With a median age at diagnosis of 68 years, a majority of patients with MCL are elderly. A single center cross-sectional study evaluated the impact of ASCT in older patients (>60 years) with lymphoma (19% with MCL) on HRQOL using two different instruments (Euroqol EQ-5D and FACT-BMT²⁰) at a median of 49 (range 17–96) months after ASCT. They found that HRQOL was well preserved after ASCT compared to an age-matched general population²¹. Similar results were reported by Farooq et al. who assessed HRQOL, using FACT-G, longitudinally in lymphoma patients who underwent ASCT vs those who did not. This study evaluated several different lymphoma histologies. Of the MCL patients included, 28 received ASCT while 51 did not. Thirty-nine percent of all autologous transplants were performed in first remission. They reported no difference in HRQOL at 3- and 6-years post-lymphoma diagnosis among patients treated with or without ASCT²².

Rituximab maintenance has become the standard of care in newly diagnosed patients after induction therapy followed by autologous transplant²³. Patients with MCL who are ineligible for ASCT are often placed on maintenance rituximab based on evidence that it improves outcomes though this remains controversial^{24–26}. HRQOL in patients receiving rituximab maintenance has been evaluated in a single center randomized study of 122 patients with CD20+ B-cell NHL (only 8 patients with MCL). This study showed that HRQOL, as measured by EORTC-QLQ-C30 and Euroqol EQ-5D, was not affected by maintenance rituximab therapy administered every 3 months for 2 years compared to observation²⁷.

For patients who are unfit or elderly and felt ineligible for transplant or cytotoxic chemotherapy for newly diagnosed disease, there is no consensus on management and little HRQOL data. Ruan et al. conducted a single arm phase 2 study of lenalidomide- rituximab

induction and maintenance and did evaluate HRQOL with FACT-Lym and FACT-Lym Trial Outcome Index⁵ (which provides a composite of physical and functional wellbeing along with FACT-Lym). Trends toward improvement were noted in patient HRQOL scores but these changes were not statistically or clinically significant²⁸.

HRQOL in Patients with Relapsed/Refractory MCL

As opposed to frontline treatment where standard approaches typically include conventional cytotoxic chemotherapy, chronically administered targeted agents are often used in second line treatment of patients with relapsed or refractory MCL. Many of these drugs have been approved based on single-arm phase 2 study results. In the absence of data establishing superiority of one treatment approach over another, HRQOL data may be valuable in making therapy decisions for individual patients. Additionally, the toxicity profile, burden of AEs and impact on the patient of continuously administered targeted therapies or immunomodulators is entirely different compared to cytotoxic chemotherapy, and the concept of not just safety but tolerability is particularly relevant when a therapy is continuous or chronic. A recent multi-stakeholder group including clinicians and patients established that the tolerability of a cancer treatment is defined as “the degree to which symptomatic and non-symptomatic AEs associated with the product’s administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy.”²⁹ By definition, understanding tolerability requires the patient perspective, in addition to safety data and knowledge about dose modifications, discontinuation and interruptions³⁰. There exists limited data on some agents to guide us in this regard in the relapsed/refractory MCL population.

Three BTK inhibitors - ibrutinib, acalabrutinib and zanubrutinib are currently FDA approved for relapsed MCL. No head-to-head comparisons of these drugs are available and therefore choice of BTK inhibitor is often based on the anticipated toxicity and tolerability of the drug in individual patient situations. There are no published data on HRQOL with the 2nd generation BTK inhibitors acalabrutinib and zanubrutinib. However, HRQOL data were reported from RAY (MCL3001), a phase 3 international randomized trial of ibrutinib vs temsirolimus in previously treated MCL³¹. This trial used FACT-Lym and EQ-5D-5L to provide longitudinal assessments of HRQOL on day 1 of the first 6 cycles, then every 9 weeks for 15 months and then every 24 weeks until disease progression, death or clinical cutoff. Results showed that patients treated with ibrutinib had substantial improvements in FACT-Lym subscale and total scores, EQ-5D-5L scores from baseline as well as compared with temsirolimus patients. It is interesting to note that the positive changes initially observed in physical wellbeing decreased with time and even dropped below the baseline after about 20 cycles of ibrutinib. For reference, the median progression-free survival for the ibrutinib arm in this trial was 14.6 months [95% CI 10.4–not estimable]. This raises the question of whether cumulative toxicity or AEs over time from ibrutinib may have affected physical wellbeing after long-term chronic therapy even though there was an improvement at the beginning of therapy due to reduction in disease symptom burden.

As discussed previously, use of lenalidomide has been explored in elderly or unfit patients in the frontline. However, lenalidomide is more commonly used in patients with relapsed or

refractory mantle cell lymphoma. Rule et al. presented data from the MCL-002 (SPRINT) trial³² that did collect HRQOL data using the EORTC QLQ-C30. Patients with relapsed/refractory MCL in this trial were randomized 2:1 to lenalidomide as a single agent vs investigator's choice chemotherapy. HRQOL was measured at baseline, alternate cycles from 2–8 and at the end of treatment. They found that HRQOL was maintained with lenalidomide from baseline through last treatment cycle. HRQOL was similar among patients treated with lenalidomide vs chemotherapy except for higher rates of clinically meaningful improvement in HRQOL for physical function and pain in the lenalidomide group³².

To our knowledge, HRQOL data, if available, for many of the other targeted agents approved and in the pipeline for MCL such as acalabrutinib, zanubrutinib, venetoclax and bortezomib has not been published to date, and is often not systematically collected in trials. This is especially concerning as these therapies, given for months to years in the relapsed setting and can have chronic, at times cumulative, toxicities. For example, although no long-term studies of bortezomib specifically in MCL patients are available, neuropathy is a well-known and established AE of bortezomib use that can severely affect physical and functional wellbeing domains of HRQOL. As targeted agents typically reserved for the relapsed/refractory setting are now being brought forth to the frontline setting, including HRQOL as a predefined endpoint for clinical trials is increasingly important. Establishing the impact of these novel therapies on HRQOL in MCL patients specifically may help to guide treatment decisions and patient counseling.

Allogeneic stem cell transplantation is sometimes offered as a potentially curative intent therapy for young fit patients with MCL who have relapsed after multiple lines of therapy or have poor prognostic markers such as p53 mutations. Short and long-term impact of allogeneic stem cell transplant on HRQOL in other hematologic malignancies are well established³³. Although no studies specific to allogeneic transplantation in MCL are reported, allogeneic transplantation is expected to lead to early moderate declines in HRQOL, which largely return to baseline at 100 days post-transplant. Long-term impact on HRQOL is largely driven by acute and chronic graft-versus-host-disease.

Chimeric antigen receptor T-cell (CAR-T) therapy is upcoming as a treatment option for relapsed MCL patients³⁴. Early data on HRQOL changes during the first few weeks post-CAR-T show that HRQOL dips in the first two weeks after CAR-T therapy, similar to autologous transplant, but recovers after week two, unlike allogeneic transplantation where the trend toward decrease in HRQOL is deeper and sustained^{35,36}. Although there were no MCL patients among this cohort, it is encouraging to have some helpful HRQOL data on CAR-T as it represents an exciting potential therapeutic modality for patients with MCL whose disease has progressed through multiple lines of therapy.

Challenges in the Evaluation of HRQOL in MCL

The existing literature of HRQOL assessments in patients with MCL demonstrates findings of interest, but mainly highlights the need for further systematic, consensus evaluation of PROs evaluating HRQOL to understand better the MCL patient experience specifically in

both newly diagnosed and relapsed/refractory disease. Many therapeutic clinical trials group MCL with indolent NHL histologies making it difficult to interpret HRQOL results in the specific context of MCL, which has a unique biology and disease course. Routine inclusion of HRQOL measures as a secondary, key or at least exploratory endpoints in MCL specific trials is the best way to address this knowledge gap. However, there are challenges inherent to instrument selection and data analysis for PROs in MCL trials. Yost et al. prospectively validated the FACT-G as a tool in NHL patients and included about 5% MCL³⁷. The FACT-Lym has been validated as an instrument to assess HRQOL in patients with relapsed/refractory MCL and was shown to differentiate patients based on performance status and worsening health status³⁸. Most instruments have not been validated in a lymphoma population specifically, but this should not be a barrier to their use. Previously discussed instruments such as EORTC QLQ-C30, EQ-5D-5L, many of which have been used in the research reviewed above, are also appropriate choices for assessment of HRQOL in MCL patients.

HRQOL is a composite outcome that is influenced by multiple other variables including social support, lifestyle such as physical activity, diet, body weight, tobacco and alcohol use^{39–41}, each of which is relevant in MCL and other types of NHL. These factors are likely both determinants as well as effects of an individual's HRQOL, which adds complexity. HRQOL is impacted by treatment-related AEs and disease-related symptoms, which can also be more specifically addressed by tools such as the Patient Reported Outcomes Version of the CTCAE (PRO-CTCAE)⁴², whereby patients self-report frequency, severity and interference of multiple symptomatic AEs that can be graded similarly to clinician reported AEs per CTCAE. Tools such as the FACT-GP5 item that asks patients to rate the “overall burden of side effects” over time may elucidate a more global impact of AEs on HRQOL in patients on chronic therapy⁴³. Patient reporting of AEs may improve the accuracy toxicity assessment, and constitutes a key element of tolerability evaluation⁴⁴. Knowing which instrument to use, how often to administer it and what data results is not always straightforward. In the future, it would be optimal to have consensus on which tools should be used in which types of studies or for which type of Hodgkin and non-Hodgkin lymphoma, but for now investigators should involve health outcomes research specific colleagues including biostatisticians for expertise on the selection of the tool and analysis of data during protocol development where possible. If not, it is reasonable to select tools based on the level of comfort with the implementation of the instrument.

Collecting the right PROs at the right frequency is only part of the challenge to understanding HRQOL in patients with MCL. Knowing how to analyze and present the PRO data in a clinically meaningful way is another.^{45,46} Longitudinal PRO analysis and display is important. AEs influence HRQOL, and understanding them better is vital for patients on long-term therapy for MCL. To understand the experience of a patient with MCL on a chronically administered targeted agent, a conventional maximum grade table demonstrating incidence of high grade cytopenias and clinician-rated AEs, is insufficient for evaluation of tolerability and the time profile of AEs.³ For example, CTCAE defines grade 2 diarrhea as more than 4–6 stools a day above baseline. While this may be a tolerable side effect in the short term and is often not reported in conventional toxicity tables, over months to years of treatment this AE may become intolerable and have substantial ramifications on multiple

domains of a patient's HRQOL. Knowing that headache from acalabrutinib may come on early and dissipate in the first couple of weeks or that neuropathy from bortezomib has a late onset and cumulative burden, is relevant to patients, yet there is often little data on toxicity over time, including burden of chronic low grade AEs over time.⁴⁷ Simple approaches to analysis of CTCAE, PRO AE and HRQOL data over time are available.⁴⁸ Additionally, there has been recent emphasis on understanding the burden of AEs overall on the patient and their HRQOL, which may provide greater insights, to better understand the MCL patient's treatment experience over time.^{49–51}

Future Directions and Summary

In the future, the goal should be systematic real-time collection of PROs in patients with MCL on and off clinical studies to understand HRQOL better. In addition to being important endpoints in clinical trials of agents for MCL, the ultimate goal of HRQOL data is to improve the experience of patients with MCL in the real world. Mobile technology, electronic platforms and wearable devices are all being investigated and implemented to facilitate the collection of PROs from patients⁵². This will make improved understanding of HRQOL in MCL and other cancers more feasible in the imminent future in patients on trials and those in routine practice. HRQOL data can guide treatment selection for patients in the clinic and be part of shared decision-making on a treatment strategy. Understanding AEs, including their time profile and overall burden from the patient perspective, can guide education on a treatment regimen so patients know what to anticipate. This knowledge can help to optimize the selection and timing of symptom control for toxicities in which an AE intervention is available. There is increasing evidence for supportive interventions such as physical activity programs during and after treatment to help with AEs such as peripheral neuropathy, fatigue and thus improve HRQOL^{53,54}. Better knowledge of AE data from patient perspective could prevent the development of late, longer term, or cumulative toxicity as it could guide clinicians on the appropriate time for dose reductions, treatment holidays or dose discontinuation where necessary to improve HRQOL while maintaining disease control.

Ultimately, there is substantial room for improvement in understanding the patient experience with treatment for MCL. In this disease with distinct biological features and a heterogeneous clinical course among patients, understanding HRQOL is particularly relevant. For patients with newly diagnosed MCL, without clearly established strategies for optimal induction and frontline treatment, further knowledge about HRQOL could afford patients and clinicians with tools to individualize treatment decisions. In the relapsed, refractory setting, the use of numerous chronically administered agents to treat disease sometimes for months to years at a time highlights the relevance of understanding treatment tolerability and its impact on HRQOL in this population. Limited data on HRQOL in MCL, which we have reviewed here, exist but many unanswered questions remain. Broad, systematic and scientifically rigorous implementation of HRQOL assessment in mantle cell studies in development has the potential to provide better understanding of and improvement in the experience of MCL patient at the bedside.

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Key points

- Understanding HRQOL is important for patients with mantle cell lymphoma, an incurable malignancy managed with a spectrum of approaches, from observation to aggressive chemo-immunotherapy to chronic targeted therapies.
- Optimal, consensus management strategies for mantle cell lymphoma are not clearly defined. HRQOL data can provide important complementary information to individualize the treatment selection for a given patient.
- Existing data on HRQOL in patients with mantle cell lymphoma is limited and many unanswered questions remain.
- Clinical trials in development for mantle cell lymphoma should routinely incorporate HRQOL endpoints in their study design.

Synopsis

Mantle cell lymphoma (MCL) is a unique lymphoma that is heterogeneous in its clinical course, and lacks consensus treatment approaches. It is often treated aggressively with immunochemotherapy at diagnosis and managed with chronic therapies taken for months to years at a time in relapse. Despite significant advances in therapy, MCL remains incurable and, therefore, maintaining patients' quality of life is an important treatment goal. Assessment of health-related quality of life (HRQOL) provides insight into patients' perspectives on the impact of their illness and its treatment on their lives. This review highlights the relevance of HRQOL assessment in MCL, evaluates existing evidence, examines current knowledge gaps and challenges in HRQOL assessment, and defines future directions for improving the evaluation of HRQOL in patients with MCL.