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Recommendation Report SCT-9 REQUIRES UPDATING

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

First-Line Therapy, Autologous Stem Cell Transplantation, and Post-Transplant Maintenance in the Management of Patients Newly Diagnosed with Mantle Cell Lymphoma

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An assessment conducted in March 2025 indicated that Recommendation Report SCT-9 REQUIRES UPDATING. It is still appropriate for this document to be available while this process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

RR SCT-9 is comprised of 3 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/66326

Section 1:	**Recommendations and Key Evidence**
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First-Line Therapy, Autologous Stem Cell Transplantation, and Post-Transplant Maintenance in the Management of Patients Newly Diagnosed with Mantle Cell Lymphoma

Section 1: Recommendations and Key Evidence

OBJECTIVES

To provide guidance based on the available evidence with respect to the best practices for the first-line therapy, conditioning regimen, timing of autologous stem cell transplantation (ASCT), and maintenance therapy for patients with mantle cell lymphoma (MCL).

TARGET POPULATION

Patients with newly diagnosed MCL who are eligible for ASCT.

INTENDED USERS

This recommendation report is targeted for physicians and medical teams who see, evaluate, and treat patients with MCL (transplant and non-transplant teams). This guidance may also inform funding decision for Ontario Health (CCO) (e.g., supporting best regimens in quality-best procedures [QBP] or through other mechanisms).

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1
Alternating cycles of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) with R-DHAP (rituximab plus dexamethasone, high-dose cytarabine (AraC), and cisplatin) is the recommended first-line treatment for symptomatic patients newly diagnosed with MCL prior to ASCT.
Qualifying Statements for Recommendation 1
Alternating cycles of R-CHOP/R-DHAP is the only regimen supported by the evidence. Alternative regimens have not been evaluated in prospective randomized controlled trials (RCTs) published to date; thus, there remains uncertainty in the clinical benefit/risk of alternative regimens when compared to the R-CHOP/R-DHAP regimen.
Key Evidence for Recommendation 1
The R-CHOP/R-DHAP recommendation is supported by evidence obtained from a randomized, open label, parallel-group phase 3 trial conducted by the European Mantle Cell Lymphoma Network [1]. In this trial, 466 patients, age 65 years or younger, were randomly allocated to receive either six courses of alternating R-CHOP or R-DHAP followed by a high-dose cytarabine-containing conditioning regimen and ASCT, or six courses of R-CHOP followed by myeloablative radio-chemotherapy and ASCT. After a median follow-up of 6.1 years, the addition of high-dose cytarabine to immunochemotherapy before ASCT was associated with improved outcomes in terms of time to treatment failure when compared with R-CHOP alone; 143 patients in the R-CHOP group and 85 patients in the cytarabine group had treatment failure (median years 9.1 vs. 3.9; 5-year rate 65% vs. 40%; hazard ratio [HR], 0.56; p=0.038). The cytarabine-containing regimen increased grade 3/4 hematological toxicities (hemoglobin

29% vs. 8%, leukocytes 75% vs. 50%, granulocytes 74% vs. 57%, platelets 73% vs. 9%) and grade 1/2 renal toxicities (creatinine 43% vs. 9%) when compared with the R-CHOP regimen, but these toxicities were manageable and the proportion of patients undergoing ASCT was similar in both groups.

After ASCT, patients treated with the cytarabine-containing conditioning regimen (84%) had significantly longer progression-free survival (PFS) compared to those treated with R-CHOP (85%) (median years 9.1 vs. 4.3; 5-year rate 65% vs. 44%; HR, 0.55; 95% confidence interval [CI], 0.42 to 0.71, p<0.0001). The proportion of ASCT-related deaths in remission was the same in both groups (3.4%). At the time of the analysis, overall survival (OS) was not significantly different between the two groups as the trial was not powered to detect relevant differences in survival.

Justification for Recommendation 1

The outcomes considered to inform this recommendation include time to treatment failure (TTF), PFS, OS, and adverse effects. It is the opinion of the members of the Working Group that the patients would highly value longer TTF over the manageable hematological toxicities.

Alternating cycles of R-CHOP and R-DHAP was associated with an expected increased grade 3/4 hematological and grade 1/2 renal toxicity but, these events were not associated with excess mortality and did not prevent subsequent ASCT. Adverse events were otherwise similar across the study arms.

The certainty of the evidence surrounding the R-CHOP/R-DHAP regimen as induction therapy for patients newly diagnosed with MCL is moderate because of imprecision – evidence came from only one RCT.

The RCT comprised patients aged 18-65 years, making the recommendation generalizable to all patients aged 65 years or younger with newly diagnosed MCL who are eligible for ASCT.

Recommendation 2

Rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD) alternating with methotrexate (MTX) and cytarabine (AraC) is not recommended for the treatment of patients with newly diagnosed MCL.

Key Evidence for Recommendation 2

This recommendation is the consensus of the Working Group, based on the evidence from one randomized phase II trial conducted by the Southwestern Oncology Group S1106 (evidence appraised at two time points) [2,3].

The S1106 trial aimed to select an induction regimen followed by ASCT consolidation as a platform for development in future trials. This study compared R-hyper-CVAD/MTX/AraC to rituximab plus bendamustine, both followed by ASCT, in patients newly diagnosed with stage IV MCL. The trial was closed early due to significant toxicities and an unacceptable high stem cell mobilization failure rate (29%) among patients treated with the R-hyper-CVAD/MTX/AraC regimen.

Justification for Recommendation 2

Rituximab plus hyper-CVAD/MTX/AraC regimen is not recommended as the first-line treatment of patients with newly diagnosed MCL because this regimen has been associated with significant toxicities and inadequate stem cell mobilization.

Recommendation 3
BEAM (carmustine, etoposide, cytarabine, and melphalan), BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide), and total-body irradiation (TBI)-based regimen) are reasonable conditioning regimen options for patients with MCL who have responded to first-line therapy and are undergoing ASCT.
Key Evidence for Recommendation 3
There are limited data on which to base a recommendation regarding the optimal conditioning regimen prior to ASCT.
Justification for Recommendation 3
The optimal conditioning regimen and timing for mobilization prior to ASCT is not known due to the lack of prospective comparative data. BEAM, BEAC, and TBI-based are commonly used conditioning regimens. In the absence of comparative, prospective studies, a definitive standard regimen cannot be recommended.

Recommendation 4
Maintenance therapy with rituximab is recommended for patients with newly diagnosed MCL who had undergone ASCT.
Qualifying Statements for Recommendation 4
There is insufficient evidence to support or refute the optimal rituximab maintenance schedule. The evidence supports 18 doses of rituximab administered over 3-years. In Ontario, rituximab is funded up to a maximum of 8 doses over 2-years.
Key Evidence for Recommendation 4
This recommendation is supported by one randomized phase III trial comparing a three-year course of rituximab maintenance therapy administered every two months after ASCT versus no maintenance. The authors reported that maintenance therapy with rituximab after R-DHAP induction therapy followed by R-BEAM consolidation therapy and ASCT significantly improved PFS (83% vs. 64%; HR, 0.4; 95% CI, 0.23 to 0.68; p<0.001) and OS (89% vs. 80%, HR, 0.5; 95% CI, 0.26 to 0.99; p=0.04) at four years, when compared to no maintenance [4]. Thirteen of 16 relapsed patients died in the rituximab group, as compared to 24 out of 37 relapsed patients who died in the observation group; the major cause of death in each group was lymphoma.
Justification for Recommendation 4
The certainty of the evidence on the efficacy of rituximab as maintenance therapy for patients with MCL who had undergone ASCT is moderate because of imprecision: evidence came from only one RCT with a relatively small sample size (n=299). However, given the improved disease control and survival rates in patients treated with rituximab after ASCT, and recognizing the relatively high relapse rates in MCL, the members of the Working Group recommend rituximab maintenance after ASCT.

The RCT comprised patients aged 27 to 65 years, making the recommendation generalizable to patients aged 65 years or younger with newly diagnosed MCL who had undergone ASCT.

IMPLEMENTATION CONSIDERATIONS

Funding for longer maintenance regimen should be considered based on the existing evidence. In Ontario, the public reimbursement of rituximab as maintenance therapy for previously untreated patients with MCL is eight doses, but there is evidence showing that extended regimen (18 doses over 3 years of maintenance) should be considered.

The use of DHAP in transplant-eligible patients with MCL may result in increased inpatient resources for chemotherapy. Using carmustine in high-dose chemotherapy regimens pre-ASCT may result in increased transplant-related costs.

RELATED GUIDELINES

- Kouroukis CT, Rumble RB, Kuruvilla J, Crump M, Herst J, Hamm C. Stem cell transplantation in lymphoma. Toronto (ON): Ontario Health (Cancer Care Ontario); 2012 December 13. Program in Evidence-Based Care: Recommendation Report SCT-4. Available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/971

FURTHER RESEARCH

Future research is required to support the evidence of the effectiveness of first-line and post-transplant maintenance therapy in the management of patients newly diagnosed with MCL.

Prospective trials examining ideal conditioning regimens should be considered, as current practice in Ontario is guided by retrospective data [5], leading to significant practice heterogeneity.

First-Line Therapy, Autologous Stem Cell Transplantation, and Post-Transplant Maintenance in the Management of Patients Newly Diagnosed with Mantle Cell Lymphoma

Section 2: Recommendation Report Methods Overview

This section summarizes the methods used to create the recommendations. For the systematic review, see Section 3.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

BACKGROUND FOR RECOMMENDATION REPORT

The initiation of this recommendation report was prompted by the need to harmonize practice in Ontario around the management of patients with newly diagnosed MCL who are eligible for stem cell transplantation. There is no clearly defined standard of care for transplant-eligible patients with MCL, and substantial variability in approach to first-line therapies exists from centre to centre within Ontario; high-dose chemotherapy regimens prior to ASCT varies from centre to centre. This recommendation report was developed to address variability among transplant centres across Ontario with respect to first-line, conditioning, and post-transplant maintenance therapy.

RECOMMENDATION REPORT DEVELOPERS

This recommendation report was developed by a Working Group consisting of five hematologist-oncologists, a patient representative, and a health research methodologist at the request of the OH (CCO) Stem Cell Transplant Advisory Committee.

The Working Group was responsible for reviewing the evidence base, drafting the recommendations and responding to comments received during the document review process. Conflict of interest declarations for all authors are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

RECOMMENDATION REPORT DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [6,7]. For Recommendation Reports this process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by a methodology experts and final approval by the Stem Cell Transplant Advisory Committee.

The PEBC uses the AGREE II framework [8] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original

evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Guidelines

As a first step in developing this recommendation report, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Only guidelines based on systematic review of the literature and published after 2016 were considered for endorsement. Guidelines including malignancies other than MCL, and/or based on consensus or expert opinion were excluded. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: Canadian Partnership Against Cancer (CPAC), Epistemonikos, National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology, and National Health and Medical Research Council – Australia.

One guideline produced in 2016 by NICE that focused on the diagnosis and management of non-Hodgkin lymphoma (NHL) was identified as potentially relevant and considered for full-text review [9]. The guideline was reviewed by members of the MCL Working Group and agreement with the recommendations contained in the NICE guideline led to the Working Group members' decision to use its evidence as a source of reference for the primary studies portion of the present document rather than as the main evidence source for the accompanying evidentiary base, as it was the opinion of the members of the Working Group that current evidence from RCTs (phase II and III) and large prospective observational studies may lead to a change of some of the recommendations.

RECOMMENDATION REPORT REVIEW AND APPROVAL

Internal Review

The recommendation report was reviewed by the Directors of the PEBC, the Guideline Methodology Lead and two additional health research methodologists. The Working Group was responsible for ensuring the necessary changes were made. If those changes were made without substantially altering the recommendations, the altered draft was not resubmitted for approval.

Report Approval by the Stem Cell Transplant Advisory Committee

After internal review, the report was presented to the OH (CCO)–Stem Cell Transplant Advisory Committee. The members of the OH (CCO)-Stem Cell Transplant Advisory Committee reviewed the document during a meeting held on May 7, 2020, and formally approved the document on May 28, 2020.

PATIENT AND CAREGIVER-SPECIFIC CONSULTATION GROUP

One patient participated as active member of the MCL Working Group. The patient representative attended and participated in Working Group meetings and teleconferences. He provided feedback on draft documents throughout the entire recommendation report development process, communicating the perspective of patients and members of the public.

DISSEMINATION

The recommendation report will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

ACKNOWLEDGEMENTS

The members of the OH (CCO) Stem Cell Transplant Advisory Committee and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Judy Brown, Sheila McNair, Jonathan Sussman, Emily Vella, for providing feedback on draft versions.
- Faith Maelzer for conducting a data audit.
- Sara Miller for copy editing.

First-Line Therapy, Autologous Stem Cell Transplantation, and Post-Transplant Maintenance in the Management of Patients Newly Diagnosed with Mantle Cell Lymphoma

Section 3: Systematic Review

INTRODUCTION

MCL is an uncommon and often aggressive subtype of B-cell NHL that results from a malignant transformation of a B lymphocyte in the outer edge of a lymph node follicle known as the mantle zone. The median age at diagnosis is approximately 60 years. Many affected patients usually have widespread disease at diagnosis involving multiple lymph nodes, the spleen, bone marrow, liver and/or regions of the gastrointestinal tract. According to Cancer Statistics, in 2019, there were approximately 10,000 and 74,200 new cases of NHL expected to occur in Canada and the United States, respectively [10,11]; and MCL represented approximately 6% of the NHL cases.

In Ontario, there is no clearly defined standard of care for transplant-eligible patients with newly diagnosed MCL. A variety of first-line chemo-immunotherapy induction and consolidative ASCT approaches are utilized in young, fit patients. Induction treatments in the upfront management prior to transplant have included rituximab-bendamustine, R-HyperCVAD, and R-CHOP alternating with R-DHAP; conditioning regimens can vary and practice in Ontario is guided by retrospective data supporting BEAM (carmustine, etoposide, cytarabine, and melphalan), BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide), and TBI-based [5]. The evidence surrounding consolidative ASCT has demonstrated a PFS benefit in eligible patients who underwent ASCT [12].

ASCT in MCL was established as standard of care based on the evidence from the European MCL Network Trial [13] that demonstrated improved PFS with a median of 39 months in patients who underwent ASCT compared with 17 months for patients who received interferon (IFN)-alpha instead of transplant. Consolidation with ASCT is frequently utilized in most transplant-eligible patients with newly diagnosed symptomatic MCL to improve outcomes and prolong remission. Decisions regarding eligibility for ASCT should be made on a case-by-case basis considering factors such as age, disease stage (III, IV), functional status, and organ function criteria; patients should also be accounted for when considering ASCT to discuss potential benefits and risks of proposed treatment and treatment alternatives, if any.

The optimal management of patients with newly diagnosed MCL who are eligible for ASCT is uncertain. This recommendation report was developed to review the most-current evidence with respect to the best practices with respect to induction, ASCT, and post-transplant maintenance therapy for patients with MCL to inform a consistent and optimized approach to management. Based on the objectives of this recommendation report, the members of the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. For patients with newly diagnosed MCL who are eligible for ASCT, what is the preferred induction regimen (dose/schedule/frequency)?
2. For patients with MCL who achieved partial or better response to induction therapy, does the addition of ASCT lead to longer and better PFS/OS in comparison to those who do not receive ASCT? If so,
    a. What is the preferred conditioning regimen for those undergoing ASCT?

b. What is the most appropriate timing for mobilization prior to ASCT (ideal number of induction chemotherapy cycles prior to stem cell collection and stem cell transplantation)?

3. For patients with MCL in remission after ASCT, does the addition of rituximab/IFN- alpha maintenance therapy lead to longer and better PFS/OS in comparison to those who do not receive maintenance therapy? If so, what is the preferred maintenance therapy in this population?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

A search was conducted for existing systematic reviews. The website Cochrane Database of Systematic Reviews (CDSR) (https://www.cochrane.org/evidence), along with the electronic databases MEDLINE (OVID) and EMBASE (OVID) were searched from January 2013 to January 2019. The full literature search strategy used to identify potential relevant systematic reviews from OVID MEDLINE and EMBASE is presented in Appendix 2. The website of the CDSR was searched using the keywords "Mantle Cell Lymphoma". Systematic reviews older than six years were considered not relevant because the main goal of the search for systematic reviews is to identify recent secondary sources covering the primary literature that may be helpful in the development of the recommendations.

Systematic reviews were included if they met the following criteria:

1. Reported on patients newly diagnosed with MCL who are eligible for ASCT.
2. Searched for studies assessing any of the following indications in the management of MCL: induction therapies, addition of ASCT to induction therapies, and maintenance with rituximab or IFN-alpha after ASCT.
3. Comprehensively searched at least one database with relevant search terms and dates.
4. Extracted relevant outcome information (OS, PFS, quality of life, toxicities) from each study.

Search for Primary Literature

A search for primary literature was planned if no suitable guidelines or systematic reviews were identified. If a suitable guideline or a systematic review was found, a systematic review of the primary literature would be conducted from the end date of the reported search to update the evidence from the identified guideline(s) and/or systematic review(s). In the case where missing information was identified from the reporting of any suitable guideline or systematic review, a new search for primary literature to address the limitation in scope would be conducted and appropriate information extracted.

Literature Search Strategy

The electronic databases MEDLINE (OVID) and EMBASE (OVID) were searched for relevant articles from the completion date of the search for the 2016 NICE (2015) to January 2019 for research questions 1 and 2, and from 1996 to 2019 for question 3. The literature search was updated in January 2020.

The search strategy included a logical combination of terms for the condition (MCL), and the intervention (systemic therapy, ASCT, maintenance, rituximab, IFN-alpha). The full literature search strategy used to retrieve potential primary studies is presented in Appendix 2.

Study Selection Criteria and Process

Inclusion Criteria

Articles identified in this systematic review were eligible if they met all of the following criteria:

1. Published full report or abstracts of phase II and phase III RCTs evaluating any of the following indicators in the management of ASCT-eligible patients with newly diagnosed MCL: first-line therapy, conditioning regimen, timing to ASCT, and/or maintenance. If no randomized evidence was available, the following criteria were considered from fully published primary observational studies:
    - Prospective comparative studies with at least 25 participants per arm, and single-arm studies with at least 100 participants for question 1 and 50 participants for question 2.
    - Prospective comparative observational studies with an appropriate contemporaneous or historical control group and with at least 25 participants in each arm for question 3.
2. Studies should report on at least one of the outcomes of interest: OS, PFS, quality of life, and toxicities (mainly hematological).

Exclusion Criteria

Studies were excluded if they were:

1. Retrospective, letters, case reports, comments, books, notes or editorial publication types;
2. Abstracts of non-randomized studies;
3. Articles published in a language other than English; or
4. Studies using rituximab-chemotherapy only, or including patients with malignancies other than MCL, or including patients who have already been treated for MCL.

A review of the titles and abstracts was conducted by one reviewer (NV). For studies that warranted full-text review, one author (NV) reviewed each study independently and consulted members of the Working Group whenever there was uncertainty.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by one author (NV), with all extracted data and information audited subsequently by an independent auditor.

Risk of bias for each included RCT was assessed using the Cochrane Collaboration risk of bias assessment tool, focusing on randomization process, allocation concealment, blinding, data availability, and outcome measurement [14]. Single-arm evidence was assessed according to full reporting of the patient selection criteria, the intervention, the follow-up period, and the reporting of all relevant outcomes together with the methods used to measure them.

Synthesizing the Evidence

Due to the between-study clinical heterogeneity in terms of the interventions, research settings, and inconsistent reporting of outcomes among studies, no meta-analysis was conducted as part of this evidentiary base. Instead, data were synthesized in tables and described narratively in the text.

RESULTS

Search for Systematic Reviews

Sixteen citations were identified from the MEDLINE, EMBASE, and Cochrane Library Database search of systematic reviews. From these, one systematic review focused on the efficacy of rituximab maintenance therapy in patients with MCL [15], but differences in the target population and study eligibility from the one in this evidentiary base prevented its inclusion.

Search for Primary Literature

For research question 1 and 2, the primary literature search was used to update the evidence from the guideline [9] used as a source of references for this evidentiary base; therefore, only primary literature published from 2015 (research questions 1 and 2) was considered because it corresponded to the end date of the search in the identified guideline (January 2015). For research question 3, a systematic review of the primary literature was conducted.

Literature Search Results

The initial literature search, after removal of duplicates, resulted in 3520 citations from which 246 were identified to be eligible for full-text review. From these, five full-report publications from four studies were found to be relevant and therefore included in this review to inform recommendations surrounding the management of patients newly diagnosed with MCL (Appendix 3). The remaining 241 publications were excluded because they failed to pass the predefined inclusion criteria. Studies selected for inclusion are listed in Table 3-1.

Table 3-1. Studies selected for inclusion

Question	Number of Included Studies (ref)
1. For patients with newly diagnosed MCL who are eligible for ASCT, what is the preferred induction regimen?	1 Randomized phase III trial [1] 2 Reports assessing the evidence from one randomized Phase II trial at two time points [2,3] 1 Prospective single-arm trial with a 15-year follow-up [16]
2. For patients with MCL who achieved partial or better response to induction therapy, does the addition of ASCT lead to longer and better PFS/OS in comparison to those who do not receive ASCT? If so, a. What is the preferred conditioning regimen for those undergoing ASCT? b. What is the most appropriate timing for mobilization prior to ASCT (ideal number of induction chemotherapy cycles prior to stem cell collection and stem cell transplantation)	None
3. For patients with MCL in remission after ASCT, does the addition of rituximab/interferon-alpha	1 Randomized phase III trial [4]

Question	Number of Included Studies (ref)
maintenance therapy lead to longer and better PFS/OS in comparison to those who do not receive maintenance therapy? If so, what is the preferred maintenance therapy in this population?	

Abbreviations: ASCT, autologous stem cell transplantation; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival.

Study and Patients Characteristics

This systematic review identified five publications from four studies assessing the management of patients with MCL who are eligible for ASCT, and assessed three of the outcomes of interest (PFS, OS, toxicities). One randomized phase III trial [1], two randomized multi-institutional phase II trials appraising the same evidence at two time points [2,3], and one large prospective single-arm trial with a 15-year follow-up period (Nordic MCL2 trial) [16] focused on first-line therapy, while only one randomized phase III trial focused on post-transplant maintenance [4]. No studies reported on conditioning regimens or number of induction chemotherapy cycles for mobilization prior to ASCT. None of the identified studies reported on quality of life. See Table 3-2 for details.

Table 3-2. Characteristics of studies assessing the management of ASCT-eligible patients newly diagnosed with MCL.

RQ 1 and 2. Induction and Conditioning Regimens (Chemotherapy and ASCT)				
Randomized Controlled Trials				
1st Author, year Trial ID [enrol. period]	**Number of pts Study Design**	**Baseline Characteristics**	**Interventions**	**Comparator**
Hermine, 2016 [1] The European Mantle Cell Lymphoma Network, NCT0020922 [2004-2010]	N=466 Randomized, open-label, parallel-group, phase 3 trial Aimed to investigate whether a regimen containing high-dose cytarabine before ASCT improves outcome	Median age: 55 y (49-60) Cytarabine: Age 56y (50-60); Control: Age 55y(48-60) Ann Arbor Stage — Cytarabine N / %; Control N / %: II: 10 / 4; 7 / 3 III: 31 / 13; 31 / 13 IV: 191 / 82; 196 / 84 MIPI Low Risk: 150 / 65; 141 / 60 Intermediate: 51 / 22; 60 / 26 High Risk: 31 / 13; 33 / 14 Cytarabine Alternating cycles of R-CHOP or R-DHAP + AraC + MRCT: 232 Control: R-CHOP + MRCT: 234	Cytarabine: (R-CHOP or R-DHAP) + AraC + MRCT + ASCT: 232 **Induction** R-CHOP - Six cycles; 3-week interval between cycles RTX: 375 mg/m^2 IV d1 CPH: 750 mg/m^2 IV d1 DOX: 50 mg/m^2 IV d1 VDS: 1.4 mg/m^2; 2mg IV d1 PRED: 100 mg orally d1-d5 R-DHAP - Six cycles; 3-week interval between cycles RTX: 375 mg/m^2 IV d1 DEXA: 40 mg orally d1-d4 AraC: 2 g/m^2/12h IV d2 CIS: 100 mg/m^2 over 24h d1 G-CSF: 5-10 µg/kg on day 11 until stem cell collection (from day 6 of the third R-DHAP cycle) **Myeloablative Conditioning MRCT W** Within 4-6 weeks of mobilization TBI: 10Gy fractionated d -7 to -5 before ASCT; pulmonary dosage limited to 8Gy HD-AraC: 1.5 g/m^2 IV/12h d -4 and -3 MEL: 140 mg/m^2 IV d -2 **NOTE:** After induction, 223 patients achieved an overall response and 187 (84%) proceed to ASCT	Control: R-CHOP + MRCT + ASCT: 234 **Induction** R-CHOP - Six cycles; 3-week interval between cycles RTX: 375 mg/m^2 IV d1 CPH: 750 mg/m^2 IV d1 DOX: 50 mg/m^2 IV d1 VDS: 1.4 mg/m^2 IV d1 PRED: 100 mg orally d1-d5 Intensified Mobilization Chemotherapy with Dexa-BEAM within 6 weeks after completion of induction CT DEXA: 3×8 mg orally d1-d10 BCNU: 60 mg/m^2 IV d2 MEL: 20 mg/m^2 IV d3 ETO: 75 mg/m^2 IV d4-d7 AraC: 2×100 mg/m^2 IV d4-d7 G-CSF: 5-10 µg/kg on day 11 until stem cell collection **Myeloablative Conditioning MRCT -** within 4-6 weeks of mobilization TBI: 12 Gy fractionated d -6 to -4 before ASCT; pulmonary dosage was limited to 8Gy HD-CPH: 60 mg/kg IV d -3 and -2 **NOTE:** After induction, 215 patients achieved an overall response and 182 (85%) proceed to ASCT

<table>
<tr>
<td rowspan="3">Chen 2017 [2]; Kamdar 2019 [3].

SWOG Study S1106
NCT01412879

[2012-2013]</td>
<td rowspan="3">N=52

Randomized Phase II multi-institutional trial

Aimed to test the hypothesis that either RH or RB would yield a high PFS rate with few toxicities, allowing sufficient stem cell mobilization for ASCT consolidation</td>
<td>Median age: RB 57 (33-64) y, RH 59 (44-66) y

<table>
<tr><th></th><th colspan="2">RB</th><th colspan="2">RH</th></tr>
<tr><td>N</td><td colspan="2">35</td><td colspan="2">17</td></tr>
<tr><td>Ann Arbor Stage</td><td>N</td><td>%</td><td>N</td><td>%</td></tr>
<tr><td>III</td><td>3</td><td>8.5</td><td>1</td><td>5.9</td></tr>
<tr><td>IV</td><td>32</td><td>91.4</td><td>16</td><td>94.1</td></tr>
<tr><td>MIPI</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Low Risk</td><td>22</td><td>63</td><td>11</td><td>65</td></tr>
<tr><td>Interm/high Risk</td><td>13</td><td>37</td><td>6</td><td>35</td></tr>
</table>
</td>
<td>RB: six cycles

RTX: 375 mg/m^2 IV d1,7,35,63,91,120
BND: 90 mg/m^2 as 30-min infusion d8+9, 36+37, 64+65, 92+93

Bendamustine administered over a 2-day period, 1 day after rituximab. Cycles were administered 1 week before the first cycle and 4 weeks after the last cycle.</td>
<td>RH: four cycles

<u>Cycle 1 and 3</u>
RTX: 375 mg/m^2 IV d1
CPH: 300 mg/m^2 IV d2-d4
DOX: 16.6 mg/m^2 IV d5-d7
VDS: 1.4 mg/m^2 (cap 2) IV d5 and d12
DEXA: 40 mg IV or PO d2-d5 and d12-d15

<u>Cycle 2 and 4</u>
RTX: 375 mg/m^2 IV d1
MTX: 200 mg/m^2 over 2 hours, 800 mg/m^2 over 22 hours IV d2
AraC: 3 g/m^2 IV d3-4
RTX: 375 mg/m^2 IV d1</td>
</tr>
<tr>
<td colspan="3">ASCT versus No ASCT</td>
</tr>
<tr>
<td><u>RB</u> 23 vs. 12

ASCT on protocol: 21
ASCT off protocol: 2
No ASCT: 12

<u>RH</u> 9 vs. 8

ASCT on protocol: 5
ASCT off protocol: 4 (discontinued therapy early for toxicities)
No ASCT: 8</td>
<td><u>RB</u>

Stem cell mobilization after cycle 6 (within 8 weeks of last dose of RB) using 375 mg/m^2 rituximab + 1.5 mg/m^2 cyclophosphamide.

Plerixafor or a second mobilization attempt was allowed but not required per protocol
Patients 61-65 years: either CBV or BEAM was used as the sole preparative regimen
Patients <61 years: CBV, BEAM, or total body irradiation/cyclophosphamide/etoposide as the sole preparative regimen

</td>
<td><u>RH</u>

Chemotherapy-based stem cell mobilization after cycle 3 with granulocyte colony-stimulating factor (dose/schedule per institutional standard)</td>
</tr>
</table>

Prospective Observational Studies				
1st Author, year (reference)	**# of pts and Study Design**	**Patient Characteristics**	**Arms or Interventions**	**Comparator(s)/Control N**
Eskelund, 2016 [16]. Nordic MCL2 trial [2000-2006]	N=159 Completed ASCT= 145 Non randomized single arm with 15-year follow-up	Median age: 56 (32-65) y Ann Arbor Stage: IV 136 (85); MIPI: Low Risk 79 (50), Intermediate Risk 41 (26), High Risk 37 (24)	**Induction** – Alternating courses of maxi-CHOP and HD-AraC, 3 of each Maxi-CHOP: given as bolus according to local routine. Forced diuresis and Mesna is optional. CPH : 1200 mg/m^2 IV d1 DOX: 75 mg/m^2 IV d1 VDS: 2 mg total IV d1 PRED: 100 mg total orally d1-d5 High-dose AraC • Patients 60 years of age or younger: AraC 3 g/m^2 every 12 hours for two days as 3-hour infusions (total of 4 infusions) • Patients greater than 60 years: AraC 2 g/m^2 every 12 hours for two days as 3-hour infusions **Stem Cell Harvest / Mobilization** – performed after cycle 6 RTX (375 mg/m^2 IV co-administered on d1 in cycle 4 and 5and on d1 and d9 in cycle 6 (after amendment in 203, it was administered also in cycles 2 and 3)) and High-dose Ara-C **Consolidation** – Allowed 1 or 2 series In case of delay in the transplant unit, one extra immunochemotherapy cycle of Maxi-CHOP, HD-AraC, or both were allowed **High-dose Regimen before ASCT** – BEAM (90 pts)/BEAC (55 pts) BEAM: BCNU 300 mg/m^2 d1, etoposide 100 mg/m^2 X 2 d2-d5, AraC 400 mg/m^2 d2-d5, melphalan 140 mg/m^2 d6, all IV	

Q 3. Maintenance Therapy Post-ASCT – Randomized Controlled Trials

<table>
<tr><th>1st Author, year (reference)</th><th># of pts and Study Design</th><th>Patient Characteristics</th><th>Conditioning Regimen before ASCT</th><th>Post-Transplant Maintenance</th><th>Comparator(s) / Control</th></tr>
<tr><td>Le Gouill, 2017 [4].

The Lymphoma Study Association LYSA

[2008-2012]</td><td>N=240

Randomized Phase III trial

Aimed to investigate the role of rituximab maintenance therapy in patients with MCL who had undergone ASCT.</td><td>Median age: Rituximab 58 (27-64), Observation 56 (29-65) y

<table><tr><th></th><th colspan="2">Rituximab</th><th colspan="2">Observation</th></tr><tr><td>N</td><td colspan="2">120</td><td colspan="2">120</td></tr><tr><td>Ann Arbor Stage</td><td>N</td><td>%</td><td>N</td><td>%</td></tr><tr><td>II</td><td>7</td><td>6</td><td>5</td><td>4</td></tr><tr><td>III</td><td>15</td><td>13</td><td>16</td><td>13</td></tr><tr><td>IV</td><td>97</td><td>82</td><td>99</td><td>82</td></tr><tr><td>MIPI*</td><td></td><td></td><td></td><td></td></tr><tr><td>Low Risk</td><td>70</td><td>58</td><td>63</td><td>52</td></tr><tr><td>Intermediate Risk</td><td>34</td><td>28</td><td>31</td><td>26</td></tr><tr><td>High Risk</td><td>16</td><td>13</td><td>26</td><td>22</td></tr></table></td><td><u>R-BEAM Regimen</u>
RTX: 500 mg/m² d -8
BCNU: 300 mg/m² d -7
ETO: 400 mg/m² d -6 to d -3
AraC: 400 mg/m² d -6 to d -3
MEL: 140 mg/m² d -2

<u>Peripheral Stem Cell</u>
Injected on d 0</td><td><u>Rituximab</u>
375 mg/m² every 2 months for 3 years

Total number of Rituximab planned doses: 23
4 doses administered with induction therapy, 1 dose with the preparative regimen for transplantation, and 18 doses over 3 years of maintenance therapy.</td><td>Observation (no maintenance)</td></tr>
<tr><td colspan="6"><u>INDUCTION REGIMEN</u> R-DHAP: four courses, repeated every 21 days
• Investigators were allowed to use carboplatin or oxaliplatin instead of cisplatin
• Stem cells were obtained after the third or fourth course of R-DHAP
• Chemotherapy regimen for stem-cell mobilization was not allowed

Patients having partial response or whose tumour was reduced by less than 75% received rescue induction therapy with four courses of R-CHOP, administered as one course every 14 days.</td></tr>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; **MIPI**, MCL prognostic index (age, performance status, S-lactate dehydrogenase, and white blood cell count; **R-CHOP**, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; **R-DHAP**, rituximab, dexamethasone, high-dose cytarabine, and platinum derivate; **AraC**, cytarabine; **MRCT**, myeloablative radio chemotherapy; **RTX**, rituximab; **CPH**, cyclophosphamide; **DOX**, doxorubicin; **VDS**, vincristine; **PRED**, prednisolone; **DEXA**, dexamethasone; **CIS**, cisplatinum; **G-CSF**, granulocyte colony-stimulating factor; **TBI**, total body irradiation; **MEL**, melphalan; **BCNU**, carmustine; **ETO**, etoposide; **RB**, rituximab bendamustine; **RH**, rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyperCVAD) alternating with high dose cytarabine and methotrexate (MTX); **CVB**, carmustine, cyclophosphamide, and etoposide; **BEAM**, carmustine, etoposide, cytarabine, and melphalan; **maxi-CHOP**, cyclophosphamide, doxorubicin, vincristine and prednisolone; **BEAC**, carmustine, etoposide, cytarabine, cyclophosphamide;

Outcomes: Management of Patients Newly Diagnosed with Mantle Cell Lymphoma who are Eligible for Stem Cell Transplantation

1. *Preferred Induction Front-line Therapy for Patients with Newly Diagnosed MCL who are Eligible for ASCT*

R-CHOP

Alternating R-CHOP, R-DHAP + AraC vs. R-CHOP

First-Line Treatment - One randomized, open-label, phase III trial by the European Mantle Cell Lymphoma Network [1] demonstrated that, in 466 patients aged 65 years or younger, alternating courses of 3× R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) and 3× R-DHAP (rituximab plus dexamethasone, high-dose cytarabine, and cisplatin) followed by high-dose cytarabine resulted in a significant longer time to treatment failure (also observed across MIPI [MCL prognostic index (age, performance status, S-lactate dehydrogenase, and white blood cell count)] risk groups), when compared to R-CHOP without cytarabine (median 9.1 vs. 3.9 years, 5-year rate 65% vs. 40%, HR, 0.56, p=0.038) (Table 3-3). TTF from randomization to stable disease after at least four induction cycles, progression, or death for any cause, rather than PFS, was used as the primary outcome to avoid second-line treatment (ASCT) interaction with the primary analysis of first-line therapy. Significant hematological (grade 3-4) and renal toxicities (grade 1-2) were more common in patients treated with the cytarabine-containing regimen, but the authors reported that these toxicities were not associated with excess mortality and did not prevent subsequent ASCT; the same proportion of patient underwent stem cell transplantation in both groups (84% in the R-CHOP + R-DHAP + AraC regimen and 85% in the R-CHOP regimen).

Conditioning Regimen - Toxicities for both conditioning regimes (TBI+AraC+MEL vs. TBI+high-dose cyclophosphamide) were similar, except for increased liver toxicity – transaminases (grade 1-2) and constipation in the R-CHOP regimen.

Post-ASCT - After stem cell transplantation, a statistically significant improvement in PFS was observed in patients treated with the R-CHOP+R-DHAP+AraC regimen when compared to the R-CHOP regimen (median years PFS from randomization 9.1 vs. 4.3; 5-year rate 65% versus 44%; HR, 0.55; 95% CI, 0.42 to 0.71, p<0.0001; median PFS from ASCT not reached versus 4.5%; 5-year rate 73% versus 45%; HR, 0.45; 95% CI, 0.33 to 0.63; p<0.0001), but no significant difference was observed in the OS between the two regimens (median 9.8 years vs. not reached; 5-year rate 76% vs. 69%; HR, 0.78; 95% CI, 0.57 to 1.07; p=0.12). The proportion of ASCT-related deaths in remission was reported to be the same in both groups (3.4%).

The quality of evidence of the European Mantle Cell Lymphoma Network trial is considered high: subjects were adequately randomized resulting in comparable study groups, subjects were treated according to intended interventions, patients were followed for an extensive period of time with few lost to follow-up, and data were analyzed in accordance with a pre-specified plan (see Appendix 5 for details).

RB vs. RH

A randomized phase II trial (S1106) comparing R-Hyper-CVAD (rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with high-dose cytarabine and methotrexate) (RH) to rituximab plus bendamustine regimen (RB) at two time points [2,3], provided very low-quality evidence against RH as a feasible induction regimen prior to ASCT due to an unacceptable high mobilization failure rate (29%), which prompted the premature closure of the study (Table 3-3). Although there were no significant differences between two- and five-year PFS and OS among patients treated with RB versus those treated with the RH regimen, the RH regimen was more toxic and had higher stem cell

mobilization failure rates when compared to the RB regimen. Only 53 out of a planned 160 patients were accrued (RH 18 and RB 35) and therefore, the small sample size limited the precision of the estimates as true significance of the data could not be assessed. Evidence from the S1106 trial was considered to be of very low quality because the data were not analyzed in accordance with the pre-specified plan; an unacceptably high mobilization failure rate on one arm of the study (RH) prompted the premature study closure.

Nordic MCL2

One single-arm phase II multicentre study [16] was identified that investigated the efficacy of the MCL2 regimen, which consists of dose-intensified induction immunochemotherapy with rituximab plus maxi-CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone] alternating with rituximab plus high-dose cytarabine), in the treatment of patients newly diagnosed with MCL (Table 3-3). The study, conducted by the Nordic Lymphoma Group, reported that the use of the MCL2 regimen resulted in a median PFS and OS of 8.5 and 12.7 years, respectively. The median post-transplant PFS was 11 years, while median OS was not reached. However, this regimen was associated with a continuous pattern of relapse and disease-related mortality [16]. The evidence presented by the Nordic MCL2 study was considered very low quality due to the nature of its study design (noncomparative).

2. *Addition of Autologous Stem Cell Transplantation in the First-Line Treatment*

The literature review did not identify any relevant studies evaluating the addition of ASCT to first-line therapy compared to no ASCT that met our inclusion criteria.

3. *Post-Transplant Maintenance*

Only one RCT was identified that investigated the efficacy of post-transplant maintenance therapy for patients with newly diagnosed MCL [4]. In this randomized phase III trial, 240 patients were treated with four courses of D-HAP every 21 years (additional rescue induction therapy with four courses of R-CHOP was administered to patients with partial response to immunochemotherapy), followed by R-BEAM (rituximab, carmustine, etoposide, cytarabine, and melphalan) consolidation therapy before ASCT. After ASCT and up to three months later, patients were randomized to receive rituximab, a three-year course of rituximab maintenance therapy administered every two months after ASCT or to undergo observation. At a median follow-up of four years, a statistically significant improvement in PFS and OS were observed in patients treated with rituximab maintenance when compared to those who underwent observation (PFS, 83% vs. 64%; HR, 0.4; 95% CI, 0.23 to 0.68; $p<0.001$; OS, 89% vs. 80%; HR, 0.5; 95% CI, 0.26 to 0.99; $p=0.04$). No late effect of rituximab was reported in either arm. After randomization, 16 patients had disease progression and 13 patients died in the rituximab arm, as compared with 37 patients who had disease progression and 24 died in the observation arm. The major cause of death in each arm was lymphoma; eight patients in the rituximab group and 16 in the observation arm.

The quality of the evidence of this trial was considered high: subjects were adequately randomized resulting in comparable study groups, subjects were treated according to intended interventions, patients were followed for an extensive period of time with few lost to follow up, and data was analyzed in accordance with a pre-specified plan (see Appendix 5 for details) (Table 3-3).

Table 3-3. Summary of the outcomes reported by studies assessing the management of ASCT-eligible patients newly diagnosed with MCL.

RQ 1 and 2. Induction and Conditioning Regimens (Chemotherapy and ASCT) - Randomized Control Trials				
Author, year (reference) **Trial ID**	**Intervention and Median follow-up**	**PFS (95%CI)**	**OS (95%CI)**	**Toxicities**
Hermine, 2016 [1]. European MCL Network NCT00209222	Cytarabine Alternating R-CHOP/R-DHAP + AraC + MRCT + ASCT **vs.** Control R-CHOP + MRCT + ASCT Median follow-up: 6.1 (95% CI 5.4-6.4) y.	**R-CHOP/R-DHAP vs. R-CHOP*** Time to Treatment Failure Median 9.1 (6.3-NR) vs. 3.9 (3.2-4.4) y 5-year rate 65% vs. 40% HR 0.56; p=0.038 **R-CHOP/R-DHAP + ASCT VS. R-CHOP+ASCT** From Randomization Median 9.1 (6.5-NR) vs. 4.3 (3.8-5.0) y 5-year rate 65% vs. 44% HR 0.55 [0.42, 0.71]; p<0.0001 From ASCT Median NR (8.6-NR) vs. 4.5 (3.6-6.0) 5-year rate 73% vs. 45% HR 0.45 [0.33, 0.63]; p<0.0001	**R-CHOP/R-DHAP + ASCT vs. R-CHOP+ASCT** Median 9.8 years (8.6-NR) vs. NR (7.6-NR) 5-year rate 76% vs. 69% HR 0.78 [0.57, 1.07]; p=0.12	**Induction - R-CHOP+R-DHAP + vs. R-CHOP** Grade 3-4 hematological toxicity hemoglobin 29% 8% leukocytes 75% 50% granulocytes 74% 57% platelets 73% 9% Grade 1-2 renal toxicity Creatinine 43% 10% **Conditioning - AraC vs. no AraC** Grade 3-4 hematological toxicity hemoglobin 60% vs. 45% Grade 1-2 Renal Toxicity Creatinine 33% vs. 13% Others Grade 3 or 4 mucositis 60% vs. 40%

RQ 1 and 2. Induction and Conditioning Regimens (Chemotherapy and ASCT) - Randomized Control Trials				
Author, year (reference) Trial ID	**Intervention and Median follow-up**	**PFS (95%CI)**	**OS (95%CI)**	**Toxicities**
Chen, 2017 [2]; Kamdar 2019 [3]. Southwest Oncology Group (SWOC) NCT01412879	RB (Rituximab Bendamustine) vs. RH (Hyper-CVAD/MTX/AraC) Median follow-up: 5-years RB: 33 months RH: 37 months RH + ASCT: 9 (5 on protocol and 4 off protocol – discontinued therapy due to toxicity) RB + ASCT: 23 21 on protocol 2 off protocol	**RB vs. RH** 2-year estimate 81% (63%-91%) vs. 82% (53-94%) 5-year estimate 66% (45%-80%) vs. 62% (34%- 81%)	**RB vs. RH** 2-year estimate 87% (70%-95%) vs. 88% (59%-97%) 5-year estimate 80% (62%-91%) vs. 74% (44%-89%)	**RH vs. RB Grade 3 or 4** Thrombocytopenia 71% vs. 17%; Anemia 59% vs. 8.6% Neutropenia 65% vs. 34%; Febrile neutropenia 29% vs. 14% Grade 3-4 non-hematological in > 5% of the patients **RH (n=17)** Hypophosphatemia 24%; hypokalemia 29%; hyperglycemia 12%; AST elevation 5.9%; ALT elevation 5.9%; catheter-related infection 5.9%; dehydration 5.9%; diarrhea 5.9%; epistaxis 5.9%; nausea 5.9%; rash 5.9%; syncope 5.9% **RB (n =35)** The only grade 3-4 non-hematological in > 5% of patients was hypokalemia (5.7%) Treatment Discontinuation – Couldn't Finish Induction **RH 2**; 1 pancytopenia, 1 other **RB 8**; 2 progressive disease, 1 neutropenia, 1 allergy, 1 seizure, 1 insurance denial, 2 others
		ASCT versus No ASCT: Landmark† analysis at 3-months for RH and at 6-months for RB		
		ASCT vs. No ASCT **RH** 2-year estimate 75% vs. 88%, p=0.43 5-year estimate 50% (15%-77%) vs. 73% (28%-93%), p=0.34 **RB** 2-year estimate 81% vs. 60%, p=0.20 5-year estimate 70% (43%-86%) vs. 63% (23%-86%), p=0.44	**ASCT vs. No ASCT** **RH** 2-year estimate NI 5-year estimate 75% (31%-93%) vs. 73% (28%-93%), p=0.81 **RB** 2-year estimate NI 5-year estimate 91% (69%-98%) vs. 60% (20%-85%), p=0.05	*An unacceptable high mobilization failure rate (29%) on the RH arm prompted premature study closure* Didn't undergo ASCT per protocol **RH** 10; 5 failure to collect stem cells, 5 thrombocytopenia **RB** 6; 2 failure to collect stem cells, 4 patient choice

RQ 1 and 2. Induction and Conditioning Regimens (Chemotherapy and ASCT) - Prospective Observational Studies				
Author, year (reference)	**Intervention and Median follow-up**	**PFS (95%CI)**	**OS (95%CI)**	**Toxicities**
Eskelund, 2016 [16]. Updated results of the Nordic MCL2 trial – Single arm	Nordic MCL2 Protocol Alternating courses of maxi-CHOP and high-dose AraC, 3 of each Median follow-up: 11.4 y.	Median All 8.5 years MIPI p<0.0001 Low 12.7 y Intermediate 8.0 y High 2.5 y **Post-ASCT median** All 11 years MIPI p=0.0001 Low 13.1 y Intermediate 8.2 y High 2.7 y	Median All 12.7 years MIPI p<0.0001 Low NR y Intermediate 11 y High 4 y **Post-ASCT median** All NR MIPI p<0.0001 Low NR Intermediate 11 y High 5.3 y	Non-relapsed deaths 12 treatment-related 7 no treatment-related 5 New malignancies: 20

* Time to treatment failure from randomization to stable disease after at least four induction cycles, progression, or death from any cause, rather than PFS was used to assess the efficacy of the first-line treatment; thus, second-line treatment will not affect the primary analysis.

† Only patients on RH with at least 3-months of follow-up without progression or patients on RB with 6-months of follow-up without progression were included, and the subsequent progression free time after 3 months of follow-up for RH and after 6 months for RB were compared

RQ 3. Maintenance Therapy Post-ASCT – Randomized Control Trials				
Author, year (reference) **Trial ID**	**Intervention and Median follow-up**	**PFS (95%CI)**	**OS (95%CI)**	**Toxicities**
Le Gouill, 2017 [4]. The Lymphoma Study Association LYSA NCT00921414	Rituximab vs. Observation Median follow-up: 4.18 (3.87-4.53) y. vs. 50.2 (46.4-54.2) mo. Rituximab administered every 2 months for 3 years	Median: Not reached 4-year rate 83% (73%-88%) vs. 64% (55%-73%) HR 0.4 [0.23, 0.68]; p<0.001	Median: Not reached 4-year rate 89% (81%-94%) vs. 80% (72%-88%) HR 0.5 [0.26, 0.99]; p=0.04	A total of 25 patients stop the scheduled 3-year maintenance therapy due to disease progression (16 patients) and neutropenia (9 patients). **Rituximab vs. observation** Grade 1-2 events after transplantation Infection 126 (80 pts) vs. 67 (54 pts) Neutropenia 92 (35 pts) vs. 45 (29 pts) Grade 3-4 Hematologic 22% vs. 25% Neutropenia 12.1% vs 2.9% Thrombocytopenia 5.1% vs. 3.8% Grade 3-4 Non-Hematologic Infections 3.0% vs. 2.9% Pulmonary Infection 2.0% vs. 3.8%

Abbreviations: R-CHOP/R-DHAP, alternating courses of 3× R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) and 3× R-DHAP (rituximab plus dexamethasone, high-dose cytarabine, and cisplatin); **MRCT**, myeloablative radio chemotherapy; **AraC**, cytarabine; **RB**, rituximab bendamustine; **RH**, rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyperCVAD) alternating with high dose cytarabine and methotrexate (MTX); **AST**, aspartate aminotransferase; **ALT**, alanine aminotransferase; **HR**, hazard ratio; **MIPI**, MCL prognostic index (age, performance status, S-lactate dehydrogenase, and white blood cell count); **NI**, not information; **NR**, not reached; **OS**, overall survival; **PFS**, progression-free survival.

DISCUSSION

This document represents a review of the evidence with respect to the best practices for first-line therapy, conditioning regimen, timing of ASCT, and maintenance therapy for patients with MCL. Management of relapsed/refractory ASCT was felt to be outside of the scope of this document.

Historically, clinical research in MCL has been challenging due to low incidence. Due to heterogeneity of data and available studies, there have been significant variations in practices provincially, nationally, and internationally. There have been few large, prospective RCTs in this patient population due to disease rarity. This document was undertaken in an attempt to standardize practices across the province.

Upfront ASCT post induction therapy for MCL is now considered standard of care in fit eligible patients. There is a paucity of modern studies exploring this; however, Dreyling et al, 2005 [13] demonstrated that ASCT in first remission significantly prolongs PFS in MCL with a median of 39 months among those who underwent transplantation compared with 17 months among those received IFN-alpha instead of transplant.

The incorporation of cytarabine in induction regimens prior to consolidative ASCT is now considered standard of care for transplant-eligible patients. The European Mantle Cell Lymphoma Network trial is the first randomized trial to demonstrate the beneficial effect of alternating cycles of R-CHOP and R-DHAP as first-line treatment of patients newly diagnosed with MCL who are eligible for ASCT. Patients treated with the cytarabine-containing conditioning regimen (84%) had significantly longer PFS compared to those treated with R-CHOP (85%) (median years 9.1 vs. 4.3; 5-year rate 65% vs. 44%; HR, 0.55; 95% CI, 0.42 to 0.71; $p<0.0001$) [1]. We feel the results of this trial are important; the trial demonstrated a significantly larger PFS and provides strong evidence that cytarabine should be incorporated in induction regimens for MCL prior to consolidative ASCT.

The Working Group found little evidence to support R-HyperCVAD as an initial induction regimen for MCL prior to ASCT. The S1106 trial aimed to select an induction regimen followed by ASCT consolidation as a platform for development in future trials, compared R-hyper-CVAD/MTX/AraC to rituximab plus bendamustine followed by ASCT in patients newly diagnosed with stage IV MCL. The trial was closed early due to significant toxicities and an unacceptably high stem cell mobilization failure rate (29%) among patients treated with the R-hyper-CVAD/MTX/AraC regimen. As a result of significant toxicities and high stem cell mobilization failure rate, it was not believed to be a good initial induction regimen for fit, transplant eligible patients with MCL.

The optimal conditioning regimen for MCL was not identified through this systematic review due to the lack of prospective comparative data. In the absence of such data, a definitive standard regimen cannot be recommended, and local approaches such as BEAM, BEAC, and TBI-based are considered reasonable regimens.

With respect to maintenance therapy after consolidative autologous transplant, one randomized trial was identified that supported the use of maintenance rituximab for patients with newly diagnosed MCL who had undergone ASCT. Eighteen doses over a three-year course of rituximab therapy administered every two months after ASCT significantly prolonged PFS and OS when compared to post-transplant observation. In Ontario, public reimbursement of rituximab as maintenance therapy is eight doses. Exploration into expanding the existing maintenance rituximab schedule to 18 doses (every 2 months for 3 years) should be considered given that the evidence demonstrates improved PFS and OS with expanded access.

CONCLUSIONS

Consolidative ASCT in MCL continues to be the standard of care in fit, transplant-eligible patients. A cytarabine-containing induction regimen is considered standard of care prior to an

ASCT. R-HyperCVAD should be avoided as initial treatment due to the high rate of toxicities and high stem cell mobilization failure compared to other lines of induction chemotherapy. Maintenance rituximab post-ASCT is supported by the current evidence.

Future prospective trials in MCL could be done to explore ideal conditioning regimens in this population and could explore the effect of various induction regimens on stem cell mobilization yields.

ONGOING TRIALS

The clinical trials registry https://clinicaltrials.gov/ was searched for information on relevant studies using the terms "mantle cell lymphoma" and "stem cell transplantation" on February 27, 2020. A total of 26 studies were identified, but only one would have potentially met the inclusion criteria for this review and their details are given below.

Identifier	NCT03267433
Title	A Randomized Phase III Trial of Consolidation with Autologous Hematopoietic Cell Transplantation Followed by Maintenance Rituximab vs. Maintenance Rituximab Alone for Patients with Mantle Cell Lymphoma in Minimal Residual Disease-Negative First Complete Remission
Status	Recruiting participants
Completion	January 31, 2032
Updated	January 2019

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Appendix 1: Mantle Cell Lymphoma Working Group

Mantle Cell Lymphoma - Working Group	
Name	Affiliation
Sita Bhella Hematologist	Princes Margaret Cancer centre Princes Margaret Hospital Toronto, Ontario
Norma Varela Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario
Matt Cheung Hematologist	Odette Cancer Centre Sunnybrook Health Sciences Centre Toronto, Ontario
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Tom Kouroukis Hematologist	Malignant Hematology & Stem Cell Transplantation Juravinski Cancer Centre Hamilton, Ontario
Shawn Sajkowski	Patient Representative

Appendix 2: Conflict of Interest Declarations

In accordance with the PEBC Conflict of Interest (COI) Policy, the recommendation report authors were asked to disclose potential conflicts of interest.

Three authors declared no conflicts of interest (TK, SS, NV), and six (GF, M. Cheung, AW, CB, SB, M. Crump) declared conflicts. Aw declared that in 2017 he received travel and accommodation support of $500 or more from Janssen Inc. He also declared that he acted as site principal investigator for Pharmacyclics LLC clinical trials assessing the efficacy and safety of Ibrutinib vs. Ibrutinib plus venetoclax in relapsed/refractory mantle cell lymphoma patients. CB declared that as a transplant physician, an increase or decrease in transplant activity based on the guideline, although unlikely, could affect his income. SB reported that she had received $500 or more in a single year from Janssen Inc., Celgene, Novartis and Lundbeck, for acting in a consultant capacity, and she also reported to own a medical professional corporation. GF reported that he received $500 or more in a single year from Janssen Inc., Astra Zeneca, and Abbvie for acting in a consulting capacity, and also reported receiving research funding from Janssen and Abbvie. M. Crump reported receiving grants for clinical trial support from Roche and Celgene, and also declared that he has authored one publication involving ASCT and rituximab maintenance for MCL.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by e-mail at ccopgi@mcmaster.ca.

Appendix 3: Literature Search Strategy

Database(s): **Embase** 1996 to 2019 January 18, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Mantle cell lymphoma/ or exp lymphoma, mantle-cell/
2	mantle cell lymphoma.tw.
3	(indolent adj5 mantle).tw.
4	(blastoid adj5 mantle).tw.
5	(diffuse adj5 mantle).tw.
6	(pleomorphic adj5 mantle).tw.
7	or/1-6
8	first line treatment.tw.
9	exp radiotherapy/
10	exp drug therapy/
11	targeted therapy.tw.
12	biological therapy.tw.
13	biotherapy.tw.
14	exp immunotherapy/
15	immunotherapy.tw.
16	immunochemotherapy.tw.
17	R hyperCVAD.tw.
18	R-CHOP.tw.
19	R-DHAP.tw.
20	R-bendamustine.tw.
21	(R-CHOP and R-DHAP).tw.
22	(systemic therapy or systemic treatment).tw.
23	rituximab.tw.
24	exp interferon-alpha/
25	exp interferon-alpha/ or exp alpha interferon/
26	exp maintenance therapy/ or exp antineoplastic combined chemotherapy protocols/
27	or/8-26
28	(case report$ or editorial$ or comment$ or letter$).pt.

29 (editorial or note or letter or case study or short survey or news or newspaper article or patient education handout or historical article).pt.

30 or/28-29

31 (7 and 27) not 30

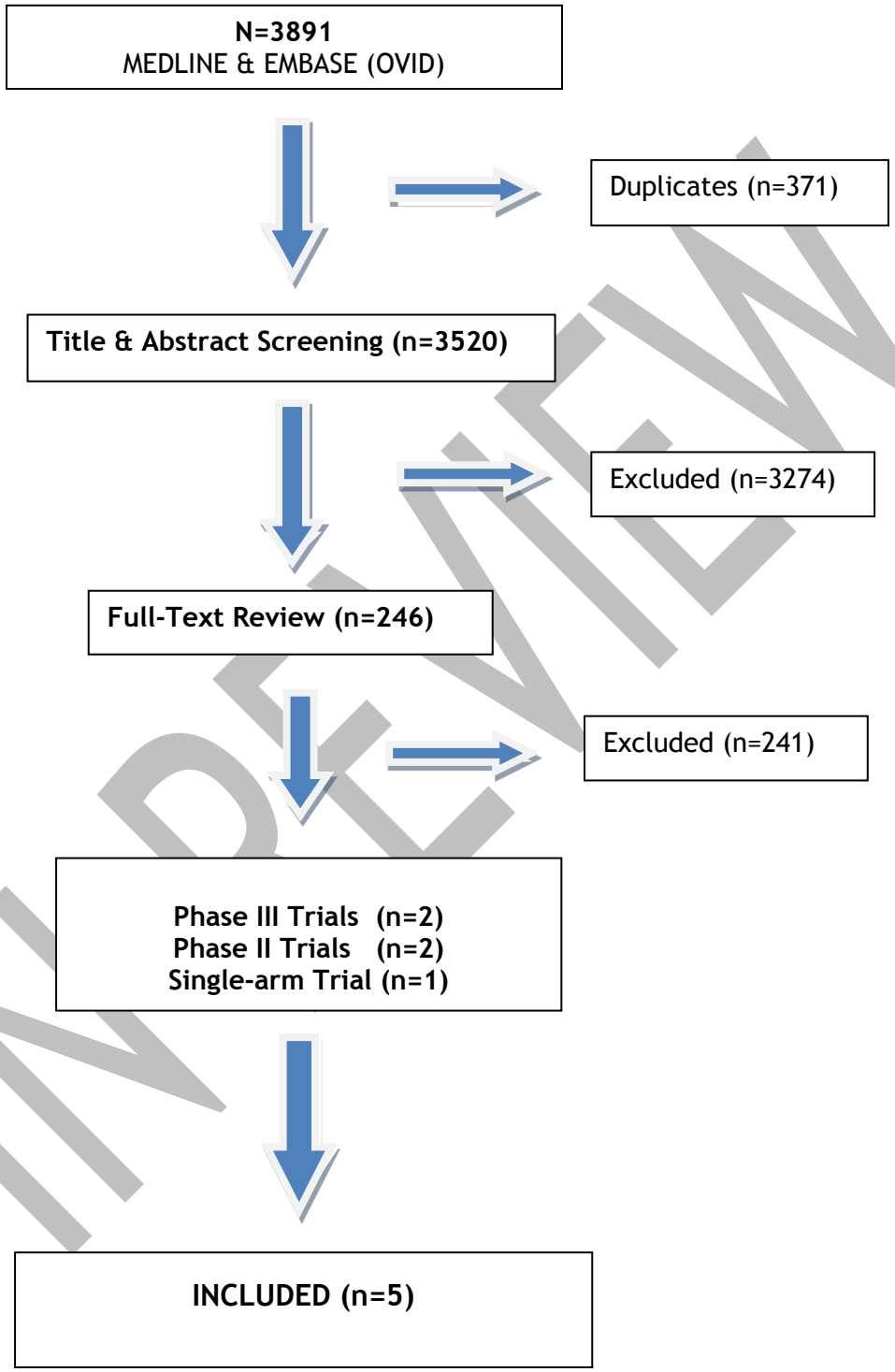
32 exp animals/ not humans/

33 31 not 32

34 limit 33 to yr="1994 -Current"

35 remove duplicates from 34

Appendix 4: PRISMA flow diagram of included studies addressing the management of patients newly diagnosed with mantle cell lymphoma



Appendix 5: Quality assessment of included randomized trials using the revised Cochrane Risk of Bias tool (RoB 2)

1st Author, year [citation]	Randomization Process	Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Reported Results	Overall Risk of Bias / Quality
Hermine, 2016 [1]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
	Allocation sequence was randomly and adequately concealed: Assigned 1:1 by computer-assisted random block selection; patients were stratified by study group and MIPI. Any baseline differences observed between intervention groups appear to be compatible with chance as randomization ensures no baseline imbalances. The authors reported similar baseline characteristics in both groups except for fewer patients in the control group with low-risk biological MIPI and ECOG performance status 0 when compared to the intervention. Even though this imbalance between the groups would help to prove efficacy of the intervention, the authors accounted for this in the analysis.	Due to previously established infusion schedule, drug combination, mobilisation, and high-dose consolidation of the two treatment groups, masking of patients and physicians was not feasible. No deviations from intended intervention arose because of the trial context. An appropriate analysis was used to estimate the effect of assignment to intervention.	Reported reasons for missing outcome data provided evidence that the result was not biased by missing outcome data. Similar proportion of patients was removed from intervention groups because the diagnosis of the MCL was excluded by the central pathology review.	The method of measuring the outcome was appropriate, and did not differ between groups. Despite the open-label design, the authors reported strategies used to minimize potential bias.	The data were analyzed in accordance with a pre-specified plan.	Good Quality

Le Gouill, 2017 [4]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
	Allocation sequence was randomly: assigned in a 1:1 ratio, according to the use or nonuse of R-CHOP before transplantation. The authors reported that patients' characteristics were comparable between the treatment groups at enrollment (randomization ensures no baseline imbalances).	Participants, carers or people delivering the intervention were aware of intervention groups during trial. An appropriate analysis was used to estimate the effect of assignment to intervention.	Outcome data were available for all randomized participants.	The method of measuring the outcome was appropriate (Kaplan-Meier) and it is unlikely that assessment of the outcome was influenced by knowledge of intervention received.	The data were analyzed in accordance with a pre-specified plan.	
Chen, 2017; Kamdar, 2019 [2,3]	Some Concerns	High Risk	Some Concerns	Some Concerns	High Risk	High Risk
	Allocation sequence was randomly but there was no information about concealment of the allocation sequence. Any baseline differences observed between intervention groups appear to be compatible with chance.	Participants, carers or people delivering the intervention were aware of intervention groups during the trial. There were deviations from intended interventions that arose because of the trial context. These deviations were unbalanced between the intervention groups, and likely to have affected the outcome.	Outcome data were not available for all randomized participants due to premature closure of the study.	The method of measuring the outcome was appropriate (Kaplan-Meier) and it is unlikely that assessment of the outcome was influenced by knowledge of intervention received.	The data was not analyzed in accordance with a pre-specified plan. Premature closure of the study limited the sample size and the precision of the estimates.	Low Quality

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MCL, mantle cell lymphoma; MIPI, MCL prognostic index (age, performance status, S-lactate dehydrogenase, and white blood cell count); R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone