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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

*S. Bhella, N. Varela, A. Aw, C. Bredeson, M. Cheung, M. Crump, G. Fraser, S. Sajkowski, T.
Kouroukis*

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An assessment conducted in February 2023 deferred the review of Recommendation Report SCT-9. This means that the document remains current until it is assessed again next year. 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
Section 2:	Recommendation Report Methods Overview
Section 3:	Systematic Review

For information about this document, please contact Dr. Sita Bhella, the lead author, through the PEBC via:

Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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or contact the PEBC office at:

Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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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

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.