About the Authors

Edward Koo, MD

Dr. Edward Koo is a fourth-year resident in the Adult Hematology Program at the University of Ottawa. He completed medical school at McMaster University followed by residency in Internal Medicine at Dalhousie University.

Affiliations: Division of Hematology, Department of Medicine, University of Ottawa, Ottawa, Ontario

David A. Macdonald, MD, FRCPC

Dr. David Macdonald is a hematologist in the Malignant Hematology Group at the Ottawa Hospital, and Assistant Professor at the University of Ottawa. He is a member of the Scientific Advisory Board for Lymphoma Canada and is a contributor to the lymphoma working group of CCTG. His clinical practice focuses on lymphoma and chronic lymphocytic leukemia, and his research interests centre on clinical trials of novel therapies in lymphoma and CLL.

Affiliations: Division of Hematology, Department of Medicine, University of Ottawa, Ottawa, Ontario

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Maintenance Therapy for CD20+ Indolent Lymphoma: Who Should Receive Maintenance?

Edward Koo, MD
David A. Macdonald, MD, FRCPC

Introduction

Maintenance rituximab (MR) has been a mainstay of treatment in Canada for CD20-positive indolent lymphoma for two decades. The adoption of MR into clinical practice occurred after the publication of the EORTC 20981 trial.[1] This trial showed a significant improvement in progression free survival (PFS) with two years of MR versus observation after induction therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with relapsed follicular lymphoma (FL). The use of MR was broadly extended to include its use in the front-line setting, following any R-containing inductions and including all CD20-positive indolent lymphoma histologies.

Automatic recommendations for MR became the standard practice for most patients. Given the recent changes to standard induction regimens in some indications, and with heightened concerns about infectious complications during B-cell depleting therapy, the recommendation for the use of MR should no longer be considered automatic. This review offers a balanced perspective of the evidence for MR.

Follicular Lymphoma

FL is the most common form of indolent non-Hodgkin lymphoma (NHL), with an estimated incidence of 38.3 cases per million individuals per year.[2] FL is incurable in most circumstances; therefore, consideration of maintenance therapy is important, given the goal to prolong the duration of response after induction therapy.

The PRIMA trial investigated MR in the front-line setting. In the trial, patients with untreated FL who received R-CHOP, rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP), or rituximab with fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) were randomized to 2 years of MR or observation without MR.[3] At 9-years of follow-up, the median PFS was 10.5 years with MR compared with 4.1 years for those who underwent observation (hazard ratio (HR) 0.61; 95% confidence interval (CI), 0.52–0.73; p<0.001), and the median time to the next line of treatment was not reached in the MR arm vs 6.1 years in the observation arm (HR 0.66; 95% CI, 0.55–0.78; p<0.001). No improvement was demonstrated in overall survival.

In Canada, most centres use bendamustine plus rituximab (BR) as the preferred induction regimen based on the BRIGHT[4] and StiL-NHL1 trials.[5] Randomized controlled trial (RCT) data comparing MR to observation does not exist for patients receiving BR. However, a post hoc analysis conducted by the BRIGHT investigators using 5-year follow-up data found that patients who received MR after responding to BR had a significantly better PFS compared with those who did not receive MR (HR 0.50, 95% CI 0.26–0.94, P=0.030), although no statistically significant difference was observed in overall survival (OS).[6] The decision to assign a patient to MR was left to the investigators' discretion, which could have introduced bias into this data.

In a retrospective multi-institution analysis of 640 FL patients who received BR for FL, outcomes were compared between patients who received MR vs those who underwent observation.[7] The 3-year PFS was higher for the MR group vs the observation group, (84.2% vs 61.2%), respectively (p<0.001), as was the OS, (94.3% vs 85.1%) respectively, (p=0.001). The decision to select patients for MR was left to the discretion of their treating physician, which prompted the investigators to conduct separate subgroup analyses of the MR effect based

on the patients' induction response. Amongst patients who achieved a complete response (CR), no difference was observed in the 3-year duration of response (DOR) or OS between those who underwent MR vs those who underwent observation. Among patients who achieved a partial response (PR), those who received MR had a longer 3-year DOR vs those who underwent observation, at 80% vs 45%, respectively (p=0.003), although no statistically significant difference in OS was observed. These findings indicated an improved DOR only in patients who achieved a PR but not a CR, compared to a PFS benefit across patients achieving both PR and CR in the randomized PRIMA study, suggests that patients who receive BR as induction therapy may not derive the same benefit from MR when compared to those receiving R-CHOP/R-CVP induction.

Regarding duration of maintenance, two years of MR has been commonly adopted, because it was used in the pivotal EORTC trial (an MR dose every 12 weeks) and in the PRIMA trial (a MR dose every 8 weeks). The retrospective analysis conducted by Hill et al. revealed heterogeneity in the administration of MR. The authors observed that MR was administered for a median of 18 months. They also observed a variety of dosing schedules, including every 2 months, every 3 months, and 4 weekly doses every 6 months. The StiL NHL7 MAINTAIN trial is currently investigating the difference between 2 and 4 years of MR. When the data was last presented in 2017, 4 years of MR demonstrated superior PFS compared with 2 years of MR, with no difference observed in OS, although it must be emphasized that the analysis is ongoing.[8]

The risks of toxicity must be considered given that most patients with FL typically have a favourable long-term prognosis.[9] In the PRIMA study, MR was associated with a higher rate of Grade 3–4 adverse events, primarily cytopenias (5.2% in the MR group vs 1.6% in the observation group) and infections (4.4% in the MR group vs 1.0% in the observation group).[3] Bendamustine has lymphodepleting effects, and when it is used in combination with anti-CD20 treatment, the risks of cytopenias, infection, and poor response to vaccination are increased. The GALLIUM study randomized FL patients to rituximab-based immunochemotherapy plus MR versus obinutuzumab-based immunochemotherapy plus maintenance obinutuzumab, in which the chemotherapy regimen was according to a centre-specific choice of CHOP, CVP or bendamustine.[10] During the maintenance phase approximately 12.8–16.7% of patients who had received bendamustine for induction experienced Grade 3–5 infections, which were almost double those of patients who received induction CVP (2.3–8.8%) or CHOP (3.9–5.9%). In a retrospective analysis comparing patients treated with BR to those treated with R-CHOP/R-CVP for FL in Ontario, admissions for infection were significantly more frequent in patients who received maintenance therapy after BR.[11]

Regarding induction with single-agent rituximab (administered as four weekly doses), the phase III RESORT RCT compared MR to rituximab re-treatment (administered as a single dose every 13 weeks until treatment failure) and showed no difference in time to treatment failure.[12] In recent studies, long-term secondary outcomes have shown superiority for MR for freedom from cytotoxic therapy and response duration; however, no OS benefit was observed. Of note, these results are less relevant to Canadian practice, in which rituximab monotherapy induction is infrequently used.

Mantle Cell Lymphoma

Standard therapy for patients with mantle cell lymphoma (MCL) includes rituximab and a chemotherapy regimen selected based on transplant eligibility. The MCL Elderly Phase III RCT randomized patients over the age of 65 to receive rituximab with fludarabine and cyclophosphamide (R-FC) or R-CHOP induction, with a second randomization to maintenance therapy with rituximab or interferon-alpha until progression. Aside from demonstrating OS improvements with R-CHOP, those who received MR after R-CHOP but not after R-FC demonstrated benefits in both PFS and OS.[13] Transplant ineligible patients are most commonly treated with BR. Subgroup analysis of the MCL cohort in the BRIGHT study showed a similar benefit in PFS but not in OS, though there appears to be more supportive evidence when compared to FL.[4] In a US real-world retrospective analysis, the combination of BR followed by MR was associated with a significantly improved real-world time to next treatment (TTNT) vs BR alone, (65.4 months, 95% CI 61.6–75.6 vs 37.7 months, 95% CI 33.1–41.2) respectively (p<0.001) and OS, (89.5 months, 95% CI 80.0–108.6 vs 78.1 months, 95% CI 62.9–93.5), respectively (p<0.001).[14]

The standard of care for transplant eligible MCL patients is rituximab and cytarabine-containing chemotherapy, followed by autologous stem cell transplantation (ASCT). The use of MR post-ASCT is strongly supported. In the phase III LyMa trial, patients aged less than 66 years were randomized to MR for 2 years versus observation following rituximab, dexamethasone, cytarabine, cisplatin (R-DHAP) induction and ASCT. At 7 years of follow-up, MR was associated with an improvement in event-free survival and PFS.[15] A systematic review and meta-analysis that examined 6 RCTs with similar inclusion criteria including MR in MCL outcomes, found PFS improvements with MR, specifically after R-CHOP or cytarabine containing induction, and after R-CHOP in the relapse setting.[16]

Waldenstrom's Macroglobulinemia

Treatment options in Waldenstrom's Macroglobulinemia (WM) differ somewhat from those for FL. WM treatment may involve more frequent use of single agent rituximab, as well as the particular activity of agents such as proteosome inhibitors and Bruton's tyrosine kinase inhibitors, among others.[17] BR remains a commonly used induction regimen. The Phase III NHL-2008 MAINTAIN RCT compared rituximab maintenance every 2 months for 2 years to observation in patients treated with 6 cycles of BR, and found no statistically significant difference in PFS or in OS (the latter was not reached with both arms).[18] MR as standard therapy for WM or lymphoblastic lymphoma is not currently recommended according to both the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines.

Marginal Zone Lymphoma

The common use of MR after induction BR in marginal zone lymphoma (MZL) in Canada is based on an extrapolation of the MR data from FL. However, no RCT has been conducted in this patient population. A subgroup of non-follicular lymphoma patients treated in the RESORT trial included 71 patients with MZL and 57 patients with small lymphocytic lymphoma (SLL).[19] Results for those with MZL and SLL were similar to those for the FL group, with MR in responders resulting in an improvement in the median time to treatment failure and the median time to first cytotoxic therapy. This study is cited by the NCCN as support for including MR as an optional first-line extended therapy in MZL. However, similar to FL, the use of single agent rituximab for induction is rarely chosen for patients with MZL in Canada, which reduces the relevance of this data.

Anti-CD20 Therapy and COVID-19

The COVID-19 pandemic has influenced the risk-benefit discussion of MR. A number of studies have demonstrated impaired responses to vaccination in patients with hematologic malignancies who have received anti-CD20 therapy,[20,21] and worse outcomes for these patients when they contract COVID-19.[22,23] A multi-centre retrospective study that included 16 French hospitals evaluated 111 lymphoma patients who were admitted to hospital in March and April 2020 with COVID-19.[20] The study reported that 85% of the patients had B-cell NHL and 71% had received treatment for lymphoma within 12 months prior to admission (63% had received anti-CD20 therapy). Recent anti-CD20 therapy was associated with prolonged length of stay (HR 2.26, 95% confidence interval 1.42–3.6, $p<0.001$) and higher risk of death (HR 2.17, C.I. 1.04–4.52, $p=0.039$).

The French cohort was an unvaccinated population who were admitted to the hospital at the onset of the pandemic. A recent meta-analysis examining COVID-19 outcomes in lymphoma and non-lymphoma indications,[21] including studies published up to June 2023, which also accounts for vaccinated patients, showed that anti-CD20 use was associated with a significantly increased risk of severe illness (pooled OR 2.95, CI 2.30–3.78) and mortality (pooled OR 2.14, CI 1.37–3.35.

Summary

Ultimately, deciding upon MR in our current era of first-line treatment for CD20-positive indolent lymphoma requires an individualized assessment of the associated risks and benefits. In MCL, the evidence that supports the benefit of MR is clear, both after ASCT, and after BR induction in non ASCT-eligible patients. In WM, RCT data has shown a lack of benefit. In MZL there is simply a paucity of data. In FL, the magnitude of benefit with MR after RCHOP/RCVP is profound, with more than a doubling of the median PFS from 4 years to 10 years. However, while MR after BR already improves PFS to nearly 6 years

Trial/Design	Patient no.	Induction Treatment	Comparison	Outcome
Rummel et al. (StiL-NHL1)/RCT[4]	447	BR vs R-CHOP	No maintenance in either arm	mPFS: 69.5 months vs 31.2 months OS: not statistically significant (p=0.249) mTTNT: NR (95% CI 124.9 –NR) vs 56 months (95% CI 39.1–82.0)
Follicular Lymphoma				
Bachy et al. (PRIMA)/ RCT[2]	1018	R-CHOP or R-CVP or R-FCM	MR x 2 years vs observation	PFS: 10.5 years vs 4.1 years (p<0.001) OS: NR vs NR (p=0.7948) TTNCT: NR vs 9.3 y (p<0.001)
Kahl et al. (RESORT)/RCT[11]	289	Rituximab x 4 doses	MR vs rituximab re-treatment	7-year freedom from first cytotoxic therapy: 83% vs 63% (p=0.001) OS: 83% vs 84% (p=0.5972)
Hill et al./ retrospective analysis[6]	640	BR	MR vs observation	3-year PFS: 84.2% vs 61.2% (p<0.001) 3-year OS: 94.3% vs 85.1% (p=0.001)
Mantle Cell Lymphoma				
Sarkozy et al. (LyMA)/RCT[14]	240	R-DHAP + autologous stem cell transplantation	MR x 2 years vs observation	EFS: NR vs 5.8 years (p<0.0001) PFS: NR vs 6.1 years 7-year OS estimate: 83.2% vs 72.2% (p=0.087)
Waldenstrom's Macroglobulinemia				
Rummel at al.(StiL-NHL7-2008 MAINTAIN)/RCT[17]	288	BR	MR vs observation	PFS: 101 months vs 83 months (p=0.32) OS: NR for both arms

Table 1. Summary of relevant randomized controlled trials addressing maintenance therapy for CD20+ indolent lymphoma; *courtesy of Edward Koo, MD and David A. MacDonald, MD, FRCPC.*

Abbreviations: BR: bendamustine, rituximab; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **R-CVP:** rituximab, cyclophosphamide, vincristine, prednisone; **R-FCM:** rituximab, fludarabine, cyclophosphamide, mitoxantrone; **R-DHAP:** rituximab, dexamethasone, cytarabine, cisplatin; **MR:** maintenance rituximab; **PFS:** progression-free survival; **OS:** overall survival; **TTNT:** time to next treatment; **TTNCT:** time to next chemotherapy treatment; **EFS:** event-free survival; **NR:** not reached

without maintenance, there is no Level 1 evidence supporting the additional benefit of MR.

A discussion about MR or observation with an FL patient after induction BR should include the following important points. An acknowledgement that the best evidence supporting MR is extrapolated from a population of patients that received inferior induction treatment. That the depth of response after induction (CR or PR) may influence the degree of benefit from MR. That there is clear evidence of potential infectious and COVID-related risks. Finally, that the goal of prolongation of the present remission status should be tempered with the knowledge that more effective subsequent treatments are emerging (**Table 1**).

Correspondence:

Dr. David Macdonald
Email: davidmacdonald@toh.ca

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