Evolving Frontline Immunochemotherapy for Mantle Cell Lymphoma and the Impact on Survival Outcomes

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Abstract:
With the advances in mantle cell lymphoma (MCL) frontline treatment over the last two decades, we sought to characterize the frontline treatment pattern change and its association with outcomes. Patients with newly diagnosed MCL from September 2002 through June 2015 were enrolled in a prospective cohort study, and clinical characteristics, treatment, and clinical outcomes were compared between patients diagnosed in 2002-2009 (Era 1) vs 2010-2015 (Era 2). Patient age, sex and simplified MIPI score were similar between the two groups. In patients with an age ≤65, there were less use of R-Hyper-CVAD (16.1% vs 8.8%) but more Nordic and R-CHOP/R-DHAP regimens (1.1% vs 26.4%), and less use of R-CHOP/R-CHOP-like regimen (64.5% vs 35.2%) but more R-Bendamustine (0% vs 12.1%) in Era 2 (p<0.001). These changes were associated with improved EFS (5-year 34.3% vs 50.0%, p=0.010) and OS (5-year 68.8% vs 81.6%, p=0.017) in Era 2. In patients with an age >65, there were less use of R-CHOP/R-CHOP-like (39.0% vs 14.3%) and non-standard systemic therapy (36.6% vs 13.0%) but more R-Bendamustine (0% vs 49.4%). These changes were associated with a trend for improved EFS (5-year 25.4% vs 37.5%, p=0.051) in Era 2. The shift from R-CHOP/R-CHOP-like regimen to R-Bendamustine was associated with improved EFS (5-year 25.0% vs 44.6%, p=0.008) in Era 2. Results from this prospective cohort study provide critical real-world evidence for improved outcomes with evolving frontline pattern of care in patients with MCL.

Conflict of interest:
COI declared - see note

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Evolving Frontline Immunochemotherapy for Mantle Cell Lymphoma and the Impact on Survival
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Running Title: Mantle Cell Lymphoma Frontline Pattern of Care

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- The pattern of frontline treatment for mantle cell lymphoma has evolved in both younger and older patients from 2002-2009 to 2010-2015.
- The change in frontline treatment was associated with improved EFS and OS in younger patients and improved EFS in older patients.

Abstract

With the advances in mantle cell lymphoma (MCL) frontline treatment over the last two decades, we sought to characterize the frontline treatment pattern change and its association with outcomes. Patients with newly diagnosed MCL from September 2002 through June 2015 were enrolled in a prospective cohort study, and clinical characteristics, treatment, and clinical outcomes were compared between patients diagnosed in 2002-2009 (Era 1) vs 2010-2015 (Era 2). Patient age, sex and simplified MIPI score were similar between the two groups. In patients with an age ≤65, there were less use of R-Hyper-CVAD (16.1% vs 8.8%) but more Nordic and R-CHOP/R-DHAP regimens (1.1% vs 26.4%), and less use of R-CHOP/R-CHOP-like regimen (64.5% vs 35.2%) but more R-Bendamustine (0% vs 12.1%) in Era 2 (p<0.001). These changes were associated with improved EFS (5-year 34.3% vs 50.0%, p=0.010) and OS (5-year 68.8% vs 81.6%, p=0.017) in Era 2. In patients with an age >65, there were less use of R-CHOP/R-CHOP-like (39.0% vs 14.3%) and non-standard systemic therapy (36.6% vs 13.0%) but more R-Bendamustine (0% vs 49.4%). These changes were associated with a trend for improved EFS (5-year 25.4% vs 37.5%, p=0.051) in Era 2. The shift from R-CHOP/R-CHOP-like regimen to R-Bendamustine was associated with improved EFS (5-year 25.0% vs 44.6%, p=0.008) in Era 2. Results from this prospective cohort study provide critical real-world evidence for improved outcomes with evolving frontline pattern of care in patients with MCL.
Introduction

Mantle cell lymphoma (MCL) is an uncommon subtype of non-Hodgkin lymphoma (NHL) that is characterized by t(11;14)(q13;q32) translocation and cyclin D1 overexpression.1-3 The clinical presentation of MCL is heterogeneous, ranging from indolent to highly aggressive.3-5 The management strategy of MCL is diverse without a universal standard approach across institutions, although there is a consensus that autologous stem cell transplant (ASCT) consolidation should be considered in young and fit patients following frontline immunochemotherapy.4,6,7

There are several notable advances in the frontline treatment of newly diagnosed MCL over the last 2 decades. (1) Addition of the anti-CD20 antibody rituximab to chemotherapy resulted in improved outcomes.8-12 (2) High dose chemotherapy followed by ASCT in first remission was proven to prolong progression-free survival (PFS) in the European MCL Network trial,13 and has been adopted in the management of young and fit patients who are eligible for ASCT, with emerging evidence of prolonging overall survival (OS).7 (3) Highly effective induction regimens containing high dose cytarabine (HiDAC) have been developed. The R-HyperCVAD alternating with R-MTX/AraC (R-MA) regimen induces high response rate and long term remission,14-16 but is associated with high toxicity.17,18 The Nordic Lymphoma Group MCL2 trial established R-maxi-CHOP alternating with R-HiDAC as an efficacious induction regimen in ASCT eligible patients.19-21 The European MCL Network confirmed the benefit of HiDAC in the randomized MCL Younger trial comparing R-CHOP alternating with R-DHAP to R-CHOP alone as induction regimens in ASCT eligible patients.22,23 (4) In ASCT ineligible patients, rituximab maintenance therapy after responding to R-CHOP improved survival.24 In ASCT eligible patients, rituximab maintenance after ASCT has demonstrated a survival benefit.25 (5) While R-CHOP improved OS compared to R-FC in older and ASCT-ineligible patients,24 the German STiL NHL1 trial and the US BRIGHT trial have demonstrated that rituximab-bendamustine (R-Benda) results in superior PFS compared to R-CHOP.26-28 In addition, the SWOG S1106 study showed that R-Benda and R-HyperCVAD/R-MA had similar induction efficacy, suggesting that R-Benda may also be an acceptable induction regimen prior to ASCT.29,30 (6) Multiple studies have demonstrated that watchful waiting or deferred initial treatment is feasible and appropriate in a subset of patients who present with indolent disease.31-34

Despite the controlled clinical trial data suggesting benefit to these therapies which require either extended treatment or use of specialized facilities, it is unclear how much either physician education, patient acceptance, therapy-required resistance or other factors may slow diffusion of these recommended management strategies. Nevertheless, as a result of the above advances, the practice pattern in managing newly diagnosed MCL may have evolved accordingly. In this study, we sought to characterize the changes in frontline treatment and the association with outcomes in patients with newly diagnosed MCL using a prospectively followed cohort.

Methods

Patients

This study was approved by the institutional review boards at Mayo Clinic and University of Iowa. It was conducted in accordance with the Declaration of Helsinki. Patients with newly diagnosed MCL were identified from the Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE). The MER is a prospective cohort study of lymphoma outcomes35 that includes consecutive patients with newly diagnosed lymphoma (within 9 months of diagnosis) since 2002. Patients enrolled on MER were managed per treating physician’s choice and were followed systematically every 6 months for the first three years and annually thereafter.
For this study, all MER patients with newly diagnosed MCL from September 2002 through June 2015 were included. Baseline clinical characteristics and treatment information were abstracted using a standard protocol. Disease progression or relapse, re-treatment, and death were verified through medical record review. Frontline treatment was classified as standard immunochemotherapy, non-standard systemic therapy, and non-systemic therapy. Standard immunochemotherapy were further classified into four categories, i.e., R-HyperCVAD, Nordic regimen or R-CHOP/R-DHAP, R-CHOP or R-CHOP-like, and R-Benda. Non-standard systemic therapy included R-2CdA, R-FCM, rituximab only, or chemotherapy without rituximab. Non-systemic treatment included surgery or radiotherapy alone, or observation. The R-Benda regimen was adopted in 2010 at our institutions; therefore, September 2002 through December 2009 was defined as Era 1 and January 2010 through June 2015 was defined as Era 2.

**Statistical analyses**

Baseline clinical characteristics and treatment categories between the two eras were compared using Chi-square test and ANOVA. Event-free survival (EFS) was defined as the time from diagnosis to disease progression or relapse, unplanned retreatment after initial treatment, or death from any cause. Overall survival (OS) was defined as the time from diagnosis to death from any cause. EFS and OS were analyzed using the Kaplan-Meier method, and hazard ratios (HR) and 95% CI were calculated through Cox regression models, with comparisons between eras adjusted for simplified MCL International Prognostic Index (sMIPI). Statistical analyses were performed using R (version 4.0.3). A P value < 0.05 was considered statistically significant.

**Results**

**Patients**

A total of 343 patients were included. Baseline clinical characteristics are shown in Table 1. 265 (77.3%) patients were male. The median age at diagnosis was 64 years (rage 32-96), and 184 (53.6%) patients were 65 years or younger. By sMIPI, 79 (27.6%) had low risk disease, 105 (36.7%) had intermediate risk, and 102 (35.7%) had high risk.

There were 175 patients from Era 1 (2002-2009) and 168 from Era 2 (2010-2015). Sex, age, and sMIPI score were similar between the two groups (Table 1).

**Treatment pattern**

Since frontline treatment of MCL depends on the age and fitness of the patients and age 65 years is considered an cutoff in considering ASCT, we evaluated the treatment pattern in Era 1 vs Era 2 in younger (age ≤65) and older (age >65) patients separately.

As shown in Table 2, for patients with age ≤65, compared with Era 1, there was less use of R-HyperCVAD (16.1% vs 8.8%) but more Nordic and R-CHOP/R-DHAP regimens (1.1% vs 26.4%) in Era 2; and less use of R-CHOP/R-CHOP-like regimen (64.5% vs 35.2%) but more R-Benda (0% vs 12.1%). Use of non-standard systemic treatment and non-systemic treatment was similar. The proportions of patients who underwent ASCT (45.2% vs 44.4%) and rituximab maintenance (5.4% vs 5.5%) were similar.

For patients with age >65, use of the intensive R-HyperCVAD (n=2, Era 1 only), Nordic or R-CHOP/R-DHAP regimens (n=2, Era 2 only) was minimal. Compared with Era 1, there was less use of R-CHOP/R-CHOP-like (39.0% vs 14.3%) and non-standard systemic therapy (36.6% vs 13.0%) but more use of R-
Benda (0% vs 49.4%). Use of non-systemic treatment was similar. The proportions of patients who underwent ASCT (7.3% vs 6.5%) and rituximab maintenance (9.8% vs 14.3%) were similar.

**Survival outcomes**

The median follow-up was 13.0 years (95% CI 12.2-15.9) for patients diagnosed in Era 1 (n=175) and 7.1 years (95% CI 6.9-8.0) for patients diagnosed in Era 2 (n=168). For the entire cohort, EFS was improved in Era 2 compared to Era 1, with a median EFS of 2.5 (95% CI 2.0-3.1) vs 3.5 (95% CI 2.8-5.4) years and a 5-year EFS of 30.2% (95% CI 24.1-37.8) vs 43.9% (95% CI 36.7-52.4) in Era 1 vs Era 2 (log-rank \( P = 0.002 \); sMIPI-adjusted HR 0.66 [95%CI 0.51-0.85], \( P = 0.002 \) (Figure 1A). There was also an improvement of OS in Era 2, with a 5-year OS of 59.2% (95% CI 52.3-67.0) vs 68.4% (95% CI 61.4-75.7) in Era 1 vs Era 2 (log-rank \( P = 0.007 \); sMIPI-adjusted HR 0.68 [95% CI 0.50-0.93], \( P = 0.016 \) (Figure 1B).

In patients 65 years or younger, there was an improvement of both EFS \(( P = 0.007 \) and OS \(( P = 0.018 \) in Era 2 (Figure 2A-B, Table 3). The improvement was primarily driven by improved EFS \(( P = 0.007 \) and OS \(( P = 0.010 \) in patients who received standard immunochemotherapy (Figure 2C-D, Table 3). EFS and OS following induction therapy with R-CHOP or R-CHOP-like regimens were similar between the two eras (Supplemental Figure 1), suggesting that there was no substantial change in supportive care over the study period. Patients who received non-standard systemic therapy or non-systemic therapy had similar EFS \(( P = 0.721 \) and OS \(( P = 0.447 \) in Era 1 and Era 2 (Figure 2E-F, Table 3).

In patients older than 65 years, there was a trend for improved EFS in Era 2 \(( P = 0.086 \) but no statistically significant difference in OS \(( P = 0.259 \) (Figure 3A-B, Table 3). The shift from R-CHOP/R-CHOP-like regimen to R-Benda was associated with an improved EFS \(( P = 0.002 \) and OS \(( P = 0.033 \) in Era 2 (Figure 3C-D, Table 3). Patients who received non-standard systemic therapy or non-systemic therapy had similar EFS \(( P = 0.091 \) and OS \(( P = 0.501 \) in Era 1 and Era 2 (Figure 3E-F).

**Discussion**

To the best of our knowledge, this is the first prospective cohort study of MCL frontline pattern of care in the rituximab era. Our data suggest heterogenous but clearly changing management approaches that were likely influenced by landmark MCL trials and clinical studies. We did observe improved treatment outcomes with evolving frontline immunochemotherapy, providing important real-world evidence that supports the use of HiDAC-containing induction regimen in ASCT eligible patients and R-Benda in ASCT ineligible patients. The change in practice pattern and the associated outcome improvement from Era 1 to Era 2 highlight the importance of conducting clinical trials to constantly improve treatments for MCL and adopting better treatments in clinical practice.

Several prior studies examined the outcomes of MCL over time using registry data. Kiel Lymphoma Study Group (1975 to 1986) and German Low Grade Lymphoma Study Group (1996 to 2004) data were primarily in the pre-rituximab era. SEER-18 registry data demonstrated an improved OS from 2000-2006 to 2007-2013 but treatment data were not available. Similarly, the Swedish Lymphoma Registry data reported an improved OS in 2006-2010 compared to 2000-2005 but only limited treatment information was available for patients enrolled in 2007 or after. A subsequent Nordic study using Swedish and Danish registry data demonstrated the benefit of rituximab and ASCT; although frontline treatment regimen was available, survival comparison between 2000-2005 vs 2006-2011, especially with relation to treatment regimen, was not performed. Data from the UK Haematological Malignancy Research Network also demonstrated an improved OS from 2004-2011 to 2012-2015, although the
treatment appeared not as intensive (50% were treated with fludarabine, cyclophosphamide and/or chlorambucil based regimens; rituximab less than 40%, HiDAC less than 20%, ASCT less than 10%). In contrast to the above, our study was based on a prospectively followed cohort with complete frontline treatment information, which allowed us to examine the treatment pattern change over time, and to correlate the treatment change with clinical outcomes, in both younger and older patients, which is more informative in analyzing and guiding clinical practice.

Several observations on the practice pattern in our study are worth noting. (1) In younger patients (age ≤65), only approximately 45% of patients underwent ASCT. Understanding the reasons for not proceeding to ASCT is important in this age group. Detailed studies of comorbidities, response to induction, treatment associated toxicities, and other factors, will aid in defining patient, disease and treatment factors that can potentially be improved in order to increase the rate of ASCT, which is known to improve PFS and potentially OS.\(^7,13\) (2) In younger patients, there was increased use of Nordic or R-CHOP/R-DHAP regimen in Era 2, but 35% of the patients still received an R-CHOP/R-CHOP-like regimen. Understanding the reasons behind the different induction choices will be important, so that the use of HiDAC-containing induction in ASCT eligible patients can be maximized to potentially further improve treatment outcomes.\(^22,23\) (3) Rituximab maintenance was utilized at a relatively low rate, less than 10% in younger and 15% in older patients. In ASCT ineligible patients, the role of rituximab maintenance is proven after R-CHOP\(^24\) but is controversial after R-Benda.\(^42,43\) The LyMa study demonstrated that rituximab maintenance improved OS following ASCT,\(^25\) but this study was published in 2017. The role of rituximab maintenance in the real-world setting warrants further studies. (4) Encouragingly, a shift from R-CHOP/R-CHOP-like regimen to R-Benda between Era 1 and Era 2 was associated with an improved EFS in older patients (age >65) receiving these regimens, consistent with the StIL NHL1 and BRIGHT trials.\(^26-28\)

The strengths of this study include the prospective cohort study design, availability of detailed frontline treatment information and sMIPI data, long follow-up, analysis stratified by age group, and the correlation of practice change with treatment outcome. The weaknesses mainly relate to the observational study design, where treatment choice and follow-up management is at the treating clinician’s discretion. In addition, the study lacked racial diversity and included nearly all white patients, and results may not generalize to other racial/ethnic groups. We also lacked detailed analysis on treatment after disease progression. The availability of the immunomodulatory drug lenalidomide,\(^34-36\) Bruton tyrosine kinase inhibitors (BTKI)\(^47-52\) and the BCL2 inhibitor venetoclax\(^53-56\) in recent years may have contributed to improved OS over time. For example, the first BTKi ibrutinib was approved in 2013, and patients diagnosed in Era 2 were more likely to have had access to BTKi at disease relapse. Better treatment options post relapse may have contributed to the improvement in outcomes in Era 2. Future studies examining pattern of care in relapsed and refractory MCL and the association with outcomes are planned at our centers.

Our study showcases the importance of validating clinical trial outcomes in routine practice with real-world evidence. In a heterogeneous disease with diverse and emerging treatment options, learning from real-world evidence can guide institutional practices that will in turn benefit the patients. As novel agents such as lenalidomide,\(^57,58\) Bruton tyrosine kinase inhibitors (e.g., SHINE, ACE-LY-308, Window-1, TRIANGLE, ECOG-ACRIN EA4181),\(^2,59\) and venetoclax (e.g., Window-2, PrECOG 0405, OAsIs)\(^60\) move to the frontline setting, continued studies of MCL frontline pattern of care will remain important and provide future guidance on clinical practice.

In summary, advances in frontline treatment for MCL were seen in both younger (less R-HyperCVAD and R-CHOP/R-CHOP-like induction, more Nordic regimen and R-CHOP/R-DHAP) and older patients (less R-CHOP/R-CHOP-like and more R-Benda). The change in induction regimens was associated with improved EFS and OS in younger patients, and a shift from R-CHOP/R-CHOP-like regimen to R-Benda was
associated with improved EFS in older patients. Results from this prospectively followed cohort provide critical real-world evidence for improved outcomes with evolving pattern of care in patients with MCL.
Data sharing statement

For data sharing, contact the corresponding author: wang.yucai@mayo.edu.

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References

1. Cheah CY, Seymour JF, Wang ML. Mantle Cell Lymphoma. J Clin Oncol. 2016;34(11):1256-1269.
2. Jain P, Wang M. Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management. Am J Hematol. 2019;94(6):710-725.
3. Cortelazzo S, Ponzoni M, Ferreri AJM, Dreyling M. Mantle cell lymphoma. Crit Rev Oncol Hematol. 2020;153:103038.
4. Maddocks K. Update on mantle cell lymphoma. Blood. 2018;132(16):1647-1656.
5. Jain AG, Chang CC, Ahmad S, Mori S. Leukemic Non-nodal Mantle Cell Lymphoma: Diagnosis and Treatment. Curr Treat Options Oncol. 2019;20(12):85.
6. National Comprehensive Cancer Network. B-Cell Lymphomas (version 4.2021).
7. Gerson JN, Handorf E, Villa D, et al. Survival Outcomes of Younger Patients With Mantle Cell Lymphoma Treated in the Rituximab Era. J Clin Oncol. 2018;36(2):1288-1294.
8. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2004;104(10):3064-3071.
9. Lenz G, Dreyling M, Hoste E, et al. Immunocytotoxic chemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol. 2005;23(9):1984-1992.
10. Schulz H, Bohlius JF, Trelle S, et al. Immunocytotoxic chemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2007;99(9):706-714.
11. Hoste E, Unterhalt M, Wörmann B, et al. The Addition of Rituximab to First-Line Chemotherapy (R-CHOP) Results in Superior Response Rates, Time to Treatment Failure and Response Duration in Patients with Advanced Stage Mantle Cell Lymphoma: Long Term Results of a Randomized GLSG Trial. Blood. 2008;112(11):3049-3049.
12. Dreyling M, Lenz G, Hoste E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood. 2005;105(7):2677-2684.
13. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol. 2005;23(28):7013-7023.
14. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol. 2010;150(2):200-208.
15. Chihara D, Cheah CY, Westin JR, et al. Rituximab plus hyper-CVAD alternating with MTX/Ara-C in patients with newly diagnosed mantle cell lymphoma: 15-year follow-up of a phase II study from the MD Anderson Cancer Center. Br J Haematol. 2016;172(1):80-88.
17. Merli F, Luminari S, Ilariucci F, et al. Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. Br J Haematol. 2012;156(3):346-353.

18. Bernstein SH, Epner E, Unger JM, et al. A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. Ann Oncol. 2013;24(6):1587-1593.

19. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemistry with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood. 2008;112(7):2687-2693.

20. Geisler CH, Kolstad A, Laurell A, et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemistry for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. Br J Haematol. 2012;158(3):355-362.

21. Eskelund CW, Kolstad A, Jerkeman M, et al. 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. Br J Haematol. 2016;175(3):410-418.

22. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood. 2013;121(1):48-53.

23. Hermine O, Hoster E, Walewski J, et al. Addition of high-dose cytarabine to immunochemistry before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. Lancet. 2016;388(10044):565-575.

24. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med. 2012;367(6):520-531.

25. Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. N Engl J Med. 2017;377(13):1250-1260.

26. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203-1210.

27. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123(19):2944-2952.

28. Flinn IW, van der Jagt R, Kahl B, et al. First-Line Treatment of Patients With Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma With Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. J Clin Oncol. 2019;37(12):984-991.

29. Chen RW, Li H, Bernstein SH, et al. RB but not R-HCVAD is a feasible induction regimen prior to auto-HCT in frontline MCL: results of SWOG Study S1106. Br J Haematol. 2017;176(5):759-769.

30. Kamdar M, Li H, Chen RW, et al. Five-year outcomes of the S1106 study of R-hyper-CVAD vs R-bendamustine in transplant-eligible patients with mantle cell lymphoma. Blood Adv. 2019;3(20):3132-3135.

31. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol. 2009;27(8):1209-1213.

32. Abrisqueta P, Scott DW, Slack GW, et al. Observation as the initial management strategy in patients with mantle cell lymphoma. Ann Oncol. 2017;28(10):2489-2495.

33. Calzada O, Switchenko JM, Maly JJ, et al. Deferred treatment is a safe and viable option for selected patients with mantle cell lymphoma. Leuk Lymphoma. 2018;59(12):2862-2870.
34. Kumar A, Ying Z, Alperovich A, et al. Clinical presentation determines selection of patients for initial observation in mantle cell lymphoma. Haematologica. 2019;104(4):e163-e166.
35. Cerhan JR, Link BK, Habermann TM, et al. Cohort Profile: The Lymphoma Specialized Program of Research Excellence (SPOR) Molecular Epidemiology Resource (MER) Cohort Study. Int J Epidemiol. 2017;46(6):1753-1754.
36. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008;111(2):558-565.
37. Herrmann A, Hoster E, Zwingers T, et al. Improvement of overall survival in advanced stage mantle cell lymphoma. J Clin Oncol. 2009;27(4):511-518.
38. Epperla N, Hamadani M, Fenske TS, Costa LJ. Incidence and survival trends in mantle cell lymphoma. Br J Haematol. 2018;181(5):703-706.
39. Abrahamsson A, Dahle N, Jerkeman M. Marked improvement of overall survival in mantle cell lymphoma: a population based study from the Swedish Lymphoma Registry. Leuk Lymphoma. 2011;52(10):1929-1935.
40. Abrahamsson A, Albertsson-Lindblad A, Brown PN, et al. Real world data on primary treatment for mantle cell lymphoma: a Nordic Lymphoma Group observational study. Blood. 2014;124(8):1288-1295.
41. Smith A, Roman E, Appleton S, et al. Impact of novel therapies for mantle cell lymphoma in the real world setting: a report from the UK’s Haematological Malignancy Research Network (HMRN). British Journal of Haematology. 2018;118(1):215-228.
42. Rummel MJ, Knauf W, Goerner M, et al. Two years rituximab maintenance vs. observation after first-line treatment with bendamustine plus rituximab (B-R) in patients with mantle cell lymphoma: First results of a prospective, randomized, multicenter phase II study (a subgroup study of the StiL NHL7-2008 MAINTAIN trial). Journal of Clinical Oncology. 2016;34(15_suppl):7503-7503.
43. Hill BT, Switchenko JM, Martin P, et al. MAINTENANCE RITUXIMAB IS ASSOCIATED WITH IMPROVED OVERALL SURVIVAL IN MANTLE CELL LYMPHOMA PATIENTS RESPONDING TO INDUCTION THERAPY WITH BENDAMUSTINE + RITUXIMAB (BR). Hematological Oncology. 2019;37(S2):405-407.
44. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol. 2013;31(29):3688-3695.
45. Witzig TE, Luigi Zinzani P, Habermann TM, et al. Long-term analysis of phase II studies of single-agent lenalidomide in relapsed/refractory mantle cell lymphoma. Am J Hematol. 2017;92(10):E575-E583.
46. Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol. 2012;13(7):716-723.
47. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507-516.
48. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood. 2015;126(6):739-745.
49. Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. Lancet Oncol. 2016;17(1):48-56.
50. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018;391(10121):659-667.
51. Wang M, Rule S, Zinzani PL, et al. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma. Leukemia. 2019;33(11):2762-2766.
52. Song Y, Zhou K, Zou D, et al. Treatment of Patients with Relapsed or Refractory Mantle-Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase. *Clin Cancer Res.* 2020;26(16):4216-4224.

53. Davids MS, Roberts AW, Seymour JF, et al. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. *J Clin Oncol.* 2017;35(8):826-833.

54. Eyre TA, Walter HS, Iyengar S, et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. *Haematologica.* 2019;104(2):e68-e71.

55. Zhao S, Kanagal-Shamanna R, Navsaria L, et al. Efficacy of venetoclax in high risk relapsed mantle cell lymphoma (MCL) - outcomes and mutation profile from venetoclax resistant MCL patients. *Am J Hematol.* 2020;95(6):623-629.

56. Tam CS, Anderson MA, Pott C, et al. Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma. *N Engl J Med.* 2018;378(13):1211-1223.

57. Ruan J, Martin P, Shah B, et al. Lenalidomide plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma. *N Engl J Med.* 2015;373(19):1835-1844.

58. Ruan J, Martin P, Christos P, et al. Five-year follow-up of lenalidomide plus rituximab as initial treatment of mantle cell lymphoma. *Blood.* 2018;132(19):2016-2025.

59. Wang ML, Jain P, Lee HJ, et al. Frontline Treatment with Ibrutinib Plus Rituximab (IR) Followed By Short Course R-Hypercvad/MTX Is Extremely Potent and Safe in Patients (age ≤ 65 years) with Mantle Cell Lymphoma (MCL) - Results of Phase-II Window-1 Clinical Trial. *Blood.* 2019;134(Supplement_1):3987-3987.

60. Le Gouill S, Morschhauser F, Chiron D, et al. Ibrutinib, obinutuzumab, and venetoclax in relapsed and untreated patients with mantle cell lymphoma: a phase 1/2 trial. *Blood.* 2021;137(7):877-887.
Figure 1. EFS and OS in the two different eras.
(A) EFS in Era 1 vs Era 2.
(B) OS in Era 1 vs Era 2.

Figure 2. EFS and OS in patients 65 years or younger in the two different eras.
(A) EFS of patients ≤65 in Era 1 vs Era 2.
(B) OS of patients ≤65 in Era 1 vs Era 2.
(C) EFS of patients ≤65 who received standard immunochemotherapy in Era 1 vs Era 2.
(D) OS of patients ≤65 who received standard immunochemotherapy in Era 1 vs Era 2.
(E) EFS of patients ≤65 who received non-standard systemic therapy or non-systemic therapy in Era 1 vs Era 2.
(F) OS of patients ≤65 who received non-standard systemic therapy or non-systemic therapy in Era 1 vs Era 2.

Figure 3. EFS and OS in patients older than 65 years in the two different eras.
(A) EFS of patients >65 in Era 1 vs Era 2.
(B) OS of patients >65 in Era 1 vs Era 2.
(C) EFS of patients >65 who received R-CHOP/R-CHOP-like or R-Benda in Era 1 vs Era 2.
(D) OS of patients >65 who received R-CHOP/R-CHOP-like or R-Benda in Era 1 vs Era 2.
(E) EFS of patients >65 who received non-standard systemic therapy or non-systemic therapy in Era 1 vs Era 2.
(F) OS of patients >65 who received non-standard systemic therapy or non-systemic therapy in Era 1 vs Era 2.
### Table 1. Clinical characteristics of MCL patients in two different eras

|                      | Total (N=343) | Era 1 (N=175) | Era 2 (N=168) | P value |
|----------------------|---------------|---------------|---------------|---------|
| **Sex**              |               |               |               | 0.64    |
| Female               | 78 (22.7%)    | 38 (21.7%)    | 40 (23.8%)    |         |
| Male                 | 265 (77.3%)   | 137 (78.3%)   | 128 (76.2%)   |         |
| **Age**              |               |               |               | 0.77    |
| Median (range)       | 64 (32-96)    | 64 (41-95)    | 64 (32-96)    |         |
| ≤65                  | 184 (53.6%)   | 93 (53.1%)    | 91 (54.2%)    | 0.85    |
| >65                  | 159 (46.4%)   | 82 (46.9%)    | 77 (45.8%)    |         |
| **ECOG Performance Status** |         |               |               | 0.44    |
| 0-1                  | 309 (90.4%)   | 156 (89.1%)   | 153 (91.6%)   |         |
| ≥2                   | 33 (9.6%)     | 19 (10.9%)    | 14 (8.4%)     |         |
| Missing              | 1             | 0             | 1             |         |
| **LDH**              |               | 0.20          |               |         |
| Normal               | 190 (67.1%)   | 88 (62.0%)    | 102 (72.3%)   |         |
| Elevated             | 93 (32.9%)    | 54 (38.0%)    | 39 (27.7%)    |         |
| Missing              | 60            | 33            | 27            |         |
| **Simplified MIPI**  |               | 0.44          |               |         |
| Low (0-3)            | 79 (27.6%)    | 44 (30.6%)    | 35 (24.6%)    |         |
| Intermediate (4-5)   | 105 (36.7%)   | 53 (36.8%)    | 52 (36.6%)    |         |
| High (6-12)          | 102 (35.7%)   | 47 (32.6%)    | 55 (38.7%)    |         |
| Missing              | 57            | 31            | 26            |         |

MCL, mantle cell lymphoma; LDH, lactate dehydrogenase; MIPI, MCL internation prognostic index.

### Table 2. Treatment pattern of MCL in two different eras

|                      | Age ≤65 (n=184) | Age >65 (n=159) |
|----------------------|----------------|----------------|
| **Frontline treatment** | Era 1 (n=93) | Era 2 (n=91) | P value | Era 1 (n=82) | Era 2 (n=77) | P value |
| R-HyperCVAD          | 15 (16.1%)    | 8 (8.8%)     | <0.001  | 2 (2.4%)     | 0 (0.0%)     | <0.001  |
| Nordic regimen or R-CHOP/R-DHAP | 1 (1.1%) | 24 (26.4%) | 0 (0.0%) | 2 (2.6%) |
| R-CHOP or R-CHOP-like | 60 (64.5%) | 32 (35.2%) | 32 (39.0%) | 11 (14.3%) |
| R-Benda              | 0 (0.0%)      | 11 (12.1%)   | 0 (0.0%) | 38 (49.4%)   |
| Non-standard systemic therapy | 8 (8.6%) | 3 (3.3%) | 30 (36.6%) | 10 (13.0%) |
| R-2CdA               | 5             | 1             | 21       | 5             |
| R-FCM                | 1             | 1             | 3        | 1             |
| R only               | 0             | 1             | 5        | 4             |
| Chemo without R      | 2             | 0             | 1        | 0             |
| Non-systemic treatment |  |  |  |  |  |
|------------------------|----------------|----------------|----------------|----------------|----------------|
|                        | 9 (9.7%)       | 13 (14.3%)     | 18 (22.0%)     | 16 (20.8%)     |
| Surgery                | 3              | 2              | 0              | 1              |
| RT                     | 0              | 0              | 3              | 2              |
| Observation only       | 6              | 0              | 15             | 13             |

| ASCT consolidation     | 0.87           | 0.84           |
| Yes                    | 42             | 40             | 6 (7.3%)       | 5 (6.5%)       |
|                        | (45.2%)        | (44.0%)        |                |                |

| Induction regimen before ASCT |  |  |  |  |
| R-HyperCVAD | 2 | 6 | 0 | 0 |
| Nordic regimen or R-CHOP/R-DHAP | 1 | 15 | 0 | 1 |
| R-CHOP or R-CHOP-like R-Benda | 39 | 15 | 6 | 2 |
|                        | 0 | 4 | 0 | 2 |

| No                     | 51 | 51 | 76 (92.7%) | 72 (93.5%) |
|                        | (54.8%) | (56.0%) |                |                |

| Rituximab maintenance | 0.97           | 0.38           |
| Yes                   | 5 (5.4%)       | 5 (5.5%)       | 8 (9.8%)       | 11 (14.3%)     |
|                        | (5.4%)         | (5.5%)         | (9.8%)         | (14.3%)        |

| No                     | 88 | 86 | 74 (90.2%) | 66 (85.7%) |
|                        | (94.6%) | (94.5%) |                |                |

MCL, mantle cell lymphoma; ASCT, autologous transplant.
|                                | Younger patients (≤65 years) | Older patients (>65 years) |
|--------------------------------|------------------------------|---------------------------|
|                                | Era 1 | Era 2 | Log-rank P | sMIPI-adjusted HR (95% CI) | Cox regression P | Era 1 | Era 2 | Log-rank P | sMIPI-adjusted HR (95% CI) | Cox regression P |
| **All patients**               |       |       |            |                             |                  |       |       |            |                             |                  |
| Median EFS (95% CI), years     | 2.9   | 4.3   | 0.010      | 0.60 (0.41-0.87)             | 0.007            | 2.0   | 3.0   | 0.051      | 0.73 (0.51-1.04)             | 0.086            |
| 5-year EFS (95% CI), %         | 34.3  | 50.0  |            | 25.4 (17.5-36.9)             | 0.051            | 25.4  | 37.5  |            | 37.5 (28.1-50.1)             |                  |
| 5-year OS (95% CI), %          | 68.8  | 81.6  | 0.017      | 0.55 (0.33-0.90)             | 0.018            | 48.2  | 53.2  | 0.136      | 0.79 (0.53-1.19)             | 0.259            |
| **Patients treated with standard immunochemotherapy* | | | | | |
| Median EFS (95% CI), years     | 3.1   | 6.4   | 0.012      | 0.56 (0.37-0.85)             | 0.007            | 1.3   | 4.2   | 0.008      | 0.42 (0.24-0.73)             | 0.002            |
| 5-year EFS (95% CI), %         | 36.8  | 53.8  |            | 25.0 (13.7-45.6)             | 0.233            | 25.0  | 44.6  |            | 44.6 (32.6-61.1)             |                  |
| 5-year OS (95% CI), %          | 69.7  | 83.7  | 0.013      | 0.48 (0.27-0.84)             | 0.010            | 46.9  | 53.0  | 0.076      | 0.54 (0.30-0.95)             | 0.033            |
| **Patients treated with non-standard systemic therapy or non-systemic therapy** | | | | | |
| Median EFS (95% CI), years     | 1.9   | 3.3   | 0.424      | 0.85 (0.35-2.08)             | 0.721            | 2.3   | 1.7   | 0.233      | 1.57 (0.93-2.66)             | 0.091            |
| 5-year EFS (95% CI), %         | 23.5  | 28.6  |            | 24.4 (14.8-40.4)             | 0.233            | 23.5  | 23.1  |            | 23.1 (11.4-46.6)             |                  |
| 5-year OS (95% CI), %          | 64.7  | 68.6  | 0.767      | 1.65 (0.46-5.94)             | 0.447            | 49.1  | 50.0  | 0.980      | 1.24 (0.67-2.29)             | 0.501            |

*Regimens included R-HyperCVAD, Nordic regimen or R-CHOP/R-DHAP, R-CHOP or R-CHOP-like, and R-Benda. Data in older patients were based on R-CHOP or R-CHOP-like and R-Benda outcomes only.

†EFS, event-free survival; OS, overall survival; sMIPI, simplified mantle cell lymphoma internation prognostic index.
