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Multi-center analysis of practice patterns and outcomes of younger and older patients with mantle cell lymphoma in the rituximab era

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Abstract

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AUTHOR CONTRIBUTIONS

All authors participated in data collection and manuscript preparation and approved the final draft. R.K., J.M.S. and J.B.C. analyzed and interpreted the data. J.M.S. and S.G. performed statistical analyses.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Clinical outcomes and predictors of survival in patients with newly diagnosed mantle cell lymphoma (MCL) treated in the rituximab era (2000–2015) at 12 US academic centers were assessed to identify determinants of survival across age groups. Objectives were to characterize and compare practice patterns, outcomes and prognostic factors for survival in younger patients (age < 65) and older patients (age ≥ 65 years). Among 1162 patients included, 697 were younger and 465 were older. In younger patients, 2-year progression free survival (PFS) and overall survival (OS) rates were 79% and 92% respectively; blastoid histology, ECOG ≥ 2, and lack of maintenance rituximab (MR) remained statistically relevant to poor OS on univariate analysis (UVA) and multivariate analysis (MVA). In older patients, 2-year PFS and OS rates were 67% and 86% respectively; lack of maintenance rituximab remained significantly associated with inferior PFS and OS on UVA and MVA ($p < 0.001$). Two-year PFS rates were 79%, and 67% and 2-year OS rates were 92% and 86% for ages < 65 and ≥ 65 respectively ($p < 0.001$). First-line high-dose cytarabine exposure and/or MR lessened the negative impact of age on survival. Taken collectively, survival outcomes for older patients remain inferior to those of younger patients in the rituximab era. However, maintenance rituximab and potentially high-dose cytarabine-based induction can mitigate the negative impact of age on survival.

1 | INTRODUCTION

Mantle cell lymphoma (MCL) is an aggressive disease that comprises approximately 6% of all B-cell non-Hodgkin lymphoma and is classically defined by the t(11;14)(q13;q32) translocation resulting in overexpression of cyclin D1.^{1,2} A “standard” first-line treatment approach has not been established with therapeutic decisions determined by the patient’s age, performance status (PS), and comorbidities.^{3,4}

In younger patients, autologous hematopoietic cell transplantation (AHCT) may be associated with improved survival outcomes.^{5–8} Randomized trials incorporating cytarabine with induction prior to AHCT have yielded 4–5 year overall survival (OS) rates of over 75%.^{6,9} However, by design, these trials excluded patients over the age of 65. With a median age of 68 years of age, therapeutic intensity poses challenges in the majority of patients with MCL. Intensive therapies including AHCT are associated with significant toxicity often making transplant unfeasible for older patients. Elderly and/or unfit patients are typically treated with less intensive therapies and rituximab maintenance, the latter supported by the results of the phase III randomized MCL Elderly trial.¹⁰ However, it remains unclear whether the effectiveness of rituximab maintenance is influenced by choice of frontline chemoimmunotherapy.^{10–12}

Several studies have evaluated targeted agents including bortezomib or lenalidomide with or without a chemoimmunotherapy backbone for frontline treatment with some benefit, although toxicity has remained a challenge particularly with chemotherapy-based combinations.^{13–16} Additionally, trials evaluating chemo-immunotherapy with Bruton’s tyrosine kinase inhibitors (BTKis) in MCL are underway (NCT 01776840). Despite these recent efforts, the prognosis for MCL remains sub-optimal for those who are elderly and/or frail and not candidates for aggressive therapies. Improved therapeutic strategies and predictors of survival in the older population need to be better defined and would likely

inform clinical practice and the design of impactful therapeutic trials in the future. Herein, we retrospectively assessed practice patterns, clinical outcomes, and predictors of relapse and survival in patients with MCL, and looked separately at younger patients defined as age < 65 and older patients defined as age ≥ 65 years, treated in the rituximab era. We compared differences in clinical characteristics and frontline treatment approaches in younger and older cohorts to identify determinants of improved survival across age groups. We showed that although survival remains superior in our younger patients, differences in outcomes according to age may be mitigated with the incorporation of rituximab maintenance and potentially high-dose cytarabine-based induction.

2 | METHODS

2.1 | Patients and data collection

We retrospectively collected data across 12 academic institutions for patients with newly diagnosed MCL treated between 2000 and 2015 to account for more conventional use of rituximab and allow for sufficient follow-up. The diagnosis of MCL was made by a hematopathologist at each institution as per routine clinical practice. From this dataset, a younger cohort, defined as < 65 years of age and an older cohort, defined as ≥ 65 years of age at the time of diagnosis, were identified. Data were collected for each patient on baseline characteristics and treatment, use of transplantation, and outcome. The MCL international prognostic index (MIPI) score was calculated for each patient with sufficient data as previously published.¹⁷ Response to induction treatment was determined by each participating center using data available from the time of treatment. The protocol was approved by the institutional review board of each participating center.

2.2 | Statistics

The primary objective of this analysis was to characterize practice patterns and survival outcomes in an elderly MCL population and secondarily to assess prognostic and predictive factors of survival across age groups. Variables examined for impact on survival included age, sex, ECOG PS, serum LDH, MIPI score and treatment received. We reported differences in baseline characteristics, prognostic markers as well as treatment received between age groups (< 65 and ≥ 65 years) using Fisher Exact and chi-square tests as appropriate. Cox multivariable regression analyses were performed to determine impact of demographic and clinical variables on survival outcomes. Survival curves were calculated using the Kaplan–Meier method. Notably, for multivariate analyses (MVA), we did exclude variables with less than 50% data capture.

3 | RESULTS

3.1 | Patients and disease characteristics

Of 1162 total patients with MCL, 697 patients were < 65 years of age and 465 patients were ≥ 65 years of age. Demographic and clinical factors for our younger and older patients are shown in Table 1.

In the younger cohort, 527 (76%) were male. In 395 younger patients with quantifiable MIPI, 218 (55%), 108 (27%) and 69 (17%) had low, intermediate and high-risk MIPI respectively. In the older cohort, 320 (69%) were male. In 281 older pts with quantifiable MIPI, 23 (8%), 110 (39%) and 148 (53%) had low, intermediate and high-risk MIPI respectively. Younger patients were more likely to have bone marrow (BM) involvement ($p = 0.031$), a better performance status ($p = 0.001$) and as expected, less likely to have diabetes, coronary artery disease, heart failure and chronic kidney disease as co-morbid conditions ($p < 0.001$ – 0.003).

3.2 | Treatment data

Younger patients: Median time from diagnosis to first treatment was 31 days (range 0–5576 days). In 643 patients < 65 years old at diagnosis with documented frontline treatment, 268 (42%) were treated with a high-dose cytarabine (HD-AraC) containing regimen (Nordic, R-CHOP/DHAP, R-HyperCVAD, BR/R-AraC, R-DHAP) and nine (1%) with a low-dose cytarabine (LD-AraC) regimen (R-BAC), 188 (29%) received R-CHOP ± methotrexate (MTX), 88 (14%) received bendamustine-rituximab (BR), five (< 1%) received lenalidomide and 85 (13%) received other treatments that excluded Bruton's tyrosine kinase inhibitors (BTKis). No patients received a BTKi as first line treatment. In 595 patients for whom autologous transplant (AHCT) status was captured, 350 (59%) received AHCT after frontline induction. In 562 patients with available data on maintenance therapy, 199 (35%) received maintenance rituximab (MR) including 94 patients post AHCT.

For younger patients with relapsed/refractory disease, treatment data across all subsequent lines of therapy were available for 257 patients who either relapsed ($n = 224$) or did not respond with either stable disease or progression after initial therapy ($n = 33$). Sixty-seven (26%) were treated with BTKi/BTKi combinations; 107 (42%) received salvage chemotherapy (BR or other); and 51 (20%) received lenalidomide and/or bortezomib based therapy. Forty-seven (18%) patients received an allogeneic hematopoietic stem cell transplantation (alloHCT) and one (< 1%) an AHCT after first relapse. One hundred seventy of 523 patients (32.5%) with data captured pertaining to clinical trial participation were enrolled on a clinical trial at some point during their disease course.

Older patients: Frontline treatment data was available in 407 patients including 222 patients between 65–69 years and 243 patients ≥ 70 years of age. Median time from diagnosis to first treatment was 31 days (range 0–2611 days). Fifty-seven (14%) were treated with a HD-AraC containing regimen (Nordic, R-CHOP/DHAP, R-HyperCVAD, BR/R-AraC, R-DHAP) and eight (2%) with a LD-AraC regimen (R-BAC). In the older cohort receiving HD-AraC ($n = 57$), 48 (84%) patients were between ages 65–69 years, and nine (16%) patients ≥ 70 years of age. Ninety-three (23%) received R-CHOP ± MTX, 148 (36%) received BR, nine (2%) received lenalidomide and 92 (23%) received other treatments that excluded BTKis. No patients received a BTKi as first line treatment. Transplant status was captured in 369 patients including 186 (50%) patients between ages 65–69 and 183 (50%) patients ≥ 70 years of age. Eighty-eight (24%) received AHCT after frontline induction. In 351 patients with available data on maintenance therapy, 155 (44%) received maintenance rituximab

(MR) including 22 post AHCT. In the older cohort consolidated with AHCT ($n = 88$), 71 (80%) patients were between ages 65–69 years and 17 (20%) patients ≥ 70 years of age.

For older patients, treatment data across all subsequent lines of therapy were available for 157 patients who either relapsed ($n = 115$) or did not respond with either stable disease or progression with initial therapy ($n = 42$). Fifty-eight (37%) were treated with BTKi/BTKi combinations; 49 (31.2%) received salvage chemotherapy (BR or other); and 25 (16%) received lenalidomide and/or bortezomib based therapy. One hundred of 350 patients (29%) with data captured pertaining to clinical trial participation were enrolled on a clinical trial at some point during their disease course. Eight (5%) patients received an alloHCT and two (1%) an AHCT after first relapse.

3.3 | Response data and predictors of early relapse

In our younger cohort, the median follow-up for the cohort was 4.0 years. In 559 patients with response data available, 409 (73%) had a CR, 117 (21%) a PR, 10 (2%) SD and 23 (4%) PD after completion of front-line treatment. Eighty-one patients (12%) had early relapse/primary refractory disease (ER/RD) defined as progression within 12 months of diagnosis or stable/progressive disease (SD/PD) as best response to induction therapy. Significant predictors of ER/RD on univariate analysis included high risk MIPI ($p = 0.004$), blastoid histology ($p < 0.001$) and Ki-67 $> 30\%$ ($p = 0.004$); enrollment on clinical trial with initial therapy was protective against ER/RD ($p = 0.014$).

In our older cohort: the median follow-up for the cohort was 2.7 years. In 357 patients with response data available, 242 (68%) had a CR, 73 (20%) a PR, 16 (4%) an SD and 26 (7%) a PD. Eighty-one (33%) patients with CR and 49 (67%) with PR to frontline therapy progressed during the observation period.

Sixty-six of 370 evaluable patients (18%) had early relapse/primary refractory disease (ER/RD). Significant predictors of ER/RD on univariate analysis included blastoid histology ($p < 0.001$) and Ki-67 $> 30\%$ ($p = 0.004$). Both age cohorts were comprised of patients with similar rates of high-risk features such as blastoid histology, presence of p53, complex karyotype and Ki-67 of $> 30\%$.

3.4 | Survival outcomes

In younger patients, PFS rates at 1 and 2 years were 88.7% and 78.6% respectively. Overall survival rates at 1 and 2 years were 96.8% and 92.1% respectively. On unadjusted univariate analysis in all younger patients, high-risk MIPI, advanced stage, BM involvement, Ki-67 $> 30\%$, > 3 cytogenetic abnormalities, and lack of HSCT were associated with inferior PFS ($p < 0.001$ – 0.034). High-risk MIPI, ECOG ≥ 2 , BM involvement, blastoid histology, and lack of rituximab maintenance were associated with inferior OS ($p = < 0.001$ – 0.038). Consolidation with AHCT in CR1 did not impact OS. On MVA, ECOG ≥ 2 , blastoid histology, and lack of rituximab maintenance remained statistically relevant to poor OS.

Survival in younger AHCT patients was similar irrespective of induction regimen used: 2 year OS with BR ($n = 30$) versus HD-AraC ($n = 183$) versus R-CHOP $\pm$ MTX ($n = 114$) was 100% versus 94.4% versus 93.7% ($p = 0.99$). Survival was also compared in patients

who were treated with combined AHCT and MR (n = 94) versus MR alone (n = 102) versus AHCT alone (n = 204) versus neither (n = 110): 2-year PFS rates were 89.3% versus 85.4% versus 84.1% versus 56.4% ($p < 0.001$) and 2 year OS rates were 97.5% versus 98.9% versus 94.2% versus 85.6% ($p < 0.02$) respectively (Figure 1).

For a more direct comparison, we observed no difference in PFS ($p = 0.43$) and OS ($p = 0.45$) in younger patients treated with AHCT followed by MR (n = 94) versus MR alone (n = 102).

Although interpretability is limited by small sample sizes, we further compared PFS (Figure 2) and OS (Figure S1) according to induction regimens more routinely used in current practice with or without MR and/or AHCT: for BR alone (n = 23) versus BR + MR (n = 21) versus BR + AHCT (n = 25) versus BR + AHCT + MR (n = 4), 2-year PFS rates were 56% versus 79% versus 79% versus 100% ($p = 0.08$) and 2-year OS rates were 89% versus 100% versus 100% versus 100% respectively ($p = 0.3$). For HD-AraC alone (n = 36) versus HD-AraC + MR (n = 25) versus HD-AraC + AHCT (n = 126) versus HD-AraC + AHCT + MR (n = 42), 2-year PFS rates were 64% versus 92% versus 87% versus 86% ($p = 0.04$) and 2-year OS rates were 87% versus 100% versus 94% versus 97% respectively ($p = 0.5$). For R-CHOP ± MTX alone (n = 26) versus R-CHOP ± MTX + MR (n = 23) versus R-CHOP ± MTX + AHCT (n = 42) versus R-CHOP ± MTX + AHCT + MR (n = 37), 2-year PFS rates were 43.5% versus 86.1% versus 83.3% versus 94.4% ($p < 0.001$) and 2-year OS rates were 83.8% versus 100% versus 95.2% versus 97.2% respectively ($p = 0.039$).

In older patients, PFS rates at 1 and 2 years were 82.4% and 67.1% respectively. The OS rates at 1 and 2 years were 92.7% and 85.5% respectively. Two-year OS rates for ER/RD patients versus durable responders (non ER/RD pts) was 55 versus 91% respectively ($p < 0.001$). On unadjusted univariate analysis in all older patients, ECOG 2, advanced stage, BM involvement, blastoid histology, > 3 cytogenetic abnormalities, and lack of rituximab maintenance were associated with inferior PFS ($p < 0.001$ –0.028). High-risk MIPI, ECOG 2, BM involvement, blastoid histology, > 3 cytogenetic abnormalities, and lack of rituximab maintenance were associated with inferior OS ($p = 0.012$ – < 0.001). The 2-year PFS rates were 81% and 58% and 2-year OS rates were 96% and 80%, with and without MR, respectively ($p < 0.001$). In older patients treated with BR frontline, MR offered a PFS ($p < 0.001$) and OS ($p = 0.004$) benefit noting that only seven (5%) of these 148 patients also underwent AHCT. After MVA, MR remained significantly associated with both improved PFS and OS ($p < 0.001$) while high dose cytarabine exposure was associated with a trend for improved OS ($p = 0.065$) in older patients (Table 2).

In older patients, AHCT in first remission did not impact PFS or OS. Overall survival in older AHCT patients was similar irrespective of induction regimen used: 2 year OS with BR (n = 7) versus HD-AraC (n = 26) versus R-CHOP ± MTX (n = 48) was 100% versus 87.1% versus 95.7% ($p = 0.51$).

Survival was compared in patients who were treated with both AHCT and MR (n = 22) versus MR alone (n = 129) versus AHCT alone without MR (n = 56) versus neither (n = 109): 2-year PFS rates were 82.7% versus 79.6% versus 75.5% versus 45.9% ($p < 0.001$)

and 2-year OS rates were 100% versus 95.6% versus 86.8% versus 74.8% ($p < 0.001$) respectively (Figure 1). However, similar to what was seen in the younger cohort, we observed no difference in PFS ($p = 0.3$) and OS ($p = 0.95$) in older patients by direct comparison of survival in those treated with AHCT followed by maintenance rituximab ($n = 22$) versus maintenance rituximab alone ($n = 129$).

Once again, we further compared PFS (Figure 2) and OS (Figure S1) according to induction regimen routinely used in current practice with or without MR and/or AHCT: for BR alone ($n = 56$) versus BR + MR ($n = 59$) versus BR + AHCT ($n = 4$) versus BR + AHCT + MR ($n = 3$), 2-year PFS rates were 43% versus 78% versus 50% versus not evaluable ($p = 0.006$) and 2-year OS rates were 70% versus 96% versus 100% versus 100% respectively ($p = 0.002$). For HD-AraC alone ($n = 10$) versus HD-AraC + MR ($n = 12$) versus HD-AraC + AHCT ($n = 23$) versus HD-AraC + AHCT + MR ($n = 3$), 2-year PFS rates were 67% versus 75% versus 81% versus 100% ($p = 0.7$) and 2-year OS rates were 67% versus 100% versus 85% versus 100% respectively ($p = 0.16$). For R-CHOP ± MTX alone ($n = 9$) versus R-CHOP ± MTX + MR ($n = 16$) versus R-CHOP ± MTX + AHCT ($n = 24$) versus R-CHOP ± MTX + AHCT + MR ($n = 14$), 2-year PFS rates were 22.2% versus 73.3% versus 87.1% versus 83.3% ($p < 0.001$) and 2-year OS rates were 66.7% versus 93.3% versus 91.7% versus 100% respectively ($p = 0.014$).

We also compared PFS and OS across young and older age cohorts. The 2-year PFS rates were 79%, and 67% and the 2-year OS rates were 92% and 86% for ages < 65 and ≥ 65 respectively ($p < 0.001$, Figure 3). Older patients that were not exposed to HD-AraC or MR had inferior PFS ($p = 0.001$) and OS ($p < 0.001$) as compared to younger patients. However, there was no difference in 2-year PFS and OS rates in younger and older patients treated with HD-AraC (Figure 3) or MR (Figure 3). We also evaluated the impact of salvage therapies across age groups and demonstrated that although 2-year PFS was similar in young and older age cohorts, 2-year OS remained inferior in older patients despite BTKi exposure (93.5 vs. 77.7%, $p = 0.04$; Figure S2).

4 | DISCUSSION

To our knowledge, this is the first retrospective analysis describing outcomes in older patients with MCL in the rituximab era. We chose age ≥ 65 to define older patients in our cohort as larger prospective studies that have evaluated and reported on intensive chemo-immunotherapy and more specifically the use of high dose chemotherapy with stem cell rescue in MCL, have typically excluded patients above the age of 65.^{8,9} In this large cohort, we demonstrate that survival outcomes in older patients are poor and remain inferior to younger patients with MCL.

Most younger and older patients were treated with chemoimmunotherapy upfront with R-CHOP favored given the time period of data capture. Those with early relapse/primary refractory disease (ER/RD) had dismal OS as compared with those who responded to frontline therapy and/or maintained a more durable response of ≥ 12 months. Factors associated with worse OS in both younger and older ER/RD cohorts included blastoid histology ($p < 0.001$) and Ki-67 $> 30\%$ ($p < 0.001$ – 0.004). These findings support the

need for enrichment of such populations in clinical trials focused on identifying effective novel therapeutics. We did not identify correlations between chemotherapy resistance and other high-risk features such as the presence of *TP53* mutations and/or complex karyotype (defined as > 3 cytogenetic abnormalities). However, results may have been skewed by limited data capture for such variables. As expected, we found that the lack of either AHCT or maintenance rituximab significantly correlated with ER/RD disease as patients with inherent chemo-immunotherapy resistance are not typically moved on to transplant consolidation and/or maintenance.

In our older cohort, those who received maintenance rituximab derived improvement in OS on MVA independent of consolidation with AHCT. We demonstrated that rituximab maintenance after BR induction impacted survival in older patients essentially in the absence of AHCT as almost all patients treated with BR in this age cohort did not receive AHCT consolidation. This is in contrast to the StiL study that evaluated maintenance rituximab in an MCL subset treated with BR. The median age of the StiL MCL subset was 70 years, reflective of an older population. No survival benefit was noted with maintenance rituximab in this study leaving the question of rituximab maintenance after BR in older patients unsettled.¹² Furthermore, we could not discern the optimal schedule and duration of rituximab maintenance for this cohort given the retrospective nature of these data.

We also demonstrated that exposure to frontline high-dose cytarabine and/or maintenance rituximab in older patients appeared to mitigate differences in outcome between younger (age < 65 years) and older patients (age ≥ 65 years). We did not identify a survival disadvantage with the use of high versus low-dose cytarabine in our dataset although interpretability is limited by the small number of patients in the latter group. Our findings are in line with several trials that point to the benefit of cytarabine upfront, irrespective of age.^{6,9,18,19} Building on results of the MCL Younger trial which demonstrated success of adding high-dose cytarabine to induction therapy in younger fit patients, Visco et al. explored a lower dose of cytarabine with a BR backbone in elderly patients.^{3,6,19} In patients with a median age of 71, this approach resulted in acceptable hematological toxicity that allowed 95% of patient to complete four cycles of therapy and achieved a 3 year PFS of approximately 75%.^{3,19} A number of randomized trials continue to build on these findings by adding targeted adjuncts including ECOG 4181 (NCT04115631). Using the BR platform, the ECOG 4181 trial will explore adjunctive BTKi and/or cytarabine in patients up to the age of 70 and may yield sustainable remissions translatable to all ages. This trial may shed some light on whether cytarabine is necessary as a component of induction in either the younger or older age groups when novel agents such as BTK inhibitors are incorporated.

Overall, our findings support the use of maintenance rituximab irrespective of age, much like the LYSA Group and European MCL Elderly Trials^{9,10} and also rationalize ongoing trials evaluating novel maintenance strategies. In older patients, such efforts include the SHINE study with ibrutinib-rituximab maintenance post induction with BR with or without ibrutinib (NCT 01776840) in patients >65 years of age as well as the MCL-R2 Elderly trial that will not only evaluate the use of cytarabine (R-CHOP ± cytarabine induction) but also compare maintenance strategies of lenalidomide with rituximab versus rituximab monotherapy (NCT 01865110) in patients >60 years of age. These studies will likely

inform whether targeted agents represent more effective and safe alternatives to rituximab maintenance in the frontline setting.

We sought to determine the impact of AHCT in our younger and older patients. In our older cohort, AHCT did not impact PFS and OS. We showed that AHCT combined with rituximab maintenance offered no benefit in survival over rituximab maintenance alone across all age groups. This lack of survival benefit with AHCT in our younger patients is reminiscent of prior reports which showed no benefit to AHCT after intensive high-dose cytarabine containing induction.²⁰ Additionally, we did not identify a difference in survival according to induction therapy used in patients undergoing AHCT. It is unclear how the use of R-CHOP induction without cytarabine in the majority of our younger and older patients impacted these findings. With the inherent limitations of this retrospective dataset, the question of whether combined AHCT consolidation and rituximab maintenance offers benefit over maintenance alone remains a valid one. The utility of maintenance $\pm$ AHCT in minimal residual disease negative first CR is being assessed by the cooperative group trial EA4151 (NCT 03267433) and it is expected that the majority of patients included will have received induction with a high-dose cytarabine containing regimen. While the trial excludes patients over the age of 70, we expect that results from the EA4151 trial will guide management in fit older patients deemed candidates for transplant.

In an attempt to capture outcomes with treatment as a combination approach reflective of more routine practice, we compared survival outcomes in patients treated with chemo-immunotherapy induction followed by AHCT and/or MR in both age cohorts. In older patients, we showed that BR + MR $\pm$ AHCT performed better than BR alone for impact on PFS ($p = 0.006$) and OS ($p = 0.002$). Though not statistically significant, similar trends were seen in the younger cohort treated with BR induction. However, provider treatment selection bias typically associated with a retrospective dataset of this nature limits the interpretation of our observations across induction and consolidative strategies.

Lastly, we did obtain data on salvage treatment when available. Only a small number of patients received BTKi salvage therapy and no patients were managed with chimeric antigen receptor (CAR) T-cell therapy. As such, our data do not reliably reflect the potential gains in survival achieved with the introduction of BTKis and cellular therapies for relapsed/refractory disease.^{21–24} That being said, the objective of our study was to characterize treatment approaches and determinants of outcomes in the frontline setting across all ages. Accordingly, our findings maintain relevance to current clinical practice for treatment naïve MCL.

5 | CONCLUSION

In this large cohort of patients treated in the rituximab era, older patients with MCL have inferior outcomes as compared with their younger counterparts. Although this difference can be circumvented with use of maintenance rituximab, more effective therapies are needed. Use of maintenance rituximab appears to have the greatest impact on survival in older patients while the utility of high-dose cytarabine and/or AHCT remains less clear across all age groups. Focused clinical trials are necessary to identify more effective induction

regimens that achieve durable responses and should incorporate maintenance strategies in the older patient population. It is anticipated that the more widespread use of BTK inhibitors and cellular immunotherapies will lead to advancements in survival, likely to become evident with longer follow-up. However, the next wave of clinical trials exploring novel therapeutics should focus on enriching for those with high risk features including older patients to better serve MCL subsets of high unmet need.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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FIGURE 1.

Survival outcomes in (A,B) younger (age < 65 years of age) and (C,D) older (age ≥ 65 years of age) patients differed according to use of AHCT (auto) and/or rituximab maintenance (ritux)

FIGURE 2.

In younger patients, use of AHCT (auto) and/or rituximab maintenance (MR) showed (A) a trend for improved PFS after induction with BR, and a statistically significant improvement in PFS after either (B) high-dose cytarabine (HD-Ara) or (C) R-CHOP $\pm$ methotrexate. In older patients, use of AHCT (auto) and/or rituximab maintenance (MR) (D) improved PFS in patients treated with either BR, (E) but not in patients treated with high-dose cytarabine (HD-Ara); use of AHCT (auto) and/or rituximab maintenance (MR) also improved PFS in older patients treated with (F) R-CHOP $\pm$ methotrexate containing induction

FIGURE 3.

(A) PFS and (B) OS was inferior in older patients when compared to younger patients with MCL. The OS was comparable in younger and older patients exposed to either (C) HD-AraC with frontline treatment or (D) post-induction/consolidation rituximab maintenance)

TABLE 1

Demographic, clinical and treatment data for MCL patients

	Age < 65		Age ≥ 65		p value
	N	%	N	%	
Sex					
Male	527	75.6	320	68.8	0.011
Female	170	24.4	145	31.2	
MCL international prognostic index (MIPi)					
<5.7	218	55.1	23	8.2	<0.001
5.7, <6.2	108	27.3	110	39.1	
≥6.2	69	17.5	148	52.7	
ECOG					
0-1	571	96.0	372	89.6	<0.001
2	24	4.0	43	10.4	
Ann Arbor stage					
I/II	36	5.4	31	6.8	0.276
III/IV	648	94.7	424	93.2	
Bone marrow involvement					
Yes	481	84.5	307	79.1	0.031
No	88	15.5	81	20.9	
Blastoid histology					
Yes	56	11.2	53	15.5	0.067
No	446	88.8	290	84.5	
TP53 present					
Yes	31	32	24	32.4	0.984
No	66	68	50	67.6	
>3 cytogenetic abnormalities					
Yes	40	15.2	35	17.8	0.463
No	223	84.8	162	82.2	
Ki-67					
<30	188	62.5	134	57.8	0.271
>30	113	37.5	98	42.2	

	Age < 65		Age ≥ 65		p value
	N	%	N	%	
Induction regimen					
Nordic regimen	20	3.1	7	1.7	-
R-CHOP/R-DHAP	35	5.4	10	2.5	
R-HyperCVAD	206	32	32	7.9	
R-BAC	9	1.0	8	2.0	
BR/R-AraC	4	1.0	4	1.0	
BR	88	13.7	148	36.4	
R-CHOP ± methotrexate	188	29.2	93	22.9	
Lenalidomide	5	0.8	9	2.2	
R-DHAP	3	0.5	4	1.0	
Other	85	13.2	92	22.6	
Cytarabine containing in frontline					
Yes	277	43.1	65	16	<0.001
No	366	56.9	342	84.0	
Auto transplant in first remission					
Yes	350	58.5	88	23.8	<0.001
No	245	41.2	281	76.2	
Post-induction rituximab					
Yes	199	35.4	155	44.2	0.008
No	363	64.6	196	55.8	
Salvage therapy					
BTKi exposure	67	26.1	58	36.9	0.04
Chemo	107	41.6	49	31.2	
Lenalidomide/bortezomib	51	19.8	25	15.9	
Other	32	12.5	25	15.9	
Was patient enrolled in a therapeutic clinical trial at ANY time?					
Yes	170	32.5	100	28.6	0.218
No	353	67.5	250	71.4	

TABLE 2

Factors associated with improved overall survival in younger and older patients on multivariate analysis

Covariate	Younger Patients ^a		Older Patients ^b	
	Hazard Ratio	HR <i>p</i> value	Hazard Ratio	HR <i>p</i> value
ECOG > = 2	4.56 (1.72–12.11)	0.002	2.26 (0.94–5.40)	0.068
Bone marrow involvement	3.10 (0.95–10.08)	0.061	2.10 (0.93–4.71)	0.073
Blastoid histology	2.95 (1.51–5.74)	0.001	1.96 (0.98–3.91)	0.058
Post-induction rituximab	0.24 (0.11–0.52)	<0.001	0.20 (0.10–0.40)	<0.001
Cytarabine containing	0.88 (0.49–1.58)	0.666	0.34 (0.11–1.07)	0.065
Autologous hematopoietic stem cell transplantation in first remission	0.92 (0.51–1.66)	0.779	0.68 (0.34–1.36)	0.281

^aNumber of observations in the original data set = 697. Number of observations used = 313 (only significant variables in univariate analyses with >50% of data capture along with AHCT were utilized in multivariate analyses).

^bNumber of observations in the original data set = 465. Number of observations used = 211 (only significant variables in univariate analyses with >50% of data capture along with AHCT were utilized in multivariate analyses).