REGULAR ARTICLE

blood advances

Ibrutinib maintenance after frontline treatment in patients with mantle cell lymphoma

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Key Points

- Fixed-duration I-M 560 mg daily for 4 years is feasible in patients with MCL who respond to frontline treatment with manageable toxicities.
- Changes in NGS-MRD were noted in a small number of patients during 4 years of maintenance with few survival events.

Maintenance rituximab in mantle cell lymphoma (MCL) has improved survival and supports exploration of maintenance with novel agents. We evaluated the safety and efficacy of ibrutinib maintenance (I-M) after induction in patients with treatment-naive MCL. Patients with MCL with complete response (CR) or partial response to frontline chemoimmunotherapy ± autologous stem cell transplantation (auto-SCT) received I-M 560 mg daily for up to 4 years. Primary objective was 3-year progression-free survival (PFS) rate from initiation of I-M. Minimal residual disease (MRD) assessments by next-generation sequencing (NGS) on peripheral blood were measured before I-M initiation and at 1, 6, and 18 to 24 months after initiation. Among 36 patients, the median age was 60 years (range, 46-90). For frontline treatment, 18 patients (50%) had consolidation with auto-SCT in CR1 before I-M. At median follow-up of 55.7 months, 17 patients (47%) completed full course I-M (median, 37.5 cycles; range, 2-52). The 3-year PFS and overall survival (OS) rates were 94% and 97%, respectively. With prior auto-SCT, 3-year PFS and OS rates were both 100%. The most common treatment–related adverse event with I-M was infection (n = 31; 86%), typically low grade; the most common grade 3/4 toxicities were hematologic. In 22 patients with MRD assessments, all were MRD negative after induction. Six became MRD positive on I-M, with 2 reverting to MRD-negative status with continued I-M, and all maintain radiographic CR with the exception of 1 with disease progression. I-M is feasible in MCL after frontline chemoimmunotherapy with manageable toxicities although significant. Changes in NGS-MRD were noted in limited patients during maintenance with few progression and survival events. This trial was registered at www.clinicaltrials.gov as #NCT02242097.

Introduction

Mantle cell lymphoma (MCL) is an uncommon but aggressive mature B-cell non-Hodgkin lymphoma that accounts for about 6% of all non-Hodgkin lymphoma cases in the United States. Despite high response rates with induction chemotherapy, this disease entity is incurable with high relapse rates.[1-3]

Submitted 19 July 2023; accepted 24 August 2023; prepublished online on *Blood Advances* First Edition 27 September 2023; final version published online 12 December 2023. https://doi.org/10.1182/bloodadvances.2023011271.

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Original data are available upon request from the corresponding author, Reem Karmali (reem.karmali@northwestern.edu). Individual participant data will not be shared.

The full-text version of this article contains a data supplement.

Although there is no consensus on the ideal frontline therapy for MCL, multiagent chemoimmunotherapy combinations are the standard of care based on multiple phase 2 and phase 3 trials. In 2 phase 3 studies, B-R (bendamustine-rituximab) was shown to be noninferior to R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone) in nontransplant eligible patient populations.[4,5] More intensive cytarabine-based regimens are widely used in transplant eligible patients based on prospective phase 2 and phase 3 studies demonstrating prolonged PFS, including R-maxi-CHOP alternating with R-HiDAC (rituximab, high-dose cytarabine per Nordic regimen) or R-CHOP/R-DHAP (rituximab, dexamethasone, high-dose cytarabine, cisplatin).[6,7]

Younger patients with good performance status are routinely considered for consolidation therapy with autologous stem cell transplant (auto-SCT); however, auto-SCT has not clearly improved survival and is not an option for many patients with MCL because of their age and comorbidities.[8-10]

Although guidelines continue to emphasize aggressive treatment approaches in fit patients as they provide durable remissions, a pattern of continuous relapse over months to years is expected, suggesting that all patients are at risk of eventual relapse.[11-13] These high relapse rates support the concept of undetectable minimal residual disease (MRD) that precedes development of clinical relapses. Once the disease has progressed after first-line therapy, the prognosis remains dismal despite significant advances in treatment options. Consequently, it remains prudent to focus on improving the therapeutic effect of upfront strategies.

Maintenance strategies have been studied in patients with MCL with the goal of prolonging durability of response. In particular, maintenance rituximab in MCL has improved survival and supports the exploration of maintenance with novel targeted agents in this disease.[2,6]

Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling in MCL and strongly influences B-cell differentiation, proliferation, and survival, thus representing an appealing target. Accordingly, multiple BTK inhibitors (BTKis) have been approved by the US Food and Drug Administration for this disease over the years.[14-16] Ibrutinib is a first-in-class BTKi that has demonstrated profound activity in relapsed or refractory MCL.[16,17] More recently, the SHINE trial demonstrated that the addition of ibrutinib to induction chemoimmunotherapy followed by indefinite maintenance significantly prolonged progression-free survival (PFS) but was associated with significant additional toxicity and offered no overall survival (OS) benefit.[18]

To date, fixed-duration ibrutinib maintenance (I-M) after frontline chemoimmunotherapy induction for MCL has neither been explored as a means of mitigating toxicity nor has the impact of maintenance on MRD status over time. We evaluated I-M as a single agent at a dose of 560 mg once daily after induction in patients with treatment-naive MCL for fixed duration of 4 years. This approach was intended to treat beyond median PFS historically expected with less intensive chemoimmunotherapy at the time of study conception while better balancing efficacy and safety with fixed duration.[4] We report results of a multicenter phase 2 trial assessing safety and efficacy including measures of MRD by next-generation sequencing (NGS) for I-M in MCL after frontline induction.

Methods

Study population and study design

This was a multi-institutional study (NCT02242097). Patients with MCL who achieved a complete response (CR) or partial response (PR) to frontline intensive induction chemoimmunotherapy with or without auto-SCT were enrolled to receive I-M dosed at 560 mg daily for up to 4 years.

To be eligible, patients had to have received induction therapy that could have included at least 4 cycles of either R-CHOP (with or without cytarabine-containing cycles), R-HyperCVAD/MA (rituximab, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high doses of methotrexate and cytarabine), or bendamustine + rituximab (BR). Patients could also be consolidated with auto-SCT per investigator choice before enrollment. However, the last dose of cytotoxic chemotherapy had to be given ≥14 days but no more than 120 days before enrollment, and patients who underwent auto-SCT consolidation had to show engraftment and meet required baseline hematologic parameters before enrollment. Patients with underlying hypertension or atrial fibrillation could be enrolled if deemed well controlled by the investigator.

Patients were evaluated monthly for the first 6 months on treatment and then every 3 months thereafter for up to 4 years. Patients who went off treatment continued to be followed for survival for up to a maximum of 4 years after the first dose of ibrutinib. Follow-up for off-treatment patients occurred every 3 months for up to 2 years and then every 6 months thereafter for up to 4 years after the first dose of ibrutinib.

This study was performed in accordance with the Declaration of Helsinki. Institutional review board approval was received for the protocol, amendments, and consent forms before initiating the study at each site. All patients gave written informed consent. Data were analyzed by the study statistician and R.K.; all authors had access to primary clinical trial data.

End points

The primary objective was to evaluate the efficacy of I-M as determined by 3-year PFS rate defined as the absence of disease progression or death from any cause from the start of I-M. PFS was defined as the length of time from ibrutinib initiation to the time of clinical disease relapse, progression, or death from any cause. Disease progression was evaluated using Cheson 2007 criteria,[19] documented by imaging (CT or MRI) for those with measurable disease or bone marrow assessment, if obtained. Any patient who received at least 1 dose of study treatment was evaluable for this end point. For disease status assessment, imaging was performed at baseline, after cycles 3 and 6, every 6 months per cycle for the first 2 years, once at 3 years, and as clinically indicated thereafter.

MRD assessments were not used to determine progression. The proportion of patients alive and progression-free at 3 years was calculated with a 2-sided 90% confidence interval (CI). In addition, a Kaplan-Meier curve was generated for PFS.

Secondary objectives were to characterize PR to CR conversions based on Cheson 2007 criteria while on I-M, determine median OS, and to assess safety. To determine rates of conversion from PR to CR, only patients who had a PR at the time of registration

Table 1. Patient clinical and demographic characteristics total number

Median age (range)	60 (46-90)
Male, n (%)	28 (78)
ECOG, n (%)	
0/1	34 (94)
2	2 (6)
Stage at initial diagnosis, n (%)	
I/II	5 (14)
III/IV	28 (78)
Unknown	3 (8)
MIPI	
Low	18 (50)
Intermediate	7 (19)
High	11 (31)
Extranodal disease at initial diagnosis, n (%)	9 (25)
Induction therapy, n (%)	
BR	17 (47)
R-HyperCVAD	9 (25)
Nordic Regimen (maxi-RCHOP/HiDAC)	7 (19)
R-CHOP/DHAP	2 (6)
R-CHOP	1 (3)
auto-SCT consolidation before enrollment, n (%)	18 (50)
Best response to induction therapy before enrollment, n (%)	
CR	34 (94)
PR	2 (6)
MRD status after induction therapy (n = 22)	
MRD (–)*	17 (77)
MRD indeterminate (defined as <1 × 10^6 cells assayed)	4 (18)
MRD (+)†	1 (5)

BR, bendamustine-rituximab; ECOG, Eastern Cooperative Oncology Group; MIPI, Mantle Cell Lymphoma International Prognostic Index.
*1 with PR radiographically by CT.
†Induced with BR before enrollment; radiographic CR by CT.

and who completed ≥1 complete cycle of ibrutinib maintenance were evaluable for this end point. OS was defined as the time from ibrutinib initiation until death or up to 4 years of follow-up after first dose of ibrutinib. Kaplan-Meier curves were generated for OS.

All patients who receive at least 1 dose of ibrutinib were evaluable for toxicity. Toxicity was assessed by the incidence of treatment-related adverse events (TRAEs) from the time of first dose of ibrutinib to 30 days after cessation of I-M. The frequency and severity of AEs and attribution to ibrutinib were assessed once per cycle according the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE, version 4.03).

Correlative studies

As an exploratory objective, MRD assessments using an NGS-MRD Assay (polymerase chain reaction method with detection resolution of 1 in 100 000 cells; Adaptive Biotechnologies) on peripheral blood, and/or peripheral blood mononuclear cells were measured at 4 time points: before I-M initiation and at 1, 6, and 18 to 24 months after initiation of I-M. Negative MRD was defined as no identifiable clone with a resolution of 1 in 100 000. Dynamic changes in MRD status over time were compared and correlated with PFS and OS.

Statistical considerations

The primary end point was to determine the 3-year PFS rate. The study had Type 1 error of 10% and a power of 90% to detect an effective treatment using a 1-stage design based on the true proportion of patients achieving 3-year PFS of at least 80% vs the null hypothesis that the true CR rate was at most 60%. Based on these parameters, a sample size of 36 evaluable patients was deemed appropriate. For the final analysis, if ≤25 patients were alive and without progression among 36 evaluable patients accrued, maintenance with ibrutinib would be considered ineffective for this patient population. In contrast, if ≥26 patients were alive and without progression, this would provide sufficient evidence for this regimen to warrant further investigation. To correlate MRD with either PFS or OS, proportional hazards regression with a time dependent covariate were used.

Results

Patient characteristics

Patients were enrolled between 2015 and 2018. Patient clinical and demographic data are summarized in Table 1. The median age was 60 years (range, 46-90), and 28 patients (78%) were male. Twenty-eight patients (78%) had advanced stage and 9 (25%) had extranodal disease. Eighteen (50%), 7 (19%), and 11 patients (31%) had low vs intermediate vs high risk Mantle Cell Lymphoma International Prognostic Index (MIPI), respectively. For induction, 17 (47%) received bendamustine-rituximab (BR), 18 (50%) a cytarabine-based regimen, and 1 (3%) R-CHOP. Eighteen patients (50%) had auto-SCT in CR1 before enrollment.

Responses and survival outcomes

Thirty-four (94%) and 2 patients (6%) had CR and PR to induction, respectively. With I-M, there were 1 PR to CR conversion and 1 patient progressed, resulting in a total of 35 patients in continued CR at their last assessment.

With a median follow-up of 55.7 months from the date of initiation of induction therapy, 17 patients (47%) completed their full course of I-M (median, 37.5 cycles; range, 2-52). Twenty-five patients (69%) completed at least 2 years of maintenance therapy, and all patients discontinued treatment.

Only 1 patient has progressed on our study thus far; 3 patients have died during I-M, 2 deaths deemed unrelated to I-M (aspiration pneumonia, second malignancy), and 1 from unknown cause. One patient was lost to follow-up.

Three-year PFS and OS rates were 94% and 97%, respectively, for the whole cohort (Figure 1). With additional follow-up, 5-year PFS and OS rates were 89% and 91%, respectively. No difference in PFS or OS was identified according to age (<65 [n = 24] vs ≥65 years [n = 12]; $P = .2$) or MIPI score (low, intermediate, or high; $P = .7$). PFS was improved in patients who received auto-SCT before enrollment (n = 18) compared with those who did not; 5-year PFS rates were 77% vs 100% ($P = .04$) with a trend for

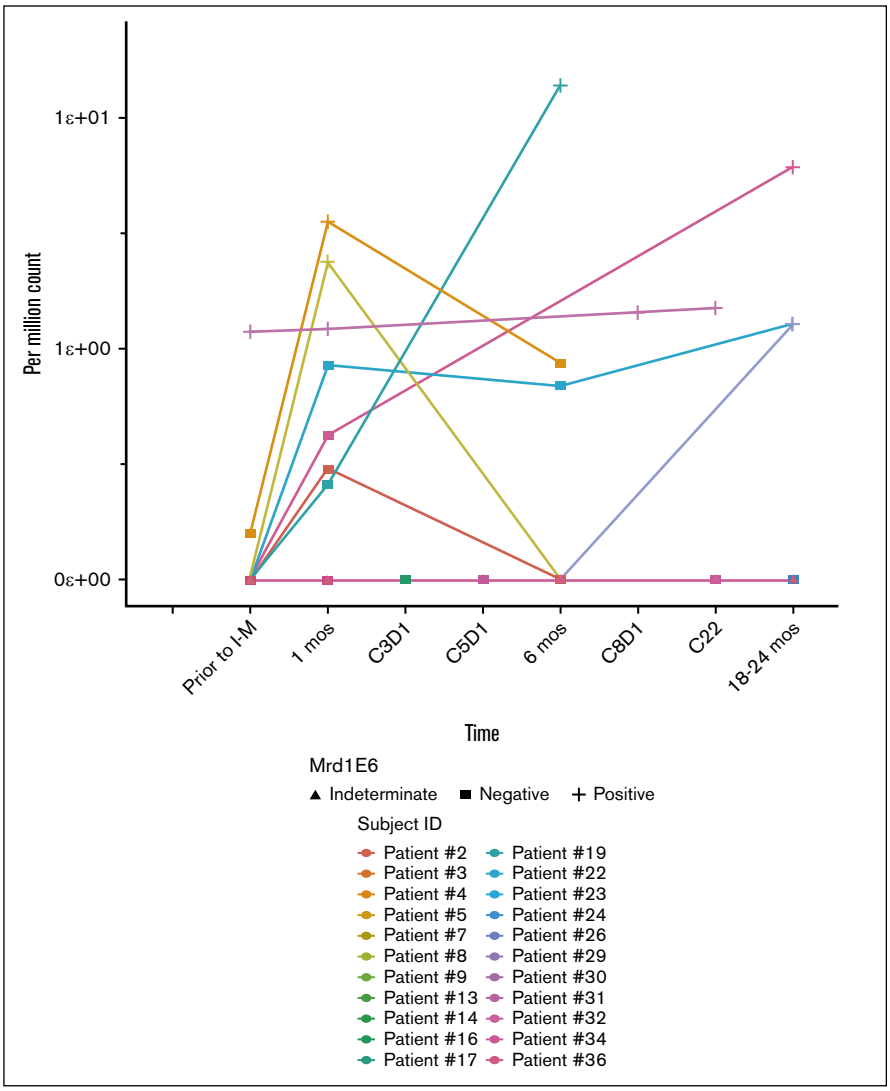

Figure 1. Sequential MRD assessments in 22 patients on I-M. All 22 patients were positive at diagnosis at a level of >100 000 tumor cells/million total cells. Six patients who were MRD (–) prior to I-M became MRD (+) with subsequent follow-up, 2 reverting back to MRD (–) status; of the 4 pts with persistent MRD (+) disease, 1 had clinical progression and the others maintain clinical response though MRD was not rechecked in these patients.

improved OS at 5 years for prior auto-SCT vs none (5-year OS rate of 100% vs 83%; $P = .07$; Figure 1).

Exploratory MRD assessments

At time of data cutoff, tissue was available in 22 patients at diagnosis (including 9 patients with prior auto-SCT), and a trackable dominant clone(s) was identified in all 22 patients. MRD status was assessed in these 22 patients at varying time points (Figure 2). For patients evaluated before I-M initiation (n = 21), MRD was assessed after induction chemoimmunotherapy and transplantation if applicable (n = 9). Before I-M maintenance, all patients with intermediate MRD (n = 4) were MRD negative when checked after 1 month on I-M. The only patient who was MRD positive after frontline treatment (with BR), remained MRD positive with assessment of MRD status at 1 month; although no further assessments for MRD were obtained beyond this time point, this patient remained in clinical remission and completed 48 cycles of I-M.

Six patients who were MRD negative before I-M became MRD positive, all within 24 months of starting I-M. Of these 6 patients, 2 were treated with hyperCVAD, 2 with BR, 1 with R-maxiCHOP/R-HiDAC + auto-SCT, and 1 with R-CHOP + auto-SCT before I-M; dose interruption or nonadherence was captured in 5 of these 6 patients before MRD-positive status was captured (supplemental Table 1). All were maintained on I-M subsequently as none demonstrated clear radiographic relapse at the time of MRD-positive status. With subsequent follow-up and ongoing I-M, 2 of these patients with MRD-positive status reverted back to MRD-negative status. Of note, 1 of these patients with MRD-positive status discontinued I-M for toxicity after 12 months and after reversion back to MRD-negative status; this patient was switched to rituximab maintenance after discontinuation of I-M without evidence of progression. This patient was not counted as an event for PFS, given no evidence of clinical relapse.

Of the 4 remaining patients, 1 had disease progression based on imaging and is the only patient on our trial to have disease progression. The others maintained radiographic CR, and MRD was not rechecked in these particular patients to better gauge the

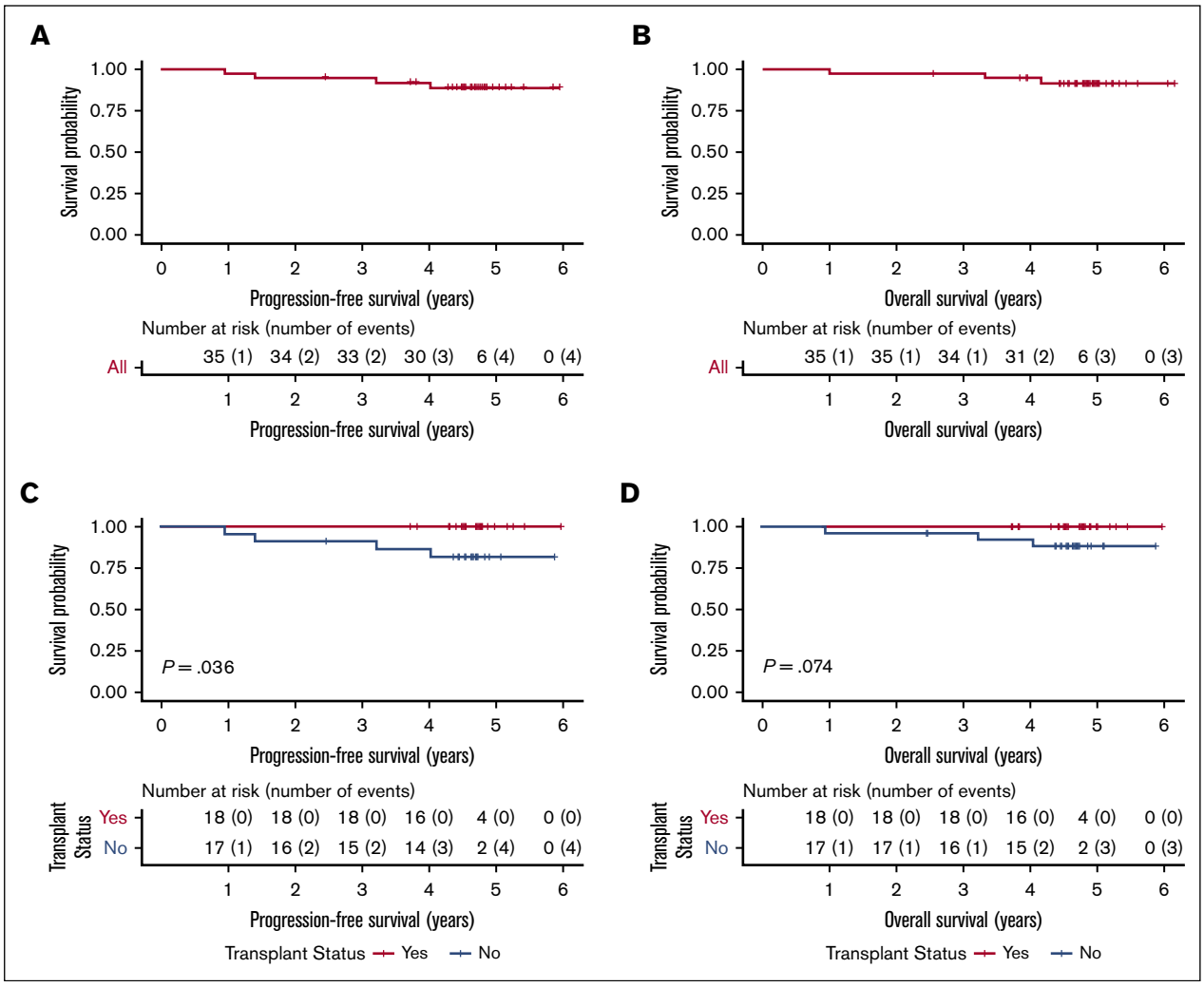

Figure 2. PFS and OS in patients treated with I-M. Four-year PFS (A) and OS (B) rates were 91% and 94% respectively for the whole cohort. PFS was improved in patients who received autologous SCT prior to enrollment (C) with a trend for improved OS (D).

possibility of reversion back to negative status. Overall, MRD did not correlate with PFS and OS, given few events.

Toxicity

The most common TRAEs were infection (n = 31; 86%), lymphopenia (n = 29; 81%), leukopenia (n = 26; 72%), diarrhea (n = 24; 67%), and thrombocytopenia (n = 23; 64%). The most common grade (G) 3-4 toxicities were hematologic including lymphopenia (n = 21; 58%) and neutropenia (n = 13; 36%; Table 2).

TRAEs attributed to ibrutinib resulted in temporary dose interruptions in 14 patients, in some patients more than once. Reasons by toxicity included neutropenia (n = 7), infection (n = 5), fatigue (n = 1), hypertension (HTN; n = 1), cramping (n = 1), and bleeding event (n = 3).

TRAEs led to permanent dose reductions in 9 patients (25%): 2 from neutropenia, 2 from fatigue, 2 from myalgias, and 1 each from infection, diarrhea, and mucositis. Fifteen patients (42%) permanently discontinued I-M from TRAEs, most commonly for new-onset atrial fibrillation/flutter (n = 8, 22%; 5 for G1-2, followed by 1 each from pneumonia, myalgias, rash, pericardial effusion, mucositis, trasient ischemic attack (TIA), and subdural hematoma/bleed. I-M was discontinued in the majority of patients who developed new-onset atrial fibrillation/flutter. Notably, atrial fibrillation/flutter occurred in 10 patients (28%; G1-2, n = 6 [17%]; G3, n = 4 [11%]) and included 2 with baseline atrial fibrillation/flutter with increase in grade attributed to I-M and accounted for incidence. HTN occurred in 20 patients (56%; G1-2, n = 12 [33%]; G≥3, n = 8 [22%]) and included 5 with baseline HTN with increase in grade attributed to I-M. Incidences of both atrial fibrillation/flutter and HTN increased over time with ongoing I-M exposure (supplemental Table 2). Incidence of baseline cardiovascular disorders in our patients are noted in supplemental Table 3.

Four additional patients discontinued I-M prematurely, not as a result of toxicity, but rather, 1 for endometrial adenocarcinoma and 1 to pursue therapy for prostate cancer, (deemed unrelated AE),

Table 2. TRAEs occurring with any grade incidence of ≥20% in patients treated with ibrutinib maintenance (n = 36)

TRAE, n (%)	All grade	Grade 3	Grade 4
Infection	31 (86)	4 (11)	1 (3)
Lymphocyte count decreased	29 (80)	12 (33)	9 (25)
White blood cell decreased	26 (72)	7 (19)	1 (3)
Diarrhea	24 (67)	0	0
Platelet count decreased	23 (64)	0	0
Neutrophil count decreased*	21 (58)	4 (11)	9 (25)
Hypertension	20 (56)	8 (22)	0
Hemorrhage	16 (44)	2 (6)	1 (3)
Skin rash	16 (44)	1 (3)	0
Bruising	13 (36)	0	0
Myalgia	13 (36)	0	0
Fatigue	12 (33)	2 (6)	0
Anemia	12 (33)	0	0
Aspartate aminotransferase increased	11 (31)	1 (3)	0
Atrial fibrillation/atrial flutter	10 (28)	4 (11)	0
Alanine aminotransferase increased	8 (22)	0	0

*Includes 1 event of febrile neutropenia.

1 for disease progression, and 1 for death of unknown cause. Four patients had a secondary solid malignancy; 2 while on treatment and 2 after stopping I-M. This included cases of intrahepatic cholangiocarcinoma, endometrial adenocarcinoma, prostate cancer, and anal squamous cell carcinoma; all felt to be unrelated to I-M considering patient risk factors.

When accounting for prior therapy during induction, 7 of 17 patients treated with bendamustine-containing induction required discontinuation of therapy because of toxicity; reasons included atrial fibrillation (n = 3), infection (n = 2), mucositis (n = 1), and syncope (n = 1). However, 2 additional patients treated with bendamustine-containing induction incurred a second malignancy during their maintenance phase. These malignancies were not attributed to I-M by the treating investigator. For patients who received auto-SCT consolidation (n = 18), 4 patients stopped I-M prematurely because of toxicity (2 for atrial fibrillation, 1 for myalgias, and 1 after a transient ischemic attack).

Discussion

Our study evaluates I-M intended as fixed duration in patients with MCL who have achieved a response to frontline chemoimmunotherapy. To our knowledge, it is the first that has attempted to evaluate the impact of maintenance of BTKis on dynamic changes in MRD over time and correlate this with survival outcomes.

In our study, patients who did not receive prior auto-SCT had 5-year PFS and OS rates of 77% and 83%, respectively, which compare favorably with the MCL Elderly Trial evaluating rituximab maintenance after conventional chemoimmunotherapy.[20] Patients with prior auto-SCT demonstrated improvement in PFS (rate of 100% with 4 years of follow-up) with a trend for improvement in OS compared with patients without prior auto-SCT. Results may have been driven by patient selection with fitter patients selected for transplant. Our sample size, however, was too small to provide any further insight on this finding. With similar length of follow-up (~50 months) in the LYMA study that treated patients with auto-SCT and randomized them to either rituximab maintenance for 3 years vs observation, the rate of PFS was 83% (95% CI, 73-88) in the rituximab group, compared with 64% (95% CI, 55-73) in the observation group (hazard ratio for disease progression, relapse, or death, 0.40; 95% CI, 0.23-0.68; $P < .001$).[6]

Although our data compare favorably with data from the MCL Elderly and LYMA studies for rituximab maintenance, the significance of our findings are unclear given the small sample size in our study. Specifically, our data clarify neither the utility of transplant with concurrent BTKi exposure nor the best practice for maintenance therapy after conventional induction chemoimmunotherapy. Whether I-M is better than rituximab maintenance has yet to be determined. The TRIANGLE study randomized patients to standard of care transplant vs transplant with ibrutinib vs ibrutinib alone. In the ibrutinib arms, patients received ibrutinib with induction followed by 2 years of fixed-duration I-M. Approximately half the patients received rituximab maintenance when the protocol was amended to reflect changes in standard practice.[21] We do expect that more mature data from the TRIANGLE study, along with results from E4151 (NCT 03267433) and E4181 (NCT 04115631) combined, will collectively provide greater insight on whether transplant can be omitted with the incorporation of BTKi therapy with induction and/or maintenance.

With the use of fixed-duration I-M after standard induction therapy, the PFS rate at 4 years was 89% for our whole cohort. In patients who did not receive consolidation with auto-SCT, the PFS rate was 77%. In comparison, the SHINE study randomized patients aged ≥65 years to receive either ibrutinib daily until disease progression or unacceptable toxicity vs placebo in combination with bendamustine and rituximab followed by rituximab maintenance every 2 months for 2 years. In the SHINE ibrutinib cohort, the 4-year PFS rate was <70%. I-M improved PFS although not OS.[18] In our cohort, 1 patient progressed while on maintenance. For the remaining patients (n = 35), despite cessation of therapy after 4 years of maintenance, no patients have relapsed. Longer follow-up will provide insight on whether fixed-duration therapy in patients with ongoing response is feasible.

The concern regarding fixed-duration therapy is particularly important given ibrutinib's toxicity profile. In the SHINE study, despite intent for indefinite therapy, there was a high rate of ibrutinib discontinuation (n = 220; 84.3%) with median duration of treatment of 24 months (range, 0.2-95.2). In our cohort, patients received a median of 37.5 cycles (range, 2-52). In the SHINE study, the incidence of grade 3 or 4 AEs during treatment was 81.5% in the ibrutinib group. Atrial fibrillation was reported in 13.9% and hypertension in 13.5% of the patients in the ibrutinib group.[18] In our patient cohort, 31 (86%) had grade 3 or 4 AEs, similar to the incidence reported in SHINE. However, rates of atrial fibrillation/atrial flutter and hypertension were particularly higher in our cohort. We would attribute this to longer treatment duration in our patients, recognizing that the incidence of atrial fibrillation/flutter increases with ongoing exposure. In addition, incidence rates included 5

patients with baseline HTN and 2 patients with baseline atrial fibrillation/flutter with increase in grade attributed to I-M.

Notably, despite significant PFS improvement observed with addition of ibrutinib to induction and as maintenance in the SHINE trial, patients incurred additional AEs leading to voluntary withdrawal of the agent for MCL in the United States. Although there are no head-to-head studies assessing the efficacy and tolerability of newer BTKis in MCL, one may argue for the consideration of using newer BTKis with a shorter course of maintenance to better balance therapeutic effect with safety.

We demonstrated high rates of MRD negativity after standard induction therapy with or without the inclusion of auto-SCT. Among the 22 patients with available samples for MRD monitoring, 6 became MRD positive within 24 months of initiating I-M. Two of these patients had documented reversion back to MRD-negative status. Of interest, nonadherence and/or dose interruption were present before positive conversion. Among the remaining 4 patients, 3 remain in CR radiographically >2 years beyond MRD detection and 1 progressed. Unfortunately, we were unable to collect additional samples in these patients to clarify the possibility of MRD reversion. It is therefore uncertain whether MRD status has added value as a predictive marker of relapse in our data set. However, it is encouraging that only 1 patient progressed. Longer follow-up may likely clarify this issue. Other limitations of our data set include the paucity of molecular data, including *TP53* mutation status, for our patients.

To conclude, we demonstrated that fixed-duration I-M at a dose of 560 mg daily for 4 years was feasible in patients with MCL who respond to frontline chemoimmunotherapy with or without auto-SCT. Toxicities including rates of high-grade atrial fibrillation/flutter and HTN were consistent with ibrutinib's known safety profile. Further studies evaluating maintenance as a shorter course or the use of next generation BTKis as alternatives to ibrutinib should be explored as they may mitigate toxicity. Changes in NGS-MRD were noted in a small number of patients during maintenance. Correlation of changes in MRD with PFS and OS in a larger sample of patients with extended follow-up are needed to determine clinical relevance of I-M and MRD status.

Acknowledgments

Pharmacyclics/Janssen financially supported the current research.

Authorship

Contribution: A.M.P. contributed to conception and design of the study; all authors collected and assembled the data; R.K. and X.M. analyzed the data; all authors interpreted the data; R.K. prepared the first draft of the manuscript; and all authors provided critical and insightful comments, contributed to manuscript writing, and gave the final approval of the manuscript.

Conflict-of-interest disclosure: R.K. reports advisory board membership in BeiGene, Genentech/Roche, AstraZeneca, Miltenyi, Lilly, Calithera, Kite/Gilead, and Bristol Myers Squibb; speakers bureau fee from BeiGene, AstraZeneca, and MorphoSys; and institutional research support from BeiGene, Takeda, Calithera, Kite/Gilead, and Bristol Myers Squibb. B.P. reports honoraria from Seattle Genetics and Takeda; and consultant fee from BioSecura. The remaining authors declare no competing financial interests.

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