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Original Article

Novel therapeutic agents and intensive chemotherapy improve survival outcomes in patients with mantle cell lymphoma

Zi-Chi Lin[1], Ming-Chung Wang[2], Tung-Liang Lin[1], Ming-Chung Kuo[1,3], Hsiao-Wen Kao[1], Hung Chang[1,3], Yu-Shin Hung[1,3], Ming-Chun Ma[2], Yuen-Chin Ong[1], Che-Wei Ou[4], Ching-Yuan Kuo[2], Yi-Yang Chen[5], Yen-Min Huang[3,6], Hsuan-Jen Shih[1]

[1]Division of Hematology, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital, Taoyuan 33305, Taiwan; [2]Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung-Chang Gang Memorial Hospital, Kaohsiung 83301, Taiwan; [3]School of Medicine, Chang Gung University, Taoyuan 33302, Taiwan; [4]Division of Hematology-Oncology, Department of Internal Medicine, New Taipei Municipal TuCheng Hospital, New Taipei 23652, Taiwan; [5]Division of Hematology and Oncology, Department of Medicine, Chiayi Chang Gung Memorial Hospital, Chiayi 613016, Taiwan; [6]Division of Hematology and Oncology, Department of Internal Medicine, Keelung Chang Gung Memorial Hospital, Keelung 204201, Taiwan

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Abstract: Mantle cell lymphoma (MCL) is a rare type of mature B-cell lymphoma. This multicenter retrospective cohort study aimed to analyze the epidemiological characteristics, treatment patterns, and survival outcomes of patients with MCL in Taiwan. We collected baseline information, treatment modalities, and response evaluation of patients with MCL. A total of 204 patients who were diagnosed with mantle cell lymphoma between November 2001 and July 2022 were included. When divided into low, intermediate, and high-risk groups according to the Mantle Cell Lymphoma International Prognostic Index, their median overall survival times were 83.7 (95% confidence interval [CI]: 77.7-NR), 72.7 (95% CI: 30.7-NR), and 19.3 (95% CI: 14.2-45.6) months, respectively. In this multicenter retrospective cohort, first line rituximab containing regimens, higher chemotherapy intensity, and ASCT were associated with longer PFS/OS, although the magnitude and statistical significance varied after adjustment and by transplant eligibility. Given potential confounding by indication, era effects, and missing data, these findings should be interpreted as observational associations rather than causal effects. Prospective or target trial emulation studies are warranted.

Keywords: Mantle cell lymphoma, high-intensity chemotherapy, rituximab, bortezomib, autologous stem cell transplantation

Introduction

Mantle cell lymphoma (MCL) is a rare type of mature B-cell lymphoma that ac-counts for ~2-6% of all lymphomas in a number of Asian countries [1]. It is characterized by the translocation of chromosomes 11 and 14 [t(11;14)(q13;q32)], which leads to the overexpression of the cyclin D1 gene. This disease exhibits a highly variable clinical course, histological and pathological features, and immunophenotype [2].

First-line treatment choices for young and fit patients with MCL include aggressive cytarabine-based induction chemotherapy and rituximab (R), with or without autologous stem cell transplantation (ASCT) and maintenance therapy. For patients who are deemed unfit for aggressive induction therapy, other treatment options included combinations of bendamustine and R (BR); cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); and bortezomib, R, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) [3]. For patients who are considered frail, other treatment options include best supportive care, R with attenuated chemotherapy, and radiotherapy for symptom relief. MCL is considered an incurable neoplasm characterized by recurrent relapses. Several

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types of treatments have been explored and shown to be effective for relapsed and refractory disease - including Bruton tyrosine kinase inhibitors (BTKi), B-cell lymphoma 2 inhibitors, chimeric antigen receptor T-cell therapy, and bispecific antibodies [4]. The role of frontline BTKi use is currently under investigation.

Several clinical and biological factors have been found to have prognostic significance for MCL. The most commonly used prognostic index for the condition is the MCL International Prognostic Index (MIPI), which contains four independent clinical and laboratory prognostic factors: age, performance status, lactate dehydrogenase (LDH) level, and leukocyte count. This index was used to classify the patients into the risk groups: low, intermediate, and high [5]. Other known prognostic factors include Ki-67 score (a marker to ascertain tumor proliferation rate), TP53 gene mutation, and pleo-morphic or blastoid morphological variants [6].

While international studies have established the prognostic utility of MIPI and demonstrated the efficacy of cytarabine-based induction and maintenance strategies, real-world data from Asian populations remain scarce. Given potential differences in genetic profiles, treatment accessibility, and healthcare systems, there is a pressing need to validate these findings in region-specific cohorts. To address this gap, we conducted a multicenter retrospective study involving four member hospitals of Taiwan's Chang Gung Medical Foundation. This study aimed to analyze the epidemiological characteristics, treatment patterns, and long-term survival outcomes of patients with MCL, thereby providing clinically relevant insights from an underrepresented Asian population.

Materials and methods

We recruited 204 patients with pathologically confirmed diagnoses of MCL made between November 2001 and July 2022 at Linkou Chang Gung Memorial Hospital, Keelung Chang Gung Memorial Hospital, Chiayi Chang Gung Memorial Hospital, and Kaohsiung Chang Gung Memorial Hospital. A pathological review was conducted for the referred cases. Those who received more than one line of systemic chemotherapy at other medical institutions were excluded.

Computed tomography and positron emission tomography-fluorodeoxyglucose (FDG-PET) were adapted for image staging based on the Lugano staging classification [7]. Bone marrow and gastrointestinal involvement were confirmed by reviewing pathological reports or FDG-PET results. Baseline patient information such as age at diagnosis, sex, performance status, LDH level, disease staging, and treatment was collected by medical record review. Response assessments were performed according to the Lugano criteria using local radiology reports. Radiology interpretations from routine clinical reads were used for response categorization; no centralized independent imaging review was performed.

Systemic therapies were classified into three predefined intensity groups - high, intermediate, and low - based on the chemotherapy intensity framework outlined in the NCCN Clinical Practice Guidelines for B-Cell Lymphomas (MCL discussion). Patients were assigned to these categories according to the agents used and high-dose cytarabine exposure. High-intensity regimens included those with high-dose cytarabine or multi-agent protocols commonly used in transplant-intended settings; intermediate-intensity regimens comprised multi-agent therapies without high-dose cytarabine; and low-intensity regimens consisted of single-agent or doublet therapies such as BR. The specific chemotherapy regimens used in these groups are detailed in **Table 1**.

The patients' characteristics were summarized using frequencies and percentages. Progression-free survival (PFS) was defined as the time from diagnosis to the earliest occurrence of death from any cause, relapse, disease progression, or initiation of the next line of treatment, with patients censored at the final follow-up. Overall survival (OS) was defined as the time from diagnosis to death from any cause, with the patients censored at the final follow-up, based on the Kaplan-Meier method. Differences in PFS and OS according to disease severity and treatment approach were analyzed using the log rank test. A multivariate Cox proportional model was used to evaluate the associations between PFS and OS with severity and treatment approach while controlling for age.

In order to explore survival between the transplant-eligible and ineligible patient groups, we also stratified the patients into two subpopula-

Table 1. Chemotherapy regimens by intensity

Chemotherapy	Regimen
High intensity	CHOP/DHAP +/- R, hyper-CVAD +/- R or V, BR/HiDAC, ESHAP +/- R
Conventional intensity	CHOP +/- R, CVOP +/- R, VR-CAP
Low intensity	BR, COP +/- R, cyclophosphamide +/- steroid, chlorambucil +/- steroid

Abbreviations: DHAP: dexamethasone, high dose cytarabine, platinum; hyper-CVAD: cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine; V: bortezomib; BR/HiDAC: bendamustine, high-dose cytarabine; ESHAP: etoposide, methylprednisolone, high-dose cytarabine, cisplatin; CVOP: cyclophosphamide, etoposide, vincristine, prednisone; COP: cyclophosphamide, vincristine, prednisone; R: rituximab.

tions: age ≤70 years and Eastern Cooperative Oncology Group (ECOG) of 0-1, and age >70 years or ECOG of >1. A multivariate Cox proportional model was also used to evaluate the associations between PFS and OS with severity and treatment patterns in these alternate stratifications, while once again controlling for either age or autologous transplantation.

This retrospective study was approved by the institutional review board of Chang Gung Medical Foundation (approval no.: 202300109B0). The requirement for informed consent was waived owing to the anonymous nature of the data.

Results

Patient characteristics

The median age of the 204 patients was 66.5 years, with 82 (40.2%) being >70 years and 172 (84.3%) being male. Bone marrow involvement was confirmed in 122 patients (59.8%). Forty-nine patients (24.0%) had gastrointestinal involvement, with the small intestine (20/49), stomach (19/49), and colon (27/49) representing the most affected sites. Twenty-three patients had >1 gastrointestinal site involvement. Liver involvement was observed in eight patients (3.9%), while splenic involvement was seen in 92 (45.1%). Most of the patients (88.7%) were diagnosed at an advanced cancer stage (stage III or IV). Additionally, 37 (18.1%) presented with bulky disease. There were 24 patients (11.7%) with the blastoid variant and 25 (12.3%) with the pleomorphic one.

The patients were classified into three risk groups based on the MIPI approach, which yielded 44 (21.6%), 37 (18.1%), and 69 (33.8%) patients, respectively, in the low-, medium-, and high-risk groups. MIPI scores could not be calculated in 54 (26.5%) patients, owing to missing LDH and leukocyte count data. Ki-67 index data were available for 106 of the patients. Fifty-eight of these had Ki-67 indexes of <30%, while 48 had Ki-67 indexes of ≥30% (**Table 2**).

Stem cell transplantation

Twenty-seven patients received ASCT. Of these, 22 received it after first-line therapy and four received it after second-line treatment. One patient underwent a second ASCT. Two patients received allogeneic stem cell transplantation - one after fourth-line immune-chemotherapy and one after first-line therapy, with neither having previously received ASCT.

First-line treatment pattern

For first-line treatments, 83 of our patients (40.7%) received low-intensity chemotherapy (including 19 who received BR), 84 (41.2%) received conventional chemotherapy (most of whom received CHOP or CHOP-like regimens, with 23 having received VR-CAP), and 22 (10.8%) received high-intensity chemotherapy (including hyper-cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine [CVAD] with or without R and R-dexamethasone, high-dose cytarabine, platinum [DHAP]/R-CHOP alternative regimens with etoposide, methylprednisolone, high-dose cytarabine, cis-platin [ESHAP]). Fifteen of the patients (7.4%) did not receive immunochemotherapy because of their frail clinical conditions, of which one of these patients received venetoclax alone. There was a total of 11 first-line treatment-related mortalities. Most of these patients had been treated with COP or CHOP, although three had received high-intensity chemotherapy, including ESHAP and hyper-CVAD (**Table 2**).

Bruton tyrosine kinase inhibitor

Among the 51 patients who received BTKi, 26 were treated with these drugs as a second-line

Table 2. Baseline characteristics of 204 patients with MCL across four Taiwanese centers

Characteristic	No. (%)
Age	
≤70	122 (59.8%)
>70	82 (40.2%)
Sex	
Female	32 (15.7%)
Male	172 (84.3%)
Eastern Cooperative Oncology Group	
0-1	161 (78.9%)
2-4	40 (19.6%)
N/A	3 (1.5%)
Stage	
I, II	20 (9.8%)
III, IV	181 (88.7%)
N/A	3 (1.5%)
Bone marrow involvement	
Yes	122 (59.8%)
No	62 (30.4%)
N/A	20 (9.8%)
Liver involvement	
Yes	8 (3.9%)
No	193 (94.6%)
N/A	3 (1.5%)
Spleen involvement	
Yes	92 (45.1%)
No	109 (54.4%)
N/A	3 (1.5%)
Gastrointestinal involvement	
No involvement	155 (76.0%)
Gastrointestinal involvement	49 (24.0%)
Esophagus	2
Stomach	19
Small intestine	20
Large intestine	27
Appendix	3
Bulky disease	
Yes	37 (18.1%)
No	151 (74.0%)
N/A	16 (7.8%)
Pathological subtype	
Blastoid	24 (11.8%)
Pleomorphic	25 (12.3%)
Others	155 (76.0%)
Ki-67 index	
<30%	58 (28.4%)
≥30%	48 (25.5%)
N/A	98 (48.0%)

Original Mantle Cell Lymphoma International Prognostic Index score	
Low	44 (21.6%)
Intermediate	37 (18.1%)
High	69 (33.8%)
N/A	54 (26.5%)
Autologous stem cell transplantation	
Yes	27 (13.2%)
No	177 (86.8%)
Chemotherapy (first line)	
Low intensity	83 (40.7%)
Conventional intensity	84 (41.2%)
High intensity	22 (10.8%)
Rituximab use (first line)	
Yes	120 (63.2%)
No	70 (36.8%)
Bortezomib use (first line)	
Yes	31 (16.3%)
No	159 (83.7%)

Abbreviations: N/A: data not available.

therapy. The overall response rate was 73.1%. The median duration of use was 13.5 months (range, 0.5-100.8). The most common adverse effects included infection and cytopenia. Hepatitis B virus flare-ups were noted in three of the patients. Atrial fibrillation was observed in three patients who were treated with ibrutinib. One of them switched to acalabrutinib. Most of the patients who discontinued BTKi use (21/51) did so because of disease progression. Other causes for treatment discontinuation included poor performance, infection, disease, old age, and other such factors.

Survival analysis

The median PFS and OS values for those patients who were aged ≤70 years at diagnosis were 27.0 (95% confidence interval [CI]: 17.1-39.8) and 79.1 months (95% CI: 46.7-102.4), respectively. The corresponding values were 7.4 (95% CI: 5.8-11.6) and 18.1 months (95% CI: 7.3-37.8). The median PFS and OS values related to first-line treatments were 49.2 (95% CI: 29.2-[not reached]) and 95.3 months (95% CI: 67.8-[not reached]), respectively, in the high-intensity group; 25.1 (95% CI: 16.2-38.9) and 61.4 months (95% CI: 46.2-80.1), respectively, in the conventional-intensity one; and 9.9 (95% CI: 7.4-15.0) and 25.1 months (95% CI: 14.2-72.7), respectively, in the low-intensity one (p values <0.001 for PFS and 0.003 for OS). The median PFS and OS values for the patients who received R in their first-line treatments were 27.1 (95% CI: 19.5-43.7) and 67.8 months (95% CI: 56.6-83.7), compared with 12.0 (95% CI: 9.6-16.3) and 30.6 months (95% CI: 19.3-48.2) for those who did not (P<0.001 for PFS, P=0.006 for OS). Similarly, the median PFS and OS values for the patients who were treated with bortezomib in their first-line therapy regimens were 43.9 (95% CI: 19.9-[not reached]) and 61.4 months (95% CI: 56.6-94.2), respectively - vs 15.3 (95% CI: 12.2-25.1) and 46.7 months (95% CI: 30.9-76.8) for those who did not (P=0.069 for PFS, P=0.186 for OS) (**Figure 1**).

The median PFS for the patients who underwent ASCT was 57.5 months (95% CI: 43.7-[not reached]), vs 13.2 months (95% CI: 11.0-19.1) for those who did not (P<0.001). The median OS of the patients who received ASCT was 115.9 months (95% CI: 100.0-[not reached]), vs 41.0 months (95% CI: 26.1-59.3) for those who did not (P<0.001) (**Figure 2**).

In the low-risk MIPI group, the median PFS and OS values were 49.2 (95% CI: 33.2-100.0) and 83.7 months (95% CI: 77.7-[not reached]), respectively. In the intermediate-risk one, the median PFS was 31.5 months (95% CI: 13.2-61.5), and the median OS was 72.7 months

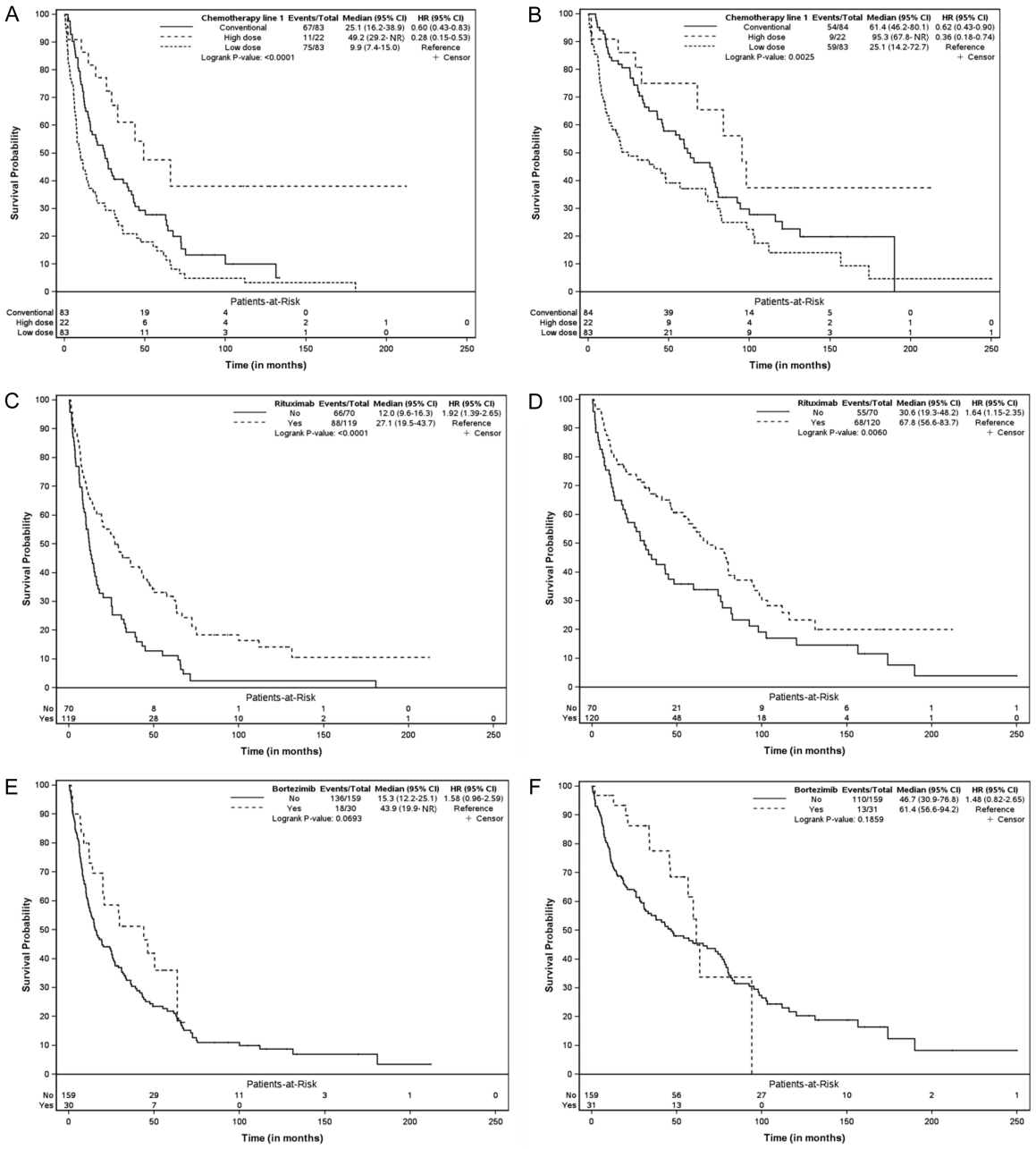

Figure 1. Survival with different systemic treatment. A. Progression-free survival with different chemotherapy intensities; B. Overall survival with different chemotherapy intensities; C. Progression-free survival in patients with or without rituximab; D. Overall survival in patients with or without rituximab; E. Progression-free survival in patients with or without bortezomib; F. Overall survival in patients with or without bortezomib.

(95% CI: 30.7-[not reached]). For the high-risk group, the median PFS was 7.8 months (95% CI: 6.5-14.5), and the median OS was 19.3 months (95% CI: 14.2-45.6). All of these values reached statistical significance as well ($p< 0.001$) (**Figure 3**).

For the patients with Ki-67 indexes of ≥30%, the median PFS was 7.5 months (95% CI: 4.6-14.5), and the median OS was 16.3 months (95% CI: 7.0-59.3). By contrast, those with Ki-67 indexes of <30% had a median PFS of 32.4 months (95% CI: 13.7-46.1) and a median OS of 76.8 months (95% CI: 43.1-97.9), with significant differences observed both in terms of PFS (P=0.004) and OS (P=0.011). The patients with the blastoid and pleomorphic variants had significantly shorter PFS and OS val-

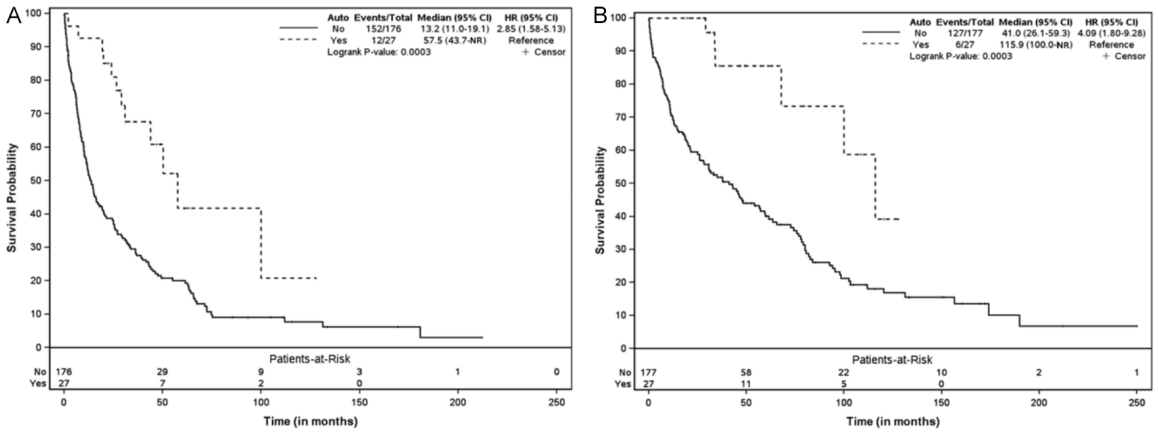

Figure 2. Survival with ASCT. A. Progression-free survival in patients with or without ASCT; B. Overall survival in patients with or without ASCT. Abbreviations: ASCT, autologous stem cell transplantation.

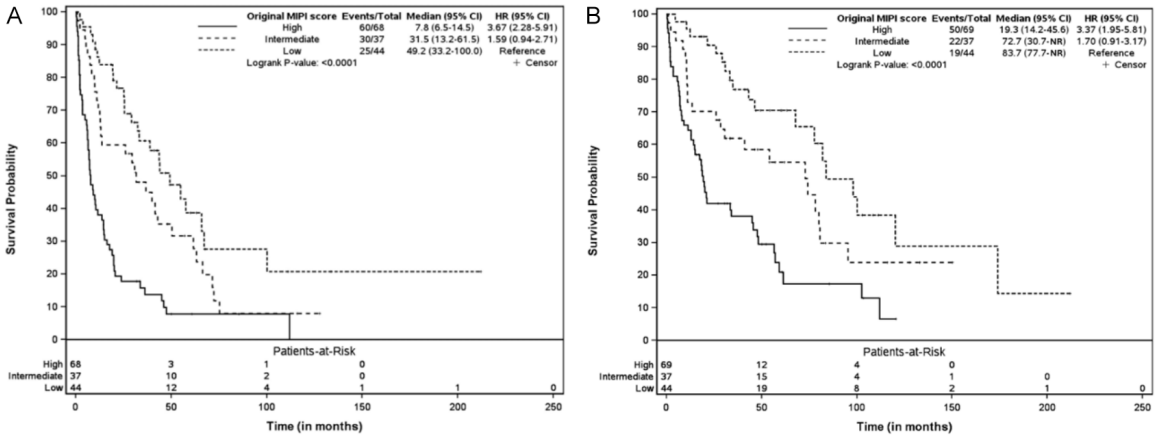

Figure 3. Survival in different MIPI. A. Progression-free survival in different MIPI groups; B. Overall survival in different MIPI groups. Abbreviations: MIPI, MCL International Prognostic Index.

ues. For those with the blastoid variant, the median PFS was 7.2 months (95% CI: 2.4-15.3), and the median OS was 10.9 months (95% CI: 5.7-37.7). For those with the pleomorphic variant, the median PFS was 9.0 months (95% CI: 3.2-57.5), and the median OS was 26.1 months (95% CI: 9.5-112.0). In comparison, the patients with other pathological MCL subtypes had a median PFS of 20.2 months (95% CI: 14.8-30.8) and a median OS of 59.7 months (95% CI: 43.1-76.8) - which represented statistically significant differences both in terms of PFS (P=0.015) and OS (P=0.017; **Table 3**).

In our bivariate analysis of the transplant-eligible group (i.e., age ≤70 years and ECOG of <2), significant differences in PFS or OS were observed across the different first-line chemotherapy intensity groups (median PFS values: 9.9 (95% CI: 7.4-14.5), 25.1 (95% CI: 16.0-36.6), and 49.2 (95% CI: 26.0-[not reached]) months in the low-, conventional-, and high-intensity groups, respectively [P<0.001]; OS: 25.1 (95% CI: 12.8-57.0), 61.4 (95% CI: 45.6-79.1), and 95.3 (95% CI: 33.1-[not reached]) months, respectively [P=0.001]). The median PFS was 57.5 months (95% CI: 30.9-[not reached]) in the patients who received ASCT, vs 14.5 months (95% CI: 11.3-19.3) in those who did not (P<0.001) - with corresponding OS values of 115.9 (95% CI: 67.8-[not reached]) vs 45.6 (95% CI: 30.6-61.4) months (P<0.001). Similarly, a median PFS of 27.1 months (95% CI: 19.3-41.6) was observed for the patients who received R as part of their first-line therapy, vs 12.0 (95% CI: 9.0-16.0) months for those who did not (P<0.001) - with corresponding OS values of 67.8 (95% CI: 54.2-80.5) vs 31.6

Table 3. Survival analysis

	Median progression-free survival (95% CI)	P	Median overall survival (95% CI)	P
Age		<0.001		<0.001
≤70	27.0 (17.1, 39.8)		79.1 (46.7, 102.4)	
>70	7.4 (5.8, 11.6)		18.1 (7.3, 37.8)	
Bulky disease		0.007		0.168
Yes	7.6 (5.4, 13.7)		20.2 (8.0, 79.1)	
No	20.5 (14.8, 30.8)		57.0 (37.8, 75.6)	
Ki-67 index		0.004		0.011
<30%	32.4 (13.7, 46.1)		76.8 (43.1, 97.9)	
≥30%	7.5 (4.6, 14.5)		16.3 (7.0, 59.3)	
Pathological subtype		0.015		0.017
Blastoid	7.2 (2.4, 15.3)		10.9 (5.7, 37.7)	
Pleomorphic	9.0 (3.2, 57.5)		26.1 (9.5, 112.0)	
Others	20.2 (14.8, 30.8)		59.7 (43.1, 76.8)	
Mantle Cell Lymphoma International Prognostic Index score		<0.001		<0.001
Low	49.2 (33.2, 100.0)		83.7 (77.7, NR)	
Intermediate	31.5 (13.2, 61.5)		72.7 (30.7, NR)	
High	7.8 (6.5, 14.5)		19.3 (14.2, 45.6)	
Chemotherapy		<0.001		0.003
Low intensity	9.9 (7.4, 15.0)		25.1 (14.2, 72.7)	
Conventional	25.1 (16.2, 38.9)		61.4 (46.2, 80.1)	
High intensity	49.2 (29.2, NR)		95.3 (67.8, NR)	
Rituximab (first line)		<0.001		0.006
Yes	27.1 (19.5, 43.7)		67.8 (56.6, 83.7)	
No	12.0 (9.6, 16.3)		30.6 (19.3, 48.2)	
Bortezomib (first line)		0.069		0.186
Yes	43.9 (19.9, NR)		61.4 (56.6, 94.2)	
No	15.3 (12.2, 25.1)		46.7 (30.9, 76.8)	
Autologous stem cell transplantation		<0.001		<0.001
Yes	57.5 (43.7, NR)		115.9 (100.0, NR)	
No	13.2 (11.0, 19.1)		41.0 (26.1, 59.3)	

Abbreviations: NR: not reached.

(95% CI: 18.1-44.9) months (P=0.014). The median PFS values were 49.2 (95% CI: 29.2-67.3), 27.7 (95% CI: 11.9-50.3), and 13.8 (95% CI: 6.5-23.9) months in the low-, intermediate-, and high-risk MIPI groups, respectively (P< 0.001), with corresponding OS values of 83.7 (95% CI: 67.8-174.0), 74.3 (95% CI: 13.3-[not reached]), and 34.0 (95% CI: 17.3-[not reached]) months (P<0.001). The median PFS was 13.6 months (95% CI: 2.1-30.9) in the patients with Ki-67 indexes of ≥30%, vs 50.3 months (95% CI: 29.5-66.4) for those with Ki-67 indexes of <30% (P=0.004) - with corresponding OS values of 37.7 (95% CI: 9.1-95.3) vs 174.0 (95% CI: 79.9-[not reached]) months (P=0.011). Significant differences in OS and PFS were observed between the subgroups with different pathological MCL subtypes (PFS values for blastoid, pleomorphic, and other subtypes: 17.1 (95% CI: 0.6-27.1), 41.3 (95% CI: 1.4-67.3), and 32.4 (95% CI: 21.4-43.9) months, respectively [P= 0.015]; corresponding OS values: 34.9 (95% CI: 0.6-79.1), 80.1 (95% CI: 1.4-120.3), and 81.8 (95% CI: 67.8-115.9) months, respectively [P=0.017]; **Table 4**).

In our bivariate analysis of the transplant-ineligible group (defined as age >70 years or ECOG of >1), we found no significant benefits related to PFS or OS from first-line R or bortezomib use. The median PFS for first-line R use was 15.0 months (95% CI: 6.3-36.1), vs 9.0 months (95% CI: 4.0-11.6) for those who did not receive R (P=0.088). Similarly, the median PFS was 19.9 months (95% CI: 1.4-63.4) for those who received bortezomib, vs 7.8 months (95% CI:

Table 4. Survival outcomes (PFS and OS) in transplant-eligible patients (age ≤70 and ECOG 0-1), n=116

	Median progression-free survival (95% CI)	P	Median overall survival (95% CI)	P
Bulky disease		0.007		0.168
Yes	12.7 (4.9, 27.1)		46.7 (10.4, NR)	
No	32.4 (21.4, 49.2)		79.9 (59.3, 97.9)	
Ki-67 index		0.004		0.011
<30%	50.3 (29.5, 66.4)		174.0 (79.9, NR)	
≥30%	13.6 (2.1, 30.9)		37.7 (9.1, 95.3)	
Pathological subtype		0.015		0.017
Blastoid	17.1 (0.6, 27.1)		34.9 (0.6, 79.1)	
Pleomorphic	41.3 (1.4, 67.3)		80.1 (1.4, 120.3)	
Others	32.4 (21.4, 43.9)		81.8 (67.8, 115.9)	
MIPI score		<0.001		<0,001
Low	49.2 (29.2, 67.3)		83.7 (67.8, 174.0)	
Intermediate	27.7 (11.9, 50.3)		74.3 (13.3, NR)	
High	13.8 (6.5, 23.9)		34.0 (17.3, NR)	
Chemotherapy		<0.001		0.001
Low intensity	9.9 (7.4, 14.5)		25.1 (12.8, 57.0)	
Conventional	25.1 (16.0, 36.6)		61.4 (45.6, 79.1)	
High intensity	49.2 (26.0, NR)		95.3 (33.1, NR)	
Rituximab (first line)		<0.001		0.014
Yes	27.1 (19.3, 41.6)		67.8 (54.2, 80.5)	
No	12.0 (9.0, 16.0)		31.6 (18.1, 44.9)	
Bortezomib (first line)		0.135		0.217
Yes	43.9 (13.8, 63.4)		61.4 (46.2, 94.2)	
No	16.0 (11.9, 25.1)		47.7 (30.9, 75.6)	
Autologous stem cell transplantation		<0.001		<0.001
Yes	57.5 (30.9, NR)		115.9 (67.8, NR)	
No	14.5 (11.3, 19.3)		45.6 (30.6, 61.4)	

Abbreviations: NR: not reached.

6.2-14.8) for those who did not (P=0.135). The median OS for first-line R use was 45.6 months (95% CI: 12.8-63.4) vs 19.3 months (95% CI: 7.0-31.6) without (P=0.082). The median OS was 56.6 months (95% CI: 1.8-61.4) in the patients who received bortezomib, vs 19.3 months (95% CI: 9.5-41.0) in those who did not (P=0.217).

Only conventional-intensity chemotherapy demonstrated significant PFS and OS benefits in the first-line setting. The median OS for the patients who received conventional chemotherapy was 59.7 months (95% CI: 18.7-78.2), vs 15.0 months (95% CI: 7.8-37.8) in the low-intensity group (P=0.021). Similarly, the median PFS was 20.5 months (95% CI: 8.4-42.8) in the patients who received conventional chemotherapy, vs 7.3 months (95% CI: 5.8-11.3) in the low-intensity group (P=0.020). (**Table 5**).

Only the MIPI risk group remained significant in terms of statistically significant survival differences in our multivariate analysis of the transplant-eligible group. MIPI risk group showed statistically significant PFS differences in multivariate analysis of transplant-ineligible group but showed no statistically significant of OS.

Discussion

MCL is a relatively rare type of lymphoma with a poor prognosis that predominantly affects older male patients. It is typically in advanced stages by the time it is diagnosed, with spread to the bone marrow and gastrointestinal tract

Table 5. Survival outcomes (PFS and OS) in transplantineligible patients (age >70 or ECOG ≥2), n=88

	Median progression-free survival (95% CI)	P	Median overall survival (95% CI)	P
Bulky disease		0.007		0.168
Yes	6.3 (1.6, 9.0)		8.5 (1.6, 47.7)	
No	11.3 (6.1, 16.3)		20.9 (11.5, 48.2)	
Ki-67 index		0.004		0.011
<30%	10.7 (5.7, 20.2)		16.6 (7.0, 56.6)	
≥30%	6.5 (2.2, 10.1)		8.5 (3.5, NR)	
Pathological subtype		0.015		0.017
Blastoid	5.4 (1.4, 7.6)		6.5 (1.8, 10.9)	
Pleomorphic	4.8 (1.9, 10.1)		19.3 (6.0, 112.0)	
Others	11.5 (6.3, 17.7)		20.9 (12.8, 48.2)	
MIPI score		0.013		0.046
Intermediate	42.8 (5.4, 63.2)		72.7 (8.5, 80.5)	
High	7.0 (3.5, 10.1)		14.6 (7.0, 20.2)	
Chemotherapy		0.020		0.021
Low intensity	7.3 (5.8, 11.3)		15.0 (7.8, 37.8)	
Conventional	20.5 (8.4, 42.8)		59.7 (18.7, 78.2)	
Rituximab (first line)		0.088		0.082
Yes	15.0 (6.3, 36.1)		45.6 (12.8, 63.4)	
No	9.0 (4.0, 11.6)		19.3 (7.0, 31.6)	
Bortezomib (first line)		0.135		0.217
Yes	19.9 (1.4, 63.4)		56.6 (1.8, 61.4)	
No	7.8 (6.2, 14.8)		19.3 (9.5, 41.0)	

being common [2]. Treatment modalities for this malignancy vary widely in real-world clinical settings, owing to differing conditions and courses. The introduction of novel therapeutic agents - R, bortezomib, and BTKi - has changed the prognosis and treatment paradigms of MCL.

R has been considered a feasible treatment agent for MCL, owing to the high expression of CD20 that characterizes the malignancy. One study of 147 patients compared treatment using fludarabine, cyclophosphamide, mitoxantrone (FCM) to an R-FCM approach in cases of relapse and refractory follicular lymphoma, as well as MCL. That trial reported an improved response rate and OS in the R-FCM arm [8]; however, another study that investigated the role of R in MCL induction with CHOP revealed an improved response rate that did not translate into prolonged PFS [9]. This discrepancy may have arisen either because of the smaller number of cases in the R-FCM trial vs the FCM one, or as a result of potential synergism between specific chemotherapy agents and R [9]. Another study, for example, showed that fludarabine demonstrated synergism with R-induced complement lysis in vitro [10].

In this study, higher PFS and OS rates were noted in the patients who received R as part of their first-line treatment, but this benefit did not remain significant in our multivariate analysis. The potential synergistic effect noted earlier may have affected this result, although it is difficult to separate the effects of R from those of other chemotherapy agents when administered in conjunction to generate combined effects.

Bortezomib is a proteasome inhibitor that has been suggested to be effective for treating MCL through mechanisms that include the inhibition of cell-cycle progression, induction of apoptosis, blockading of NF-κB, and inhibition of angiogenesis [11]. When compared with the R-CHOP regimen, VR-CAP showed a significant prolongation of survival but a higher rate of hematological toxicity in the LYM-3002 trial [12, 13]. In the present study, first-line bortezomib use was not associated with significant

benefits to both PFS and OS, which may have been because of the small sample size of only 31 patients in the patient subgroup who received bortezomib as part of their first-line treatment.

ASCT, cytarabine-based induction therapy, and maintenance R therapy have been recommended by a number of national and international guidelines for younger and fitter patients with MCL. The role of consolidative ASCT in terms of prolonging PFS and OS was established based on the results of a randomized control trial that compared ASCT to interferon-alpha therapy during the first MCL remission following CHOP-like induction therapy [14, 15]. The importance of high-dose cytarabine-based induction therapy was demonstrated in the MCL Younger trial, which compared R-CHOP alternating with R-DHAP to R-CHOP alone, with both regimens being followed by consolidative ASCT. The time to treatment failure was significantly longer in the cytarabine group, although no significant difference in OS was reported [16, 17]. R maintenance therapy showed significantly improved event-free survival, PFS, and OS after four cycles of R-DHAP and ASCT in the LyMa trial, high-lighting the beneficial role of maintenance R therapy during MCL treatment [18].

In our cohort, high-dose cytarabine-based chemotherapy demonstrated a PFS and OS benefit in the subgroup of younger and fitter patients. In a retrospective comparison of two independent cohorts of younger patients with MCL, no significant differences in outcomes were reported between a first-line BR with ASCT and maintenance R approach vs R-CHOP/R-DHAP with ASCT [19]. Whether higher doses of cytarabine provide additional survival benefits therefore remains uncertain, as previous trials of the R-BAC regimen have demonstrated preserved efficacy even with reduced doses [20].

Although consolidative ASCT after first remission is commonly recommended as a treatment strategy for younger and fitter patients by several guidelines, its benefit remained unclear in certain real-world analyses [21]. The question of whether consolidative ASCT remains beneficial in the rituximab era was raised in a subgroup analysis of the longterm followup of the MCL European Network ASCT study, which reported that the overallsurvival benefit of ASCT was not statistically significant among patients who received rituximab [15]. There is currently no definitive clinical trial evidence that consolidative ASCT improves survival following R plus highdose cytarabine based induction therapy. In our study, ASCT showed significant benefits in terms of both PFS and OS in our transplant-eligible patients - although the significance of this benefit disappeared in our multivariate analysis. This may also have been because of the relatively small sample size.

Compared with the LyMA trial (R-DHAP induction + ASCT; 7-year PFS 47%) and the MCL Younger trial (R-CHOP/R-DHAP induction + ASCT; time-to-treatment-failure 8.4 years), outcomes in our transplant-eligible, high-intensity chemotherapy group were inferior: median PFS 49.2 months and median OS 95.3 months. The proportion of MIPI-high patients was similar between our cohort and LyMA (22% vs 18%) but higher than in the MCL Younger cytarabine group (13%).

Possible explanations for the inferior outcomes observed in our cohort include differences in transplant-eligibility criteria and patient selection. We defined transplant-eligible as age ≤70 years (vs ≤65 years in the LyMA and MCL Younger trials), and the retrospective design limited precise assessment of organ function and other clinical condition, increasing cohort heterogeneity. Furthermore, not all patients in our transplant-eligible, high-intensity chemotherapy group underwent ASCT consolidation (n=10; all received rituximab as part of first-line induction).

Despite these differences, the survival gap between our real-world cohort and the clinical trials suggests that consolidative ASCT after rituximab-containing, high-dose cytarabine-based induction may still confer additional long-term benefit. However, the retrospective design, potential selection biases, and treatment-delivery differences preclude causal inference; confirmation using prospective studies or larger real-world datasets is therefore warranted.

One study reported superior efficacy when ibrutinib was added to standard in-duction immunochemotherapy with ASCT for treating MCL; however, it remains un-clear whether ASCT provides additional benefits when added to ibrutinib-based treatments [22].

Age plays a significant role in the prognosis of MCL. In the MIPI scoring system, age is included as a continuous variable with a relative survival risk of 1.04 per year, rather than using the age 60 cutoff approach adopted by the International Prognostic Index. Compared with younger patients, older ones tend to experience higher toxicity from chemotherapy, not only because of potential comorbidities that affect renal and cardiac function, but also because of reduced bone marrow reserves, changes in body composition, increased body fat, and decreased total body water [23, 24]. Balancing the benefits and risks of treatment in this patient group is highly challenging. The median OS in our transplant-ineligible patient subgroup, for example, was only 18.1 months. Although conventional chemotherapy yielded significantly longer PFS and OS in these patients, this significance disappeared in our multivariate analysis that included the MIPI score. This likely reflects the clinical strategy of using conventional chemotherapy in relatively fit patients. First-line R use showed a trend toward improved PFS and OS but this trend did not reach statistical significance. Though only eight of our transplant-ineligible patients received BR in their first-line treatments, these results nevertheless support the safety and efficacy of BR use in relatively frail and older patients. In the SHINE trial, the addition of ibrutinib to BR, followed by ibrutinib plus R maintenance, significantly prolonged PFS compared with placebo plus BR and rituximab maintenance, albeit with a higher overall incidence of adverse events [25]. The ECHO study showed improved PFS but no OS benefit for acalabrutinib plus BR versus BR alone; adverse events were more frequent with acalabrutinib, while rates of key events of clinical interest (atrial fibrillation/flutter, hypertension, and infection) were similar between arms [26]. Given their improved selectivity and tolerability, second-generation BTK inhibitors such as acalabrutinib and zanubrutinib merit further evaluation in combination with immunotherapy or lower-intensity chemotherapy for transplant-ineligible patients.

As was expected, our older patients exhibited poorer overall outcomes. Incorporating novel treatments with lower toxicities and reliable levels of efficacy in first-line treatment contexts may represent a promising future direction - particularly since MCL predominantly affects older individuals.

One limitation of this retrospective study is the potential for selection bias, as treatment decisions were made based on the judgments of the attending clinicians and therefore were not predefined. Additionally, the retrospective nature of the study limits our ability to control all confounding factors such as comorbidities and variations in supportive care, further complicating the interpretation of its results. Our relatively small sample size, particularly regarding certain patient subgroups, reduced our power to detect statistically significant differences and thus may have contributed to the lack of significance noted in some of the analyses. Very few patients received maintenance R (n=9), limiting any meaningful assessment of its effect on outcomes in this cohort.

We acknowledge that our operational definition of transplant eligibility (age ≤70 years and ECOG 0-1) was pragmatic and based on available chart data and therefore does not capture other important clinical determinants of candidacy such as comorbidities, organ-function metrics, or patient preference.

Another key limitation is our absence of genetic and cytogenetic data, as well as missing LDH level and leukocyte count information in ~25% of our patients. These limitations are common in retrospective studies and emphasize the need for more comprehensive data collection in future prospective studies.

Clinical implications and future directions

Our study found that high-dose cytarabine-based induction, R, bortezomib, and consolidative ASCT were each associated with improved outcomes in this cohort. However, whether the combination of R plus high-dose cytarabine induction followed by consolidative ASCT and R maintenance represents the optimal first-line strategy remains unresolved. The relative merits of BR versus R + cytarabine based induction, the frontline use of BTK inhibitors, and the necessity and role of ASCT after different induction regimens need confirmation in prospective trials. Because MCL is still generally regarded as incurable with standard approaches, later-line modalities such as bispecific antibodies and CAR T-cell therapy are important areas for research and clinical development. Older patients in particular had worse outcomes in our cohort - likely reflecting poorer organ function,

greater comorbidity, and reduced tolerance of intensive therapy and its complications (for example, tumor lysis and infection). Given the disease's predilection for older adults (median age at diagnosis 66.5 years in our cohort), developing lower-toxicity, well-tolerated regimens for this population is an important future research direction. These results underscore the value of prospective Asian registries and pragmatic trials to define optimal induction-consolidation-maintenance pathways and to evaluate cost-effectiveness in local healthcare contexts.

Conclusions

The use of high-intensity chemotherapy, R, and ASCT during first-line treatments for MCL was associated with significantly improved PFS and OS in our patient cohort, also in subgroup of transplant-eligible patients. Among our transplant-ineligible patients, conventional chemotherapy intensity showed a survival benefit that later lost its statistical significance when we performed a multivariate analysis that included the MIPI score. First-line R use showed a trend toward improved PFS and OS, though this also did not reach statistical significance (P=0.082 for OS, P=0.088 for PFS).

MCL treatment decisions concerning chemotherapy intensity and ASCT are typically based on the clinical performance of and comorbidities present in each patient. Novel therapeutic agents are often well tolerated by most patients. Our results suggest that incorporation of novel agents and use of tolerable, risk adapted chemotherapy are associated with improved outcomes in routine practice. After addressing time dependent exposure to ASCT, era and center effects, and missingness, we anticipate that the strength and precision of these associations will be clarified.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yen-Min Huang, Division of Hematology and Oncology, Department of Internal Medicine, Keelung Chang Gung Memorial Hospital, Keelung 204201, Taiwan. E-mail: 8902004@cgmh.org.tw; Dr. Hsuan-Jen Shih, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital, Taoyuan 33305, Taiwan. E-mail: samuelshih@cgmh.org.tw

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