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Original Article

Real-world Evidence of Treatment Outcomes in Mantle Cell Lymphoma: A Single-center Experience in Southern Taiwan

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Abstract

Background: Mantle cell lymphoma (MCL) is a rare and aggressive B-cell lymphoma often diagnosed at an advanced stage. Standard first-line treatment includes bendamustine-rituximab or cytarabine-based regimens, sometimes followed by autologous stem cell transplantation (autoSCT). The TRIANGLE trial suggested that Bruton's tyrosine kinase inhibitor (BTKi)-based, transplant-free strategies may be similarly effective. In Taiwan, the use of BTKis is limited to relapsed disease due to reimbursement policies. This study analyzes the characteristics, event-free survival from first-line treatment (EFS1), and the impact of BTKis on EFS from the start of second-line treatment (EFS2) in patients with MCL. **Materials and Methods:** This retrospective cohort study included 58 MCL patients treated at Kaohsiung Chang Gung Memorial Hospital from January 2001 to December 2023. Clinical characteristics, treatment regimens, and outcomes were reviewed using the electronic medical records. EFS1, EFS2, and overall survival (OS) were analyzed. Survival curves were generated using the Kaplan–Meier method. **Results:** The median age of the patients was 65 years and 81% were male. Most patients presented with advanced-stage disease (87.9%) and 47.3% were classified as high risk according to the MCL International Prognostic Index. The median OS (mOS) and EFS1 were 45.4 months and 14.2 months, respectively. Patients who underwent frontline autoSCT had better EFS; however, more follow-up data were needed to analyze the mOS. Comparisons of different first-line regimens (cytarabine, bendamustine, and bortezomib) were not conducted due to the small number of patients. In the second-line setting, treatment with BTKis was not superior to other therapies regarding EFS. **Conclusion:** In conclusion, our real-world data suggest that frontline autoSCT may improve EFS in patients with MCL. While BTKis remain standard in relapsed settings, their benefit over chemotherapy was not evident in this cohort. These findings reflect treatment patterns and outcomes in patients in southern Taiwan and further evaluations are needed.

Keywords: Autologous stem cell transplantation, Bruton's tyrosine kinase inhibitor, mantle cell lymphoma

Introduction

Mantle cell lymphoma (MCL) is a rare and aggressive subtype of B-cell nonHodgkin lymphoma, accounting for

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approximately 5%–7% of all cases.[1] It is characterized by the t (11;14)(q13;q32) translocation, which leads to cyclin D1 overexpression and uncontrolled cell proliferation.[2] MCL typically presents in older adults, with a median age in the mid-60s and shows a male predominance.[3] At diagnosis, most patients have advanced-stage disease with frequent extranodal involvement such as bone marrow[3] and gastrointestinal (GI) tract.[4]

While MCL may respond initially to treatment, it remains incurable with standard regimens, and most patients eventually relapse. Initial treatment strategies have traditionally included immunochemotherapy such as bendamustine-rituximab, which is considered a less intensive option, or R-CHOP. In younger fit patients, treatment generally follows the approach established by the MCL Younger trial, with R-CHOP followed by cytarabine-based regimens and then autologous stem cell transplantation (autoSCT).[5] However, the optimal frontline approach continues to evolve. The recent TRIANGLE trial evaluated whether adding the Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib to standard immunochemotherapy (with or without autoSCT) could improve outcomes in previously untreated MCL. The trial demonstrated that an ibrutinib-containing autoSCT-free based approach resulted in significantly improved failure-free survival (FFS) compared to the conventional autoSCT-based approach, challenging the need for transplantation in the era of targeted therapy.[6]

However, the integration of BTKis into frontline treatment remains challenging in Taiwan. Although agents such as ibrutinib, acalabrutinib, and zanubritinib are reimbursed by the National Health Insurance (NHI) program as second-line therapy for relapsed or refractory MCL, their use in the first-line setting is not currently supported. As a result, most newly diagnosed patients continue to receive conventional chemoimmunotherapy regimens. This disconnect between evolving international standards and local reimbursement policies underscores the importance of analyzing real-world outcomes based on available therapies.

Few studies have reported the real-world outcome data in Taiwan, and none have specifically focused on southern Taiwan.[7,8] Therefore, the aim of this study was to evaluate the clinical characteristics, treatment patterns, and survival outcomes of patients with MCL treated at our center. We focus on first-line treatment modalities and report overall survival (OS) and event-free survival from first-line treatment (EFS1). For second-line treatment, we report the clinical outcomes of BTKis on EFS from the start of second-line therapy (EFS2).

Materials and Methods

Study design and participants

Patients aged 18 years or older with newly diagnosed MCL between January 1, 2001 and December 31, 2023 at Kaohsiung Chang Gung Memorial Hospital (KCGMH) were enrolled, after excluding those with a history of other malignancies. Follow-up continued until death, loss to follow-up, or the end of the study (December 31, 2024). This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. Mortality data were obtained through linkage to the National Death Registry. The Institutional Review Board (IRB) of KCGMH approved the process of acquiring data from the participants (Number: 202300712B0, approval date: June 6, 2023). Patient consent was waived due to the nature of the study design and IRB regulations.

Data including patient characteristics (age, diagnosis data, gender, white blood cell count (WBC), lactate dehydrogenase (LDH), and lymphoma involved site), immunochemical staining results, and treatment type were collected.

Treatment

The first-line treatments included cytarabine and bendamustine-containing regimens (for example, RBAC with rituximab 375 mg/m^2 intravenously on day 1, bendamustine intravenously 90 mg/m^2 on days 1 and 2, and cytarabine 0.5 g/m^2 intravenously QD on days 1 and 2), cytarabine-containing regimens (for example, R-DHAP with rituximab 375 mg/m^2 intravenously on day 1, dexamethasone 40 mg orally on days 1–4, cytarabine 2 g/m^2 intravenously every 12 h on day 2, and cisplatin 100 mg/m^2 by continuous infusion over 24 h on day 1 of 3-week cycle), bendamustine-containing regimens (for example, RB with rituximab 375 mg/m^2 intravenously on day 1 and bendamustine intravenously 90 mg/m^2 on days 1 and 2 of a 4-week cycle), CHOP-like regimens (for example, R-CHOP with rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1·4 mg/m^2 (maximum 2·0 mg), all given intravenously on day 1, and oral prednisone 60 mg/m^2 on days 1–7, 3-week cycle), bortezomib-based regimens (for example, VR-CAP with intravenous bortezomib 1·3 mg/m^2 on days 1, 4, 8, and 11 of each cycle, and rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, all given intravenously on day 1, and oral prednisone 60 mg on days 1–7, 3-week cycle), and others (for example, including radiotherapy, prednisolone alone). The choice of treatment was according to the clinician's evaluation.

The requirements for autoSCT were patients under 65 years old with normal liver and renal function, Eastern Cooperative Oncology Group (ECOG) 0, and agreeing to undergo autoSCT after fully discussion. We collected stem cells during the bone marrow recovery period after intensive chemotherapy treatment as R-DHAP. All of the patients received BCNU, etoposide, cytarabine, and melphalan as the conditioning chemotherapy regimen before autoSCT.

Second-line treatments included the first-line treatments and the BTKis ibrutinib, acalabrutinib, and zanubrutinib.

Response assessment

The treatment response for each patient was documented based on the treating physician's evaluation. The standard

lymphoma staging workup included whole-body computed tomography (CT) or positron emission tomography-CT (PET-CT), along with a bone marrow trephine biopsy. Final response evaluations were conducted following the completion of first-line therapy using PET-CT or CT. Clinical outcomes were categorized based on internationally recognized response criteria: complete response (CR) was defined as the disappearance of all evidence of disease, partial response (PR) as a ≥50% reduction in the sum of diameters of measurable lesions, stable disease (SD) as failure to achieve CR or PR, and progressive disease as worsening of the condition.

EFS was defined as the time from the initiation of therapy to the occurrence of any predefined event, including disease progression during first-line treatment, disease progression after achieving a PR, relapse following a CR, initiation of a new anti-cancer therapy, death from any cause (such as lymphoma progression, complications, or unknown cause), adverse events during treatment that required treatment cessation, or the development of a second primary malignancy. EFS was calculated from the start of therapy to the date of the first event. The time from frontline treatment was defined as EFS1, and the time from second-line treatment was defined as EFS2. OS was defined as the duration from the date of diagnosis to death from any cause, providing a comprehensive measure of survival across the study period.

Statistical analysis

Categorical data were evaluated using the Chi-square test or Fisher's exact test. Time-to-event end points were follow-up time and PFS. Analyses and graphical representations were made using the Kaplan–Meier method. Statistical significance was evaluated by the log-rank test. Analyses were performed using SPSS version 26 (IBM Inc., Armonk, NY, USA).

Results

Characteristics

A total of 58 patients were enrolled and following up until December 31, 2024. Their median age was 65 years and the majority were male (81.0%). Based on the MCL International Prognostic Index (MIPI), 25.5% of the patients were categorized as low-risk, 27.3% as intermediate-risk, and 47.3% as high-risk (n = 55). Based on histology, the classic type of MCL was identified in 75% of the patients, the pleomorphic type in 17.9%, and the blastoid type in 7.1% (n = 56). Regarding performance status, 86.0% of the patients had an ECOG score of 0–1, while 14% had a score of ≥2 (n = 57). Most patients presented with advanced-stage disease, with 87.9% in stage 3–4, and only 12.1% in stages 1–2 [Table 1]. Lymphoma with bone marrow involvement was identified in 60.3% of the patients, and spleen involvement was identified in 44.8%. GI organ involvement was noted sometimes, however only 21 patients were evaluated by endoscopy. Three patients had gastric involvement, 2 had colon involvement, and 4 had duodenum involvement [Table 2]. All patients had not only GI tract lesions but also multiple lymph node involvement or at least 2 extranodal lesions.

Among the immunophenotypic and histological markers, CD5 positivity was observed in 88.9% of the patients (n = 54), cyclin D1 positivity in 96.4% (n = 54), and CD23 negativity in 92.3% (n = 36). Of those tested for Ki-67 proliferation index (n = 28), 42.9% had a value ≥30%, and 57.1% had a value <30%. The median WBC was 8.8 × 10^3/μL (range 5.8–17.6), and the median LDH level was 213 mg/dL (range 176–309) [Table 3].

Outcomes

The median OS (mOS) of all patients was 45.4 months [Figure 1a] and the median EFS1 (mEFS1) was 14.1 months [Figure 1b]. The median follow-up OS was 126.5 months and the median follow-up EFS1 was 125.8 months. We collected clinical data and divided the patients according to MIPI score. The results showed that the mOS was 90.8 months in those with a low MIPI score, 59.8 months in those with an intermediate MIPI score, and 24.4 months in those with a high MIPI score (P = 0.013) [Figure 2a]. Eight patients received frontline autoSCT. The median follow-up time in these patients was

Table 1: Clinical basic characteristics of patients with mantle cell lymphoma

Clinical parameters	*n* (%)
Total	58
Age	65±12
Gender	
Male	47 (81.0)
Female	11 (19.0)
MIPI (total 55)	
Low	14 (25.5)
Intermediate	15 (27.3)
High	26 (47.3)
Pathology classification (total 56)	
Classic	42 (75)
Pleomorphic	10 (17.9)
Blastoid	4 (7.1)
ECOG (total 57)	
0–1	49 (86.0)
≥2	8 (14.0)
Stage	
1–2	7 (12.1)
3–4	51 (87.9)

ECOG: Eastern Cooperative Oncology Group, MIPI: Mantle Cell Lymphoma International Prognostic Index

Table 2: Organ effected by mantle cell lymphoma

Clinical parameter	*n* (%)
Bone marrow involvement	35 (60.3)
Splenomegaly	26 (44.8)
GI system involvement (total 21)	
Positive	10 (47.6)
Gastric	3 (14.4)
Colon	6 (28.6)
Duodenum	4 (19.1)

GI: Gastrointestinal

43.0 months, and the median follow-up time in those who did not receive autoSCT was 161.8 months. The mOS was not reached in the autoSCT group and 45.1 months in the no autoSCT group. The 3-year OS in the autoSCT group was 85% compared to 57% in the no autoSCT group. Due to insufficient follow-up time, we did not show *P* values [Figure 2b].

Table 3: White blood cell, lactate dehydrogenase, and immunochemical stain of mantle cell lymphoma

Laboratory	*n* (%)
CD5 (total 54)	
Positive	48 (88.9)
SOX11 (total 24)	
Positive	21 (87.5)
CyclinD1 (total 56)	
Positive	54 (96.4)
CD23 (total 39)	
Negative	36 (92.3)
P53 (total 9)	
Positive	4 (44.4)
Ki-67 (%) (total 28)	
≥30	12 (42.9)
<30	16 (57.1)
WBC (1000/μL)	8.8 (5.9–17.6)
LDH (mg/dL)	213 (170–301)

WBC: White blood cell, LDH: Lactate dehydrogenase

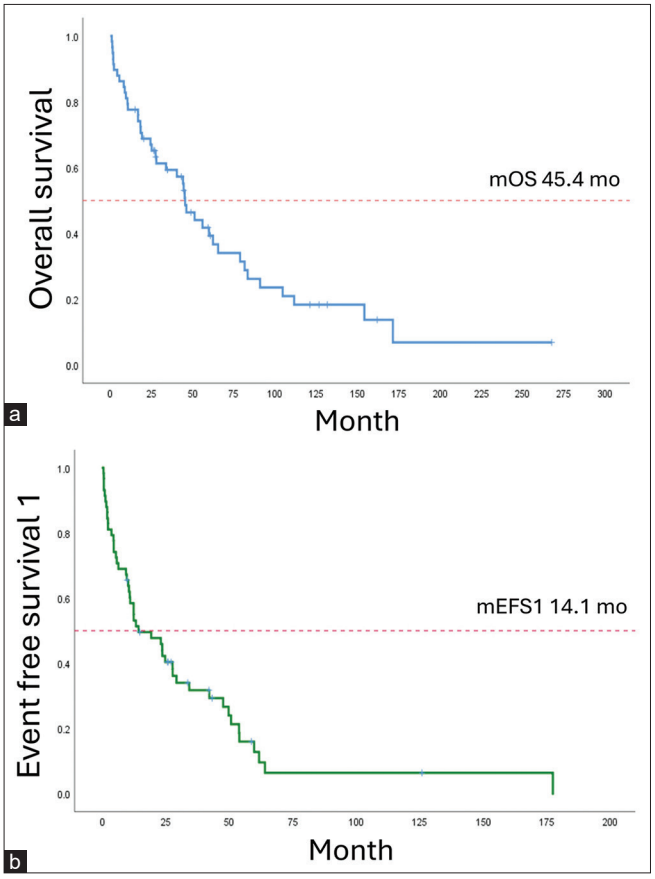

Figure 1: Kaplan–Meier estimation of all patient outcomes, (a) Overall survival analysis (the median follow-up time 126.5 months), (b) Eventfree survival 1 (of first line treatment) (the median follow-up time 125.8 months)

For EFS1, two patients who died before they received any treatment and one patient who died during treatment cycle 1 were excluded from the treatment efficacy analysis. We analyzed the impact of autoSCT on EFS1. The median follow-up time was 41.9 months in the autoSCT group and 125.8 months in the no autoSCT group. The mEFS1 was not reached in the autoSCT group and was 12.2 months in the no autoSCT group ($P = 0.030$) [Figure 3]. We also compared different first-line treatments, including cytarabine and bendamustine combination regimens, cytarabine-based regimens, bendamustine-based regimens, anthracycline-based regimens, and others [Table 4]. The CR rate with frontline treatment was 29.1%, and the PR rate was 34.5% [Table 5]. Four patients received cytarabine and bendamustine combination regimens; however, the follow-up time was too short for analysis. These patients were excluded in analysis of mEFS1. We also excluded the patients who received autoSCT from further mEFS1 analysis because of the statistical impact. We then classified the patients by those who did and did not receive cytarabine, and those who did and did not receive bendamustine. The mEFS1 of the patients who received cytarabine was 49.7 months compared to 12.1 months in those who did not ($P = 0.123$), and the mEFS1 of the patients who received bendamustine was 27.5 months compared to 10.9 months ($P = 0.189$). In addition, the mEFS1 values

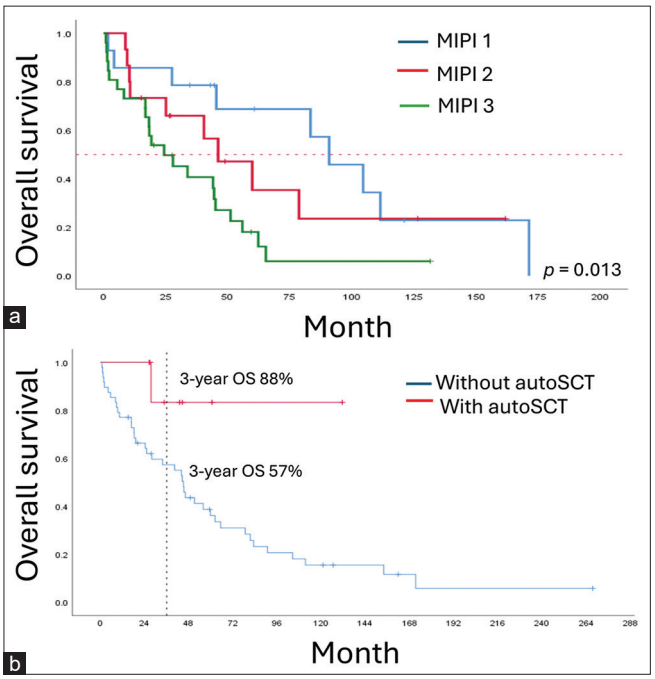

Figure 2: Kaplan–Meier estimation of patient outcomes of overall survival analysis, (a) stratified according to Mantle Cell Lymphoma International Prognostic Index score ($n = 55$) ($P = 0.013$, the median follow-up time 126.5 months), (b) stratified according to autologous stem cell transplantation or not (The median follow-up time 126.5 months)

of the patients who received cytarabine-based regimens, bendamustine-based regimens, CHOP-like regimens, bortezomib-based regimens, and others were 10.3 months, 24.6 months, 9.1 months, 9.5 months, and 12.2 months, respectively, and the mOS values were 24.3 months, 55.9 months, 44.1 months, 44.5 months, and 33.8 months, respectively. Because of the small patient number, we did not compare each treatment.

Thirty-five patients received second-line treatment, including cytarabine combined with bendamustine-based regimens (14.3%), bendamustine-based regimens (17.1%), CHOP-like regimens (28.6%), bortezomib-based regimens (11.4%), and BTKi alone or in combination (28.6%) [Table 6]. The median follow-up time was 14.4 months. The mEFS2 was 12.1 months [Figure 4a]. Comparing the patients who did and did not receive BTKis, the mEFS2 of those who used BTKis was 7.0 months compared to 14.4 months in those who did not use BTKis ($P = 0.036$) [Figure 4b].

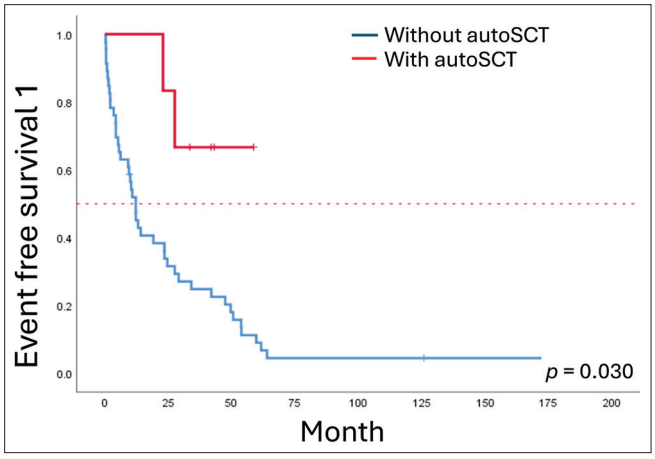

Figure 3: Kaplan–Meier estimation of patient outcomes of event free survival 1 analysis stratified according to autologous stem cell transplantation (autoSCT) or not ($n = 51$) ($P = 0.03$, the median follow-up time of autoSCT 41.9 months, of not autoSCT 125.8 months)

Discussion

The results of this retrospective study suggest that without frontline BTKi treatment, autoSCT as part of first-line management seems to benefit EFS1 when treating MCL. Although the mOS seemed to be between different between the patients who did and did not receive autoSCT, the follow-up time was insufficient. Univariable and multivariable analyses of OS showed that ECOG and EFS1 were independent prognostic factors [Supplementary Table 1]. We also performed univariable and multivariable analyses of EFS1. The prognostic factors in univariable analysis were age, autoSCT, ECOG 0–1, and MIPI. Multivariable analysis of EFS1 revealed that age and ECOG 0–1 were independent prognostic factors [Supplementary Table 2]. However, we could only adjust for autoSCT or not. After we excluded frontline autoSCT patients, there was no difference in mEFS1 between each kind of treatment. A previous cohort study in Taiwan also revealed that patients who received autoSCT had better OS compared to those who had not.[7] However, nearly half of the patients (18) in that study relapsed after autoSCT, including 7 within 12 months. In our study, 2 of the 8 patients who received frontline autoSCT had events. Despite the small number of patients in our study, frontline autoSCT seemed to be associated with clinical improvement.

As the first-line regimen for MCL, cytarabine, bendamustine, and bortezomib have been widely discussed. The MCL Younger trial investigated the outcomes when using cytarabine-based regimens, including one arm with R-CHOP and another arm with R-CHOP alternating with R-DHAP. After 10 years of follow-up, the patients in the R-DHAP arm had a longer OS (median not reached, 10-year rate 60% [95% confidence interval (CI), 53–67]) compared to those in the R-CHOP arm (median 11.3 years, 10-year rate 55% [95% CI, 48–62]).[9] For bendamustine, a previous multicenter, randomized, noninferiority, open-label, phase 3 study revealed that the effect of bendamustine plus rituximab was superior to R-CHOP.[10] The mPFS of bendamustine plus rituximab

Table 4: Different regimen and containing drugs of frontline treatment

Regimen (total 56 patients)	*n* (%)	Common regimen and dosage
Cytarabine and bendamustine based	4 (7.1)	RBAC: Rituximab 375 mg/m^2, Bendamustine 90 mg/m^2 for 2 days, Cytarabine 0.5 g/m^2 for 2 days
Cytarabine based	9 (16.1)	R-DHAOx: Rituximab 375 mg/m^2, Cytarabine 2 g/m^2 Q12H, Oxaliplatin 100 mg/m^2, Dexan 40 mg for 4 days
		HyperCVAD/MA: Cyclophosphamide 300 mg/m^2 Q12H for 3 days, Doxorubicin 50 mg/m^2, Vincristine 1.4 mg/m^2 (max: 2 mg), Dexan 40 mg for 4 days; Methotrexate 1 g/m^2, Cytarabine 3 g/m^2 Q12H for 2 days
Bendamustine based	10 (17.9)	R-B: Rituximab 375 mg/m^2, Bendamustine 90 mg/m^2 for 2 days
CHOP-like regimen*	18 (32.1)	R-CHOP: Rituximab 375 mg/m^2, Cyclophosphamide 750 mg/m^2, Doxorubicin 50 mg/m^2, Vincristine 1.4 mg/m^2 (max: 2 mg), prednisolone 60 mg for 7 days
Bortezomib based*	6 (10.7)	VR-CAP: Bortezomib 1.3 mg/m^2 for 4 days (D1, 4, 8, 11), Rituximab 375 mg/m^2, Cyclophosphamide 750 mg/m^2, Doxorubicin 50 mg/m^2, Prednisolone 60 mg for 7 days
Others	9 (16.1)	Prednisolone alone or RT alone
With rituximab	31 (57.4)	
With frontline autoSCT	8 (14.3)	

*If patient was poor performance (ECOG >2), poor cardiac function (LVEF ≤50%), or old age (≥80 years old), anthracycline was considered to be omitted. autoSCT: Autologous stem cell transplantation, ECOG: Eastern Cooperative Oncology Group, RT: Radiation therapy, LVEF: Left ventricular ejection fraction

Table 5: Frontline treatment response

	*n** (%)
Complete response	16 (29.1)
Partial response	19 (34.5)
Stable disease	5 (9.1)
Progression disease	15 (27.3)

*Total patient number for analysis was 55. 2 patients were expired before they received any treatment and 1 patient was expired during treatment cycle 1

Table 6: Different regimen and containing drugs of second-line treatment

Regimen (total 35)	*n* (%)
Cytarabine and bendamustine based	5 (14.3)
Bendamustine based	6 (17.1)
CHOP-like based	10 (28.6)
Bortezomib based	4 (11.4)
BTKi alone or combined	10 (28.6)

BTKi included Ibrutinib, acalabrutinib, zanubrutinib. BTKi: Bruton's tyrosine kinase inhibitor

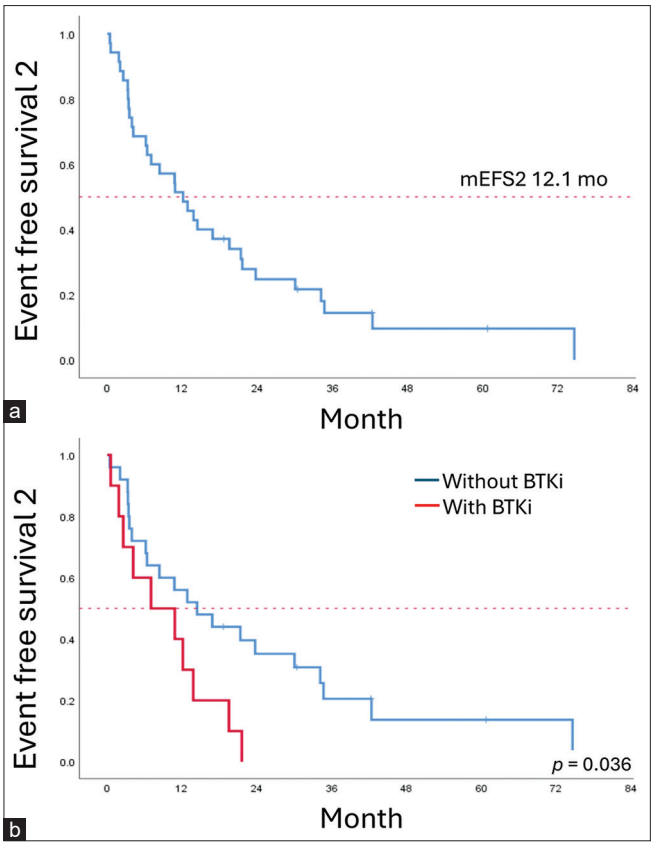

Figure 4: Kaplan–Meier estimation of patient outcomes of event free survival 2 analysis (a) with all patients (n = 35) (The median follow-up time 14.4 months), (b) stratified according to Bruton's tyrosine kinase inhibitor or not

was 35.4 months compared to 22.1 months for R-CHOP (HR 0.49, 95% CI 0.28–0.79; P = 0.0044). Another study compared bortezomibs combined with cyclophosphamide, rituximab, vincristine, and prednisolone (regimen as VR-CAP) to R-CHOP as the first-line treatment for MCL.[11] The mOS was 90.7 months in the VR-CAP group and 55.7 months in the R-CHOP group. However, no clinical trial was compared first-line treatment efficacy directly between those treatments and combined with or without autoSCT.

The TRIANGLE trial challenged the role of autoSCT in MCL frontline treatment.[6] In this phase 3 study conducted by the European MCL Network, treatment-naïve, transplant-eligible MCL patients were randomized to receive standard immunochemotherapy with autoSCT, ibrutinib in combination with immunochemotherapy followed by autoSCT, or ibrutinib-containing therapy without transplantation. The results demonstrated that both ibrutinib-containing arms had significantly improved FFS compared to the standard arm. Notably, the ibrutinib-based regimen without autoSCT achieved comparable FFS to the transplant-containing groups, suggesting that a transplant-free approach may be a viable alternative in selected patients.

Some case reports and reviews have reported the indolent presentation of MCL as GI tract polyposis.[12,13] However, MCL with additional GI tract involvement has been associated with poor outcomes in previous studies. One multicenter study from Taiwan revealed that MCL patients with gastric involvement had relatively poor outcomes.[14] Another single-center study from Austria showed no difference in OS between patients with and without GI involvement, with an OS of 116.0 months in the GI involvement group and 74.0 months in the no GI involvement group.[15] In our study, the number of patients with GI tract involvement was low. Only 21 patients received panendoscopy or colon fiberscopy and 10 patients had positive results. Among these patients, 3 had gastric involvement, 6 had colon involvement, and 4 had duodenum involvement. A relatively higher incidence but lower frequency of endoscopy examinations was noted. Clinically, physicians did not routinely arrange endoscopy examinations except for patients with abdominal discomfort or positive PET scan findings. Because of the small number of patients, we did not perform further analysis of clinical outcomes by different sites of MCL involvement.

For relapsed or refractory MCL (R/R MCL), treatments such as BTKi[16-18] are now standard. A phase II study showed the benefit of ibrutinib for R/R MCL,[16] with a medium progression-free survival of 13.9 months in all patients and 7.4 months in patients without previous bortezomib treatment. The data of the patients without previous bortezomib treatment are similar to our study, and this could explain why our patients who received second-line BTKis had a relatively shorter mEFS2 compared to those treated with other regimens. Beyond covalent BTKis, non-covalent BTKis such as pirtobrutinib have been approved by the FDA for patients with R/R MCL after at least two lines of systemic therapy, including a BTKi according to the BRUIN study.[19] The phase 3 BRUIN MCL-321 trial is currently underway

to compare pirtobrutinib with the investigator's choice of covalent BTKi (acalabrutinib or zanubrutinib) in patients with previously treated BTKi-naïve MCL.

CAR-T, Cereblon E3 Ligase Modulatory Drugs (CELMoDs) and T-cell–engaging bispecific antibodies have recently been shown to be beneficial for R/R MCL. However, currently approved CAR-T, including Brexucabtagene Autoleucel[20] and Lisocabtagene Maraleucel,[21] are not available in Taiwan. CELMoDs such as lenalidomide are usually combined with rituximab, and this regimen has been used for R/R MCL.[22] T-cell–engaging bispecific antibodies have been shown to be beneficial for diffuse large B-cell lymphoma. A phase I/II study showed that glofitamab monotherapy could be used to treat patients with R/R MCL who had previously received BTKis.[23] The results of the trial revealed a CR rate of 78.3% and overall response rate of 85% in 60 patients. However, in 31 patients who had received BTKis before, the CR rate was 71% and overall response rate was 74.2%.

The OS and treatment response rates in our study were different to a previous MCL retrospective study conducted in Taiwan.[7] Our study included older patients with higher MIPI scores. Age may be a more important cause of the difference in results because older patients could have more comorbidities, and thus lower treatment dose. Regarding second-line treatment, BTKis were found to be more effective compared with other treatment in a previous clinical trial.[16] However, this benefit was not seen in our study. This may be because more critical patients received BTKis in our study. Before November 2017, patients who wanted to use ibrutinib as second-line treatment in Taiwan needed to buy it by themselves without NHI support. Some patients may have been unable to afford the cost or chose the treatment only when facing a critical condition.

There are several limitations to this study, including the retrospective design, small number of patients, treatment heterogeneity, short follow-up, and missing molecular data. First, the retrospective study design introduced the potential for selection and recall bias inherent to historical data collection. Second, the small number of patients combined with treatment heterogeneity, meaning that the patients received a variety of different therapeutic regimens, significantly increased the risk of confounding factors and limits the statistical power and generalizability of the results. These factors made it challenging to isolate the effect of any single variable or treatment approach. The short follow-up period also presented a major difficulty, as it restricted our ability to fully assess long-term outcomes, such as OS or late-stage treatment-related toxicities, thereby complicating a comprehensive comparison of different treatment groups. Finally, the considerable amount of missing molecular data was a significant limitation. This absence of critical genetic and molecular information may have obscured important underlying biological differences between patients and could potentially have contributed to or complicated the assessment of treatment efficacy and choice.

Conclusion

Frontline autoSCT seemed to benefit EFS1 in the MCL patients in this study. Cytarabine, bendamustine, and bortezomib-containing treatments as first-line chemotherapy were effective. However, the small sample size of each treatment group and short follow-up period made subgroup analysis difficult. Although BTKi treatment was standard second-line treatment, there was no benefit in EFS2 compared to chemotherapy in our study. Despite some limitations, our study provides valuable real-world data from Southern Taiwan, reflecting actual clinical practice and offering insights into the challenges of managing MCL outside of controlled clinical trial settings.

Author contributions

Concepts - Chien-Lin Lee, Chin Yuan Kuo, Ming Chun Ma, Hung Lin Liu, Ling Jung Chiu, Pi-Han Liao, Ming-Chung Wang; Design - Chien-Lin Lee, Chin Yuan Kuo, Ming Chun Ma, Hung Lin Liu, Ling Jung Chiu, Pi-Han Liao, Ming-Chung Wang; Definition of intellectual content - Chien-Lin Lee, Chin Yuan Kuo, Ming Chun Ma, Hung Lin Liu, Ling Jung Chiu, Pi-Han Liao, Ming-Chung Wang; Literature search - Chien-Lin Lee; Data acquisition - Chien-Lin Lee, Chin Yuan Kuo, Ming Chun Ma, Hung Lin Liu, Ling Jung Chiu, Pi-Han Liao, Ming-Chung Wang; Data analysis - Chien-Lin Lee; Statistical analysis - Chien-Lin Lee; Manuscript preparation - Chien-Lin Lee; Manuscript editing - Chien-Lin Lee, Ming-Chung Wang; Manuscript review - Ming-Chung Wang. All authors have read and agreed to the final version of the manuscript.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Univariant and multivariant analysis of overall survival

OS	Univariant		Multivariant	
	HR	*P*	HR	*P*
Age	1.04 (1.01-1.08)	0.009		
Gender	1.03 (0.45-2.34)	0.946		
autoSCT	0.17 (0.02-1.21)	0.076		
ECOG (0-1)	0.17 (0.07-0.41)	<0.001	0.27 (0.11-0.965)	0.004
1st treat with R	0.92 (0.49-1.75)	0.805		
EFS1	0.96 (0.94-0.98)	<0.001	0.96 (0.94-0.98))	<0.001
Stage (III & IV)	1.31 (0.51-3.40)	0.577		
MIPI	1.82 (1.28-2.57)	0.001		
1st line with Ara-C	0.50 (0.18-1.41)	0.19		
1st line with bendamustine	0.94 (0.43-2.07)	0.881		

Supplementary Table 2: Univariant and multivariant analysis of EFS1

EFS1	Univariant		Multivariant	
	HR	*P*	HR	*P*
Age	1.04 (1.01-1.07)	0.008	1.03 (1.00-1.06)	0.24
Gender (male)	0.85 (0.39-1.84)	0.671		
autoSCT	0.24 (0.06-0.98)	0.047		
ECOG (0-1)	0.27 (0.12-0.62)	0.002	0.32 (0.14-0.76)	0.009
1st treat with R	0.67 (0.37-1.21)	0.181		
Stage (III & IV)	0.85 (0.36-2.01)	0.706		
MIPI	1.56 (1.15-2.12)	0.004		
1st line with Ara-C	0.35 (0.13-0.99)	0.047		
1st line with bendamustine	0.74 (0.35-1.56)	0.422		