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ORIGINAL ARTICLE

Continuous R-DA-EDOCH alternated with high-dose Ara-C induces deep remission and overcomes high-risk factors in young patients with newly diagnosed mantle cell lymphoma

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ABSTRACT

Objective: Our previous studies have indicated potentially higher proliferative activity of tumor cells in Chinese patients with mantle-cell lymphoma (MCL) than those in Western. Given the success and tolerability of R-DA-EDOCH immunochemotherapy in treating aggressive B-cell lymphomas, we designed a prospective, phase 3 trial to explore the efficacy and safety of alternating R-DA-EDOCH/R-DHAP induction therapy for young patients with newly diagnosed MCL. The primary endpoint was the complete remission rate (CRR) at the end of induction (EOI).

Methods: A total of 55 patients were enrolled. The CRR at the EOI was 89.1% [95% confidence interval (CI) 78%–96%], and the overall response rate was 98.1% (95% CI 90%–100%). Most patients with bone marrow involvement quickly attained minimal residual disease (MRD) negative status, with a 95.7% rate at the EOI.

Results: The 3-year progression-free survival (PFS) and overall survival rates were 66.3% and 83.2%, respectively. No patients discontinued treatment because of adverse events. Univariate analysis identified pathologic morphology and TP53 mutations as risk factors for PFS. However, high tumor proliferative activity and certain cytogenetic abnormalities showed no significant adverse prognostic significance.

Conclusions: Intensive therapy based on a high cytarabine dose and continuously administered EDOCH achieved a high MRD-negative rate and provides an optional induction choice for young patients with MCL with high-risk factors.

KEYWORDS Mantle cell lymphoma; immunochemotherapy; high-risk factors; minimal residual disease; adverse events

Introduction

Mantle-cell lymphoma (MCL) is a rare subtype of non-Hodgkin's lymphoma, with a median overall survival (OS) of only 3–5 years in the era of chemotherapy[1]. MCL is clinically characterized by its heterogeneity. Over the past 2 decades, substantial advances have been made in the prognosis of patients with MCL, with the advent of rituximab[2-7]. Currently, both the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines advocate for multiple immunotherapy regimens containing high-dose cytarabine (Ara-C) as the first-line treatment for transplantation-eligible patients with MCL. These treatments include combinations such as RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)/R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin), R-maxi-CHOP/R-HD-Ara-C (rituximab plus high-dose cytarabine), BR (rituximab and bendamustine)/R-HD-Ara-C, R-Hyper CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone)/R-MA (high-dose methotrexate and cytarabine), and R-BAC (rituximab, bendamustine, and cytarabine)[8,9]. Among these treatments, the regimen of RCHOP/R-DHAP followed by autologous stem cell transplantation (ASCT) has frequently

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been used in clinical studies. In observations over as many as 15 years, half the treated patients remained alive, and 40% remained in their first remission after more than a decade[10]. The recently proposed BR/R-HD-Ara-C regimen has also achieved high remission rates and favorable survival outcomes[11]. Although these regimens have substantially improved the prognosis of patients with MCL, the optimal regimen remains elusive; no definitive cure is close to being available, and relapses are inevitable. Moreover, high-risk individuals, particularly those with MIPI-c, TP53, MYC abnormalities, and aggressive histology, frequently have poor prognosis[12].

With deepening understanding of the mechanism of MCL, researchers are increasingly focusing on this field, and more targeted agents have been applied clinically, thus offering promise for improving MCL outcomes (**Figure 1**). Recently, Bruton's tyrosine kinase inhibitors (BTKi) have been trialed as first-line recommendations. Results from the TRIANGLE regimen trial have shown that incorporating BTKi into induction regimens enhances patient outcomes, particularly for high-risk patients[13]. However, for young patients who are transplant candidates, the traditional intensified treatment regimens already offer considerable extension in disease-free survival. Integrating BTKi might compromise patient tolerance to rigorous immunotherapy regimens, amplify the risk of infection or complications, and pose added financial burden. Precisely identifying the appropriate populations for target therapy is

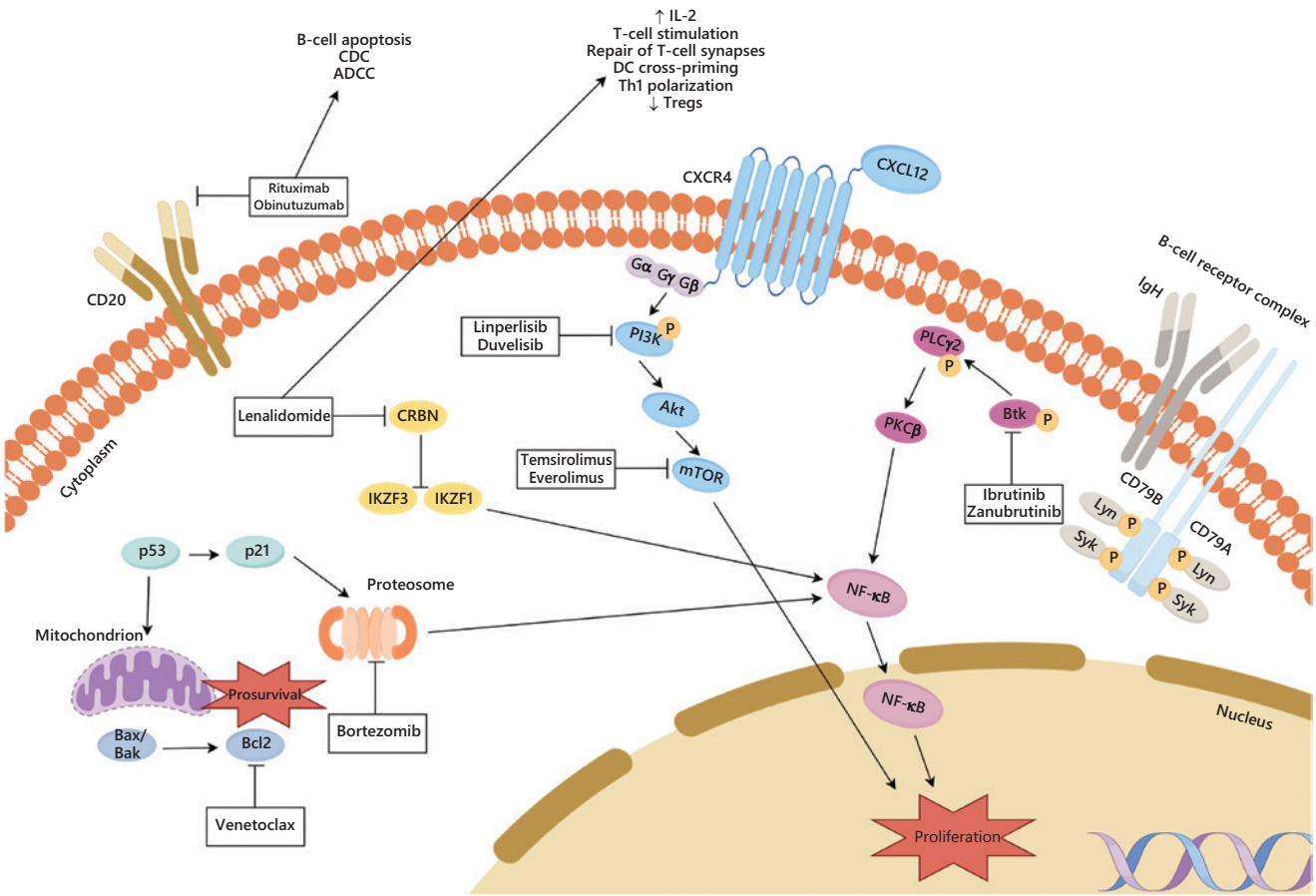


Figure 1 Key molecular mechanisms/rationales for targeted agents in mantle cell lymphoma (MCL). In MCL, sustained activation of the B-cell receptor complex results in cellular growth and survival through multiple downstream signaling pathways. This figure shows the main signaling pathways and molecules involved in B cell receptor activation, such as Btk and NF-κB. Arrows point to downstream signaling molecules or their roles. White boxes indicate novel therapies that inhibit critical elements of this signaling pathway. Akt, protein kinase B; Bak, B-cell lymphoma-2 homologous antagonist killer; Bax, B-cell lymphoma-2–associated X protein; Bcl2, B-cell lymphoma protein-2; Btk, Bruton's tyrosine kinase; CRBN, cereblon; DC, dendritic cell; IgH, immunoglobulin heavy chain; IL-2, interleukin-2; IKZF3, Aiolos; IZKF1, Ikaros; Lyn, Src-family kinase p53/56Lyn; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; PI3K, phosphatidylinositol 3-kinase; PKCβ, protein kinase Cβ; PLCγ2, phospholipase Cγ2; Syk, spleen tyrosine kinase; Th, T-helper cell; Treg, T-regulatory cell.

essential, to ensure that patients unlikely to benefit from solo immunochemotherapy receive the best tailored treatment, thus helping patients achieve maximal survival benefits at the lowest cost, and achieving personalized treatment.

Our published data have indicated that Chinese patients with MCL tend to be younger with a higher prevalence of TP53 deletion and MYC abnormalities than Western patients with MCL[14]. Given the efficacy and tolerability of the dose-enhanced immunochemotherapy R-DA-EDOCH regimen (dose-adjusted regimen, rituximab plus etoposide, dexamethasone, doxorubicin, cyclophosphamide, and vincristine) in patients with multiple high-risk aggressive B-cell lymphomas[15] and the potentially elevated tumor cell activity in Chinese patients, we designed alternating R-DA-EDOCH/R-DHAP induction therapy as an enhanced version of the RCHOP/R-DHAP regimen for young patients with newly diagnosed MCL. We conducted a phase III study (NCT02858804) of this regimen by using the new induction procedure followed by ASCT. In this context, we examined the regimen's efficacy and safety.

Patients and methods

Patients

The "EDOCH Alternating with DHAP for Newly Diagnosed Younger MCL (BDH-MCL01)" clinical trial was registered on July 17, 2016 (registration No. NCT02858804). Trial enrollment was completed in June 2020, with an estimated enrollment of 55 patients. Eligible patients 18–65 years of age who had a confirmed diagnosis of MCL with translocation breakpoints at t (11;14) or cyclin D1 expression were enrolled. The main inclusion criteria included Ann Arbor stage II–IV and Eastern Cooperative Oncology Group performance-status score (ECOG) ≤ 1. All details regarding the inclusion and exclusion criteria are outlined in the Supplementary material.

Trial design and treatments

This open-label, nonrandomized trial was conducted in accordance with the Declaration of Helsinki. The trial protocol was approved by the institutional ethics committees (IIT2021030-EC-1), and all involved patients provided written informed consent.

During induction, patients received alternating R-DA-EDOCH/R-DHAP for 2 cycles (4 courses in total). Specific drug dosages and use are listed in the Supplementary material. Patients who achieved less than partial remission (PR) stopped the trial, whereas the other patients continued with another cycle of treatment. After the 3 cycles of inductive treatment, patients decided whether to continue ASCT consolidation therapy or another cycle of consolidation. R maintenance therapy (375 mg/m^2, every 3 months for as many as 8 additional doses) was recommended to all patients. Supportive care, including the use of polyethylene glycol recombinant human granulocyte stimulating factor and prophylactic anti-infective agents, was provided at the discretion of the investigator. The clinical trial process is illustrated in **Figure 2**.

Endpoints and assessments

The primary endpoint of this study was the complete response rate (CRR) at the end of induction (EOI). Secondary endpoints included the objective response rate (ORR) at the EOI, progression-free survival (PFS), OS, and safety and tolerability. Efficacy evaluation was performed according to the Lugano 2014 criteria with positron emission tomography-computed tomography (PET-CT) and/or computed tomography (CT) after every 2 courses of treatment. PFS was defined as the time from the initiation of therapy to progression, relapse, transformation, death, or the last visit. OS was measured from the initiation of therapy to the date of death for any reason or the last follow-up. Safety and tolerability were assessed throughout the trial and as many as 90 days after the end of treatment. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events, version 5.0.

Minimal residual disease (MRD) status was the exploratory efficacy endpoint for this trial. We conducted MRD testing on the bone marrow (if involved) at 3 time points: after the 2nd and 4th courses of treatment, as well as after the completion of induction therapy. MRD was assessed in bone marrow with eight-color multiparameter flow cytometry, as previously described[16]. MRD negativity was defined as a clonal malignant cell count of $< 10^{-4}$ (0.01%).

Statistical analysis

Patients were continuously enrolled according to the eligibility criteria. We calculated the sample size on the basis of the primary endpoint, CRR. On the basis of the assumption of a CRR of 75% in this trial and a CRR of 55% as historical reference values[2], at least 50 patients were found to be required for the primary analysis. This sample size was calculated according to

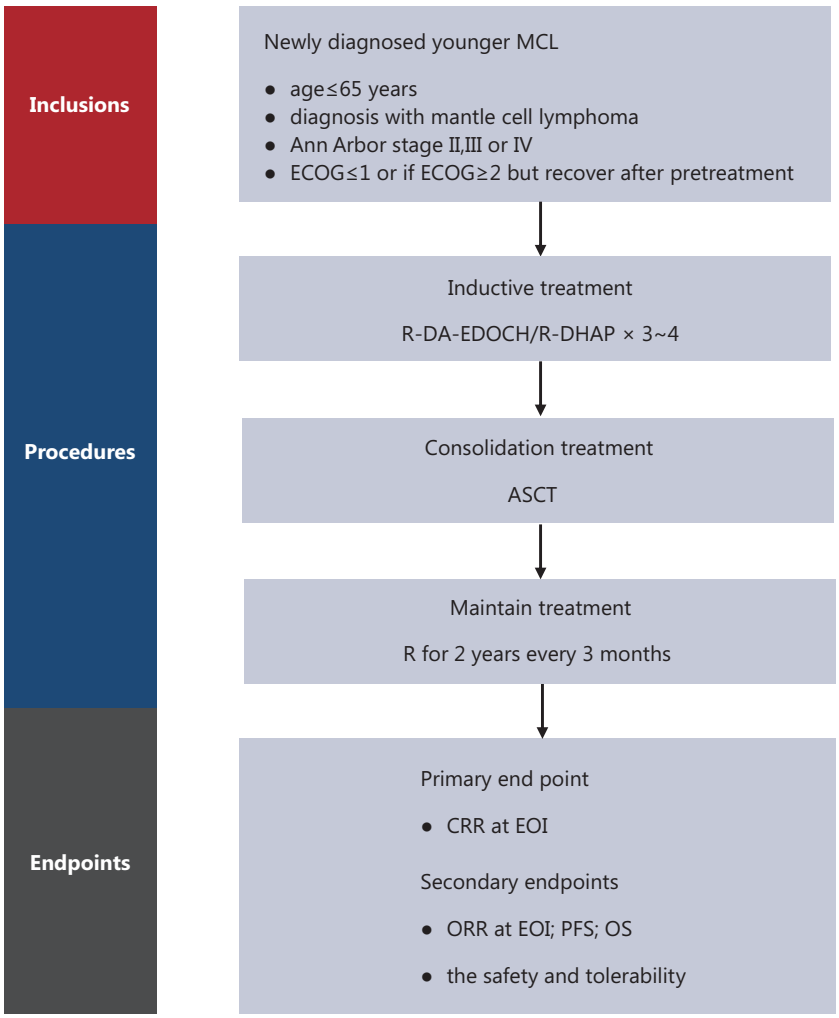


Figure 2 Clinical trial diagram. MCL, mantle cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance-status score; ASCT, autologous stem cell transplantation; R maintain, rituximab maintenance treatment; CRR, complete response rate; EOI, end of induction; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.

a test power (1-β) of 0.80, significance level (α) of 0.05 (two-tailed test), and dropout rate as 0.10. A total of 55 patients were enrolled in this study.

All efficacy endpoints were analyzed in the intention-to-treat population (defined as all patients who had undergone induction therapy), and safety was assessed in all patients who received at least one course of treatment.

Survival distributions were estimated with the Kaplan-Meier method and compared with the two-sided log-rank test. The hazard ratio and associated two-sided 95% confidence interval (CI) were calculated with a stratified Cox proportional-hazards model. Comparisons of categorical variables among subgroups were conducted with Fisher's exact test. For continuous variables, Mann-Whitney U test was used. *P* values < 0.05 (two-sided) were considered statistically significant. All calculations were performed in the Statistical Package for the Social Sciences (SPSS®) version 26.0 (IBM Corp., Armonk, NY, USA), STATA software version 15.0 (Stata Corp., College Station, TX, USA), and R version 4.0.1.

Results

Patients and treatment

We enrolled 55 patients with a median age of 53 years (range: 37–65 years). The male to female ratio was 2.2:1, as detailed in **Table 1**. Fifty-three patients (94.6%) had advanced-stage disease (Ann Arbor stage III–IV), and 38.2% patients exhibited B

Table 1 Baseline characteristics and risk stratification

Characteristics	*n*/N (%)
Sex	
Male	38/55 (69.1)
Ann Arbor	
II	3/55 (5.4)
III	4/55 (7.3)
IV	48/55 (87.3)
B symptoms	21/55 (38.2)
Pathological type	
Blastoid	6/52 (11.5)
Pleomorphic	2/52 (3.8)
Classic	44/52 (84.7)
Immunohistochemistry	
Ki-67 ≥ 30%	17/39 (43.6)
p53 ≥ 50%	18/36 (50.0)
Karyotype	
Complex	9/46 (19.6)
IGHV	
Unmutated	22/33 (66.7)
FISH	
17p deletion	10/53 (18.9)
9p deletion	14/41 (34.1)
17p deletion and 9p deletion	5/41 (12.2)
MYC translocation/amplification	9/30 (30.0)
Gene mutation	
TP53	11/42 (26.2)
TP53 and 17p-	7/42 (16.7)
CDKN2A	0/37 (0.0)
MIPI	
Low	32/55 (58.2)
Intermediate	11/55 (20.0)
High	12/55 (21.8)
MIPI-c	
Low	19/39 (48.7)
Low-intermediate	12/39 (30.7)
Intermediate-high	4/39 (10.3)
High	4/39 (10.3)
HR*	34/55 (61.8)

HR*, including at least one high-risk factor as follows: (1) MIPI-high; (2) MIPI-c-high; (3) blastoid/pleomorphic pathological type; (4) TP53 mutation; (5) 17p deletion; (6) immunohistochemistry p53 ≥ 50%; (7) 9p deletion; (8) MYC translocation/amplification; (9) complex karyotype. IGHV, immunoglobulin heavy-chain variable region.

symptoms. A total of 11.5% (6/52) of cases were of blastocytic subtype and 3.8% (2/52) of cases were of pleomorphic subtype. Immunohistochemical studies revealed a Ki-67 index ≥ 30% and p53 ≥ 50% in 43.6% (17/39) and 50.0% (18/36) of patients, respectively. TP53 mutation detection was available in 42 patients, and the mutation frequency was 26.2% (11/42). Other molecular findings included MYC rearrangements/amplifications in 30.0%, 17p deletions in 18.9%, and 9p deletions in 34.1%. Notably, 16.7% of patients exhibited both TP53 mutations and 17p deletion, denoted TP53 double-allele abnormalities. Immunoglobulin heavy-chain variable region (IGHV) somatic hypermutation analysis was performed in 33 patients, 22 (66.7%) of whom had unmutated IGHV genes. Overall, 61.8% of the patients were identified to have at least one high-risk factor according to risk stratification, pathological classification, and molecular genetic abnormalities (**Table 1**).

All patients underwent at least 2 cycles of alternating R-DA-EDOCH/R-DHAP immunochemotherapy, and successfully completed an efficacy and safety evaluation (**Figure 3**). One patient dropped out because of disease progression during induction therapy. A total of 28 patients underwent ASCT consolidation therapy, and 25 patients continued another cycle of R-EDOCH/R-DHAP consolidation therapy instead of ASCT. Among those not undergoing ASCT, 13 opted for R maintenance. Baseline characteristics and risk stratification of patients with/without ASCT are listed in **Table S1**.

High response rate and deep remission

Among the 55 response-evaluable patients, 98.1% achieved an ORR at the end of alternating R-DA-EDOCH/R-DHAP inductive treatment (95% CI 90%–100%), and the CRR was 89.1% (95% CI 78%–96%). Calculations of CRR, ORR, and partial response rates were conducted across various

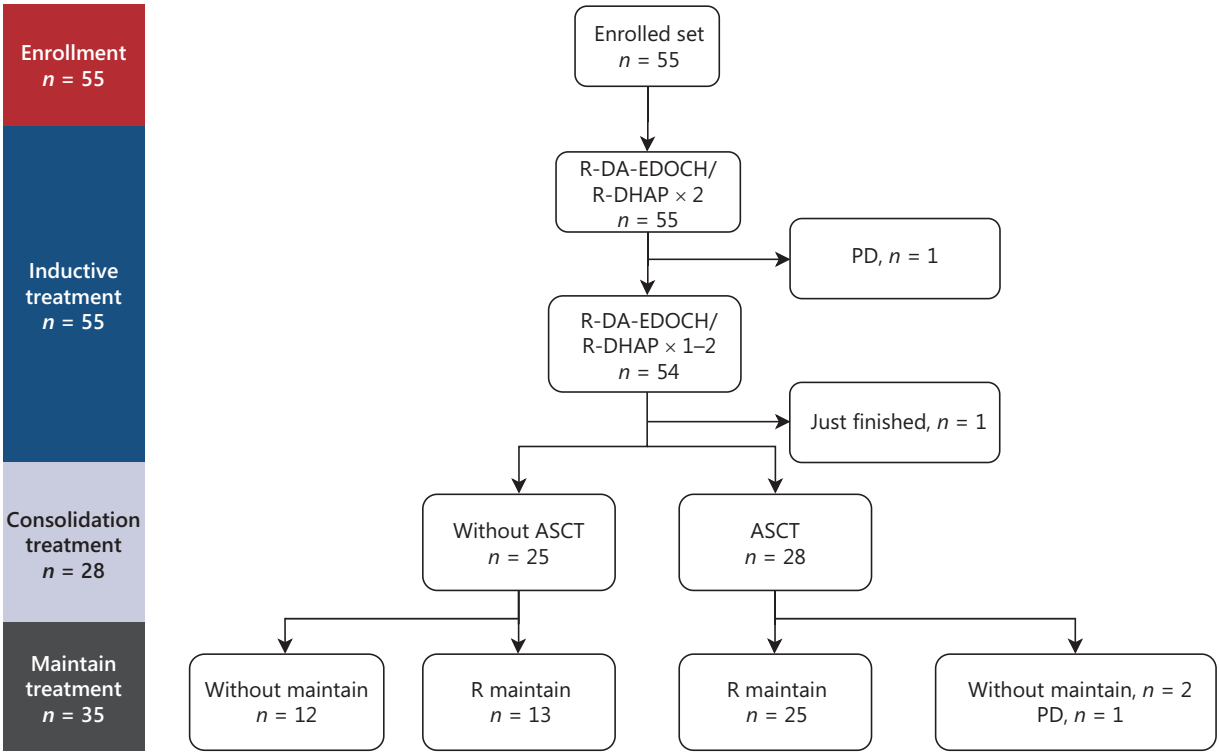


Figure 3 Patient flow. PD, progressive disease; ASCT, autologous stem cell transplantation; R maintain, rituximab maintenance treatment.

subgroups, such as MIPI, MIPI-c, pathological traits, copy number variations, and crucial tumor suppressor gene mutations. No significant differences were observed in CRR and ORR among patients with various prognostic characteristics (**Table 2**). Patients with blastoid/pleomorphic MCL displayed a relatively unfavorable treatment response, with CRR below 80% at EOI (**Table 2**).

Of the 55 patients, 48 had bone marrow involvement at their initial diagnosis. Of the 48 patients, 33 (68.8%) underwent bone marrow evaluation after 2 treatment cycles. This number increased to 45 of 48 (93.8%) after 4 treatment cycles, and further increased to 46 of 48 (95.8%) at EOI. A notable majority quickly reached MRD-negative status. Specifically, the MRD-negativity rates were 51.5% after 2 treatment cycles, 93.3% after 4 cycles, and 95.7% at EOI. Impressively, by the EOI, no detectable MRD was observed among all patients achieving a complete response (CR, *n* = 49). Additionally, of the 5 patients with PR, MRD was undetectable in the bone marrow in 3 patients. A detailed breakdown of CR and MRD-negative rates at various stages is provided in **Table S2**.

Favorable tolerability

The alternating R-DA-EDOCH/R-DHAP regimen was well tolerated, and no patients discontinued treatment because of intolerable treatment-related AEs. Hematologic AEs were predominant, and 85.5% of patients experienced at least one such event. Notably, 49.1% and 58.2% of the patients exhibited grade 3–4 leukopenia and neutropenia, respectively, whereas 14.5% experienced grade 3 neutropenic fever.

Regarding non-hematologic toxicity, we observed no instances of grade 4 AEs. The most prevalent AEs were grade 1–2 nausea/vomiting (25.4%), fatigue (17.9%), and peripheral neuritis (14.5%). Regarding infection, 15 patients developed a pulmonary infection, 7 patients had upper respiratory tract infection, 4 patients had gingivitis, and 2 patients experienced conjunctivitis and presented with a grade 3 urinary tract infection. Additionally, 2 patients (3.6%) encountered grade 2 arrhythmias during treatment. Other notable events included grade 2 thrombosis in 2 patients and grade 1 bleeding in 1 patient. Detailed hematologic and non-hematologic AEs are listed in **Table 3**.

Table 2 EOI response rates among response-evaluable patients in the indicated subgroups

Group	ORR, *n*/N (%) (95% CI)	CRR, *n*/N (%) (95% CI)	PRR, *n*/N (%) (95% CI)
Overall	54/55 (98) (90–100)	49/55 (89) (78–96)	5/55 (9) (3–20)
MIPI-low	31/32 (97) (84–100)	28/32 (88) (71–97)	3/32 (9) (2–25)
MIPI-intermediate	11/11 (100) (72–100)	10/11 (91) (59–100)	1/11 (9) (0–41)
MIPI-high	12/12 (100) (74–100)	11/12 (92) (62–100)	1/12 (8) (0–39)
Defined high risk	34/34 (100) (90–100)	32/34 (94) (80–99)	2/34 (6) (1–20)
Classic	43/44 (98) (88–100)	40/44 (91) (78–98)	3/44 (7) (1–19)
Blastoid/pleomorphic	8/8 (100) (63–100)	6/8 (75) (35–97)	2/8 (25) (3–65)
Ki-67 < 30%	21/22 (95) (77–100)	20/22 (91) (71–99)	1/22 (4) (0–23)
Ki-67 ≥ 30%	17/17 (100) (81–100)	14/17 (82) (57–96)	3/17 (18) (4–43)
IHC P53 < 50%	18/18 (100) (83–100)	16/18 (89) (65–99)	2/18 (11) (1–35)
IHC P53 ≥ 50%	18/18 (100) (82–100)	16/18 (89) (65–99)	2/18 (11) (1–35)
17p-	10/10 (100) (69–100)	9/10 (90) (56–100)	1/10 (10) (0–45)
Without 17p-	41/42 (98) (87–100)	37/42 (88) (74–96)	4/42 (10) (3–23)
9p-	14/14 (100) (77–100)	12/14 (86) (57–98)	2/14 (14) (2–43)
Without 9p-	26/27 (96) (81–100)	24/27 (89) (71–98)	2/27 (7) (1–24)
MYC abnormalities	10/10 (100) (69–100)	10/10 (100) (69–100)	0/10 (0) (0–0)
Without MYC abnormalities	19/20 (95) (75–100)	15/20 (75) (51–91)	4/20 (20) (6–44)
Complex karyotype	9/9 (100) (66–100)	9/9 (100) (66–100)	0/9 (0) (0–0)
Without complex karyotype	36/37 (97) (86–100)	34/37 (92) (78–98)	2/37 (5) (1–18)
TP53 mutation	11/11 (100) (72–100)	9/11 (82) (48–98)	2/11 (18) (2–52)
Without TP53 mutation	30/31 (97) (83–100)	27/31 (87) (70–96)	3/31 (10) (2–26)
IGHV-unmutated	22/22 (100) (85–100)	18/22 (82) (60–95)	4/22 (18) (5–40)
IGHV-mutated	10/11 (91) (59–100)	10/11 (91) (59–100)	0/10 (0) (0–0)

EOI, end of induction; ORR, objective response rate; CRR, complete response rate; PRR, partial remission rate; 95% CI, 95% confidence interval; MIPI, Mantle cell lymphoma International Prognostic Index; IHC, immunohistochemistry; 17p-, 17p deletion; 9p-, 9p deletion; MYC abnormalities, MYC translocation and/or amplification; IGHV, immunoglobulin heavy-chain variable region.

Improved prognosis

During a median follow-up of 48 months (range: 6–112 months), the 3-year PFS and OS rates were 66.3% and 83.2%, respectively (**Figure 4**). Throughout this period, 23 patients experienced disease progression. Moreover, 15 patients died: 2 because of treatment-related secondary leukemia (MCL still in CR), 1 because of cerebral infarction, 1 because of *Pneumocystis carinii* pneumonia during post-ASCT maintenance therapy, and the remaining 11 because of disease progression.

Sequential ASCT consolidation and/or R maintenance slightly increased the CRR but significantly extended PFS (3-year PFS rate: ASCT+R 83.6% *vs.* R 61.5% *vs.* without ASCT/R 50.0%, $P = 0.009$, **Figure 5**). However, the OS did not significantly vary across these groups. No significant difference in PFS and OS was observed between patients with ($n = 34$) or without ($n = 9$) high risk factors (PFS $P = 0.735$, OS $P = 0.612$). Univariate analysis revealed that blastoid/pleomorphic pathologic morphology ($P = 0.003$), TP53 mutation ($P = 0.038$), and TP53 double-allele events ($P = 0.020$) were risk factors for PFS under this therapeutic approach (**Figure 6**).

Table 3 Hematologic and non-hematologic adverse events

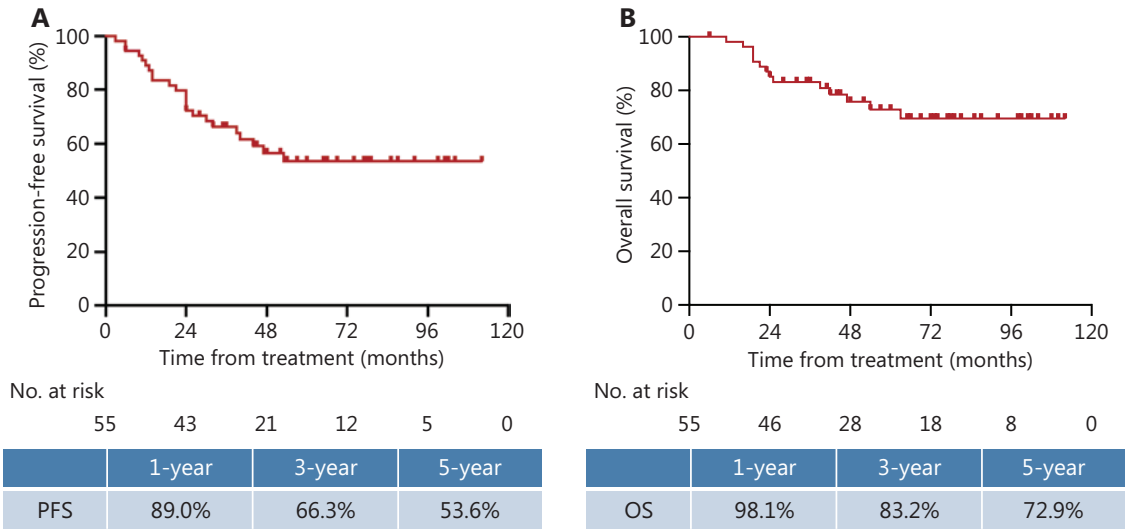
Categories	SAEs (%)	Grade 4 (%)	Grade 3 (%)	Grade 2 (%)	Grade 1 (%)
Leukocytopenia	27 (49.1)	13 (23.6)	14 (25.5)	13 (23.6)	6 (10.9)
Neutrocytopenia	32 (58.2)	19 (34.6)	13 (23.6)	8 (14.5)	3 (5.5)
Anemia	4 (7.3)	0 (0.0)	4 (7.3)	24 (43.6)	4 (7.3)
Thrombocytopenia	14 (25.5)	9 (16.4)	5 (9.1)	5 (9.1)	4 (7.3)
Febrile neutropenia	8 (14.5)	0 (0.0)	8 (14.5)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.6)	4 (7.3)
Nausea/vomiting	0 (0.0)	0 (0.0)	0 (0.0)	7 (12.7)	7 (12.7)
Abdominal distension/pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	1 (1.8)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	3 (5.5)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Hyperglycemia	2 (3.6)	0 (0.0)	2 (3.6)	3 (5.5)	3 (5.5)
Hypokalemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.3)
Elevated creatinine	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.5)	1 (1.8)
Upper respiratory infection	1 (1.8)	0 (0.0)	1 (1.8)	6 (10.6)	0 (0.0)
Pulmonary infection	13 (23.6)	0 (0.0)	13 (23.6)	2 (3.6)	0 (0.0)
Urinary system infection	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Gingivitis	1 (1.8)	0 (0.0)	1 (1.8)	3 (5.5)	0 (0.0)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Thrombus	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)
Infusion reactions	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)
Peripheral neuritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	7 (12.7)

Interestingly, factors such as high tumor proliferative activity (e.g., Ki-67 ≥ 30% and MYC abnormalities) and certain negative genetic abnormalities (e.g., deletions on chromosomes 17p and 9p) lacked statistically significant adverse prognostic implications. To further explore the effects of treatment options on the prognosis of high-risk patients, we performed a subgroup analysis of high-risk patients (with TP53 abnormalities or/and blastoid morphology). High-risk patients who completed transplantation and maintenance therapy had better prognosis than those who did not undergo transplantation or maintenance therapy (**Figure S1**). However, in this post-hoc analysis, some subgroups had very small sample sizes; therefore, statistical validity is lacking, and further research in larger sample sizes is necessary.

Because of the high proportion of patients with bone marrow MRD negativity after intensive treatment, only 2 patients were bone marrow MRD-positive after induction therapy. This finding might explain the absence of prognostic significance in the bone marrow MRD status ($P = 0.347$).

Discussion

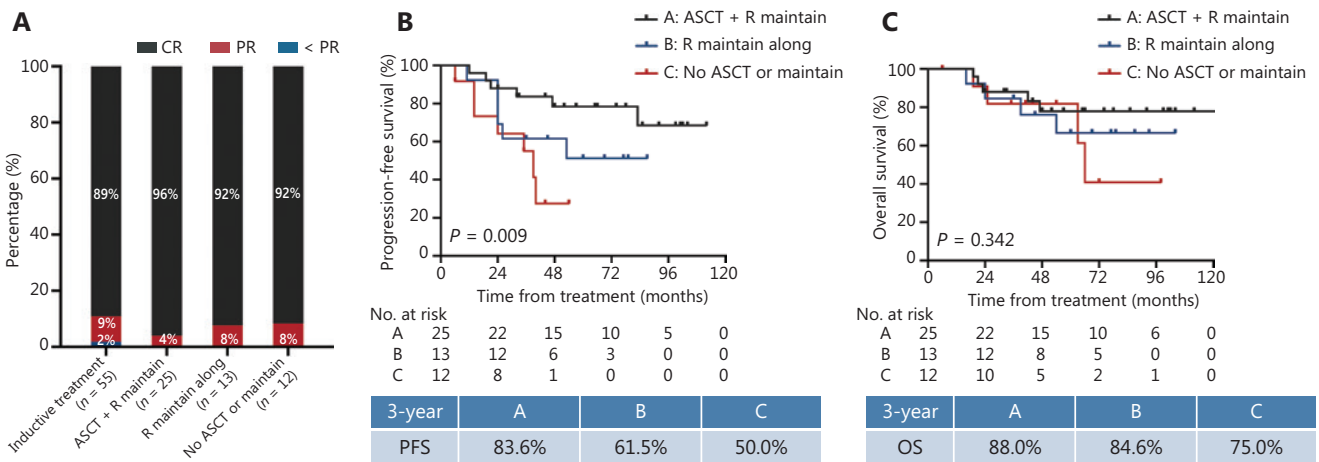
MCL is a heterogeneous disease presenting diverse pathophysiological and genetic characteristics, clinical symptoms,



	1-year	3-year	5-year
PFS	89.0%	66.3%	53.6%

	1-year	3-year	5-year
OS	98.1%	83.2%	72.9%

Figure 4 PFS (A) and OS (B) of the entire cohort. PFS, progression-free survival; OS, overall survival.



3-year	A	B	C
PFS	83.6%	61.5%	50.0%

3-year	A	B	C
OS	88.0%	84.6%	75.0%

Figure 5 Response rates (A), PFS (B), and OS (C) for the indicated treatment subgroups. ASCT + R maintain, patients received both autologous stem cell transplantation and rituximab maintenance treatment; R maintain along, patients received only rituximab maintenance treatment after induction therapy; no ASCT or maintain, patients received neither autologous stem cell transplantation nor rituximab maintenance treatment; PFS, progression-free survival; OS, overall survival.

staging, and prognosis[1]. Various clinical trials and real-world studies have assessed the potential effectiveness of various treatment approaches[2-4,17-24], yet a standardized and curative solution for MCL remains undefined. This prospective clinical trial underscores the efficacy and safety of the first-line induction therapy of alternating R-DA-EDOCH/R-DHAP for young patients with MCL. Impressively, most participants attained CR [CRR 89% (95% CI 78%–96%)] and MRD-negative status quickly, and showed notable tolerance. Except for pathologic morphology and TP53 aberrance, high tumor proliferative activity (such as Ki-67 ≥ 30% and MYC abnormalities) and certain other genetic abnormalities showed no significant adverse prognostic effects. Moreover, the sequential application of ASCT consolidation and/or R maintenance ($P = 0.019$) significantly prolonged PFS in patients with MCL.

In the era of immunochemotherapy, rituximab, high-dose cytarabine, and ASCT have emerged as the 3 cornerstones for treatment of young patients with MCL. Prior research has

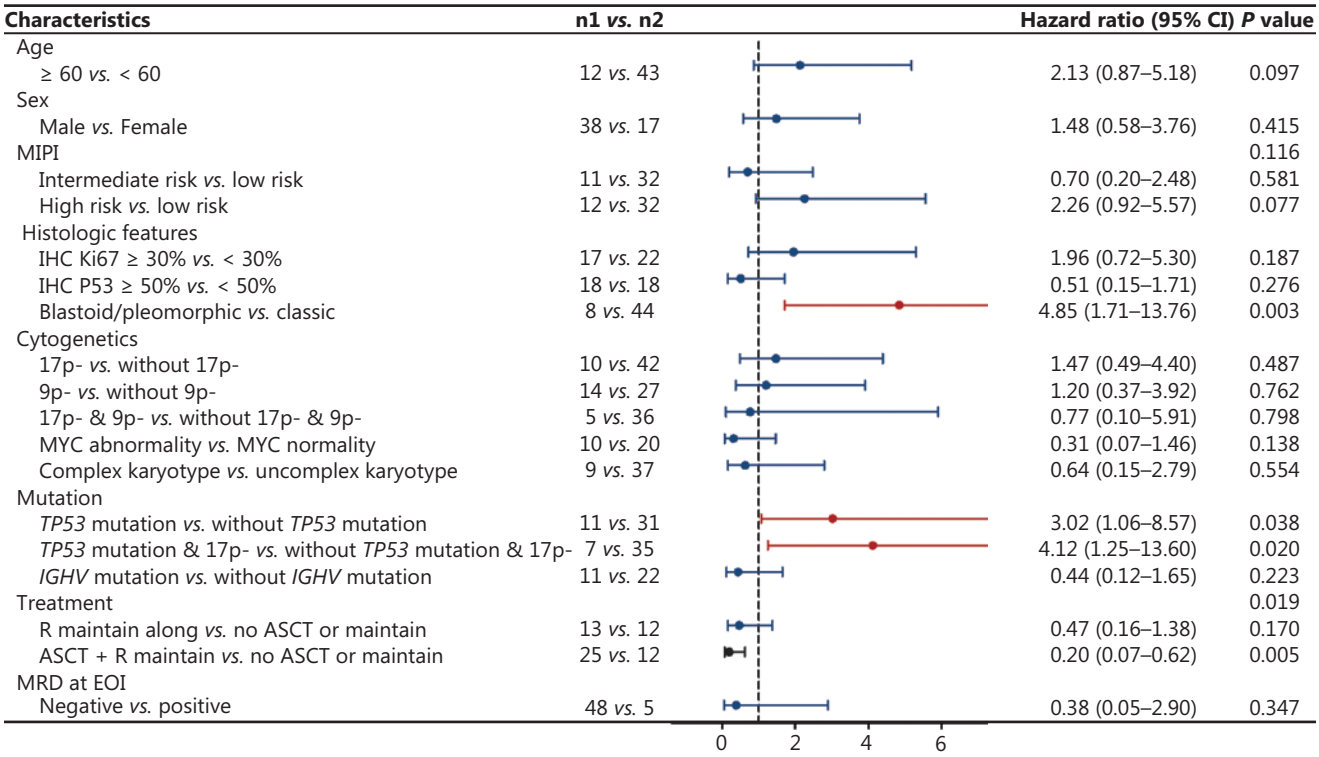


Figure 6 Univariate analysis of PFS. PFS, progression-free survival; MIPI, Mantle cell lymphoma International Prognostic Index; IHC, immunohistochemistry; 17p-, 17p deletion; 9p-, 9p deletion; MYC abnormalities, MYC translocation and/or amplification; IGHV, immunoglobulin heavy-chain variable region; ASCT + R maintain, patients received both autologous stem cell transplantation and rituximab maintenance treatment; R maintain along, patients only received rituximab maintenance treatment after induction therapy; no ASCT or maintain, patients received neither autologous stem cell transplantation nor rituximab maintenance treatment; MRD, minimal residual disease; EOI, end of induction.

indicated that approximately 55% of young patients with MCL reached CR after completing alternating R-CHOP/R-DHAP induction. However, this rate is arguably insufficient for a condition known for its high aggressiveness and unfavorable outcomes. Furthermore, our previous study has indicated that Chinese patients with MCL are younger and have a higher proportion of TP53 deletion and MYC abnormalities than western patients with MCL, both of which are unfavorable prognostic indicators, thereby suggesting potentially enhanced tumor cell proliferation in this demographic[14]. Further analyses of Alliance/GALGB 50303 clinical trial data have indicated that R-DA-EPOCH improves PFS in intermediate-high-risk and high-risk patients with untreated diffuse large B-cell lymphoma, with relatively favorable tolerance[15]. Consequently, we hypothesized that alternating R-DA-EDOCH/R-DHAP would not be inferior to alternating R-CHOP/R-DHAP as the inductive therapy for eligible patients with MCL, and specific subgroups would benefit from this regimen. The CRR and the ORR at the EOI were 89% (95% CI 78%–96%) and 98% (95% CI 90%–100%), respectively, surpassing those of other immunochemotherapeutic modalities such as alternating R-CHOP/R-DHAP (55%) and R-hyper CVAD/R-MA (87%)[2,4]. The patients who completed the ASCT and R maintenance showed comparable survival in our study, although the proportion of high-risk patients appeared to be greater than those in previous studies[10,25]. Only 51% patients underwent ASCT consolidation and/or R maintenance in this study, partially because of COVID-19 disruptions in recent years. In alignment with findings from Le Gouill et al.[6], the subgroup analysis affirmed that ASCT consolidation and/or R maintenance did prolong PFS in our study. However, no significant OS advantage was observed in the ASCT subgroup. The introduction of pioneering treatments after progression, such as BTKi and B-cell lymphoma-2 inhibitor (BCL2i), and/or participation in clinical trials, have largely improved post-relapse survival among patients in whom immunochemotherapy has failed.

As anticipated, alternating R-DA-EDOCH/R-DHAP induction was generally well-tolerated, with manageable rates of

hematologic and infectious AEs. Grade 3–4 leukopenia and neutropenia were the most prevalent severe AEs. Nonetheless, compared with previous studies, there were limit fatal infectious events under necessary support treatment, including the utilization of granulocyte-stimulating factor and prophylactic anti-infective agents. Crucially, this regimen did not impair the successful collection of stem cells for ASCT and was suitable for patients eligible for transplantation.

One pressing challenge in contemporary lymphoma treatment is ensuring a lasting response for most patients. MRD has emerged as a critical posttreatment outcome predictor[26]. Among patients with MCL, substantial evidence has highlighted that achieving deep remission, defined as a CR paired with MRD negativity, correlates with extended survival[11,27,28]. Various methods have been used for MRD monitoring in the context of MCL, but a standard detection method remains elusive. We used a prognostic evaluation approach by integrating radiologic imaging with eight-color multiparameter flow cytometry of samples with bone marrow involvement. This approach enabled comprehensive evaluation of both nodal/extranodal lesions and bone marrow involvement. The rate of CR with bone marrow MRD negativity at the EOI reached 88.7%, a value higher than those in prior studies. Compared with other studies, this result indicated deeper remission and better status for the following therapy. In particular, the longitudinal data also indicated rapid remission in our cohort, thereby demonstrating the potency of the regimen.

Given the limited sample size of our cohort, we did not perform further multivariate prognostic analysis. In our univariate prognostic analysis, traditionary risk factors[1,12] such as MIPI, 17p deletion and 9p deletion did not significantly influence survival. Notably, risk factors associated with tumor proliferative activity, such as Ki-67 ≥ 30% and MYC abnormalities, exhibited no marked prognostic significance, as expected. The CRR and MRD-negative rate were relatively high in these high-risk patients. These results suggested that R-DA-EDOCH/R-DHAP therapy was an effective induction regimen in patients with high proliferative activity. However, this intensive treatment did not work well in patients with blastoid/pleomorphic pathologic morphology and patients with TP53 mutation and/or TP53 double-allele events. Together with results from other studies, our findings highlighted that immunochemotherapy alone might not fully overcome the adverse prognostic effects of pathologic morphology and TP53 aberrance[12,29]. Over the past decade, the therapeutic landscape for MCL has considerably evolved. Targeted agents, such as immunomodulatory drugs (e.g., lenalidomide), BTKi, and BCL2i, have shown remarkable efficacy in patients with relapsed/refractory status and are now options in first line therapy, particularly for high-risk patients with MCL[29]. The key molecular mechanisms and rationale for use of targeted agents in MCL are illustrated in **Figure 1**. Encouragingly, the subgroup analysis of the ZUMA-2 clinical trial indicated comparable ORRs for patients regardless of blastoid morphology and TP53 mutation[30]. We eagerly anticipate further studies to provide deeper insights into high-risk MCL and to enhance the survival prospects of these patients.

Conclusions

In summary, alternating R-DA-EDOCH/R-DHAP inductive therapy showed impressive efficacy and favorable tolerability in young untreated patients with MCL in this prospective study. Under intensive therapy, patients showed a significant increase in the rate of deep remission and MRD-negative status. Intensive therapy based on a high dose of cytarabine and continuously administered EDOCH may partially overcome the adverse prognostic effects of high-risk factors such as high MIPI risk, high Ki-67, and MYC abnormalities. However, this treatment cannot fully overcome the negative effects of blastoid pathological subtypes and TP53 mutations. Combination therapy with targeted drugs is necessary to provide patients with additional survival benefits. The alternating R-DA-EDOCH/R-DHAP regimen presents a compelling induction choice for young patients with MCL, particularly for those with high tumor proliferative activity.

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Conflicts of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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Contributed data or analysis tools: Yi Wang, Yuting Yan, Wei Liu, Tingyu Wang, Gang An, Weiwei Sui, Wenyang Huang, Wenjie Xiong, Huimin Liu, Qi Sun, Huijun Wang, Zhijian Xiao, Jianxiang Wang, Lugui Qiu, Dehui Zou, Shuhua Yi.
Performed the analysis: Yi Wang, Yuting Yan.
Wrote the paper: Yi Wang, Yuting Yan, Shuhua Yi.

Data availability

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

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