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REVIEW

Real-World Evidence of Relapsed/Refractory Mantle Cell Lymphoma Patients and Treatments: A Systematic Review

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Introduction: Mantle cell lymphoma (MCL) is an incurable disease with an aggressive clinical course, and most patients eventually relapse after chemotherapy. Targeted therapies developed for relapsed/refractory MCL have been approved based on clinical trial data. However, real-world setting data are scarce and scattered.

Areas Covered: This systematic review aimed to collect, synthesize, and describe the characteristics and treatment outcomes of patients with relapsed/refractory MCL after receiving a second or subsequent line of therapy in the real-world setting.

Expert Opinion: R/R MCL is clinically and biologically heterogeneous and still represents a therapeutic challenge, with high-risk and early relapsed patients remaining an unmet medical need. This systematic review is limited by the quality of the available data and the difficulty of comparing outcomes in R/R MCL due to the heterogeneity of the disease, but the results suggest that covalent BTKis should be positioned as second-line therapy, followed by CAR T-cells in BTK-i-relapsed patients. Chemo-free and combination therapies with established chemoimmunotherapy backbones in the relapsed and front-line settings have been recently developed, and front-line options are being improved to move targeted and cellular therapies to earlier lines, including front-line therapy, in elderly and younger fit patients. In the upcoming years, many new targeted agents will play an important role and will be incorporated to the routine practice as their sequence, and outcomes in unselected patients are determined.

Keywords: CAR-T cells, ibrutinib, mantle cell lymphoma, real-world evidence, relapsed/refractory mantle cell lymphoma (R/R MCL), treatment efficacy

Introduction

Mantle cell lymphoma (MCL) is an infrequent subtype of non-Hodgkin lymphoma (NHL) that accounts for approximately 5 to 7% of lymphoid malignancies in Western Europe,[1] but its incidence seems to be increasing over time.[2] It is an incurable disease with a median age at diagnosis of 68 years,[3] more common in men than in women (ratio around 3:1).[1,2]

Although two types of clinically indolent MCL variants have been recognized —leukemic non-nodal MCL and in situ mantle cell neoplasia— most patients with MCL present with an aggressive clinical course.[1,4] Moreover, MCL patients usually experience multiple relapses, and survival outcomes worsen with increasing lines of therapy.[5] Some clinical and pathological features have been identified as prognostic factors of MCL, such as the MCL International Prognostic Index (MIPI), the Ki-67 index, aberrations in the TP53 tumor suppression gene (eg, TP53 mutations and del17p), presence of blastoid or pleomorphic histologic variants, and an early progression of disease after first-line therapy, especially within the first one or two years.[6]

Historically, several chemotherapy-based strategies have been used for MCL depending on the patient's age, functional status, and number of previous lines of therapy, but most patients eventually relapse.[1] In the last few years, several targeted treatment approaches have been developed for relapsed/refractory MCL (R/R MCL), including Bruton's tyrosine kinase (BTK) inhibitors, B-cell lymphoma 2 (BCL-2) inhibitors, lenalidomide and bortezomib-based approaches, m-TOR inhibitors, and chimeric antigen receptor (CAR) T-cell therapy.[6] Of those, the first–in–class BTK inhibitor ibrutinib has been positioned

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as the standard of care in the second line of therapy for MCL, based on the data from a pooled analysis of three clinical trials of R/R MCL patients treated with ibrutinib.[7]

The recommendations of treatment guidelines for R/R MCL are usually based on clinical trial data.[1] Nevertheless, it is considered useful to validate the efficacy and safety of treatments in real-world studies to adopt them in routine clinical practice. In this regard, the real-world evidence currently available on R/R MCL treatments is scarce and scattered,[8–14] and it is often difficult to compare due to the diversity of the approaches and the patients' characteristics. Therefore, this systematic review aimed to collect, synthesize, and describe the characteristics and treatment outcomes of patients with R/R MCL after receiving a second or subsequent line of therapy in the real-world setting.

Materials and Methods

A systematic literature search was performed and reported in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, a guideline for standard reporting of systematic literature reviews.[15]

Eligibility Criteria

Real-world studies including patients with confirmed R/R MCL, written in English, published between 2010 and 2022, and indexed in PubMed or corresponding to 2021 congress publications of the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), the European Hematology Association (EHA), or the International Conference on Malignant Lymphoma (ICML) were eligible for inclusion. Conversely, clinical trials, case studies, or case series of <10 patients (excepting those considered relevant to mention in this review due to their uniqueness), and publications not reporting original data (eg, letters, editorials, comments, or systematic reviews) were excluded from the study. Other exclusion criteria were patients naïve to MCL treatment, outdated treatment regimens, and studies not reporting outcomes regarding survival or treatment response. Moreover, we excluded studies assessing transplantation strategies, given that they are mostly consolidation therapies with outcomes depending on previous rescue treatments, precluding direct comparisons.

Information Sources and Search Strategy

The literature search was performed on 15 May 2022 using the MEDLINE database through PubMed and websites with relevant conference materials on the subject —ie, the proceedings of the biennial International Conference on Malignant Lymphoma (ICML)[16] and the annual meetings of the American Society of Hematology (ASH),[17] the American Society of Clinical Oncology (ASCO),[18] and the European Hematology Association (EHA).[19]

The search strategy in MEDLINE was as follows: ("relapsed" AND/OR "refractory") AND "mantle cell lymphoma" AND ("retrospective" OR "real life" OR "real world" OR "case report"). In addition, for the manual search of ICML, ASH, ASCO, and EHA conference proceedings, the keywords "relapsed", "refractory", mantle cell lymphoma, "real world", "retrospective", "real life", and "case series" were used.

In order to cover the most relevant pharmacological strategies for R/R MCL in current daily clinical practice, the search was limited to articles written in English, with full text available, published between 2010 and 2022. Furthermore, if the most relevant results presented to international congresses before 2021 would have already been published as journal articles, the abstracts of the proceedings were manually searched only for studies published since 2021.

Study Selection, Data Collection, and Data Items

Two reviewers independently screened all titles/abstracts and the full text of the retrieved publications potentially relevant for inclusion. Any disagreements were resolved by consulting with a third author. Similarly, the data were independently collected by two reviewers in predefined table disagreements, if any, were resolved by discussion with a third author.

The data collected related to the study included the first author, the year of publication, the treatment, and the sample size. Data regarding the baseline characteristics of study patients included age, gender, Eastern Cooperative Oncology Group (ECOG) score, stage of the disease according to the Ann-Arbor classification, number of previous lines of therapy,

previous autologous or allogeneic stem cell transplantation (auto-SCT or allo-SCT, respectively), refractoriness to previous lines of therapy, progression of disease within 24 months (POD24), MIPI or simplified MIPI (sMIPI), Ki-67 index, TP53 aberrations, and presence of aggressive histologic variants (ie, blastoid or pleomorphic MCL). Clinical outcomes related to treatment efficacy were as follows: progression-free survival (PFS), overall survival (OS), overall response rate (ORR), complete response (CR), and follow-up.

Risk of Bias Assessment

The risk of bias of the included studies was assessed by two reviewers using the Joanna Briggs Institute (JBI) critical appraisal tool for case series.[20] Any discrepancies were resolved by discussion with a third author.

Data Synthesis and Analyses

Data were presented as a narrative synthesis of the available data reported for each retrieved treatment regimen.

Results

A total of 300 publications were identified using the described search strategies. After removing all duplicates and excluding studies that did not meet the inclusion criteria, a total of 25 journal articles —18 original articles,[8–11,14,21–33] 3 letters to the editor,[34–36] 3 short reports,[13,37,38] and 1 case report[39] and 5 conference publications[40–44] were included in the systematic review. All the 30 studies allowed the data collection of 37 treatment regimens for R/R MCL patients. Of them, 15 were based on BTK inhibitors, 14 on chemotherapy or immunochemotherapy, and 8 on other strategies. Table 1 summarizes the general characteristics of the treatment regimens and patients included in the systematic review.

BTK Inhibitor Regimens

All studies on BTK inhibitors analyzed the use of ibrutinib, either as monotherapy (n = 13 treatment regimens)[8–11,14,21–24,34,37,40,41] or combined (n = 2).[24,39]

Ibrutinib Monotherapy

The treatment regimens based on ibrutinib monotherapy included from 33 to 211 patients (n = 12), mostly males (65% to 82%, n = 12), with a median age at treatment between 65 and 74 years (n = 8) (Table 1). The percentages of patients with an ECOG score ≥2 and a III–IV stage R/R-MCL according to the Ann-Arbor classification ranged from 5.2% to 34% (n = 9) and from 68.1% to 93% (n = 10), respectively. The median number of previous lines of therapy varied from 1 to 3 (n = 10), and the proportion of patients with a previous auto-SCT was between 13% and 66% (n = 11), and between 0% and 11% (n = 4), for allo-SCTs. Regarding response to previous treatments, between 16% and 48.1% of the patients were refractory to first-line therapy (n = 3) and between 18.2% and 47.1% were refractory to the most recent treatment line (n = 3); 47.8% to 54% of the patients were POD24 regarding their front-line therapy (n = 3). Additionally, the percentage of patients with an intermediate-high MIPI/sMIPI and a Ki-67 index ≥30% ranged between 44% and 87% (n = 7), and between 33.3% and 55.6% (n = 5), respectively. The proportion of patients presenting with high-risk blastoid or pleomorphic histology differed considerably among studies (from 3.4% to 32.6%, n = 9), with only three studies reporting TP53 aberrations, which ranged from 0 to 20%.

The efficacy outcomes of patients treated with ibrutinib alone were also quite variable and included a median PFS ranging from 7.9 to 30.8 months (n = 13), a median OS from 12.4 to 38 months (n = 12), an ORR from 36.4% to 95.9% (n = 10), and a CR from 15% to 39.5% (n = 9), with median follow-ups ranging from 12.6 to 60 months (Table 2).

Ibrutinib in Combination

Two studies analyzed the efficacy of ibrutinib in combination with other agents. The first one reported the outcomes of ibrutinib combined with several other agents (rituximab, lenalidomide, bortezomib, and/or bendamustine) in 53 patients (75.5% males, median age of 56 years),[24] of which 28.3%, 84.9%, 51.0%, and 54.7% had an ECOG score ≥2, a III–IV stage R/R-MCL, an intermediate-high sMIPI, and a Ki-67 index ≥30%, respectively. In addition, the percentages of patients with a previous auto-SCT, refractoriness to the most recent line of therapy, and blastoid histology were 9.4%, 47.2%, and 19.2%.

Table 1 General Characteristics of the Assessments and Patients Included in the Systematic Review According to the Type of R/R MCL Treatment[a]

First author, publication date	Treatment	Patients, N	Age (years), *median (range)*	Male gender, n (%)	ECOG score ≥2, n (%)	Ann-Arbor stages III–IV, n (%)	No. of previous LoT, *median (range)*	Previous auto-SCT, n (%)	Previous allo-SCT, n (%)	Refractoriness to previous LoT, n (%)	POD24, n (%)	MIPI or sMIPI intermediate–high, n (%)	Ki-67 index ≥30%, n (%)	TP53 aberrations n (%)	Blastoid or pleomorphic histology, n (%)
BTK inhibitors															
Ibrutinib monotherapy															
Broccoli 2018[10]	Ibrutinib	77	65.2 (34.6–81.3)	59 (76.6)	16 (20.7)	69 (89.6)	3 (1–10)	27 (35)	NR	37 (48.1) to 1LT; 17 (22.1) to most recent LoT	NR	NR	NR	NR	3 (3.9), blastoid
Yi 2021[34]	Ibrutinib	88	71 (42–92)	71 (80.7)	8 (9.1)	77 (87.5)[b]	1 (1–6)	12 (13.6)	NR	NR	NR	70 (79.5)	*median (range): 35.0 (10.0–95.0)*[b]	0 (0.0)[b], TP53/del(17p)	3 (3.4), blastoid[b]
McCulloch 2021[11]	Ibrutinib	211	73 (33–96)	147 (70)	46 (24)	194 (93)[b]	1 (1–1)	50 (24)	3 (1)	NR	109 (52) with 1LT	123 (87)	76 (54)[b]	NR	29 (14), blastoid[b]
Tucker 2021[37]	Ibrutinib	65	67 (48–90)	76%[c]	34%[c]	NR	2 (1–6)	Approx. 66%[c]	NR	NR	NR	0 (0)	NR	NR	18%, blastoid[c]
Jeon 2019[21]	Ibrutinib	33	65 (40–79)[b]	27 (81.8)	4 (12.1)[d]	28 (84.9)[b]	33% 1 prior LoT*	6 (18.2)	0 (0.0)	NR	NR	19 (57.6)[d]	11 (33.3)[d]	NR	NR
Epperla 2017[14]	Ibrutinib	97	63 (39–87)[b]	80 (82)	14 (14)[b]	88 (91)[b]	2 (1–8)	38 (39)	11 (11)	7 (7) primary refractory disease	NR	43 (44)[b]	37 (38)[b]	NR	15 (16), blastoid[b]
Visco 2021[9]	Ibrutinib	50	58 (19–70)[b]	37 (74.0)	NR	NR	1 (1–1)	23 (46)	NR	8 (16) to 1LT	27 (54) with 1LT	*High: 16 (33)*[d]	NR	NR	20 (20)[d]
Sancho 2022[22]	Ibrutinib	66	69.3 (60.9–76.2)	52 (78.8)	0–1: 59 (93.7)[d]	61 (92.4)[d]	2 (1–7)	14 (21.2)	NR	12 (18.2) to most recent LoT	12 (18.2)	42 (63.6)[b]	20 (55.6)[b]	2 (9.1)[d], TP53/del(17p)	12 (24.5), blastoid; 4 (8.2), pleomorphic[b]
Sharman 2021[23]	Ibrutinib 2L+3L	117	*2nd LoT: 71.6 (48.2–>90); ≥3rd LoT: 68.5 (53.3–88.3)*	117 (79.6)	21 (14.3)	129 (87.8)[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cencini 2021[8]	Ibrutinib	69	70 (41–89)[d]	45 (65.2)	NR	47 (68.1)	1 (1–4)	9 (13.0)	1 (1.5)	12 (17.4) to 1LT	33 (47.8) with 1LT	*High: 21 (30.4)*	NR	NR	7 (10.2)[d]
Janssens 2021[40]	Ibrutinib	76	74.0 (47.0–88.0)	58 (76.3)	3 (5.2)[d]	NR	1 (1–3)	NR	NR	NR	NR	NR	NR	2 (20)[d], TP53/del(17p)	NR
Obr 2021[41]	Ibrutinib	77	68 (40–81)[b]	NR	NR	80%[c,d]	2 (1–8)	24.7%[c,d]	NR	NR	61%[c,e]	84.7%[c,d]	NR	NR	NR
Zhang 2022[24]	Ibrutinib	68	63 (34–81)	45 (66.2)	15 (22.1)	61 (89.7)	60.3% 1 prior LoT;	3 (4.4)	NR	32 (47.1) to most recent LoT	NR	42 (61.8)	31 (45.6)	NR	7 (11.5), blastoid

Ibrutinib in combined therapy															
Zhang 2022[24]	Ibrutinib + Other agents	53	56 (42–80)	40 (75.5)	15 (28.3)	45 (84.9)	66% 1 prior LoT	5 (9.4)	NR	25 (47.2) to most recent LoT	NR	27 (51.0)	29 (54.7)	NR	10 (19.2), blastoid
Fabbri 2020[39]	Ibrutinib + Venetoclax	4	47 (40–59)[b]	3 (75.0)	0 (0.0)[d]	IV: 4 (100)[d]	NR	NR	NR	4 (100) to 1LT and most recent LoT	NR	*High: 3 (75)*[d]	4 (100)[d]	NR	3 (75)[d]
Chemotherapy/immunochemotherapy															
Bendamustine-based approaches															
Rigacci 2012[25]	Bendamustine ± R	30	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Warsch 2012[26]	Bendamustine ± R	25	NR	NR	NR	20 (80)	1 (1–5)	5 (20)	NR	NR	NR	NR	NR	NR	NR
García-Noblejas 2014[29]	Bendamustine ± R	58	71 (43–90)	38 (67)	16 (28)	48 (87)	2 (1–6)	13 (21)	NR	15 (26) to most recent LoT	NR	39 (69.5)	NR	NR	9 (15), blastoid
Smith 2018[29]	Bendamustine ± R	20	68.6[f]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Karadurmus 2019[28]	Bendamustine ± R	18	65.6[d, f] (49–79)	15 (83.3)	7 (38.9)[b]	16 (88.9)[b]	1 (1–4)	5 (27.8)	NR	9 (50) to most recent LoT	NR	NR	NR	NR	NR
Visco 2021[9]	R-B	54	61 (35–70)[b]	42 (78)	NR	NR	1 (1–1)	22 (41)	NR	5 (9) to 1LT	22 (41) with 1LT	*High: 17 (32)*[d]	NR	NR	13 (25)[d]
Visco 2021[9]	R-BAC	76	55 (37–68)[b]	61 (80)	NR	NR	1 (1–1)	16 (22)	NR	10 (13) to 1LT	31 (41) with 1LT	*High: 26 (35)*[d]	NR	NR	17 (24)[d]
McCulloch 2020[13]	R-BAC	36	66 (43–81)	29 (80.6)	7 (20)	36 (100)[b]	2 (1–6)	15 (41.7)[g]	2 (5.6)	NR	16 (44.4) with 1LT	21 (80.8)	NR	NR	7 (19.4), blastoid
Other chemotherapy/immunochemotherapy-based approaches															
Smith 2018[29]	FC ± R	30	73.9[f]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smith 2018[29]	CHOP ± R	37	72.8[f]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smith 2018[29]	Chlorambucil ± R	19	83.9[f]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smith 2018[29]	Cytarabine (DHAP, CHOP/DHAP, HyperCVAD) ± R	38	62.5[f]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kroschinsky 2019[30]	DHAP	10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lamm 2013[38]	R-ADOx	12	69 (57–87)[d]	12 (100)	2: 11 (91.7)[d]	12 (100)[d]	3 (1–9)	NR	NR	NR	NR	6 (50.0)[d]	NR	NR	1 (8.3), pleomorphic[d]

(*Continued*)

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Table 1 (Continued).

First author, publication date	Treatment	Patients, N	Age (years), *median (range)*	Male gender, n *(%)*	ECOG score ≥2, n *(%)*	Ann-Arbor stages III–IV, n *(%)*	No. of previous LoT, *median (range)*	Previous auto-SCT, n *(%)*	Previous allo-SCT, n *(%)*	Refractoriness to previous LoT, n *(%)*	POD24, n *(%)*	MIPI or sMIPI intermediate–high, n *(%)*	Ki-67 index ≥30%, n *(%)*	TP53 aberrations n *(%)*	Blastoid or pleomorphic histology, n *(%)*
Other strategies															
Skarbnik 2017[35]	Bortezomib	53	70.8[f]	37 (70)	NR	28 (97)	1[f]	5 (9)	NR	21 (40) to the most recent LoT	NR	NR	NR	NR	NR
Stefoni 2018[31]	Lenalidomide	70	67 (45–85)	50 (71.4)	20 (28.6)[d]	56 (80)[d]	2.5 (1–10)	36 (51.4)	NR	16 (22.8) to 1LT; 32 (45.7) to most recent LoT	NR	NR	NR	NR	NR
Zinzani 2015[32]	Lenalidomide	33	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hughes 2019[33]	Venetoclax	10	NR	NR	NR	10 (100)	NR	NR	0 (0)	NR	NR	NR	NR	NR	6 (60), blastoid
Iacoboni 2020[36]	CAR-T	33	67 (47–79)	29 (88)	≥1: 18 (55)	29 (88)[d]	2 (1–8)	12 (36)	5 (15)	7 (21) primary refractory disease	NR	23 (70)	16 (49)[d]	4 (12)[d], TP53	9 (27)
Romancik 2021[42]	CAR-T	52	66 (47–79)[d]	43 (82)	5 (10)[d]	IV: 41 (78)[b]	3 (2–8)	21 (40)	2 (4)	NR	26 (50) with 1LT	20 (68)[d]	30 (83)[d]	9 (39)[d], del(17p)	12 (30)[d]
Herbaux 2021[43]	CAR-T	47	67 (45–79)[h]	93.6%[c]	21.1%[c,d]	NR	3 (2–8)	34%[c]	NR	NR	NR	NR	78.60%[c,d]	NR	NR
Wang 2021[44]	CAR-T	93	67 (34–89)[d]	75 (81)	8 (9)[d]	81 (88)[d]	3 (1–9)	25 (27)	4 (4)	41 (44) to most recent LoT	NR	63 (88)[d]	66 (77)[d]	31 (46)[d]	38 (40.8)[d]

Notes: [a]Unless otherwise specified, the variables correspond to the time of relapse or treatment initiation, [b] at diagnosis; [c] n not reported; [d]unclear time of assessment; [e]line of therapy not reported; [f]range not reported; [g]in first-line therapy; [h]at registration in DESCAR-T French national registry.

Abbreviations: 1LT, first-line therapy; allo-SCT, allogenic stem cell transplantation; auto-SCT, autologous stem cell transplantation; BTK, Bruton's tyrosine kinase; CAR-T, chimeric antigen receptor T-cell therapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; DHAP, dexamethasone, cytarabine, and cisplatin; ECOG, Eastern Cooperative Oncology Group; FC, fludarabine and cyclophosphamide; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; LoT, lines of therapy; MIPI, Mantle Cell Lymphoma International Prognostic Index; NR, not reported; POD24; progression of disease within 24 months; R, rituximab; R-ADOx, rituximab, Ara-C, dexamethasone, and oxaliplatin; R-B, rituximab and bendamustine; R-BAC, rituximab, bendamustine, and cytarabine; R/R MCL, relapsed/refractory mantle cell lymphoma; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index.

Table 2 Effectiveness Outcomes of Patients Treated with Bruton's Tyrosine Kinase (BTK) Inhibitors

First author and publication date	Treatment	PFS (months), *median*	OS (months), *median and/or % at the specified time*	ORR (%)	CR (%)	Follow-up (months), *median*
Ibrutinib as monotherapy						
Broccoli 2018[10]	Ibrutinib	12.9	16	36.4	18.2	38
Yi 2021[34]	Ibrutinib	20.8	79.1% at 2 years	64.8	NR	30.5
McCulloch 2021[13]	Ibrutinib	17.8	23.9	69	27	24
Tucker 2021[37]	Ibrutinib	12	18.5	NR	NR	60
Jeon 2019[21]	Ibrutinib	27.4	35.1	64	15	NR
Epperla 2017[14]	Ibrutinib	15	22	65	33	NR
Visco 2021[9]	Ibrutinib	24	Approx. 38	NR	NR	NR
Sancho 2022[22]	Ibrutinib	20	32	63.5	38.1	19.4
Sharman 2021[23]	Ibrutinib	19.6	25.8	NR	NR	16.1
Cencini 2021 [40]	Ibrutinib	17	34.8	62.3	39.1	15.6
Janssens 2021[40]	Ibrutinib	18.6	32.2	95.9	39.5	24.3
Obr 2021[41]	Ibrutinib	7.9	12.4	66	30	12.6
Zhang 2022[24]	Ibrutinib	18.5	28.2	41 (60.3)	11 (16.2)	20.5[a]
Ibrutinib in combination						
Zhang 2022[24]	Ibrutinib + Other agents	30.8	Not reached	45 (84.9)	23 (43.4)	20.5[a]
Fabbri 2020[39]	Ibrutinib + Venetoclax	NR	NR	100	50	NR

Notes: [a]For all patients in the study regardless of treatment.
Abbreviations: CR, complete response; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

The second study described the cases of four patients treated with ibrutinib and venetoclax, who were mostly males with a median age of 47 years at diagnosis.[39] All of them had previously been treated with rituximab, high dose cytarabine, and anthracycline and presented an ECOG score between 0 and 1, as well as an IV stage MCL. Three patients out of four presented with three high risk features: high MIPI value, Ki-67 index >30%, and blastoid or pleomorphic histology (Table 1).

The survival outcomes of both studies are also shown in Table 2. The treatment strategies reported in the first study resulted in a median PFS of 30.8 months, an ORR of 84.9%, and a CR of 43.4%, with a median follow-up of 20.5 months (for the overall study population).[24] Moreover, the efficacy of ibrutinib plus venetoclax in the second study was reported in terms of ORR and CR, which were 100% and 50%, respectively.[39]

Chemotherapy/Immunochemotherapy-Based Strategies

The strategies based on chemotherapy/immunochemotherapy included eight assessments of bendamustine regimens reported in seven studies;[9,13,25–29] one of fludarabine and cyclophosphamide (FC) regimens alone or combined with rituximab;[29] one of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimens alone or combined with rituximab;[29] one of chlorambucil regimens alone or combined with rituximab,[29] two of cytarabine-based regimens;[29,30] and one of rituximab, Ara-C, dexamethasone, and oxaliplatin (R-ADOx) regimens[38] (Table 1).

Bendamustine-Based Strategies

Seven studies assessed eight bendamustine-based approaches, five with bendamustine either with or without rituximab (bendamustine ± R);[25–29] one with bendamustine and rituximab (B–R);[9] and two with rituximab, bendamustine, and cytarabine (R-BAC).[9,13] These treatment regimens included between 18 and 76 patients (n = 8), predominantly males (between 67% and 83.3%, n = 5), with median ages at treatment initiation varying from 66 to 71 years (n = 3). The percentages of patients with an ECOG score ≥2 and a III–IV Ann-Arbor stage ranged from 20% to 38.9% (n = 3), and from 80% to 100% (n = 4), respectively. The patients had received a median of one to three previous lines of therapy (n = 6), and 20% to 41.7% of them, a previous auto-SCT (n = 6). As for response to previous lines of therapy, between 9% and 13% of the patients were

refractory to first-line therapy (n = 2), whereas 26% to 50% of them were refractory to the most recent therapy/chemotherapy (n = 2). In addition, 41% to 44.4% of the individuals were POD24 to their first-line therapy (n = 3). The proportion of patients presenting with an intermediate-high MIPI/sMIPI and a blastoid or pleomorphic MCL ranged from 69.5% to 80.8% (n = 2), and from 15% to 25% (n = 4), respectively (Table 1).

Patients treated with bendamustine-based approaches presented considerably variable survival outcomes, with a median PFS ranging from 10.1 to 25.9 months (n = 5) and a median OS from 12.5 to 43 months (n = 4). The ORR and CR ranged from 70% to 86% (n = 6), and from 40% to 61.1% (n = 5), respectively (Table 3). Median follow-ups ranged from 10 to 22 months.

Other Chemotherapy/Immunochemotherapy-Based Approaches

The general characteristics of the remaining chemotherapy/immunotherapy-based treatment regimens can also be seen in Table 1, whereas their corresponding outcomes are summarized in Table 3. The study of Smith et al included the assessments of FC, CHOP, chlorambucil, and cytarabine-based regimens.[29] The analysis of FC was performed on 30 patients with a median age at treatment onset of 73.9 years, resulting in a median OS of 9.6 months. Similarly, the assessment of CHOP included 37 patients with a median age at treatment initiation of 72.8 years; their median OS was 9.6 months as well. In contrast, the assessment on chlorambucil included a lower number of patients (n = 19), who were older than those described before (median of 83.9 years) and reported a shorter survival (median OS of 7.2 months). Moreover, the analysis of cytarabine-based regimens —DHAP, CHOP/DHAP, and HyperCVAD, alone or combined with rituximab— was performed among 38 younger patients (median age of 62.5 years) and yielded a median OS of 6.0 months. The other analysis of a cytarabine regimen (specifically, a modified DHAP regimen) included 10 patients and reported a 5-year PFS and OS of approximately 60%, along with an ORR of 50%, and a CR of 10%, with a median

Table 3 Effectiveness Outcomes of Patients Treated with Chemotherapy or Immunochemotherapy

First author and publication date	Treatment	PFS (months), *median and/or % at the specified time*	OS (months), *median and/or % at the specified time*	ORR (%)	CR (%)	Follow-up (months), *median*
Bendamustine-based approaches						
Rigacci 2012[25]	Bendamustine ± R	10% at 4 months	39% at 10 months	70	40	12/10[a]
Warsch 2012[26]	Bendamustine ± R	NR	Not reached	80	48	12
García-Noblejas 2014[27]	Bendamustine ± R	16	32.4	86	55	16
Smith 2018[29]	Bendamustine ± R	NR	12.0; 52.9% at 1 year	NR	NR	NR
Karadurmus 2019[28]	Bendamustine ± R	25.9	74.9% at 2 years	72.2	61.1	22
Visco 2021[9]	R-B	13	Approx. 43	NR	NR	NR
Visco 2021[9]	R-BAC	25	Approx. 38	73	NR	NR
McCulloch 2020[13]	R-BAC	10.1	12.5	83	60	18
Other chemotherapy/immunochemotherapy-based approaches						
Smith 2018[29]	FC ± R	NR	9.6; 44.7% at 1 year	NR	NR	NR
Smith 2018[29]	CHOP ± R	NR	9.6; 44.8% at 1 year	NR	NR	NR
Smith 2018[29]	Chlorambucil ± R	NR	7.2; 38.4% at 1 year	NR	NR	NR
Smith 2018[29]	Cytarabine (DHAP, CHOP/DHAP, HyperCVAD) ± R	NR	6.0; 31.7% at 1 year	NR	NR	NR
Kroschinsky 2019[30]	DHAP	Approx. 60% at 5 years	Approx. 60% at 5 years	50	10	64
Lamm 2013[38]	R-ADOx	9.3	Not reached	75	33.3	14.7

Notes: [a]For OS at 24 months and PFS at 20 months, respectively.

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CR, complete response; DHAP, dexamethasone, cytarabine, and cisplatin; FC, fludarabine and cyclophosphamide; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; R-ADOx, rituximab, Ara-C, dexamethasone, and oxaliplatin; R-B, rituximab and bendamustine; R-BAC, rituximab, bendamustine, and cytarabine.

follow-up of 64 months.[30] As for the assessment of R-ADOx regimens, it included 12 male patients with a median age of 69 years and a median of 3 previous lines of therapy. Most patients (91.7%) had an ECOG=2 and, all of them, an III–IV stage MCL, whereas only one (8.3%) presented with an aggressive MCL histology (pleomorphic). The efficacy outcomes of this approach included a median PFS of 9.3 months, an ORR of 75%, and a CR of 33.3%, with a median follow-up of 14.7 months.[38]

Other MCL Treatments

Besides the treatment regimens based on BTK inhibitors and chemotherapy/immunotherapy, we found other R/R MCL treatment approaches, including treatment regimens based on bortezomib (n = 1),[35] lenalidomide (n = 2),[31,32] venetoclax (n = 1),[33] and CAR T-cell therapies (n = 4).[36,42–44]

Bortezomib

The study of the treatment regimen based on bortezomib included 53 patients (70% males) with a median age at treatment initiation of 70.8 years, with almost all of those with available data (97%) being at stages III–IV. Patients had received a median of 1 previous line of therapy, and 9% of them had undergone a previous auto-SCT. In addition, 40% of the patients were refractory to the most recent treatment (Table 1). This study reported a median PFS of 4.7 months and a median OS of 11.3 months, with a median follow-up of 5.3 months[35] (Table 4).

Lenalidomide

The study by Stefoni et al included 70 patients (71.4% males) with a median age of 67 years. Of them, 28.6% had an ECOG score ≥2, and 80% were at an III–IV stage. Patients had a median of 2.5 lines of therapy, and more than half of them (51.4%) had received an auto-SCT. In this regard, 22.8% and 45.7% of the patients were refractory to the first and the most recent line of therapy, respectively (Table 1). The authors reported a median PFS of 13.8 months, a median OS of 32.5 months, an ORR of 47.1%, and a CR of 31.4%[31] (Table 4). Similarly, the study of Zinzani et al, which included 33 patients with R/R MCL treated with lenalidomide, reported a PFS of 13.9 months, an ORR of 45.5% and a lower CR of 12.1%[32] (Table 4).

Venetoclax

The study on venetoclax included 10 patients, of which 90% had previously been treated with ibrutinib, 60% presented with blastoid histology, and all of them were at an III–IV stage (Table 1). Venetoclax treatment resulted in a median PFS and OS of 6 months[33] (Table 4).

Table 4 Effectiveness Outcomes of Patients Treated with Other Strategies

First author and publication date	Treatment	PFS (months), *median and/or % at the specified time*	OS (months), *median and/or % at the specified time*	ORR (%)	CR (%)	Follow-up (months), *median*
Skarbnik 2017[35]	Bortezomib	4.7	11.3	NR	NR	5.3
Stefoni 2018[31]	Lenalidomide	13.8	32.5	47.1	31.4	NR
Zinzani 2015[32]	Lenalidomide	13.9	NR	45.5	12.1	NR
Hughes 2019[33]	Venetoclax	6	6	NR	NR	NR
Iacoboni 2020[36]	CAR-T	50.8% at 1 year	61.4% at 1 year	91	79	10.1
Romancik 2021[42]	CAR-T	82.7% at 6 months	89.0% at 6 months	88	69	4.2
Herbaux 2021[43]	CAR-T	57.9% at 6 months	NR	88	61.9	3.3
Wang 2021[44]	CAR-T	80.6% at 3 months	82.1% at 6 months	86	64	3

Abbreviations: CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

CAR T-Cell Therapies

Four studies evaluated the use of CAR T-cell therapies with brexucabtagene on R/R MCL patients.[36,42–44] They included 33 to 93 patients, mostly males (81% to 93.6%, n = 4), with median ages between 66 and 67 years (n = 4). The proportion of patients with an ECOG score ≥2 ranged from 9% to 21.1% (n = 3), whereas the percentage of individuals at III–IV stages was 88% (n = 2). The number of previous lines of therapy varied from 2 to 3 (n = 4), the proportion of patients who had previously received an auto-SCT and an allo-SCT ranged from 27% to 40% (n = 4) and from 4% to 15% (n = 3), respectively, and patients previously treated with BTKis ranged 82% to 100% (n = 2). Regarding prognostic factors, 68% to 88% of the individuals had a MIPI/sMIPI intermediate-high (n = 3), whereas 49% to 83% of them presented with a Ki-67 index ≥30% (n = 4). Moreover, TP53 aberrations and blastoid or pleomorphic variants were found in 12% to 46% (n = 3) and in 27% to 45% (n = 3) of patients, respectively (Table 1).

Regarding efficacy outcomes, two studies reported 6-month PFS, ranging from 57.9% to 82.7%, whereas other studies reported similar rates at different time points (3-month PFS of 80.6%, n = 1, and 1-year PFS of 50.8%, n = 1). However, the 6-month OS was relatively homogeneous among the studies (82.1% to 89.4%, n = 3). The ORR and CR were also very similar, ranging from 86 to 91% (n = 4) and from 61.9 to 79% (n = 4), respectively. Median follow-ups were variable, ranging from 3 to 10.1 months (Table 4).

Risk of Bias Assessment

Table S1 summarizes the analysis of the risk of bias of the studies included in the systematic review. Of them, 26 (86.7%) clearly described eligibility criteria, 25 (83.3%) reported consecutive inclusion of participants, and only 8 (26.7%) stated complete inclusion of participants. In addition, 16 (53.3%) studies measured the lymphoma in a standard and reliable way for all the participants, but only 9 (30.0%) studies reported using valid methods to diagnose it. Demographics and clinical characteristics of R/R MCL patients were clearly reported for each treatment regimen in 23 (76.7%) and 15 (50.0%) of the studies, respectively, although the latter would increase if we considered the whole study population (ie, not only patients with R/R MCL) and/or all the treatment regimens of the studies. All studies (n = 30, 100.0%) clearly reported efficacy outcomes (ie, treatment response and survival) and demographic information of the sites or center where the studies were conducted. Finally, the statistics were clearly reported in 18 (60.0%) studies.

Discussion

In this systematic review of the characteristics and treatment outcomes of patients with R/R MCL in the clinical practice, we found that most treatment regimens were based on BTKis (specifically, ibrutinib) or chemotherapy/immunochemotherapy strategies (especially those including bendamustine). As expected, most patients were males with a median age ranging from 65 to 75 years at treatment initiation. Of the treatment regimens reporting each variable of interest, approximately two thirds of them included a percentage of patients with an ECOG score ≥2 between 10% and 30%, most of them had ≥80% of the patients with an III–IV stage disease, reflecting the reality of the treatment of the disease in the routine clinical practice. All of them reported a median number of previous lines of therapy of between 1 and 3. The percentage of patients who had previously received an auto-SCT was quite variable, but ranged from 10% to 40% in approximately two-thirds of the treatment regimens, depending on the age and status of the patients included in the study. More than half of the patients presented with an intermediate-high MIPI/sMIPI in treatment regimens reporting it. In addition, the percentages of patients with high-risk features, such as TP53 aberrations, and a Ki67 ≥30% were reported in a small number of studies and ranged from 0% to 46%, and from 33.3% to 100% of the patients, respectively, further reflecting high variability among patients included in these studies. Additionally, the percentage of patients with blastoid or pleomorphic histology was variable, ranging from 3.4% to 27–40% in CAR T-cell studies where, as expected, patients are in later lines and have more high-risk features.

Interestingly, only studies using ibrutinib and CAR T-cells (brexucabtagene autoleucel) reported similar efficacy outcomes in RWE studies[7–10,13,28–31,33,35,36,39–43] compared to clinical trials (CTs).[6,45] When comparing the values of each outcome of interest, the real-world treatment regimens using ibrutinib monotherapy[8–11,14,21–24,34,37,40,41] yielded a wide range of values for all the studied variables where those of the pooled analysis fell.[7] As for the treatment response,

the lowest values of ORR were reported with the lenalidomide regimens[25,26] and the cytarabine regimen.[29] Of note, the ibrutinib study by Broccoli et al[10] reported an ORR of 36%, but physicians in the study erroneously considered that ibrutinib induced transient lymphocytosis as PD and stopped treatment. The highest ORR values were the ibrutinib-based regimens reported by Janssens and Fabbri et al,[38,39] all four CAR T-cell treatment regimens,[36,42–44] and one study reporting bendamustine ± rituximab.[27] Interestingly, the ORR rates reported in the bendamustine RWE studies (ranging 70% to 86%) were generally lower than those reported in clinical trials.[45–50] Regarding CR rates, the highest CR values corresponded to the CAR T-cell treatment regimens,[36,42–44] whereas the lowest ones were those reported by the ibrutinib monotherapy regimens of Jeon et al,[21] Zhang et al,[24] and the already mentioned Broccoli et al,[10] the DHAP regimen,[30] and the lenalidomide regimen reported by Zinzani et al.[32] It is important to note that, among ibrutinib studies, there was a high variability between CR rates, ranging from 39.5% to 15%[28,39] which may be due not only to the baseline characteristics of the patients and the line of therapy in which ibrutinib was used, but also to the response criteria used in the study, which may vary significantly in this type of retrospective routine clinical practice studies. Moreover, it has been widely described in the successive follow-ups of ibrutinib clinical trials[51] that ORRs and CR rates improve over time, so these differences may also be due to short follow-up periods.

Regarding survival outcomes, the highest median PFS values were found with ibrutinib[21,24] and bendamustine (median PFS ranging from 10.1 to 25.9 months)[9,28] regimens. The ibrutinib-based treatment regimens resulted in a wide range of median PFS values, from 7.9 to 30.8 months.[8–11,14,21–24,34,37,39–41] The PFS reported in the pooled analysis,[6] with a median follow-up of 9.7 years, was 12.5 months in all the population (median of 2 prior lines) and 25.4 months in patients with one prior line of therapy. Thus, the number of prior lines of therapy the patient received before ibrutinib treatment should be considered in order to contextualize PFS results of the RWE studies. In the study by Obr et al, recently updated,[52] reporting a median PFS of 7.9 months, patients were heavily pretreated, with 72% of the patients with 2 or more previous lines of therapy. On the contrary, in the studies reporting data from patients treated with ibrutinib as second-line therapy,[8,9,13,34,40] where the best PFS results are expected, PFS ranged between 17 and 24 months, in line with the results of the pooled analysis, considering unselected RWE populations. Conversely, bortezomib[35] and venetoclax[33] treatment studies yielded the lowest PFS values, potentially because in these studies they were used as monotherapy in late lines of therapy and in elderly patients.

The highest median OS values were also found among ibrutinib[8–11,14,21–24,37,40,41] and bendamustine[9,13,27] treatment regimens. All of the other treatment regimens reporting OS yielded lower median OS values, and the lowest ones were those corresponding to cytarabine,[29] bortezomib,[35] and venetoclax[33] regimens, with the last two being lower than those reported in CTs.[49–51] CAR-T regimen studies did not report median PFS and OS due to their short follow-up, but the longest follow-up by Iacoboni et al[36] reported an estimated 50.8% PFS and 61.4% OS at 12 months, very promising results in this heavily pretreated high-risk patient population. In this context, it is important to note that multivariate analysis have shown several prognostic markers to have a deleterious effect in PFS and OS besides previous lines of therapy in the context of R/R MCL and need to be considered when comparing the efficacy results reported in the different studies:[6] ECOG, sMIPI, bulky disease, early progression of disease (POD24 status), and ultra-high-risk features, such as blastoid/pleomorphic histology and TP53 mutation.

When looking at clinical trials assessing the efficacy of the same agents retrieved in this review for treating R/R MCL patients,[7,45–50,53–63] we observed some similarities in the efficacy outcomes. Regarding response outcomes, as in the real-world studies, the highest ORRs were reported by clinical trials assessing bendamustine,[47,48] CAR T-cell therapy,[61] and ibrutinib combined with rituximab.[56] Conversely, the lowest ORRs were those found in clinical studies evaluating lenalidomide[63] and bortezomib.[59] Additionally, studies using CAR T-cell therapy[61] and bendamustine[47] reported the highest CR rates, whereas the lowest CR values were those reported in clinical trials using bortezomib[59] and lenalidomide.[63] Conversely, the highest median PFS values corresponded to ibrutinib-based therapies[6,53,55] and CAR T-cell therapies, considering that CAR T-cell therapies have been tried mostly in a post iBTK setting, whereas bortezomib,[59,60] together with lenalidomide,[63] yielded the lowest median PFS values.

It is important to note that bendamustine-based therapy results in higher CR rates than ibrutinib monotherapy in RWE and CTs, which does not translate into improved PFS/OS results, which could suggest that, besides attaining a CR, a well-established endpoint that prolongs PFS,[6] continuous treatment may play an important role in delaying progression of the disease in MCL. One proof of that is that rituximab maintenance after front line therapy has been shown to delay progression of the disease and improve PFS/OS[64–66] and has thus been established as standard of care.

In the retrospective study MANTLE FIRST, Visco et al[9] compared second line ibrutinib, R-BAC, R-bendamustine, and a variety of other treatments in young R/R MCL patients. The CR rates obtained with R-BAC and R-Benda were 63% and 43%, respectively, whereas ibrutinib yielded a lower CR rate of 38%, which did not translate into a better PFS for R-BAC (mPFS2: 25 m.) and R-bendamustine (mPFS2: 13 m.) in comparison with ibrutinib (mPFS2: 24 m.); conversely, ibrutinib resulted in a significantly longer PFS in POD24 patients compared to those attained with R-BAC and R-bendamustine (p=0.02) besides CR rates, reflecting that the attainment of deep responses, in the setting of targeted continuous therapies, may not be the only goal of therapy and may be achieved later in time without direct impact on PFS.

This study has some limitations, mainly associated with the quality of the data but also with the difficulty of comparing outcomes in R/R MCL due to the heterogeneity of the disease. First, the methods to assess the treatment outcomes were not always described accurately in the retrieved studies, which may entail a measurement bias and affect results. Secondly, not all the studies reported the same data on the characteristics of patients and the studied outcomes. In this regard, most studies did not report the Ki-67 index or the presence of TP53 aberrations, which are prognostic factors of MCL and, thus, may affect the efficacy of the treatment. Besides, many studies were basket studies and not only involved patients with R/R MCL and one treatment regimen, but also patients with other types of lymphomas, treatment-naïve MCL, and/or different treatment approaches. Given that not all these studies reported the variables by type of lymphoma, naïve or relapsed status, or treatment approach, we could not always retrieve the data corresponding to R/R MCL patients for a given treatment approach. Another limitation relies on the high variability of real-world data, making it difficult to compare the different treatment regimens among them and from those obtained in clinical trials. However, most of these limitations are inherent to real-world data, which are essential to complement those of clinical trials.

Conclusion

To our knowledge, this is the first systematic review of the real-world evidence on R/R MCL treatments. Baseline characteristics of patients included in the studies reflect the reality of R/R MCL in a real-world setting and the heterogeneity of the disease. A very important part of the studies retrieved were ibrutinib monotherapy studies, maybe due to the increasing importance in the last few years of real-world evidence and the need to confirm clinical trial results in a routine clinical practice setting with unselected patient populations. Furthermore, ibrutinib was a first-in-class BTK inhibitor and its first publication in 2013[67] raised interest in the medical community due to the unprecedented efficacy results reported for a targeted agent in monotherapy, its favorable tolerability profile, and its convenience compared to classic chemoimmunotherapy strategies, something that may have boosted interest in confirming those results in the routine clinical practice. Chemoimmunotherapy is still being widely used in the R/R setting, as evidenced by the broad range of studies considered in this review, but the use of other targeted therapies is very limited. Regarding efficacy outcomes, the best results obtained in RWE studies are those of ibrutinib, CAR T-cells and bendamustine-based regimens, the first two similar to those reported in clinical trials. Those results have led to expert/guidelines recommendations prioritizing BTKis at first relapse and CAR T-cells as the best option after BTKi relapse.[68–71] However, these results should be interpreted with caution since they are limited by the quality of the real-world data available and the difficulty of comparing outcomes in R/R MCL due to the heterogeneity of the disease.

Expert Opinion

Despite recent advances that have prolonged survival, R/R MCL is clinically and biologically heterogeneous and is still a therapeutic challenge, with high-risk and early relapsed patients remaining an unmet medical need. There is no standard treatment for R/R MCL, but considering patients' advanced age, tolerability profile, and convenient administration, BTKis should be positioned as second line of therapy,[6] and CAR T-cells should be the approach to BTKi-relapsed patients.[61] However, access to CAR T is not universal, and more therapies in this setting are still needed.

In this sense, there is a huge development in the MCL field with many chemo-free and combination regimens with established chemoimmunotherapy backbones being studied not only in the relapsed setting, but to improve front-line treatment options and to move forward to earlier lines targeted and cellular therapies. For instance, the randomized Phase 3 SHINE study, where

continuous ibrutinib or placebo was combined with rituximab-bendamustine followed by rituximab maintenance in front-line elderly MCL patients, showed a promising 80.6-month median PFS for the ibrutinib + BR arm, which is the longest PFS ever reported for this type of non-candidate to auto-SCT patients. The results of the TRIANGLE trial, evaluating the use of ibrutinib alone or in combination with auto-SCT in the front-line setting in candidates to auto-SCT[72] are also worth mentioning. These trial results seem to indicate that auto-SCT, currently the most efficacious standard of care for front-line transplant-eligible patients, is not superior to front-line ibrutinib monotherapy in young fit MCL patients. This is an unprecedented result leading us to hypothesize that auto-SCT may be replaced with the addition of ibrutinib to the induction therapy in these patients as front-line treatment, avoiding auto-SCT-associated morbidities and mortality. These results, along with other promising clinical trials including new targeted agents in combination with other therapies, may bring these therapies to the front-line setting and help improve patient outcomes since diagnosis (MANGROVE, NCT04002297; SYMPATICO, NCT03112174; OAsIs, NCT02558816; ENRICH, BOVEN, NCT03824483). Furthermore, these new therapeutic schemes could decrease toxicity compared to the standard chemotherapy mentioned in this study, being more convenient and tolerable, opening new venues towards improving both efficacy and tolerability in the newly diagnosed MCL population, often enriched in non-transplant eligible, elderly unfit patients.

Additionally, many new targeted agents will play an important role in the upcoming years (the non-covalent BTKis such as pirtobrutinib, anti-ROR1 conjugate zilovertamab, bispecific antiCD20-CD3 antibodies epcoritamab, glofitamab, other CAR T-cells like lisocabtagene and other small molecules) and will eventually evolve to be used in the front-line setting, where therapies have been proved more efficacious. Conversely, it can be hypothesized that chemoimmunotherapy will have a small role, while targeted agents along with CAR-T cells will have a major role in the front-line setting and the first relapse, where the best results will be achieved, and the life of MCL patients will be prolonged. How these therapies will be incorporated to the daily clinical practice will depend on many factors, including access to novel therapies in different geographical regions. Irrespective of access, these agents and their combinations will have to be added to the treatment strategies according to patients' status and age. Furthermore, optimal sequencing will have to be determined, and those results will have to be confirmed in non-selected MCL populations, which are usually elderly and have comorbidities and use concomitant medications that may affect the outcomes of these treatments. The rise of RWE studies has been very positive to the medical community, expanding knowledge about these therapies, not only in terms of effectiveness, but also of their long-term security profile in real-world populations.

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