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A Systematic Review of Treatments of Relapsed/Refractory Mantle Cell Lymphoma

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Abstract

A systematic review was conducted to evaluate the clinical effectiveness and safety of treatments for patients with relapsed/refractory mantle cell lymphoma (MCL) unsuitable for intensive treatment. The criteria for inclusion of the trials were established before the review. A search of Medline, Embase, and the Cochrane library databases was conducted to identify phase II or III randomized controlled trials (RCTs), reported from January 1, 1994 to May 29, 2016. Relevant conference abstracts, citation lists from the included articles, published guidelines, and on-going clinical trial databases were also searched. Studies were included if they had evaluated any single agent or combination of treatments for adult patients with relapsed/refractory MCL who had received $\geq$ 1 previous line of therapy. Seven RCTs were identified. Only 1 treatment appeared in > 1 trial; therefore, the results from each trial could not be quantitatively pooled for meta-analysis. The lack of common comparators, differences in baseline characteristics and inclusion and exclusion criteria, and variances in the response criteria used to measure outcomes made comparison of the results difficult. Although the direction of effect for progression-free survival (PFS) and overall survival (OS) was in favor of the experimental drug in all trials, the difference in PFS was statistically significant in 5 and OS in 2. None showed statistical significance for both. A noticeable lack of RCTs evaluating treatments for patients with relapsed/refractory MCL made meaningful comparisons of effectiveness across trials rather difficult. This trend continues, because all, bar 1, of the 85 ongoing trials in this area are single-arm studies. RCTs are required to enable better evaluation of the optimal treatment regimen for this group of patients.

Introduction

Mantle cell lymphoma (MCL) is a rare B-cell malignancy belonging to the non-Hodgkin lymphoma (NHL) group of diseases.[1] MCL represents 3% to 10% of all newly diagnosed NHL cases,[2,3] with an incidence of approximately 1 per 100,000 persons in Europe[4] and the United States.[5] MCL more commonly affects men, with a median age at presentation of 65 years[2] and is typically at an advanced stage at diagnosis, Ann Arbor stage III and IV.[6]

The hallmark of MCL is the chromosomal translocation t(11;14)(q13;q32), resulting in overexpression of the cell cycle protein

cyclin D1 and cell cycle dysregulation.[7] MCL has 2 main variants. Classic MCL is the more common form[2] and has an overall survival (OS) of approximately 4.5 years. The blastoid variant of MCL is rarer but has been associated with a more aggressive clinical course and poorer prognosis, with an OS of approximately 15 months.[8]

MCL frequently has an aggressive clinical course. Although initial therapy can achieve high overall response rates (ORRs) of 60% to 97%,[9] these tend to be short lived, and most patients will eventually develop relapse and die of their disease. Some patients, however, have a more indolent form of MCL. Although it is difficult to identify this group, some markers (eg, SOX11 negativity) might help to distinguish this indolent form from a more aggressive phenotype. Ongoing research in the United Kingdom[10] aims to characterize the differences in a prospective trial. Some clinicians have now adopted a "watch and wait" management approach with these patients if they are asymptomatic.[4]

The first-line treatment options will depend on the age and fitness of the patient. Intensive frontline cytarabine-based treatments are reserved for younger, fitter patients because of their associated toxicity and are commonly consolidated with autologous transplantation.[2,4,7] However, most patients are older or

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Figure 1	PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Diagram

Potentially relevant records identified:
- Medline (n=703)
- Embase (n=632)
- Cochrane (n=58)
- PubMed (n=353)   Total n=1746

Unique records after duplicates removed:
n = 1316

Records excluded: n= 1289
- Biomarker/prognosis (n=31)
- Reviews/Commentary/Letters (n=156)
- Study Design (n=147)
- Population (n=603)
- Intervention (n=296)
- Preclinical (n=25)
- Outcomes/Analysis (n=31)

Records retrieved for full text screening:
n =27

Records excluded from full text screening:
n=16
- Population (n=7)
- Study Design (n=6)
- Intervention (n=3)

Records for review:
n = 11

Records excluded: n=4
- Dose scheduling studies (n=4)

Total trials for final review:
n = 7

more frail at presentation; thus, this approach is not feasible. A number of immunochemotherapy options are available for this group of patients,[4] including B-R (bendamustine, rituximab), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone) regimens, with response rates ranging from 60% to 95% and a median progression-free survival (PFS) of ≤ 5 years. Rituximab maintenance also plays a role in sustaining the response after R-CHOP induction.[11] For the more frail patients who are unsuitable for immunochemotherapy,

less intensive therapies have been recommended, including chlorambucil, bendamustine, or cladribine, usually given in combination with rituximab,[2,7,12] and the R-CVP regimen (rituximab, vincristine, cyclophosphamide, prednisolone).[2]

No consensus has yet been reached regarding the optimal standard of care for relapsed/refractory (R/R) disease. Experts have recommended an alternative immunochemotherapy regimen from that which was used initially,[6] and the selection of treatment will depend on a number of factors, including the presence of comorbidities, patient fitness, and patient wishes. Because many patients are not suitable for an intensive treatment approach, several options for the R/R setting have been recommended in the guidelines for older patients.[2,4,13] In the present systematic review, we, therefore, evaluated the available evidence for therapeutic options for patients with R/R MCL unsuitable for an intensive treatment approach.

Materials and Methods

The review method was predefined in a protocol available in the Supplemental Data section (available in the online version) and registered in the Prospero website (available at: https://www.crd.york.ac.uk/PROSPERO/). Randomized controlled trials (RCTs) were included if they met the following criteria: (1) study population, adult patients with R/R MCL who had received ≥ 1 previous line of therapy and not eligible for intensive treatment or transplantation; (2) intervention, any single agent or combination of agents, including chemotherapy, immunotherapy, immunochemotherapy, targeted agents, excluding intensive treatment and transplantation; (3) comparator, any single agent or agents, as stated; and (4) outcomes, OS, PFS, ORR, and safety. Electronic searches were undertaken in Medline, Embase, and the Cochrane Library from January 1994 (MCL was accepted as a separate entity in 1994[14]) to May 29, 2016. In addition, conference proceedings from the annual congresses of the American Society of Hematology (ASH), European Hematology Association, American Society of Clinical Oncology, and European Society of Medical Oncology were searched for the preceding 5 years to find unpublished trials. Citation lists from the included studies, review articles, and published guidelines from the National Comprehensive Cancer Network, European Society of Medical Oncology, ASH, British Society of Haematology, and European Mantle Cell Lymphoma Network were also searched. Ongoing trials were identified from 2 research databases (available at: www.clinicaltrials.gov and www.clinicaltrialregister.eu) up to December 24, 2016.

The search terms for the population included "lymphoma, mantle-cell lymphoma, non-Hodgkin lymphoma, B-cell lymphoma" for the intervention. The control search terms included "drug therapy [MeSH] OR immunotherapy [MeSH] OR molecular targeted therapy [MeSH] OR biological therapy [MeSH] OR combined modality therapy [MeSH] OR antineoplastic agents [MeSH] OR lenalidomide OR ibrutinib OR thalidomide OR bortezomib OR temsirolimus OR everolimus OR BTK [Bruton's tyrosine kinase] inhibitor OR proteasome inhibitor." Full details of the search strategies used are shown in Supplemental Tables 1 and 2 (available in the online version). No language restrictions were used in the search.

Two reviewers (M.P. and M.K.) independently screened the search results for potential inclusion and exclusion using the title and abstract, with full paper copies obtained to confirm inclusion in the review. The final decision for the inclusion of articles was determined by agreement between the 2 reviewers.

Results

A total of 1746 articles were identified from the search as outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram (Figure 1). After 430 duplicates were removed, 1316 articles were initially screened for inclusion from the title and abstract, with 27 published articles retrieved for full text screening. Seven RCTs met the inclusion criteria and were included in the present review.[15-21] Full agreement had been reached between the 2 reviewers regarding the included articles. The concordance between reviewers resulted from both the clearly defined criteria and the paucity of trials available in this setting.

A summary of the trial design for the included trials is provided in Table 1, with the treatment regimens for each trial listed in Table 2. The follow-up duration among the trials varied, with the shortest median follow-up of 15.9 months in the trial conducted by Trneny et al[21] and the longest median follow-up of 96 months reported by Rummel et al.[20] All 3 trials that had included a variety of NHL subtypes[16,17,20] reported separate outcomes for the MCL subpopulation and were included in the present review. Only 1 treatment, temsirolimus, appeared in > 1 trial.

Data were extracted from the articles by 1 reviewer (M.P.) and were checked by a second reviewer (M.K.). The study and patient characteristics and the details of the intervention and control were extracted. The outcomes data collected included OS, PFS, tumor responses, and data on safety, restricted to grade 3 and 4 hematologic toxicity.

Only a descriptive analysis of the included trials was feasible owing to the heterogeneity of the study populations and interventions.

Quality Assessment of Studies

The quality of each trial was evaluated using the Cochrane Collaboration's tool for assessing the risk of bias.[22] Assessment of the blinding of participants and personnel was not applicable, because all trials were open label and were therefore listed as unclear owing to the restrictions of choice within the tool. A full assessment of each trial is given in Supplemental Table 3 (available in the online version). Overall, 2 trials[15,21] were judged to have a low risk of bias across all domains, 5 trials[16-20] provided insufficient information on which to judge bias in some domains, and 2 trials[18,20] were judged to have some elements of a high risk of bias (some trials were in > 1 category). The study by Rummel et al[20] was judged to have detection bias because it had not reported the response criteria. The study by Furtado et al[18] was judged to have selection and reporting bias because of differences in the baseline characteristics between the 2 groups and because they did not report prespecified outcomes. A summary of the risk of bias is shown in Figure 2.

Baseline Characteristics

The inclusion criteria were broadly similar among the trials, with a couple of notable differences. Hess et al[19] required patients to have received ≥ 2 previous therapies, the remaining trials only required 1. All trials, where stated, included patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS)

		Treatment		MCL Patients (n)		
Investigator	**Design**	**ID**	**Control**	**ID**	**Control**	**Inclusion Criteria**
Dreyling et al,[15] 2016	Phase III, multicenter, open label, randomized 1:1, ITT, IWG 2007	Ibrutinib	Tems	139	141	R/R MCL, ≥1 previous rituximab-containing therapy, ECOG PS 0-1
Forstpointner et al,[16] 2004	Phase III, multicenter, open label, randomized 1:1, ITT, IWG 1999	R-FCM	FCM	24	26	R/R MCL (35%), FL (49%), lymphoplasmacytic (11%), other (5%); ≥1 previous chemotherapy, including HSCT; PS not stated
Forstpointner et al,[17] 2006	Phase III, multicenter, open label, randomized 1:1, ITT, IWG 1999	Rituximab maintenance	No Tx	24	26	R/R MCL, FL; patients achieving CR or PR on induction R-FCM; PS not stated
Furtado et al,[18] 2014	Phase II, multicenter, open label, randomized 1:1, ITT, IWG 2007	V-CHOP	CHOP	23	23	R/R MCL, ≥1 previous therapy, ECOG PS ≤2
Hess et al,[19] 2009	Phase III, multicenter, open label, randomized 1:1:1, ITT, IWG 2007	Tems HD vs. LD	IC[a]	HD 54; LD 54	53	R/R MCL, 2-7 previous therapies, must have included an alkylating agent, an anthracycline, and rituximab; ECOG PS ≤2
Rummel et al,[20] 2016	Phase III, multicenter, open label, randomized 1:1, per protocol analyses; response criteria not stated	B-R	F-R	24	23	R/R MCL (21%), FL (51%), MZL (8%), WM (11%), unclassified (9%), ≥1 previous therapy, WHO PS 0-2
Trneny et al,[21] 2016	Phase II, multicenter, open label, randomized 2:1, ITT, IWG 2007	Lenalidomide	IC[a]	170	84	R/R MCL, ≥1 previous combination chemotherapy with an alkylating agent plus ≥1 of anthracycline, cytarabine, or fludarabine with or without rituximab; ECOG PS 0-2

Abbreviations: B-R = bendamustine, rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; CR = complete response; ECOG = Eastern Cooperative Oncology Group; FCM = fludarabine, cyclophosphamide, mitoxantrone; FL = follicular lymphoma; F-R = fludarabine, rituximab; HSCT = hematopoietic stem cell transplantation; IC = investigator's choice chemotherapy; ID = investigational drug; ITT = intention-to-treat (analyses); IWG 1999 = international working group response criteria 1999; IWG 2007 = IWG revised response criteria 2007; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; PR = partial response; PS = performance status; R-FCM = rituximab, fludarabine, cyclophosphamide, mitoxantrone; R/R = relapsed or refractory disease; Tems = temsirolimus; Tx = treatment; V-CHOP = bortezomib plus CHOP; WHO = World Health Organization; WM = Waldenström's macroglobulinemia.
[a]Rates of 2-3 previous therapies versus 4-7 previous therapies.

of ≤ 2. Dreyling et al[15] restricted this to an ECOG PS of 1. The median age of the included patients was similar across the trials, with median age of 67 to 70 years in most trials.

The baseline characteristics are summarized in Table 3 and were generally well balanced between the treatment arms in most trials. Three trials[18,19,21] reported an imbalance in some baseline characteristics. In 1 study,[19] the treatment groups differed with respect to blastoid variant, the median number of previous lines of treatment, and the use of previous bortezomib therapy. Another study[18] differed with respect to the proportion of male patients, interval since diagnosis, and previous rituximab. The third study differed with respect to tumour burden, bulky disease, lactate dehydrogenase levels, number of previous therapies, and number of patients with refractory disease.[21]

Effectiveness of Treatments

The PFS, OS, and ORRs reported for MCL patients in the included trials are summarized in Table 4. All the trials reported an improvement in PFS with the experimental drug, with the difference statistically significant in all, except for 2 of the trials.[16,18] All the trials reported an improvement in OS in favor of the experimental arm, although not all the trials were powered to demonstrate a statistically significant difference in OS between the 2 groups.

Dreyling et al[15] compared the oral BTK inhibitor, ibrutinib, to the intravenous mTOR pathway inhibitor, temsirolimus, in patients who had received ≥ 1 previous rituximab-containing therapy. With a median follow-up period of 20 months, PFS was significantly improved with ibrutinib compared with temsirolimus (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.32-0.58; $P < .0001$),

with a median PFS with ibrutinib of 14.6 months versus 6.2 months with temsirolimus. The relative reduction in the risk of death in patients receiving ibrutinib compared with temsirolimus was 24% (HR, 0.76; 95% CI, 0.53-1.09; $P = .1324$). The median OS was not reached in the ibrutinib arm compared with 21.3 months in the temsirolimus arm. 23% of the patients receiving temsirolimus crossed over to the ibrutinib arm. The ORR as assessed by independent review was significantly greater for ibrutinib than for temsirolimus (72% vs. 40%; $P < .0001$). Additionally, the complete response (CR) rates were superior (19% with ibrutinib vs. 1% with temsirolimus; odds ratio, 3.98; 95% CI, 2.38-6.65). At 18 months, the estimated rate of response was 58% (range, 46%-68%) for ibrutinib compared with 20% (range, 9%-35%) for temsirolimus.

Hess et al[19] compared 2 intravenous temsirolimus regimens (175 mg weekly for 3 weeks, followed by either 75 mg weekly or 25 mg weekly) and investigator's choice (IC) chemotherapy for patients who had received 2 to 7 previous therapies, which must have included an alkylating agent, an anthracycline, and rituximab. The improvement in PFS was statistically significant with the higher dose temsirolimus compared with the IC cohort (HR, 0.44; 97.5% CI, 0.25-0.78; $P = .0009$). A nonsignificant improvement in PFS was noted with the lower dose of temsirolimus (HR, 0.65; 97.5% CI, 0.39-1.10; $P = .062$). A longer median PFS was observed in the high-dose cohort compared with the IC (4.8 vs. 1.9 months) and the low-dose cohort (3.4 vs. 1.9 months with IC). Higher dose temsirolimus resulted in a 20% relative reduction in the risk of death compared with IC chemotherapy (HR, 0.80; 95% CI, 0.50-1.28; $P = .35$), but the difference did not reach statistical

Table 2	Regimens Used in Trials Listed in Table 1
Drug	**Dosage and Schedule**
Ibrutinib	Oral 560 mg daily until progression
Temsirolimus	IV temsirolimus 175 mg on days 1, 8, 15 of cycle 1, followed by 75 mg on days 1, 8, 15 of subsequent 21-d cycles until progression or unacceptable toxicity
FCM	IV fludarabine 25 mg/m² on days 1-3 plus IV cyclophosphamide 200 mg/m² on days 1-3 plus IV mitoxantrone 8 mg/m² on day 1 for 4 cycles
R-FCM	IV rituximab 375 mg/m² on day 0 plus FCM as before for 4 cycles
Rituximab maintenance	2 Courses of IV rituximab 3 and 9 mo after completion of induction; each course: 4 doses of IV rituximab 375 mg/m² for 4 consecutive weeks
CHOP	IV cyclophosphamide 750 mg/m² plus IV doxorubicin 50 mg/m² plus IV vincristine 1.4 m/m² to maximum of 2 mg on day 1 of each cycle plus oral prednisolone 100 mg/d for maximum of 8 cycles
V-CHOP	IV bortezomib 1.6 mg/m² on days 1 and 8 of 21-d cycle plus CHOP as before for maximum of 8 cycles
Temsirolimus HD	IV temsirolimus as before until progression or unacceptable toxicity
Temsirolimus LD	IV temsirolimus 175 mg on days 1, 8, and 15 of cycle 1, followed by 25 mg on days 1, 8, and 15 of subsequent 21-d cycles until progression or unacceptable toxicity
B-R	IV bendamustine 90 mg/m² on days 1 and 2 plus IV rituximab 375 mg/m² on day 1 every 4 wk for maximum of 6 cycles
F-R	IV fludarabine 25 mg/m² on days 1-3 plus rituximab as before for maximum of 6 cycles
Lenalidomide	Oral lenalidomide 25 mg on days 1-21 of 28-d cycle until progression or unacceptable toxicity
IC[a]	IV gemcitabine 1000 mg/m² on days 1, 8, and 15 every 28 d for maximum of 6 cycles OR IV fludarabine 25 mg/m² or oral fludarabine 40 mg/m² on days 1-5 every 28 d for maximum of 6 cycles OR oral chlorambucil 0.1-0.2 mg/kg daily for 3-6 wk OR IV cladribine 5 mg/m² daily for 5 d every 28 d OR IV etoposide 50-150 mg/m² daily for 3-5 d every 21-28 d OR oral thalidomide 200 mg daily OR IV vinblastine 10 mg weekly OR IV alemtuzumab 30 mg/d 3 times weekly OR oral lenalidomide 25 mg daily for 28 d
IC[b]	IV rituximab 375 mg/m² on days 1, 8, 15, and 22 and then once every 56 d until progression OR IV gemcitabine as before OR either fludarabine as before OR IV chlorambucil 40 mg/m² monthly divided over days 3-10 until progression OR IV cytarabine 1-2 g/m² on days 1 and 2 every 28 d for maximum of 6 cycles

Abbreviations: B-R = bendamustine, rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; FCM = fludarabine, cyclophosphamide, mitoxantrone; F-R = fludarabine, rituximab; HD = high dose; IC = investigator's choice; IV = intravenous; LD = low dose; R-FCM = rituximab, fludarabine, cyclophosphamide, mitoxantrone; V-CHOP = bortezomib plus CHOP.
[a]Investigator's choice in Hess et al trial.
[b]Investigator's choice in Trneny et al trial.

significance. The lower dose achieved a 4% relative reduction in the risk of death compared with the IC (HR, 0.96; 95% CI, 0.60-1.54; $P = .87$). The final median OS analysis demonstrated an improvement in favor of the higher dose of temsirolimus compared with the IC (12.8 vs. 9.7 months; $P = .35$). The median OS observed with the lower dose cohort was 10 months ($P = .87$). High-dose temsirolimus resulted in superior ORR compared with IC chemotherapy (22% vs. 2%; $P = .0019$). The ORR with low-

dose temsirolimus was 6% ($P = .61$). The CR rate with high-dose temsirolimus was comparable to that of the IC (2% vs. 2%), although the partial response (PR) rate was improved (20% vs. 0%).

The use of R-FCM (the addition of rituximab [an anti-CD20 monoclonal antibody] to FCM [fludarabine, cyclophosphamide, mitoxantrone]) chemotherapy was compared with FCM alone by Forstpointner et al[16] in a mixed population of lymphoma subtypes (49% had follicular lymphoma (FL), 35% had MCL, and 11% had lymphoplasmacytic/cytoid lymphoma) who had received ≥ 1 previous line of treatment. The trial was stopped early with 128 patients recruited owing to the significant advantage observed in favor of R-FCM. PFS was significantly improved with R-FCM compared with FCM alone in the overall population (median PFS, 16 vs. 10 months; $P = .038$) after a median follow-up of 18 months. In an exploratory analysis of the histologic subgroups, a shorter median PFS was observed for the MCL population compared with the total population (R-FCM, 8 vs. 4 months with FCM; $P = .389$). The investigators used a second randomization[17] to maintenance rituximab or no maintenance for patients who had achieved a CR or PR. Although the median duration of response for MCL patients was similar in both arms (14 months with maintenance vs. 12 months without maintenance; $P = .049$), a greater proportion of MCL patients receiving maintenance rituximab experienced ongoing remission > 2 years (45% vs. 9%). A statistically significant benefit in median OS was observed in the cohort of MCL patients receiving R-FCM compared with FCM (OS, not reached vs. 11 months [estimated]; $P = .0042$). These patients represented 35% of the total population. In addition, at 2 years, 65% of the MCL patients receiving R-FCM were still alive compared with 35% of patients treated with FCM. R-FCM resulted in an improved ORR compared with FCM alone (58% vs. 46%; $P = .282$). More MCL patients experienced a CR with R-FCM than with FCM (29% vs. 0%), although more patients in the FCM arm achieved a PR (29% vs. 46%).

Furtado et al[18] compared V-CHOP (bortezomib [an inhibitor of the 26S proteasome], cyclophosphamide, doxorubicin, vincristine, prednisolone) for a maximum of 8 cycles to CHOP in MCL patients who had been treated with ≥ 1 previous line of therapy. The phase II trial recruited 46 patients and was stopped early by the independent data monitoring committee owing to the significant differences in OS between the 2 cohorts. After a median follow-up of 34 months, a nonsignificant improvement in PFS was observed with the V-CHOP combination compared with CHOP alone (HR, 0.60; 95% CI, 0.31-1.15; $P = .12$). The median PFS observed with the V-CHOP combination was 16.5 months compared with 8.1 months with CHOP, with a significant improvement in OS achieved with V-CHOP (HR, 0.37; 95% CI, 0.16-0.83; $P = .01$). The median OS of 35.6 months with V-CHOP was substantially longer than that observed with CHOP at 11.8 months. The addition of bortezomib to CHOP resulted in a superior ORR compared with CHOP alone (82.6% vs. 47.8%; $P = .01$). A nonsignificant improvement in CR rates (34.8% vs. 21.7%; $P = .33$) and PR rates (47.8% vs. 26.1%; $P = .13$) was also noted.

Rummel et al[20] compared B-R (bendamustine, rituximab) and F-R (fludarabine, rituximab) in a mixed cohort of patients who had received ≥ 1 previous therapy. Of their patients, 51% had FL, 21% had MCL, 11% had Waldenström's macroglobulinemia, 8% had

Figure 2 Risk of Bias Summary. *Assessment of Blinding of Participants and Personnel Was Not Applicable Because All Trials Were Open Label. The Trials Were Listed as Having an Unclear Risk of Bias Owing to the Restrictions of Choice Within the Bias Tool. Green Indicates a Low Risk of Bias; Yellow, an Unclear Risk of Bias; and Red, a High Risk of Bias

marginal zone lymphoma, 8% had lymphoplasmacytic lymphoma, and 1% had low-grade disease, unclassified. A maximum of 6 cycles of either chemotherapy combination was administered to 230 patients. The protocol was amended during the course of the trial to include rituximab maintenance therapy for patients who had responded to B-R or F-R, because maintenance rituximab treatment had been approved for patients with FL. In patients with MCL, the improvement in PFS was statistically significant in the B-R arm (HR, 0.45; 95% CI, 0.22-0.76; $P = .01$), with a median PFS of 17.6 months achieved with B-R compared with 4.7 months with F-R. An improvement in median OS was also observed (B-R group, 35.3 months vs. 20.9 months for the F-R group; $P = $ not reported). The effect of maintenance rituximab was not reported for the MCL patients. A superior ORR for the MCL patients receiving B-R was achieved (70.8% vs. 26.1%). Both the CR rate (37.5% vs. 13%) and the PR rate (33.3% vs. 13%) were substantially greater for the MCL patients treated with B-R compared with those treated with F-R.

Trneny et al[21] compared oral lenalidomide to IC single-agent chemotherapy in 254 MCL patients. The patients had to have received ≥ 1 combination chemotherapy regimen comprising an alkylating agent and ≥ 1 of an anthracycline, cytarabine, or fludarabine, with or without rituximab. After a median follow-up of 15.9 months, the improvement in PFS was statistically significant with lenalidomide (HR, 0.61; 95% CI, 0.44-0.84; $P = .004$) compared with IC, with a prolonged median PFS of 8.7 months versus 5.2 months in the IC arm. A significant improvement was demonstrated in favor of lenalidomide compared with most of the individual IC therapies. A nonstatistically significant difference in OS was reported for patients treated with lenalidomide compared with patients treated with IC (HR, 0.89; 95% CI, 0.62-1.28; $P = .45$). The median OS was 27.9 months with lenalidomide compared with 21.2 months with IC. The trial was not powered to demonstrate a survival difference between the 2 arms and was further compounded by patients crossing over to the lenalidomide arm at disease progression. A significant improvement in ORR was observed for patients receiving lenalidomide compared with IC chemotherapy (40% vs. 11%; $P < .001$). The CR rate was 5% with lenalidomide versus 0% ($P = .043$). The PR rate was 35% versus 11% with IC. The duration of response was significantly prolonged with lenalidomide compared with IC (16.1 vs. 10.4 months; $P = .043$).

Safety

A summary of grade ≥ 3 hematologic toxicities observed in the trials is presented in Figure 3. Patients treated with ibrutinib had a longer duration of treatment exposure compared with the control arm in the trial by Dreyling et al[15] (14.4 vs. 3 months), with a mean relative dose intensity of 99.9% for ibrutinib versus 81.8% for temsirolimus. Adverse events caused treatment discontinuation and dose reductions in 6% and 4% of patients in the ibrutinib arm compared with 26% and 43% in the comparator group, respectively.

The median duration of temsirolimus 175/75-mg treatment was more than double that of IC (12 vs. 5 weeks) in the trial by Hess et al.[19] Significantly greater rates of thrombocytopenia and anemia were observed with temsirolimus. In contrast, leukopenia was more frequent with IC chemotherapy than with higher dose temsirolimus (all grades, 15% vs. 40% with IC), as was neutropenia (all grades, 24% vs. 40% with IC). Of the patients in the temsirolimus 175/75-mg arm, 22% discontinued treatment because of an adverse event compared with 11% in the IC arm.

The frequency of grade 3/4 hematologic toxicities was comparable across both treatment groups in the trial by Forstpointner et al,[16] except for lymphocytopenia, which was more common across grades 1 to 4 in the R-FCM arm than in the FCM arm. The extended use of rituximab during the maintenance phase of the trial[17] did not result in any significant differences in the adverse events between the 2 arms.

Furtado et al[18] reported a similar rate of grade ≥ 3 thrombocytopenia between the 2 arms. However, a significant increase in the rate of grade ≥ 3 neutropenia was observed in the experimental arm, which translated to a greater rate of febrile neutropenia with the V-CHOP regimen. Non-neutropenic infection rates were also higher; however, these were primarily low grade.

The B-R and F-R combinations were both well tolerated by patients in the trial by Rummel et al.[20] The dose intensity was 96.3% in the B-R group and 99.5% in the F-R arm, indicating good tolerability for both regimens.

Table 3 Baseline Characteristics of Trial Population

Investigator	Median Age (y)		Median Time from Original Diagnosis to Randomization (mo)		Blastoid vs. Classic Histologic Type (%)		Low vs. Med vs. High sMIPI (%)		Relapsed vs. Refractory (%)		Previous Lines of Therapy 1-2 vs. >2 (%)	
	ID	C	ID	C	ID	C	ID	C	ID	C	ID	C
Dreyling et al,[15] 2016; Ibr vs. Tems	67	68	38.9	46.23	12 vs. 88	12 vs. 88	32 vs. 47 vs. 22	30 vs. 49 vs. 21	74 vs. 26	67 vs. 33	68 vs. 32	66 vs. 34
Forstpointner et al,[16] 2004; R-FCM vs. FCM	65	63	24 for total population		NS	NS	NS	NS	NS	NS	83 vs. 17[a]	84 vs. 17[a]
Forstpointner et al,[17] 2006; R-main vs. Obs	63	63	35 for total population		NS	NS	NS	NS	NS	NS	97 vs. 4[a]	100 vs. 0[a]
Furtado et al,[18] 2014; V-CHOP vs. CHOP	69	71	24.7	19.7	NS	NS	NS	NS	NS	NS	NS	
Hess et al,[19] 2009; Tems vs. IC	HD, 68; LD, 68.5	64.5	HD, 49.6; LD, 47.7	48.5	HD, 0 vs. 85; LD, 17 vs. 65	7 vs. 74	NS	NS	NS	NS	HD 52 vs. 48[b]; LD 59 vs. 41[b]	39 vs. 61[b]
Rummel et al,[20] 2016; B-R vs. F-R	71.6	69.4	NS	NS	NS	NS	NS		96 vs. 4	95 vs. 5	79.1 vs. 20.8	87 vs. 13
Trneny et al,[21] 2016; L vs. IC	68.5	68.5	54 vs. 45[c]	52 vs. 46[c]	NS	NS	25 vs. 39 vs. 35[d]	25 vs. 44 vs. 30[d]	59 vs. 41	70 vs. 30	73 vs. 26	71 vs. 29

Abbreviations: B-R = bendamustine, rituximab; C = control; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; F-R = fludarabine, rituximab; ID = investigational drug; HD = high dose; Ibr = ibrutinib; IC = investigator's choice; L = lenalidomide; LD = low dose; NS = not stated; Obs = observation; R-FCM = rituximab, fludarabine, cyclophosphamide, mitoxantrone; R-main = rituximab maintenance; sMIPI = simplified mantle cell lymphoma international prognostic index; Tems = temsirolimus; V-CHOP = bortezomib, cyclophosphamide, doxorubicin, vincristine, prednisolone.
aPercentage of 1 previous and 2 previous therapies summed for this group.
bRates of 2-3 previous therapies versus 4-7 previous therapies.
cDuration < 3 y versus > 3 y.
dBoth arms missing data for 2%.

Table 4 Efficacy Outcomes for MCL Patients in Included Trials

Investigator	OA	PFS (mo)			OS (mo)			ORR (%)			CR (%)			PR (%)	
		M	HR (95% CI)	P Value	M	HR (95% CI)	P Value	ORR	OR (95% CI)	P Value	CR	OR (95% CI)	P Value	PR	OR (95% CI)
Dreyling et al,[15] 2016	ITT	14.6 vs. 6.2	0.43 (0.32-0.58)	<.0001	NR[a] vs. 21.3	0.76 (0.53-1.09)	.1324	72 vs. 40	NR[b]	.0001	19 vs. 1	3.98 (2.38-6.65)	NR[b]	NR[b]	NR[b]
Forstpointner et al,[16] 2004	ITT	8 vs. 4	NR[b]	.3887	NR[a] vs. 11 (est)	NR[b]	.0042	58 vs. 46	NR[b]	.282	29 vs. 0	NR[b]	NR[b]	29 vs. 46	NR[b]
Forstpointner et al,[17] 2006	Initial R-FCM therapy	14 vs. 12[c]	NR[b]	.049	45% vs. 9%[d]	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
Furtado et al,[18] 2014	ITT	16.5 vs. 8.1	0.6 (0.31-1.15)	.12	35.6 vs. 11.8	0.37 (0.16-0.83)	.01	82.6 vs. 47.8	0.14 (0.3-0.62)	.01	34.8 vs. 21.7	0.52 (0.14-1.93)	.33	47.8 vs. 26.1	0.39 (0.11-1.33)
Hess et al,[19] 2009[e]	ITT	4.8 vs. 1.9	0.44 (0.25-0.78)	.0009	12.8 vs. 9.7	0.80 (0.50-1.28)	.3519	22 vs. 2	NR[b]	.0019	2 vs. 2	NR[b]	NR[b]	20 vs. 0	NR[b]
Rummel et al,[20] 2016	Per protocol	17.6 vs. 4.7	0.45 (0.22-0.76)	.01	35.3 vs. 20.9	NR[b]	NR[b]	70.8 vs. 26.1	NR[b]	NR[b]	37.5 vs. 13	NR[b]	NR[b]	33.3 vs. 13	NR[b]
Trneny et al,[21] 2016	ITT	8.7 vs. 5.2	0.61 (0.44-0.84)	.004	27.9 vs. 21.2	0.89 (0.62-1.28)	.45	40 vs. 11	NR[b]	.001	5 vs. 0	NR[b]	NR[b]	35 vs. 11	NR[b]

Abbreviations: CI = confidence interval; CR = complete response; est = estimated; HR = hazard ratio; ITT = intent to treat; M = median; OA = outcomes analysis; OR = odds ratio; ORR = overall response rate; PFS = progression-free survival; PR = partial response; R-FCM = rituximab, fludarabine, cyclophosphamide, mitoxantrone.
[a]Not reached.
[b]Not reported.
[c]Median response duration.
[d]Ongoing remissions > 2 y.
[e]Results for higher dose.

Dose reductions were more common in the lenalidomide group (41% vs. 17%),[21] but discontinuations were more common in the IC group (5% vs. 16%). The rates of grade ≥ 3 neutropenia were greater in the lenalidomide arm, with febrile neutropenia reported in 6% of patients receiving lenalidomide compared with 2% of patients receiving IC. The rates of anemia were comparable, with the incidence of thrombocytopenia greater in the IC arm.

Unpublished and Ongoing Trials

The data from 4 trials[23-26] were presented at the 58th annual meeting of the ASH held in San Diego from December 3 to 6, 2016. All 4 trials had assessed combinations of treatments for R/R MCL.[23-26] All these trials were single-arm studies but give an indication of emerging potential future management approaches. Jerkeman et al[23] on behalf of the Nordic Lymphoma Group combined ibrutinib with lenalidomide and rituximab. The investigators reported that of the 50 patients enrolled to date, 29 were evaluable for response and had achieved an impressive ORR rate of 83% and CR of 41%, with the median PFS not reached. Morschhauser et al[26] presented the results on behalf of the LYSA (Lymphoma Study Association) group from their study combining lenalidomide with obinutuzumab, an anti-CD20 monoclonal antibody. Seven MCL patients completed the induction phase and achieved an ORR of 38.5%, with CR in 23.1%, as evaluated using the revised International Working Group (IWG) 2007 criteria.[27] These improved ORR and CR rates would indicate a deeper response with the combination of therapies, which might, in time, translate to longer PFS and OS for patients.

As of December 2016, 85 trials were ongoing (www.clinicaltrials. gov and www.clinicaltrialsregister.eu), aiming to recruit > 2300 patients with relapsed/refractory MCL to evaluate monotherapies and combinations of agents. Of these 85 trials, 53 are phase I or phase I/II trials, 26 are in phase II, 1 trial is phase III, and 1 trial is phase IV. The remaining 4 trials are either retrospective or stated as
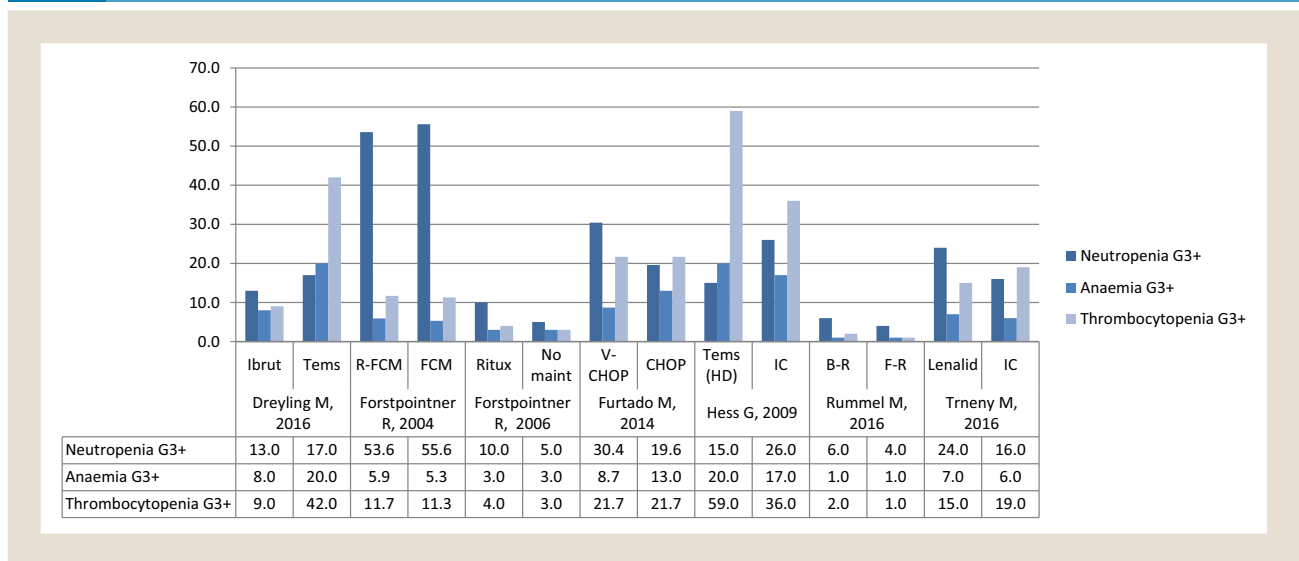
pilot studies, with no further details. Only the phase III trial is a RCT (Supplemental Table 4; available in the online version). Of the remaining 26 ongoing phase II trials, 13 are evaluating combinations of treatments and 13 are assessing monotherapies. Ibrutinib is included in 5 combination trials, lenalidomide in 3 combination studies, 1 of which is with bendamustine, and bortezomib is combined with additional treatments in 2 trials.

Discussion

No consensus has been reached about the standard of care for R/R MCL and the current UK,[2] European Union,[4] and US[13] guidelines reflect this. As demonstrated by the search results, many reported studies have assessed treatment regimens for this disease; however, the vast majority have been single-arm, non-randomized trials that relied on historical controls for comparison. Bortezomib, ibrutinib, and lenalidomide all received marketing authorization based on single-arm phase II trials,[28-30] which might have reflected the unmet medical need for this group of patients at the time. The lack of RCTs evaluating treatments for R/R MCL is noticeable and limited the scope of the present systematic review. Only 7 RCTs[15-21] were identified for the present review, 6 of which were distinct trials. Of these, only 2 met all the criteria set out in the Cochrane's Collaboration tool for assessing the risk of bias.

Three of the trials had mixed populations. MCL is a rare, but aggressive, B-cell malignancy that behaves quite differently from other subtypes of NHL, resulting in distinctive responses to treatment, as demonstrated in the trial by Rummel et al.[20] In their trial, MCL patients receiving the combination of bendamustine and rituximab achieved a median PFS of 17.6 months. In contrast, patients with FL achieved a median PFS of 54.5 months with the same regimen. These were exploratory subgroup analyses; nevertheless, this highlights the need to evaluate treatments for a pure MCL population to draw clinically meaningful conclusions. It can

| Figure 3 | Grade ≥ 3 Hematologic Toxicities |

	Ibrut	Tems	R-FCM	FCM	Ritux	No maint	V-CHOP	CHOP	Tems (HD)	IC	B-R	F-R	Lenalid	IC
	Dreyling M, 2016		Forstpointner R, 2004		Forstpointner R, 2006		Furtado M, 2014		Hess G, 2009		Rummel M, 2016		Trneny M, 2016	
Neutropenia G3+	13.0	17.0	53.6	55.6	10.0	5.0	30.4	19.6	15.0	26.0	6.0	4.0	24.0	16.0
Anaemia G3+	8.0	20.0	5.9	5.3	3.0	3.0	8.7	13.0	20.0	17.0	1.0	1.0	7.0	6.0
Thrombocytopenia G3+	9.0	42.0	11.7	11.3	4.0	3.0	21.7	21.7	59.0	36.0	2.0	1.0	15.0	19.0

Abbreviations: B-R = bendamustine, rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; FCM = fludarabine, cyclophosphamide, mitoxantrone; F-R = fludarabine, rituximab; G3+ = grade ≥ 3; HD = high dose; Ibrut = ibrutinib; IC = investigator's choice; Lenalid = lenalidomide; maint, maintenance; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-FCM = rituximab, fludarabine, cyclophosphamide, mitoxantrone; ritux = rituximab; Tems = temsirolimus.

be challenging to accrue a sufficient number of patients to a trial when the disease is rare, and collaborative research groups have been established because of this. Forstpointner et al[16] had only included 48 patients with MCL when further recruitment was halted owing to the significant advantage observed in the R-FCM arm, which had a mixed population of lymphoma subtypes. The trial by Furtado et al[18] had planned to recruit 90 patients. However, the trial was stopped early owing to a significant difference in survival observed at the first predetermined evaluation point; thus, only 46 patients were included. Neither trial was statistically designed for such small numbers; therefore, the statistical significance of the results could be unreliable. The median PFS observed with V-CHOP treatment was double that with CHOP alone in the trial by Furtado et al,[18] yet this did not achieve statistical significance.

It is difficult to make meaningful comparisons of effectiveness across the included trials in the present review because the inclusion and exclusion criteria differed among the trials. The trial by Dreyling et al[15] excluded patients with an ECOG PS > 1. The remaining trials allowed patients with an ECOG PS of 0 to 2.[18-21] Most trials included patients who had received ≥ 1 line of previous therapy[15,16,18,20,21]; however, these previous therapies differed between the trials and might have had some impact on the outcomes achieved. Previous rituximab therapy could have introduced an outcome bias to those trials allowing previous exposure. Rule et al[31] demonstrated that the addition of rituximab to fludarabine-based chemotherapy in patients with newly diagnosed MCL improved OS, resulting in a reduction in the hazard of death by 31%. In addition, it has been suggested that previous bortezomib treatment sensitizes MCL to subsequent therapies.[32] Another baseline factor that could affect the outcomes include the interval from the initial diagnosis to randomization because the longer time might suggest that these patients had more indolent disease and could safely wait to start therapy. The proportion of patients with the more difficult to treat blastoid histologic type will also affect the outcomes. The split between patients with relapsed disease and those with refractory disease will influence the outcomes, because refractory disease is generally a harder-to-treat subtype. Additional factors that should be considered when comparing trials are the differences in the MCL international prognostic index scores, the proportion of patients with high Ki-67 scores, indicating more aggressive disease, and other biologic factors such as TP53 mutation or SOX11 status, which will affect the outcomes. The ideal would be to have these balanced between the arms of each trial, and stratification before randomization might achieve this. However, in a rare disease, this can be difficult to achieve in practice. The blastoid histologic type represents a small proportion of the total MCL population; it is important that patients with this subtype are included in trials to collect data on how they respond to various treatments. It would not be feasible to perform a trial of this subtype alone; therefore, imbalances in the baseline characteristics of this nature between treatment arms should be tolerated, acknowledging that they could affect the results.

The response criteria by which outcomes were measured also differed among the studies. It is important that consistent definitions of endpoints are used to allow for comparisons among clinical trials. The 1999 IWG criteria[33] were revised in 2007[27] and eliminated the need for the response criterion, CR unconfirmed, and incorporated the assessment of extranodal disease. In a trial[23]

recently presented at the 58th Annual Meeting of the ASH in 2016, 2 analyses were conducted within the same trial, 1 using the 1999 IWG criteria[33] demonstrating an ORR of 46.2% and a CR/CR unconfirmed of 15.4%. The other analysis used the revised 2007 IWG criteria[27] and reported an ORR of 38.5% and CR of 23.2%, demonstrating some differences in the response rates according to the criteria used. Four of the trials[15,18,19,21] in the present review used the revised 2007 IWG criteria[27]; however, both trials by Forstpointner et al[16,17] used the 1999 IWG criteria.[33] The revised criteria[27] also provide clear definitions of time to event outcomes; for example, PFS and OS are measured from the point of randomization to the date of disease progression or death from any cause. The definitions of PFS were inconsistent among the trials. Three trials[15,19,21] used the IWG definition. Two trials,[16,20] however, used the definition: "progression-free survival is the interval between the start of treatment/first treatment and documentation of progressive disease or death from any cause." One trial[18] did not provide a definition of PFS. The investigators stated that one of the secondary outcomes was the "median time to progression of disease"; however, they reported the PFS in the results.

The trial by Hess et al[19] evaluated 2 different dosing regimens of temsirolimus (175/75 mg and 175/25 mg) against a control arm of IC chemotherapy. The results led to the regulatory approval of the 175/75-mg dose in the European Union. Dreyling et al[15] compared ibrutinib to temsirolimus 175/75 mg. Some similarities were found when comparing the baseline characteristics between the 2 trials; thus, it would be feasible to compare the outcomes of these 2 trials. What is striking is that across all outcome measures in the study by Dreyling et al,[15] temsirolimus outperformed those achieved in the temsirolimus 175/75-mg arm of the trial by Hess et al,[19] although the duration of response reported was similar between the 2 trials. Patients in the trial by Hess et al[19] had received 2 to 7 previous therapies (48% had received 4-7 previous treatments) compared with ≥ 1 in the study by Dreyling et al[15] (68% had received a median of 1-2), which might account for the poorer performance of temsirolimus, suggesting that earlier treatment is more effective. The abstract presented by Rule et al[34] at the 21st Congress of the European Haematology Association in 2016 supports this idea. The investigators reported survival outcomes for ibrutinib stratified by the number of lines of previous therapy, which revealed that earlier treatment is more effective. However, ibrutinib was significantly better than temsirolimus across all outcome measures in the trial by Dreyling et al.[15]

The addition of rituximab to chemotherapy regimens for the treatment of MCL has been established in a number of trials. Included in the present review were the trials by Forstpointner et al,[16,17] which demonstrated that the addition of rituximab to the combination of fludarabine, cyclophosphamide, and mitoxantrone, followed by rituximab maintenance for patients in remission improved the response rates and OS. Maintenance rituximab resulted in a greater proportion of patients experiencing ongoing remission for > 2 years. The effect of rituximab on the outcome for MCL patients influenced the decision to halt the trial by Furtado et al[18] early. The investigators had not incorporated rituximab into the design of their study; however, during the recruitment period, it had become part of standard care in the United Kingdom. Rummel

et al[20] had begun accrual for their trial in October 2003; however, the investigators amended their protocol to allow patients who had responded to either B-R or F-R chemotherapy to receive maintenance rituximab after the report by Forstpointner et al.[17] They conducted a subgroup analysis of the total population, comparing those patients who had received maintenance and those who had not. The results confirmed the effect that maintenance rituximab had on PFS and OS in the relapsed/refractory setting after remission with induction chemotherapy. Maintenance rituximab reduced the risk of death or disease progression by 48% (PFS, $P = .01$; OS, $P = .03$). The group of MCL patients who received maintenance rituximab was too small for analysis. However, the trial reported by Rummel et al[35] at the 2016 annual meeting of the American Society of Clinical Oncology, conducted in the first-line setting, might give some indication of what might be expected in MCL patients. No statistically significant difference in PFS was observed between patients receiving maintenance rituximab after B-R chemotherapy and those not receiving maintenance rituximab (HR, 0.64; 95% CI, 0.36-1.14; $P = .130$). They recruited 120 patients with newly diagnosed MCL and concluded that after a median observation time of 4.5 years, they were not able to demonstrate statistically significant evidence supporting the benefit of rituximab maintenance after B-R.

Only 1 treatment, temsirolimus, appeared in > 1 trial; thus, the results from each trial could not be quantitatively pooled by meta-analysis. Although a limited network meta-analysis could theoretically have been performed of the data from Dreyling et al[15] and Hess et al[19] because both trials included a temsirolimus arm, Hess et al[19] had included IC as a comparator. Thus, it was impossible to evaluate the effectiveness of temsirolimus against particular drugs, making the comparisons meaningless.

Because most patients with MCL are elderly, the tolerability of treatment is an important factor when comparing different therapies and should be evaluated on the per protocol population to accurately reflect the adverse events in patients actually receiving the drug. The grade ≥ 3 hematologic adverse event rates varied considerably among the included trials. The rates of grade ≥ 3 hematologic toxicities were low with the combination of bendamustine and rituximab and the combination of fludarabine and rituximab in the trial by Rummel et al,[20] with high-dose intensities achieved in both arms of the trial. Ibrutinib was also well tolerated, with low rates of myelosuppression despite a treatment exposure 3 times as long with ibrutinib than with temsirolimus 175/75 mg.[15] Dose reductions were uncommon with ibrutinib, although 43% of patients receiving temsirolimus 175/75 mg required a dose reduction because of adverse events. Nearly one quarter of patients treated with temsirolimus 175/75 mg in the trial by Hess et al[19] discontinued treatment because of an adverse event. The results from both of these trials suggest that temsirolimus at the approved dose of 175/75 mg is poorly tolerated. In the trial by Forstpointner et al,[17] it was encouraging to note that rituximab maintenance did not result in substantial additional treatment-associated hematologic toxicities, with grade ≥ 3 adverse event rates very similar between the maintenance and no maintenance arms.

Some of the novel agents identified in the present review are being evaluated in the front-line setting, which will affect the choice of agent when these patients subsequently develop a relapse. A UK study[36] evaluating ibrutinib and rituximab against a rituximab and chemotherapy combination in patients with newly diagnosed MCL who are not eligible for intensive treatment is ongoing. The results are expected in 2022. In addition, the SHINE trial (a study of the Bruton tyrosine kinase inhibitor ibrutinib given in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma) is assessing the combination of ibrutinib with B-R in patients with newly diagnosed MCL.[37] A similar trial evaluating the combination of the second-generation BTK inhibitor, acalabrutinib, with B-R[38] is ongoing, with the results due in February 2021. If these prove to be successful, the paradigm for relapsed or refractory disease will shift, and subsequent trials for relapsed/refractory MCL will need to include patients who have received previous ibrutinib or acalabrutinib treatment. A Spanish trial[39] is evaluating the combination of ibrutinib and rituximab in patients with newly diagnosed indolent MCL. That trial is expected to report results in January 2023. Several trials[40-42] are evaluating the role of lenalidomide in the first-line setting, either combined with chemotherapy or as maintenance after chemotherapy induction. The E1411 trial[43] is evaluating the combination of bortezomib with B-R as induction therapy, followed by rituximab with or without lenalidomide as maintenance. The results are expected in March 2019.

A number of new agents are being assessed for R/R MCL, either as monotherapy or combined with established treatments, including venetoclax (BCL-2 inhibitor), idelalisib, and buparlisib (PI3Kδ inhibitors), the second-generation proteasome inhibitor carfilzomib, daratumumab (an anti-CD38 monoclonal antibody), and genetically engineered chimeric antigen receptor T-cells (CAR T-cells). All are currently being evaluated in single-arm trials.

As the landscape of treatment options for the management of R/R MCL becomes more complicated, comparative studies will be required to evaluate the relative advantages of 1 treatment over another to ensure the optimal use of the available therapies. The protocol only permitted the inclusion of RCTs, because that study design provides the best evidence for the effectiveness of treatments. Single-arm trials might provide additional information to clinicians regarding the efficacy of treatment options for this rare disease; however, these are biased by the nature of their design. It is concerning that only 1 of the ongoing studies is an RCT. Careful consideration should be given to future trial designs to ensure that meaningful evaluation of effectiveness of treatments can be undertaken.

The challenging factor is that MCL remains a rare malignancy with a small pool of patients from which to recruit to trials. Collaboration between research groups and agreement of standards for clinical trials is essential. In addition to this, using adaptive trial designs to assess the relative merits of treatments could help in addressing this challenge. Multi-arm, multistage trials have been adopted in some therapeutic areas to allow the comparison of a number of novel treatments compared simultaneously to a shared control group.[44] This can result in the provision of answers to research questions more quickly and cost effectively with a smaller number of patients and might be a suitable approach to adopt for evaluating future treatments or combinations of treatments for MCL patients.

The scarcity of high-quality RCTs of MCL highlights the difficulty in evaluating the comparative efficacy and safety of new

therapies. Historical studies lack common comparators, exhibit differences in inclusion criteria, and have small sample sizes. Although prognostic indicators such as the simplified MCL international prognostic index score or blastoid variant were reported in some of the studies, none of the trials reported outcomes according to these important factors owing to the small numbers of patients in these groups. The original protocol intended to undertake a subgroup analysis for these prognostic indicators; however, owing to the lack of data, such an analysis was not possible. Nevertheless, the present review should help to guide treatment selection for elderly patients with R/R MCL unsuitable for intensive chemotherapy or transplantation.

Disclosure

M.P. is employed by Janssen-Cilag, the manufacturer of ibrutinib, as a senior Medical Scientific Liaison Manager. The present review, however, was written as part of the author's position as an MSc student at the Institute of Cancer Sciences, University of Birmingham, and all efforts have been made to take a strictly impartial view of the evidence. S.R. has provided consultancy for Janssen-Cilag, Celgene, Roche, Napp, Pharmacyclics, Gilead, Sunesis, Kite, TG Therapeutics, and Astra Zeneca. M.K. is employed by Janssen-Cilag as a senior Medical Scientific Liaison Manager. J.W. is funded by Cancer Research UK and has no conflicts of interest to declare.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2017.10.004.

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Supplemental Table 1	Medline (Ovid) Search Strategy
1. Lymphoma, Mantle-cell.mp. or *mantle cell lymphoma/	
2. Lymphoma, non-Hodgkin.mp. or *nonhodgkin lymphoma/	
3. B-cell.mp. or *B lymphocyte/	
4. 1 or 2 or 3	
5. Drug therapy.mp. or drug therapy/	
6. Immunotherapy.mp. or immunotherapy/	
7. Molecular targeted therapy.mp. or molecularly targeted therapy/	
8. Biological therapy.mp. or biological therapy/	
9. Combined modality therapy.mp. or multimodality cancer therapy/	
10. Antineoplastic agents.mp. or antineoplastic agent/	
11. Lenalidomide.mp. or lenalidomide/	
12. Ibrutinib.mp. or ibrutinib/	
13. Thalidomide.mp. or thalidomide/	
14. Bortezomib.mp. or bortezomib/	
15. Temsirolimus.mp. or temsirolimus/	
16. Everolimus/ or everolimus.mp.	
17. BTK inhibitor.mp. or Bruton tyrosine kinase inhibitor/	
18. Proteasome inhibitor.mp. or proteasome inhibitor/ or ixazomib/	
19. Immunomodulating agent/ or imid.mp.	
20. Combination chemotherapy/ or chemotherapy/ or multimodal chemotherapy/ or cancer combination chemotherapy/ or chemotherapy.mp.	
21. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	
22. 4 and 21	
23. Limit 22 to (randomized controlled trial and yr = "1994-Current")	

Supplemental Table 2	Embase (Ovid) Search Strategy
1. Lymphoma, Mantle-cell.mp. or *mantle cell lymphoma/	
2. Lymphoma, Non-Hodgkin.mp. or *nonhodgkin lymphoma/	
3. B-cell.mp. or *B lymphocyte/	
4. 1 or 2 or 3	
5. Drug therapy.mp. or drug therapy/	
6. Immunotherapy.mp. or immunotherapy/	
7. Molecular targeted therapy.mp. or molecularly targeted therapy/	
8. Biological therapy.mp. or biological therapy/	
9. Combined modality therapy.mp. or multimodality cancer therapy/	
10. Antineoplastic agents.mp. or antineoplastic agent/	
11. Lenalidomide.mp. or lenalidomide/	
12. Ibrutinib.mp. or ibrutinib/	
13. Thalidomide.mp. or thalidomide/	
14. Bortezomib.mp. or bortezomib/	
15. Temsirolimus.mp. or temsirolimus/	
16. Everolimus/ or everolimus.mp.	
17. BTK inhibitor.mp. or Bruton tyrosine kinase inhibitor/	
18. Proteasome inhibitor.mp. or proteasome inhibitor/ or ixazomib/	
19. Immunomodulating agent/ or imid.mp.	
20. Combination chemotherapy/ or chemotherapy/ or multimodal chemotherapy/ or cancer combination chemotherapy/ or chemotherapy.mp.	
21. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	
22. 4 and 21	
23. Limit 22 to (randomized controlled trial and yr = "1994-Current")	

Supplemental Table 3	Quality Assessment of Included Trials of Mantle Cell Lymphoma		
Investigator	**Criteria From Cochrane Collaboration Tool**	**Assessment**	**Notes**
Dreying et al,[15] 2016	Was allocation sequence adequately generated?	Yes	Central randomization was used….based on computer-generated randomization schedule; randomization was balanced using randomly permuted blocks
	Was allocation adequately concealed?	Yes	Randomization scheme was implemented within interactive web response system
	Was participant and personnel knowledge of allocated intervention prevented during the study?	Unclear	Open label; patients and investigators were unmasked to treatment assignment
	Was knowledge of outcomes assessment adequately prevented during the study?	Yes	Outcome assessments were conducted by an independent review committee using validated IWG criteria
	Were incomplete outcomes data adequately addressed?	Yes	All data were accounted for; analysis conducted on ITT basis
	Are reports of study free of suggestion of selective outcome reporting?	Yes	All prespecified outcomes reported
	Was study apparently free of other problems that could put it at a high risk of bias?	Yes	Although protocol was amended to allow crossover to investigational arm at progression, this would have introduced bias against the investigational drug
Forstpointner et al,[16] 2004	Was allocation sequence adequately generated?	Yes	Central randomization procedure performed using computer program and random permutated blocks
	Was allocation adequately concealed?	Yes	Central allocation performed by telephone
	Was participant and personnel knowledge of allocated intervention prevented during the study?	Unclear	Open label; patients and investigators were unmasked to treatment assignment
	Was knowledge of outcomes assessment adequately prevented during the study?	Unclear	Open label; responses were evaluated using validated IWG criteria, although whether centrally or locally reviewed was not stated
	Were incomplete outcomes data adequately addressed?	Yes	Of 147 patients randomized to the trial, 128 were evaluable; investigators accounted for remaining 19 patients
	Are reports of the study free of suggestion of selective outcome reporting?	Yes	All prespecified outcomes were reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Although the trial was stopped early, this was prespecified and allowed for stopping when a level of significance was reached; treatment arms and baseline characteristics were well balanced
Forstpointner et al,[17] 2006	Was allocation sequence adequately generated?	Yes	Central randomization procedure performed using computer program and random permutated blocks
	Was allocation adequately concealed?	Yes	Central allocation performed by telephone
	Was participant and personnel knowledge of allocated intervention prevented during the study?	Unclear	Open label; patients and investigators were unmasked to treatment assignment
	Was knowledge of outcomes assessment adequately prevented during the trial?	Unclear	Responses were evaluated using validated IWG criteria, although whether centrally or locally reviewed not stated
	Were incomplete outcomes data adequately addressed?	Yes	Investigators accounted for all patients and gave reasons for those not included in the analysis
	Are reports of the study free of suggestion of selective outcomes reporting?	Yes	All prespecified outcomes were reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Analysis included 38 patients who received FCM as induction instead of R-FCM. If any bias introduced it would be against investigational arm
Furtado et al,[18] 2014	Was allocation sequence adequately generated?	Unclear	Method of sequence generation was not described; insufficient information to allow judgment
	Was allocation adequately concealed?	Unclear	Method of concealment was not described; insufficient information to allow judgment
	Was participant and personnel knowledge of allocated intervention prevented during the study?	Unclear	Open label; patients and investigators were unmasked to treatment assignment

Supplemental Table 3	Continued		
Investigator	**Criteria From Cochrane Collaboration Tool**	**Assessment**	**Notes**
	Was knowledge of outcomes assessment adequately prevented during the trial?	Unclear	Responses were evaluated using validated IWG criteria, although whether centrally or locally reviewed not stated
	Were incomplete outcomes data adequately addressed?	Yes	Of 46 patients included in the trial, 41 were assessable; the investigators accounted for the 5 nonassessable patients and included them in the analysis as nonresponders
	Are reports of the study free of suggestion of selective outcome reporting?	No	The protocol prespecified the time to progression and quality of life as secondary endpoints; these were not reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	No	Imbalances were present in the baselines characteristics, with more men in the CHOP arm (91% vs. 65%) because interval from diagnosis was shorter in the CHOP arm (19.7 vs. 24.7 mo) and fewer patients had received previous rituximab in the CHOP arm (17% vs. 43%)
Hess et al,[19] 2009	Was allocation sequence adequately generated?	Unclear	Method of sequence generation was not described; insufficient information to allow judgment
	Was allocation adequately concealed?	Unclear	Method of concealment was not described; insufficient information to allow judgment
	Was participant and personnel knowledge of allocated intervention prevented during the study?	Unclear	Open label; patients and investigators were unmasked to treatment assignment
	Was knowledge of outcomes assessment adequately prevented during the trial?	Yes	Outcomes assessments were conducted by an independent review committee using validated IWG criteria on an ITT basis
	Were incomplete outcomes data adequately addressed?	Yes	No missing outcomes data
	Are reports of the study free of suggestion of selective outcomes reporting?	Yes	All prespecified outcomes were reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Baseline characteristics were generally well balanced; imbalances were in favor of IC: fewer patients with bone marrow involvement (39% vs. 54%), fewer patients with blastoid variant (7% vs. 17%), and more patients with previous bortezomib therapy (31% vs. 19%)
Rummel et al,[20] 2016	Was allocation sequence adequately generated?	Yes	Randomization was conducted centrally according to prespecified randomization lists with permuted blocks of randomly variable block size
	Was allocation adequately concealed?	Yes	Patients were randomized centrally under concealment
	Was participant and personnel knowledge of allocated intervention prevented during the study?	Unclear	Open label; patients and investigators were unmasked to treatment assignment
	Was knowledge of outcomes assessment adequately prevented during the trial?	No	Patients were assessed locally and not by an independent review committee; response criteria were not referenced in the study
	Were incomplete outcomes data adequately addressed?	Yes	Analysis was conducted on a per protocol basis; investigators accounted for all patients and gave reasons for those not included in the analysis
	Are reports of the study free of suggestion of selective outcome reporting?	Yes	All prespecified outcomes were reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Baseline characteristics were similar between the 2 groups
Trneny et al,[21] 2016	Was allocation sequence adequately generated?	Yes	Permuted-block randomization with block size of 6, resulting in 50 blocks in each stratum
	Was allocation adequately concealed?	Yes	A centralized interactive voice-response system was used to allocate patients
	Was participant and personnel knowledge of allocated intervention prevented during the study?	Unclear	Open label; patients and investigators were unmasked to treatment assignment

Supplemental Table 3	Continued		
Investigator	**Criteria From Cochrane Collaboration Tool**	**Assessment**	**Notes**
	Was knowledge of outcomes assessment adequately prevented during the trial?	Yes	Outcomes assessments were conducted by an independent review committee using validated IWG criteria
	Were incomplete outcomes data adequately addressed?	Yes	All data were accounted for; analysis conducted on ITT basis
	Are reports of the study free of suggestion of selective outcome reporting?	Yes	All prespecified outcomes were reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Although protocol allowed crossover to investigational arm at progression, this would have introduced bias against the investigational drug

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; FCM = fludarabine, cyclophosphamide, mitoxantrone; IC = investigator's choice; ITT = intent to treat; IWG = International Working Group; R-FCM = rituximab, fludarabine, cyclophosphamide, mitoxantrone.

	Supplemental Table 4	**Ongoing Trials of Relapsed/Refractory MCL**				
NCT Identifier	**Study Design**	**Treatment Line**	**Target Patient Number**	**Primary Outcome**	**Study Completes**
Combination trials					
NCT02460276	A phase II trial of ibrutinib, lenalidomide and rituximab for patients with relapsed/refractory mantle cell lymphoma	≥1 Previous rituximab-containing treatment	50	ORR based on PET and CT	Mar 2019
NCT01880567	A phase II study of ibrutinib plus rituximab in patients with relapsed/refractory mantle cell lymphoma or elderly patients with newly diagnosed mantle cell lymphoma	≥1 Previous treatment	100	ORR	July 2019
NCT01737177	Bendamustine, lenalidomide and rituximab (R2-B) combination as a second-line therapy for first relapsed-refractory mantle cell lymphomas: a phase II study	≥1 previous treatment	42	CR based on IWG 2007 and maintenance PFS	Jan 2017
NCT01996865	A phase 3B randomized study of lenalidomide (CC-5013) plus rituximab maintenance therapy followed by lenalidomide single-agent maintenance versus rituximab in subjects with relapsed/refractory follicular, marginal zone, or mantle cell lymphoma	≥1 previous treatment	500	PFS based on IWG 1999	Mar 2023
NCT00980395	A phase II, open-label study of bortezomib (Velcade), cladribine and rituximab (VCR) in advanced, newly diagnosed and relapsed/refractory mantle cell and indolent lymphomas	NS	39	PFS at 2 y	Dec 2021
NCT02840539	A phase 2 trial to evaluate the efficacy of bortezomib, cytarabine, and dexamethasone in patients with relapsed or refractory mantle cell lymphoma	1-3 previous lines of treatment	32	ORR	Feb 2020
NCT02736617	A phase II study of obinutuzumab (GA-101) in combination with ibrutinib (I) for the treatment of relapsed mantle cell lymphoma	≥1 Previous treatment	20	Best ORR of CR/PR	July 2021
NCT02471391	A phase 2 study of ABT-199 in combination with ibrutinib in the treatment of patients with relapsed or refractory mantle cell lymphoma (AIM study)	≥1 Previous treatment	24	CR at 16 wk based on IWG 2007	June 2018
NCT01796470	A phase 2 open-label study evaluating the efficacy, safety, tolerability, and pharmacodynamics of GS-9973 (entospletinib) in combination with idelalisib in subjects with relapsed or refractory hematologic malignancies	NS	66	ORR	Dec 2016
NCT00764517	Phase II study of vorinostat (SAHA), cladribine, and rituximab (SCR) in mantle cell lymphoma, chronic lymphocytic leukemia, and relapsed B cell non-Hodgkin lymphoma	NS	66	ORR based on IWG 2007	March 2017
EudraCT: 2015-004061-87	A phase 2 study to evaluate the efficacy and tolerability of IMGN529 in combination with rituximab in patients with relapsed and/or refractory diffuse large B-cell lymphoma and other forms of non-Hodgkin lymphoma	≥1 Previous treatment	75	Safety and ORR	NS
Monotherapy trials					
NCT02601313	A phase 2 multicenter study evaluating the efficacy of KTE-C19 in subjects with relapsed/refractory mantle cell lymphoma (R/R MCL) (ZUMA-2)	≤5 Previous treatments, which must have included anthracycline or bendamustine-containing regimen, anti-CD20 mAb and ibrutinib	70	ORR based on IWG	July 2018
NCT02042950	A phase II study of carfilzomib in the treatment of relapsed/refractory mantle cell lymphoma	NS	60	ORR based on IWG 2007	Jul 2021
NCT02413489	An open label, phase 2 study to evaluate efficacy and safety of daratumumab in relapsed or refractory mantle cell lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma	≥2 Previous lines of treatment	210	ORR	June 2017

Supplemental Table 4	Continued				
NCT Identifier	**Study Design**	**Treatment Line**	**Target Patient Number**	**Primary Outcome**	**Study Completes**
NCT02488512	Peptide receptor radionuclide therapy with 90Y-dotatoc in relapsed/refractory diffuse large B cell (DLBCL) and mantle cell lymphomas (MCL)	NS	35	ORR based on IWG	Feb 2018
NCT02169180	A phase 2 study of the Bruton tyrosine kinase (BTK) inhibitor ibrutinib in subjects with relapsed or refractory mantle cell lymphoma (MCL) in Japan	≥1 Previous treatment	16	ORR based on IWG 2007	Dec 2016
NCT02267915	An open multicenter phase II study of efficacy and toxicity of maintenance subcutaneous rituximab after induction with rituximab in patients with relapsed or refractory mantle-cell lymphoma non-eligible for HSCT	1-2 Previous lines of treatment	36	TTP	Nov 2019
NCT01678417	A phase II study of 131I-rituximab for patients with relapsed or refractory follicular or mantle cell lymphoma	NS	29	ORR	Jun 2017
NCT01693614	An open-label phase II study of BKM120 in patients with relapsed and refractory diffuse large B-cell lymphoma, mantle cell lymphoma and follicular lymphoma	≥1 Previous treatment	72	ORR	July 2017
NCT02213926	An open-label, phase 2 study of ACP-196 in subjects with mantle cell lymphoma	NS	124	ORR	Sept 2019
NCT02572453	Phase 2 study of AT13387 (onalespib) in ALK$^+$ ALCL, MCL, and BCL-6$^+$ DLBCL	Previous multiagent chemotherapy and ibrutinib or other BTK inhibitor	50	ORR, change in protein levels of ALK, BCL6, and cyclin D1	Aug 2019
NCT01799889	A phase 2, open-label study evaluating the efficacy, safety, tolerability, and pharmacodynamics of GS-9973 (entospletinib) in subjects with relapsed or refractory hematologic malignancies	NS	385	PFS	May 2019
NCT02952508	An open-label, multicenter, phase 2 study of CLR 131 in patients with relapsed or refractory (R/R) select B-cell malignancies	1-2 Previous treatments	80	ORR	Mar 2019
NCT01261247	A phase II study of the histone deacetylase (HDAC) inhibitor LBH589 (panobinostat) in patients with relapsed or refractory non-Hodgkin lymphoma	≥1 Previous treatment	41	ORR	Nov 2017

Abbreviations: ALCL = anaplastic large cell lymphoma; CR = complete response; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; HSCT = hematopoietic stem cell transplantation; IWG = International Working Group; mAb = monoclonal antibody; MCL = mantle cell lymphoma; NS = not stated; ORR = overall response rate; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; R-GemOx = rituximab, gemcitabine, oxaliplatin; R/R = relapsed/refractory; TTP = time to progression.