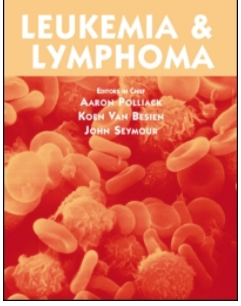

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Treatment for patients with relapsed/refractory mantle cell lymphoma: European-based recommendations

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ABSTRACT

Patients with mantle cell lymphoma (MCL) usually respond to initial combination chemotherapy, but the disease inevitably relapses and often follows an aggressive course. Here, clinical study results published since 2008 for patients with relapsed/refractory MCL were reviewed to compare available evidence for treatment guidance. Most trials identified were non-randomized, phase II studies performed at a limited number of sites, and many evaluated MCL as one of multiple non-Hodgkin lymphoma subtypes. Additional randomized, comparative trials are needed. Treatment selection generally depends on patient need, age and fitness, time of relapse, and line of therapy. Combination regimens typically produce higher response rates than single agents, and adding rituximab generally improves outcomes. The inclusion of ibrutinib, lenalidomide, temsirolimus, and bortezomib, represents an important advance for patients ineligible for, unable to tolerate, or failing high-intensity combination chemotherapy. A high need for effective treatments in relapsed/refractory MCL remains, particularly for elderly and frail patients.

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Chemotherapy; clinical trials; mantle cell lymphoma; molecular targeted therapy

Introduction

Mantle cell lymphoma (MCL) is a distinct histologic type of non-Hodgkin lymphoma (NHL), with a median age of 65 years at diagnosis and predominantly more aggressive course of disease [1,2]. Diagnosis is based on morphology and immunophenotype (CD20+, CD5+, CD23–, and FMC7+), but detection of chromosomal translocation t(11;14)(q13;q32) or the resulting cyclin D1 overexpression is mandatory [3,4]. Although technically categorized as an indolent form of NHL, MCL typically follows an aggressive clinical course and is considered incurable. The majority of patients receive treatment upon diagnosis, except for a small fraction of patients with very indolent disease identifiable by gene expression profiling [5,6] or low-risk characteristics and/or evolution of disease [7,8].

Median overall survival (OS) following initial induction therapy is 3–5 years with the use of dose-intense chemotherapy or combination therapy, incorporation of antilymphoma antibodies, and autologous stem cell transplantation [1,2,9–11]. US guidelines issued by the National Comprehensive Cancer Network® (NCCN®) categorize induction based on aggressive versus less aggressive treatment [12], whereas the European (EU) guidelines categorize induction based on the patient's age (<65 versus ≥65 years) and status (fit versus frail) [1,2,13]. Aggressive treatment in the US guidelines and treatment of fit patients ≤65 years of age in EU guidelines consist of high-dose chemoimmunotherapy followed by consolidation with high-dose therapy and autologous stem cell transplantation. R-hyperCVAD (rituximab combined with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) is also recommended as an aggressive regimen in US but not EU guidelines. Less aggressive treatment

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in the US and treatment of fit, elderly patients in the EU consist of a conventional regimen such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or BR (bendamustine and rituximab).

Although MCL generally responds to initial treatment, the disease inevitably relapses, even after an intensive intervention [14]. Treatment of relapsed or refractory disease, characterized by increasingly shorter periods of remission with successive lines of treatment and progression to more clinically aggressive phenotype, is challenging [1,2,14,15]. This review covers current treatment options in the relapsed/refractory setting, examining selection based on prior therapy, patient characteristics, performance status, and line of therapy. Conventional chemotherapy approaches as well as newer molecular-based therapies are included.

Methods

A review of the literature was carried out using PubMed to identify studies reporting clinical trial results in patients with relapsed/refractory MCL published between January 2008 and July 2017. Search terms included: title *mantle cell lymphoma*, publication type *clinical trial*, and language *English*. Abstracts from major conferences (American Society of Clinical Oncology [ASCO], American Society of Hematology [ASH], European Hematology Association [EHA], and International Conference on Malignant Lymphoma [ICML]) were also evaluated. Trials in previously untreated MCL patients, those with <10 MCL patients, pharmacokinetic studies, and publications such as letters to the editor were excluded, and the resulting list was focused on studies of key marketed and investigational agents. Studies were categorized as monotherapy, chemotherapy/chemoimmunotherapy, chemotherapy/immunotherapy combinations with molecular-based agents, and combination biologic therapies.

Study data

Chemoimmunotherapy

Chemoimmunotherapy trials in relapsed/refractory MCL are shown in Table 1, with key results discussed below [16–26]. Many recommendations regarding use of chemoimmunotherapy to treat relapsed/refractory MCL are based on limited studies and few randomized comparative trials. The most commonly used combinations in this setting are CHOP and regimens containing bendamustine, cytarabine, or fludarabine in combination chemotherapy regimens has shown improved OS [27]. These combination regimens tend to be more appropriate in first and second relapse in younger patients and elderly fit patients. While they appear to produce higher response rates than monotherapy, few comparisons have been made in randomized trials.

The alkylating agent bendamustine in combination with rituximab (BR regimen) has high activity in relapsed/refractory MCL [28]. Phase II findings with BR within this time period showed 92% overall response rate (ORR), 55% complete response (CR)/CR unconfirmed (CRu), and median duration of response (DOR) of 19 months in relapsed/refractory MCL [17]. Subsequent studies of BR showed significantly prolonged progression-free survival (PFS), producing a significantly higher ORR compared with fludarabine plus rituximab (FR) in a phase III study conducted in patients with relapsed follicular, indolent, and mantle cell lymphomas [18]. Among MCL patients who were randomized to BR or FR, ORR was 71% (38% CR) and 26% (13% CR), respectively, and median PFS was 17.6 and 4.7 months, respectively ($p = .01$). BR was also associated with improved OS (median 35.3 versus 20.9 months). Among all patients treated with BR, the most common grade 3/4 adverse events (AEs) were leukopenia (13%), neutropenia (9%), and nausea and emesis (4%). In a phase II study with relapsed or refractory MCL (median 2 prior therapies), BR treatment resulted in an 82% ORR (40% CR), median PFS of 17.2 months, and a 3-year OS rate of 55% [19]. Among patients evaluated by positron emission tomography (PET) scan, complete metabolic response was observed in 75%. Grade 3/4 neutropenia and lymphopenia occurred in 44 and 89% of patients, respectively. Serious AEs occurred in 40% of patients, but only three patients withdrew from the study due to AEs. The use of BR in the treatment of relapsed/refractory MCL has increased steadily based on recent results from the multicenter, randomized, phase III non-inferiority StiL and BRIGHT studies, which reported significantly prolonged PFS and CR rates, respectively, in comparison to R-CHOP or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), in the small subsets of previously untreated MCL [29–32].

Novel monotherapy treatment options for relapsed/refractory MCL

Pivotal trials of monotherapy options in relapsed/refractory MCL are shown in Table 2 and results from key studies are discussed below [33–54]. Multiple treatment options are available in this setting, but no

le 1. Chemotherapy and chemoimmunotherapy options: clinical trials with ≥10 patients.

men	Phase	No. of patients	Prior regimens, median (range)	ORR (CR/CRu)	Median PFS, months	Median OS, months	Grade ≥3 AEs
lamustine-based regimens							
lamustine [16]	II	11	4 (1–16)	100% (73%)	Not reported	Not reached 1-year PFS =90%	Neutropenia (72%), leukopenia (65%), thrombocytopenia (16%), anemia (6%), grade 3 infection (7%)[a]
17]	II	12	Not reported	92% (55%)	Not reported	Not reported	Neutropenia (37%), leukopenia (30%), thrombocytopenia (10%), infection (10%)
18]	III		1 (1 to >2)[a]				BR: leukocytopenia (13%), neutro-
R		24		71% (38%)	17.6	35.3	penia (9%) FR: leukocytopenia
R		23		26% (13%)	4.7	20.9	(12%), neutropenia (7%)
19]	II	45	2 (1–4)	82% (40%)	17.2	Not reported	Lymphopenia (89%), leukopenia (44%), neutropenia (44%)
C [20]	II	20	1 (1–2)	80% (70%)	Not reached	Not reached	Thrombocytopenia (83%), leukopenia (67%), neutropenia (49%)
citabine-based regimens							
m-Mitox [21]	16; 15 evaluable	Not reported	Not reported	47% (20%)	Not reached	Not reached	Neutropenia (100%), thrombocytopenia (67%), leukopenia (53%), anemia (33%)
mOx [22]	Salvage therapy	28	1 (1–4)	79% (75%)	18	30	Neutropenia (5%), thrombocytopenia (3%)
mOx [23]	Retro	30	1.8 (0–5)	83% (60%)	28	37	Efficacy presented with *ex vivo* data; no safety reported
arabine-based regimens							
arabine-based combi-ations[b] [24]	Retro	34; 31 evaluable	(1–5)	52% (19%)	Not reported	Not reported	62% grade 3 or 4 hematological toxicity; febrile neutropenia (29%)
r regimens							
C [25]	Not stated	22	2 (1 to >3)	82% (46%)	Not reported	Not reported	Myelosupression (percentages not reported), infection (14%)
perCVAD alternating ith R MTX.Ara-C [26]	II	29	1 (1–5)	93% (45%)	11	19	Neutropenia (60%), thrombocytopenia (54%), neutropenic fever (11%)

complete response; CRu: unconfirmed complete response; MCL: mantle cell lymphoma; NHL: non-Hodgkin's lymphoma; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; retro: retrotive study; R/R: relapsed/refractory.

notherapy regimens: BR: bendamustine and rituximab; FCM: fludarabine: cyclophosphamide: and mitoxantrone; FFR: flavopiridol: fludarabine: and rituximab; FR: fludarabine and rituximab; GD: gemcitabine and taxel; GDP: gemcitabine: dexamethasone: and cisplatin; PEP-C: prednisone: etoposide: procarbazine: and cyclophosphamide; R-BAC: rituximab: bendamustine: cytarabine (Ara-C); R-CVP: rituximab: cyclophospha-: vincristine: and prednisone; R-hyperCVAD: rituximab and hyperfractionated cyclophosphamide: vincristine: doxorubicin: and dexamethasone alternating with high-dose methotrexate and cytarabine (Ara-C); M – rituximab: fludarabine: cyclophosphamide: and mitoxantrone; R-GemOx: rituximab: gemcitabine: and oxaliplatin; RGM: rituximab: gemcitabine: and mitoxantrone; RiBVD: rituximab: bendamustine: bortezo- and dexamethasone; RMC: rituximab: methotrexate: and cytarabine (Ara-C).

se trials also included patients with other NHL subclasses (or occasionally other hematological malignancies); data marked by asterisk are for all patients, rather than the subset of MCL patients.

% combined with rituximab; 56% combined with anthracyclines.

le 2. Targeted monotherapy options: clinical trials with ≥10 patients.

tment	Phase	No. of points	Prior regimens, median (range)	ORR (CR/CRu)	Median DOR, months	Median PFS/OS, months	Most Common Grade ≥3 AEs
pathway inhibitor							
inib [33]	II	111; 109 eval.	3 (1–6)	68% (21%)	17.5	13.9/not reached	Neutropenia (11%), anemia (5%), diarrhea (5%), dyspnea (5%), pneumonia (5%), thrombocytopenia (5%) One grade 5 AE (pneumonia, probably treatment related).
-term follow-up [34]			3 (1–6)	67% (23%)	17.5	13.0/22.5	Neutropenia (17%), thrombocytopenia (13%), anemia (11%), pneumonia (6%)
unomodulatory agent							
lidomide [35]	II	134	4 (2–10)	28% (8%)	16.6	4.0/20.9	Neutropenia (43%), thrombocytopenia (27%), anemia (11%), pneumonia (8%), fatigue (7%)
-term follow-up [36]			4 (2–10)	28% (8%)	16.6	4.0/20.9	Neutropenia (44%), thrombocytopenia (28%); 4 SPMs (3%)
lidomide IC [37]	II	170 84	2 (IQR 1–3) 2 (IQR 1–3)	40% (5%) 11% (0)	16.1 10.4	8.7/27.9 5.2/21.2	For lenalidomide versus IC: neutropenia (44% versus 34%), thrombocytopenia (18% versus 28%), anemia (8% versus 7%), leukopenia (8% versus 11%)
lidomide (retro)[b] 8]		70	Not reported	44% (31%)	Not reported	62-month DFS = 37% 62-month OS = 26%	Not reported
lidomide [39]	II	57	3 (1–13)[a]	42% (21%)	Not reached	5.7/not reported	Neutropenia (89%), thrombocytopenia (42%), anemia (20%), leukopenia (16%), dyspnea (12%), fatigue (10%)
-term follow-up [40]			3 (1–13)	35% (12%)	16.3	8.8/not reached	Neutropenia (46%), thrombocytopenia (30%), anemia (12%), fatigue (9%), pleural effusion (7%)
lidomide [41]	II	26	3 (2–7)	31% (8%)	22.2	3.9/10.0	Neutropenia (62%), thrombocytopenia (42%), infection (42%) One grade 5 AE (neutropenic sepsis).
lidomide [42]	II	15	4 (2–7)	53% (20%)	13.7	5.6/not reported	Neutropenia (40%), thrombocytopenia (20%), leukopenia (27%), fatigue (6%)
R inhibitor							
sirolimus [43,44]	III	162					In high- and low-dose groups: thrombocytopenia (59%, 52%), neutropenia (15%, 22%), anemia (20%, 11%), asthenia (13%, 19%), infection (9%, 4%)
gher dose		54	3 (2–7)	22% (2%)	7.1	4.8/12.8	
wer dose		54	3 (2–7)	6% (0%)	3.6	3.4/10.0	
vestigator choice		53	4 (2–7)	2% (2%)	N/A	1.9/9.7	
sirolimus [45]	II	29; 27 evaluable	4 (1–9)	41% (3.7%)	6	6/14	Thrombocytopenia (39%), neutropenia (18%), anemia (15%), leukopenia (7%), fatigue (25%), infection (15%), dyspnea (11%), hyperglycemia (11%)
inib versus emsirolimus 6,47]	III	139 141	2 (1–9) 2 (1–9)	77% (23%) 47% (3%)	NR 7.0	15.6/NR 6.2/21.3	For ibrutinib versus temsirolimus: thrombocytopenia (9% versus 42%), anemia (8% versus 20%), neutropenia (13% versus 17%), fatigue (4% versus 7%)
asome inhibitor							
ezomib [48,49]	II	155; 141 evaluable	1 (1–3)	32% (8%)	9.2	6.5/23.5	Peripheral neuropathy (13%), fatigue (12%), thrombocytopenia (11%), diarrhea (7%) (34% lymphopenia at long-term follow-up)

(*continued*)

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