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REVIEW

Lifting the mantle: Unveiling new treatment approaches in relapsed or refractory mantle cell lymphoma

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ABSTRACT

The management of relapsed/refractory mantle cell lymphoma (MCL) remains a clinical challenge. A standard second-line treatment for relapsed/refractory MCL does not exist. Management of relapsed/refractory MCL requires an individualized treatment approach, incorporating factors such as: functional status, prior treatments, response to prior therapies, and disease biology. Generally, there are two categories of salvage therapy; the first, non-cross-resistant cytotoxic chemotherapeutic agents and, the second, pathway-targeted agents. For transplant eligible patients, the optimal therapy usually consists of salvage, remission re-induction phase followed, whenever possible, by a consolidation phase. Bendamustine and/or high dose cytarabine plus rituximab based chemotherapy represent the most common salvage therapy with an overall response rate of 70–80%. Consolidation with a reduced intensity conditioning allogeneic stem cell transplantation represents the only potentially curative treatment. Overall survival ranges from 30% to 50% at 5 years with this approach. For transplant ineligible patients, ibrutinib is the most effective treatment with an overall response rate of almost 70% and median response duration of 17.5 months. Lacking an effective consolidation, this approach is not considered curative. In this review we characterize the main therapeutic approaches available in this setting and summarize our preferred clinical treatment approach.

1. Introduction

Mantle cell lymphoma (MCL) is a rare B-cell lymphoma accounting for 5–10% of non-Hodgkin lymphoma (NHL) in North America and Europe. It is generally considered an incurable disease and is associated with a relatively poor prognosis. In recent years, the prognosis has improved likely due to two important breakthroughs: the incorporation of high-dose cytarabine in the induction treatment, followed by autologous hematopoietic cell transplantation (autoHCT) in first remission, and the addition of the monoclonal antibody rituximab to chemotherapy regimens. For young and fit patients eligible for cytarabine-containing chemoimmunotherapy followed by autoHCT, several studies have reported promising survival outcomes [1–4]. In particular, the MCL2 trial from the NORDIC group reported a median overall survival and response duration longer than 10 years and a median event-free survival (EFS) of 7.4 years [5].

Despite these improvements, relapse is common. The management of relapsed/refractory disease represents a challenge. The recent elucidation of pathways involved in B-cell lymphoma pathogenesis has led to the development of novel therapies targeting the NF-kB, mammalian target of rapamycin (mTOR), and B-cell receptor signaling pathways. The development of effective biologically-targeted drugs provides hope for improving outcomes in the setting of relapsed/refractory MCL. The presence of several new agents, absence of large randomized clinical trials, and the heterogeneity of patients make it difficult to define a single preferred salvage strategy for these patients. Second-line treatment approaches can include traditional chemotherapeutic agents, such as bendamustine [6] and biologically-targeted drugs, such as bortezomib [7], ibrutinib [8], and lenalidomide [9]. Moreover, there is increasing data regarding allogeneic hematopoietic cell transplantation (alloHCT) consolidation in this setting, with several studies reporting efficacy with reduced intensity conditioning (RIC) alloHCT as a second-line consolidation [10–19], due to the graft-versus-lymphoma (GVL) effect [20–25]. In this review, we present a description of salvage strategies available for the treatment of relapsed/refractory MCL. Moreover, we will discuss a practical approach to select the best treatment for both transplant eligible and ineligible patients.

2. Relapsed/refractory salvage therapy

There are a growing number of treatment options for patients with relapsed/refractory MCL that include standard chemotherapy, such as bendamustine [6], as well as novel agents including bortezomib [26],

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temsirolimus [27], lenalidomide [27], and, most recently, ibrutinib [8]. Furthermore, there are a number of other biologically-targeted agents that are currently in development such as cyclin-dependent kinase 4/6 inhibitors [28], histone deacetylase inhibitors [29], arsenic trioxide [30], drugs targeting the phosphoinositide 3-kinase (PI3K) pathway [31] and Bcl-2 inhibitors [32]. In the current review, we will focus on the FDA-approved second-line treatment options available for relapsed/refractory MCL patients and the outcomes associated with these regimens. A summary of the major trials results is reported in Tables 1 and 2.

2.1. R-FCM, R-GemOX, and R-DHAP

Until recently the therapeutic options for relapsed/refractory MCL were limited reflecting a median overall survival of patients with MCL of 3 to 4 years. There are few large studies evaluating the role of salvage chemotherapy programs in relapsed/refractory MCL. Generally, short median progression-free survival (PFS) of 5 to 12 months has been associated with salvage regimens including rituximab–fludarabine–cyclophosphamide–mitoxantrone (R-FCM), rituximab–gemcitabine–oxaliplatin (R-GemOx) and rituximab–dexamethasone–cytarabine–cisplatin (R-DHAP) [33–35]. The largest of these studies examined the efficacy of R-FCM with or without rituximab maintenance in patients with relapsed/refractory mantle cell lymphoma. This approach was associated with abbreviated median response duration of approximately one year that was not significantly different between the rituximab maintenance arm (14 months) and the observation arm (12 months) [33].

2.2. Bendamustine + rituximab

The impressive activity of bendamustine and rituximab (BR) in MCL was first demonstrated in the relapsed/refractory setting in a trial of 63 patients with indolent NHL who were treated with bendamustine 90 mg/m^2 on days 1 and 2 and rituximab 375 mg/m^2 on day 1 every 4 weeks for a maximum of 4 cycles of therapy (BR) [36]. In this study, 16 (25%) patients had MCL and the BR program was associated with an overall response rate (ORR) of 75%, with 50% complete responses (CR). With a median follow-up of 20 months, the median PFS for MCL patients was 18 months, with six patients in remission at time of study publication (range of PFS, 6 to >22 months). A similar study in the United States that included 12 patients with MCL confirmed the European results with BR in relapsed MCL, demonstrating a high ORR of 92% with 42% CR and 17% complete response unconfirmed (CRu) and a similar median duration of response of 19 months [13]. Based upon these results, BR is a commonly used salvage regimen for relapsed/refractory MCL, particularly in previously bendamustine naïve patients. Of note, BR is increasingly being used for the frontline treatment of MCL, particularly in transplant-ineligible patients, given relatively favorable ORR [6].

2.3. Rituximab, bendamustine, and cytarabine (R-BAC)

Rituximab, bendamustine, and cytarabine were combined in a phase II study including both previously untreated MCL patients who were ineligible for intensive regimens and/or autoSCT as well as relapsed/refractory MCL patients who had received only one prior immunochemotherapy treatment regimen [37]. The ORR was 80% with 70% CR in relapsed/refractory MCL patients. There was however significant myelosuppression with 87% of patients experiencing grades 3–4 thrombocytopenia and 12% incidence of febrile neutropenia. Although CR rates appear greater with R-BAC versus BR alone, the patients included in this study with relapsed/refractory disease were less heavily pretreated compared with those patients included in BR studies.

Table 1
Essential data from the major trials testing immunochemotherapy in relapsed/refractory MCL.
MCL, mantle cell lymphoma; ORR, overall response rate; CR, complete response; PFS, progression free survival; FCM, fludarabine–cyclophosphamide–mytoxantrone; Rituximab–fludarabine–cyclophosphamide–mitoxantrone; R-DHAP, rituximab–dexamethasone–cytarabine–cisplatin; NHL, non-Hodgkin lymphoma; autoHCT, autologous hematopoietic cell transplantation.

Category of drug	Reference	Type of study	# of MCL patients	Therapeutic regimen	ORR % (CR%)	Median PFS (months)	Comment
Chemotherapy	Rodriguez et al. [34]	Phase II trial	n = 14	Rituximab + gemcitabine + oxaliplatin	85% (64%)	45% at 12 months	Median follow-up 11 months
	Forstpointer et al. [33]	Phase III trial	n = 57	1st randomization: FCM vs. R-FCM	R-FCM ORR: 58–79%	Median response duration	ORR of R-FCM > ORR of FCM. No significant different +/− R maintenance
				2nd randomization: R maintenance vs. no reatment	(20–29%) FCM ORR: 46% (0%)	12–14 months	
	Witzig et al. [35]	Phase II trial	n = 4 (of 57 NHL pts)	R-DHAP	82% (33%) for all NHL pts	5.3 months	Responding pts received HDT/ASCT
	Rummel et al. [36]	Phase II trial	n = 16	Rituximab + bendamustine	75% (50%)	18 months	
	Robinson et al. [13]	Phase II trial	n = 12	Rituximab + bendamustine	92% (42%)	23 months	
	Visco et al. [37]	Phase II trial	n = 40	Rituximab + bendamustine + cytarabine	80% (70%)	2-year PFS 70% (median PFS not reached)	

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