



The current therapeutic scenario for relapsed mantle cell lymphoma

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Purpose of review

Patients with relapsing mantle cell lymphoma (MCL) still represent a demanding challenge for the hematologist. The dismal prognosis and the absence of generally accepted therapeutic standards hamper the clinical management of such cases. Moreover, the availability of many targeted approaches, in a field so far missing efficient salvage regimens, challenges current therapeutic algorithms in these patients.

Recent findings

Molecular targeted drugs provide unprecedented response rates in relapsed and even chemorefractory MCL. Many phase II studies demonstrated impressive antilymphoma activity of compounds such as bortezomib, lenalidomide and temsirolimus, whereas ongoing phase III trials currently assess the 'real world' benefit and the impact on survival, both alone and in combination with chemotherapy or monoclonal antibodies. Recently, the Bruton's tyrosine kinase inhibitor ibrutinib, targeting the B-cell receptor cascade, showed impressive response rates and will be soon available in phase III trials.

Summary

In the present review we focus on the major therapeutic discoveries of the last few years to offer a practical algorithm to select the appropriate treatment in patients with relapsed MCL.

Keywords

mantle cell lymphoma, new drugs, refractory, relapse, therapy

INTRODUCTION

During the last few years remarkable progress has been made in the development of new treatment strategies of mantle cell lymphoma (MCL), an infrequent subtype of non-Hodgkin lymphoma characterized by initial high responses but continuous relapse pattern and a dismal long-term outcome [1]. Most of the new targeted approaches available in the clinics or being tested in early phase I/II protocols result from recent molecular studies on cell proliferation and apoptosis pathways [2]. Moreover, ongoing molecular genetic investigations continue to identify new oncogenic targets, providing preclinical rationale for therapeutic application and further drugs development [3–5]. Nevertheless, a definite cure for MCL cannot be achieved so far, with the exception of potentially harmful allogeneic stem cell transplantation (allo-SCT). Even more important a satisfactory disease control can be achieved only in a subset of patients, particularly in relapsed disease.

The major clinical trials of the last decade focused on improvement of the front-line treatment, leading to the definition of a 'gold standard'

therapy, for young and fit patients consisting of anthracyclines, high doses of cytarabine and rituximab, followed by an autologous stem cell transplantation (auto-SCT) [6–8,9^a]. Similar efficiency has been shown for an even more intensified regime [10]; however, only the minority of patients was able to complete the full course in a multicenter setting [11].

Similarly the standard first-line therapy for elderly MCL patients (not eligible for auto-SCT) has been lately established consisting of rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone (R-CHOP) immunochemotherapy, followed by

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KEY POINTS

- The major biological discoveries of the last years in MCL survival pathways have led to the availability in the clinics of many effective targeted drugs.
- Phase II and III clinical trials are currently ongoing to test the efficacy of these drugs on large series of relapsed MCL patients.
- Clinical trials investigating innovative approaches should be considered in all relapsed MCL patients.
- The treatment strategies in relapsed MCL should depend on the individual risk profile and patients' comorbidities.

rituximab maintenance [12]. Both efforts resulted in a considerable improvement in overall survival.

On the contrary, lacking large randomized clinical trials, there is still no generally accepted approach in relapsed MCL. Clinical guidelines, although recently updated [9[¶]], are not specifically focused on the relapse setting, supplying only some hints. Moreover, the numerous new targeted options [2], along with the promising data for combinations with conventional chemotherapeutics and anti-CD20 immunotherapy, could generate hesitation about the optimal therapeutic approach for these patients. Thus, the present review focuses on the major therapeutic discoveries of the last few years to offer a practical algorithm to select appropriate treatment decisions in patients with relapsed MCL.

CURRENT AVAILABLE THERAPEUTIC OPTIONS

As no curative treatment can be so far offered to relapsed MCL patients, aside from allo-SCT, the therapeutic goal should be the prolonged disease control, balancing the expected efficacy with the risk of toxicity and reduced quality of life (QoL). In this perspective the most recent data on salvage regimens are discussed below.

Chemotherapy-based approaches

The addition of rituximab to conventional chemotherapy (R-FCM, R-GEMOX, R-DHAP) increases response rates up to 60–70%; however, the duration of response in relapsing disease remains limited (mainly less than 1 year) and such treatment options should be considered basically palliative [13–15]. More promising data on the contrary have been recently achieved from the new combination of

some 'old drugs' with rituximab, based on the results of the bendamustin-rituximab regimen (75% overall response rate, ORR – and 50% complete responses, CR – in relapsing disease) [16]. The impressive activity of bendamustin-rituximab has been also shown in first-line treatment [17], as well as the superior data of cytarabine in first-line young patients [6–8]. Accordingly, a new regimen combining rituximab, bendamustine and cytarabine (R-BAC) was tested in 20 relapsed and 20 first diagnosed MCL patients [18[¶]]. The activity of this combination is noteworthy, although in a limited series: an ORR of 80 with 70% CR was reported in relapsing patients (90 and 83% on the total, respectively), resulting in an excellent 2-year progression-free survival (PFS) of 70% (95% for the untreated patients). The primary toxicity was reversible myelosuppression, platelet transfusions were required in two-third of cycles and erythropoietin was applied in about half of patients. Currently, a phase II study of R-BAC in first-line for elderly patients is ongoing, but this regimen is promising also in the relapse setting.

In contrast, considering the low efficacy and the increased toxicity of an auto-SCT approach in second-line [19], such a treatment should be offered only to fit MCL patients who did not receive auto-SCT as first-line. Finally, among palliative approaches for elderly patients, the efficacy, feasibility and low toxicity of an oral low-dose metronomic polichemotherapy combination (PEP-C) is noteworthy, optionally in combination with rituximab and thalidomide [20,21].

Established molecular approaches

In this section the most recent data on salvage 'new drugs' regimens are extensively discussed.

Proteasome inhibitors

The first 'new drug' to be registered in relapsed MCL in the United States is bortezomib, since the first demonstrations of this selective and reversible proteasome 26S inhibitor's efficacy [22–25]. Even though the combination of bortezomib with rituximab and chemotherapy showed high response rates (up to 60–70%), the majority of these studies consists of small series of heavily pretreated patients and often comprises other histologies. Median PFS rates are in the range of 12 months. The published combined regimens encompass both targeted approaches, such as rituximab or rituximab-dexamethasone [26,27], as well as immunochemotherapies such as rituximab-dexamethasone-high dose-cytarabine (R-HAD), rituximab-prednisone-cyclophosphamide (R-CP), rituximab-bendamustine and gemcitabine [28–31]. The

toxicity profile predominantly consists of polyneuropathy (sometimes marked and long lasting) and neutrothrombocytopenia (when associated with chemotherapy), challenging the long-term application, for example, as maintenance in relapsed MCL. A phase III clinical trial is currently ongoing, randomizing MCL relapsed patients to receive either R-HAD ± bortezomib (NCT01449344). Other studies tested bortezomib combinations in first-line treatment, too [32–34].

Mammalian target of rapamycin inhibitors

Temsirolimus, an intravenous mammalian target of rapamycin (mTOR) inhibitor, received European Medicines Agency approval in 2009, due to its single-agent activity in patients with relapsed MCL. This approval was based on results of a large phase III trial in patients with relapsed/refractory MCL. Temsirolimus induced a significant improvement in median PFS and ORR, compared with investigator's choice monotherapy (4.8 versus 1.9 months and 22 versus 2%, respectively) [35]. Hematological adverse events were the most frequently reported, but were generally well managed by dose reductions or treatment delay. Gastrointestinal toxicity, especially diarrhea, and fatigue were also common, but incidence of grade 3–4 events was low. The addition of rituximab to temsirolimus was subsequently tested in a phase II study on 71 patients. An increased ORR of 59%, with up to 19% CR was observed, with a median time to progression (TTP) of about 10 months [36]; the toxicity profile was similar to temsirolimus monotherapy, with a slightly higher rate of pulmonary toxicity (pneumonia and pneumonitis around 10% of cases). To further improve its efficacy, temsirolimus is being currently investigated in combination with bendamustine-rituximab in a phase II clinical trial (NCT01078142) [37].

Another well tolerated oral mTOR inhibitor is everolimus. In a multicenter phase II trial of 35 MCL-relapsed patients a ORR of 20% (with 49% of stable diseases, SD) with a median PFS of 5.5 months has been reported [38], but further studies in combination with chemotherapy or other biological drugs are warranted.

Immunomodulatory drugs

A number of phase II trials have confirmed the promising response rates of lenalidomide in relapsed MCL. This immunomodulatory compound showed high antilymphoma activity in several other studies [39–41]. The ORR were around 30–50%, with promising CR rates up to 20% and PFS generally around 6–9 months. Recently a phase II study in

52 patients with relapsed MCL confirmed the impact of a chemo-free lenalidomide-rituximab combination with high response rates (57% ORR, 36% CR) and impressive response durations up to 19 months [42]. On the other hand, no clear advantages in survival were achieved by the addition of dexamethasone to lenalidomide [43]. The manageable toxicity (mainly mild, hematological) and the oral formulation make this drug an attractive option also in the context of maintenance regimens, specifically in the elderly population. A phase II trial of the rituximab-lenalidomide-bendamustine combination is presently accruing patients with relapsed MCL (NCT01737177).

Largely overshadowed by its subsequent follower lenalidomide, thalidomide, the oldest member of the immunomodulatory drugs (IMiDs), was shown active in relapsed MCL already a decade ago [44]. More recently, a retrospective French survey on 58 patients confirmed that thalidomide was effective in relapsed MCL, with a favorable side-effect profile (7% grade 3–4 adverse events, including thromboembolism). Although this survey comprised different treatment schedules (monotherapy or combinations with rituximab or bortezomib), an interesting ORR of 50% (and 29% SD) with a time to treatment failure (TTF) of 29 and 11% at 1 and 2 years, respectively, should be noticed [45]. Thus, thalidomide is well tolerated and might offer a cost-effective alternative to more expensive targeted agents, especially in countries with limited health-care resources.

Antibody-based approaches

In contrast to its favorable safety profile (mainly manageable thrombocytopenia and neutropenia) and promising data coming in other types of lymphoma, yttrium-90 (⁹⁰Y)-ibritumomab tiuxetan monotherapy does not impact substantially the prognosis of relapsed MCL. In a phase II trial of 32 patients with relapsed MCL this anti-CD20 radio-immunoconjugate showed an ORR of 32% with an event-free survival (EFS) of 6 months [46]. However, radioimmunotherapy might be more efficient as part of multimodal strategies: considering that the results were particularly poor in patients with bulky disease, recent studies are exploring the ⁹⁰Y-ibritumomab tiuxetan consolidation after successful salvage chemotherapy or first-line treatment [47] and the combination with another efficient targeted drug, such as bortezomib [48].

NEW MOLECULAR-TARGETED APPROACHES

The growing insights into the underlying molecular biology of MCL form the basis for the ongoing

exploration of targeted approaches [2]. A number of new compounds are currently being tested in MCL and are available for application within clinical trials.

B-cell receptor signaling inhibitors

The most convincing data come for the oral Bruton's tyrosine kinase (BTK) inhibitor ibrutinib. The interim results of an international phase II trial on refractory/relapsed MCL patients show impressive efficacy and excellent tolerability of this drug, which specifically blocks the B-cell receptor (BCR) signaling survival pathway [49]. In 110 evaluable patients (either bortezomib exposed or naive) ibrutinib monotherapy displayed an impressive ORR of 68%, with 22% CR; the data are even superior focusing on the initial cohort of 51 patients, with a longer follow-up of nearly 15 months. ORR and CR were 75 and 39%, respectively, clearly demonstrating an incremental CR rate under continuous treatment. Median duration of response is not yet reached with a PFS of around 14 months. Noteworthy is the favorable safety profile, with less than 15% grade 3/4 hematological toxicity and mainly mild gastrointestinal symptoms, fatigue and infections in a population of heavily pretreated patients. These outstanding results have already led to the design of phase III trials, comparing ibrutinib versus temsirolimus in relapsed patients (NCT01646021) or conventional immunochemotherapy ± ibrutinib as first-line treatment (www.clinicaltrials.gov). Moreover, the preclinical rationale for BTK-inhibitors combinations with other biological agents (such as bortezomib) has been already postulated [50].

Another disruptor of the BCR signal cascade, CAL-101, a specific inhibitor of phosphatidylinositol 3-kinase delta isoform, is currently being tested in phase I/II trials: although achieving a promising ORR of 62% [51], mature results on remission duration are not yet available.

Antibody-based approaches

New monoclonal antibodies (mAb), targeting a variety of epitopes in addition to CD20 are currently investigated in preclinical and clinical trials, but data on MCL are still scarce. GA101 (obinutuzumab), the first type II, glycoengineered and humanized anti-CD20 mAb, determined a ORR of 27% (four out of 15 patients) in a randomized phase II trial of refractory/relapsed MCL [52]. Ofatumumab, a fully human mAb targeting a unique epitope on the CD20 molecule, has been tested in phase I/II trials in combination with bendamustine [53] or

lenalidomide [54], but more mature data are still missing.

An interesting approach is the bispecific anti-CD19/anti-CD3 mAb, which showed a high efficacy in a phase I/II trial particularly in the MCL patients [55,56].

DCDS4501A is an anti-CD79b mAb conjugated to a microtubule toxin (monomethyl auristatin E), showing an acceptable toxicity profile and encouraging antitumor activity in a phase I trial on 33 heavily pretreated lymphoma patients, including four patients with relapsed/refractory MCL [57]. Nevertheless, additional studies on larger patient cohorts are warranted.

Cell cycle/apoptosis targeting drugs and others

Flavopiridol directly inhibits cyclin-dependent kinase (CDK) 4 and 6, leading to downregulation of cyclin D1. This compound showed significant activity in combination with fludarabine and rituximab or bortezomib in two phase I trials [58,59]. A direct CDK4/6 inhibitor, PD0332991, also achieved substantial responses and suggested clinical benefit in a subset of MCL patients [60].

ABT-199 is an orally bioavailable, second-generation BCL-2 specific BH3 mimetic with promising results in a phase I trial for MCL patients (six out of six patients with a >50% reduction in target lesions) [61].

Abexinostat, a novel oral pan histone deacetylase inhibitor, proved to be clinically active and well tolerated in a phase II trial in patients with refractory/relapsed MCL. ORR was 27% (three out of 11 patients) and PFS 4 months. The most common grade 3/4 adverse events were thrombocytopenia (17%), neutropenia (13%), fatigue (13%) and anemia (7%) [62].

A summary of the recent published clinical trials of targeted approaches in relapsed MCL is presented in Table 1.

ALLOGENEIC TRANSPLANTATION

Despite the high response rates obtained by the new therapeutic approaches so far described, a long-term disease control has not yet been achieved in relapsed MCL and prognosis of subsequent relapses remains poor, in particular in chemorefractory cases. The only few reported definite long-term remissions (or even cure) for at least a selected subset of relapsed patients are achieved by allo-SCT. The biological background of such an immunologic approach is based on a lymphoma-free graft as well as the supposed allogeneic reactivity of the donor T-cells

Table 1. Recent published clinical trials of targeted approaches in relapsed mantle cell lymphoma

	Author	Study features	Evaluable MCL patients	Therapeutic regimen	ORR% (CR%)	Median PFS (months)	Median OS (months)
Proteasome inhibitors	Goy <i>et al.</i> [25]	Phase II	141	bortezomib	33 (8)	6.7 (TTP)	23.5
	Baiocchi <i>et al.</i> [26]	Phase II	13	bortezomib, rituximab	29 (29)	1.9	na
	Lamm <i>et al.</i> [27]	Phase II	16	bortezomib, rituximab, dexamethasone	81 (44)	12.1	38.6
mTOR inhibitors	Weigent <i>et al.</i> [28]	Retrospective	8	rituximab, high-dose cytarabine, dexamethasone, bortezomib	50 (25)	5	15.5
	Gerecitano <i>et al.</i> [29]	Phase I	10	rituximab, cyclophosphamide, prednisone, bortezomib	60 (50)	na	na
	Friedberg <i>et al.</i> [30]	Phase II	7	bendamustine, rituximab, bortezomib	71 (na)	na	na
IMiDs	Kouroukis <i>et al.</i> [31]	Phase II	25	bortezomib, gemcitabine	60 (11)	11.4	na
	Hess <i>et al.</i> [35]	Phase III, randomized	54	temsirolimus 175/75	22 (2)	4.8	12.8
	Ansell <i>et al.</i> [36]	Phase II	54	temsirolimus 175/25	6 (0)	3.4	10
	Renner <i>et al.</i> [38]	Phase II	53	investigator's choice	2 (2)	1.9	9.7
	Witzig <i>et al.</i> [40]	Phase II	69	temsirolimus, rituximab	59 (19)	9.7	29.5
	Eve <i>et al.</i> [41]	Phase II	35	everolimus	20 (6)	5.5	na
	Wang <i>et al.</i> [42**]	Phase II	57	lenalidomide	42 (21)	5.7	na
	Zaja <i>et al.</i> [43]	Phase II	26	lenalidomide	31 (8)	3.9	10
	Harel <i>et al.</i> [45]	Phase II	44	lenalidomide, rituximab	57 (36)	11.1	24.3
	Ruan <i>et al.</i> [20]	Phase II	33	lenalidomide, dexamethasone	52 (24)	12	20
Antibody-based approaches	Wang <i>et al.</i> [46]	Retrospective	58	thalidomide +/-bortezomib +/- rituximab	50 (21)	(1-y TTF 29%)	(1-y OS 62%)
	Cartton <i>et al.</i> [52]	Phase II	22	metronomic prednisone, etoposide, procarbazine, cyclophosphamide, rituximab, thalidomide	73 (32)	10	(2-y OS 45%)
	Wang <i>et al.</i> [46]	Phase II	32	90Y-ibritumomab iuxetan	31 (16)	6 (EFS)	21
B-cell receptor signaling inhibitors	Cartton <i>et al.</i> [52]	Phase II	15	GA-101	27 (na)	2.5	na
	Viardot <i>et al.</i> [56]	Phase I	7	blinatumomab	43 (14)	na	na
	Wang <i>et al.</i> [49***]	Phase II	110	ibrutinib	68 (22)	13.9	na
Kahl <i>et al.</i> [51]	Phase I	16	Cal-101	62 (na)	3 (DOR)	na	

Cell-cycle/apoptosis targeting drugs and others	Lin <i>et al.</i> [58]	Phase I	10 ^a	flavopiridol, fludarabine, rituximab	80 [70]	21.9	na
	Holkova <i>et al.</i> [59]	Phase I	6	flavopiridol, bortezomib	33 [17]	na	na
	Davids <i>et al.</i> [61]	Phase I	6	ABT-199	100 [na]	na	na
	Evens <i>et al.</i> [62]	Phase II	11	abexinostat	27 [na]	4	na

CR, complete response; DOR, duration of response; EFS, event-free survival; IMiDs, immunomodulatory drugs; MCL, mantle cell lymphoma; na, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure; TTP, time to progression; Y, years.
^aSix patients received the schema as first-line therapy.

against the tumor, a phenomenon known as ‘graft-versus-lymphoma’ reaction, potentially overcoming also chemoresistance. However, the application of allo-SCT in MCL is hampered by the therapy-related high toxicity of both reduced-intensity conditioning (RIC) and nonmyeloablative (NMA) approaches. Moreover, limitations come from advanced patient age (median at diagnosis is 65–68 years), availability of a compatible donor and the high relapse rate even after this procedure.

In the retrospective single center experience of M.D. Anderson [19] 35 most-chemosensitive (88%) patients (median age 58 years) received a NMA allo-SCT (fludarabine, cyclophosphamide and high-dose rituximab). A 6-year PFS rate of 46% was reported, with a plateau phase after 3 years and no relapse after 63 months of follow-up, whereas the 6-year overall survival (OS) was 53%. The 1-year treatment-related mortality (TRM) rate was 9% but no long-term nonrelapse mortality (NRM) rate was stated.

A recent retrospective multicenter French report [63] assessed the outcome of 70 MCL patients (79% chemosensitive, median age 56 years) receiving a RIC allo-SCT following various regimens (94% fludarabine-containing). In this series, the 2-year EFS and OS rates were 50 and 53%, respectively, but no plateau phase was achieved at any time point after transplantation. The 1-year and 2-year TRM rates were 22 and 32%, respectively.

Interestingly, in a recent large retrospective study of 202 patients with chemorefractory MCL, the Center for International Blood and Marrow Transplant Research found no significant differences between patients receiving conventional and RIC/NMA allo-SCT in terms of 3-year PFS (20 versus 25%), OS (25 versus 30%) and NRM (47 versus 43%) [64[■]].

In conclusion, although the discussed studies may be hampered by selection bias in single center series, heterogeneity of patients and procedures, it is noteworthy that an allo-SCT approach achieves durable remissions in approximately a fourth of young chemorefractory patients [64[■]]. The addition of radioimmunotherapy (RIT) to allo-SCT procedures has shown only conflicting results so far [65,66]. In conclusion, the issue of tolerability of such an immunological strategy is essential, as the high NRM (along with the high relapse rate) remains the major limitation for the application of allo-SCT in relapsed MCL.

ONGOING EUROPEAN CLINICAL TRIALS FOR RELAPSED MANTLE CELL LYMPHOMA

As MCL is a rare entity and relapsed MCL patients are difficult to treat with conventional immunotherapy, an enrollment in a prospective clinical

Table 2. Ongoing European clinical trials for relapsed mantle cell lymphoma

NCT code	Study features	Estimated enrollment (patients)	Estimated primary completion date (month/year)	Therapeutic regimen	Sponsor	Location countries
01449344	Phase III, randomized	157	09/2016	R-HAD versus R-HADB	European MCL Network	France, Germany
01646021	Phase III, randomized	280	08/2014	Ibrutinib versus temsirolimus	Janssen Research & Development LLC	Worldwide
01078142	Phase I/II, single arm	72	03/2014	BERT	German Low Grade Lymphoma Study Group (GLSG) & European MCL Network	Germany
01737177	Phase II, single arm	42	07/2014	R-2B	Fondazione Italiana Linfomi ONLUS, Italy	Italy
01389427	Phase I/II, single group assignment	63	06/2013	R-CHOP/R-FC/R-HAD + temsirolimus	Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang GOELAMS, France	France

BERT, bendamustine-rituximab-temsirolimus; MCL, mantle cell lymphoma; NCT, national clinical trial; R-HAD ± B, rituximab high-dose cytarabine-dexamethasone ± bortezomib; R-2B, rituximab-lenalidomide-bendamustine; R-CHOP, rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone; R-FC, rituximab-fludarabine-cyclophosphamide. Details of the studies can be found at the internet site: <http://www.clinicaltrials.gov>

trial is strongly recommended. This option allows applying new effective and expensive medications, sometimes not yet exploitable in routine clinical practice. Thus, a list of the major European actively recruiting clinical trials for relapsed MCL is reported in Table 2. The details of each study can be found at: <http://www.clinicaltrials.gov>

Prospective, multicenter, randomized, open-label phase III clinical trials

'Efficacy and Safety of R-HAD Alone or in Combination With Bortezomib in Patients With Relapsed or Refractory MCL' (NCT01449344), compares the efficacy and safety of bortezomib in combination with rituximab, high-dose cytarabine and dexamethasone (R-HAD) to R-HAD alone in patients with relapsed or refractory MCL after or not eligible for myeloablative treatment. Estimated enrollment: 200 patients. Sponsor: European MCL Network.

'Study of Ibrutinib (a Bruton's Tyrosine Kinase Inhibitor), Versus Temsirolimus in Patients With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy' (NCT01646021), evaluates the efficacy and safety of ibrutinib when compared with temsirolimus in patients with relapsed or refractory MCL who have received at least one prior rituximab-containing chemotherapy regimen. Estimated enrollment: 280 patients. Sponsor: Janssen Research & Development LLC.

Prospective, multicenter, single arm, open-label phase II or I/II clinical trials

'Temsirolimus, Bendamustine and Rituximab for Relapsed Follicular Lymphoma or Mantle Cell Lymphoma' (NCT01078142): the efficacy of the combination regimens will be evaluated in a first cohort of 30 patients with relapsed MCL and in a second cohort of 30 patients with relapsed follicular lymphoma. Estimated enrollment: 72 patients. Sponsor: German Low Grade Lymphoma Study Group (GLSG) and European MCL Network.

'Bendamustine/Lenalidomide/Rituximab: Combination as a Second-Line Therapy for First Relapsed-Refractory MCL' (NCT01737177), evaluates the safety and activity of the combination of bendamustine, lenalidomide and rituximab (R2-B) in patients with first relapsed/refractory MCL and the efficacy and safety of a maintenance treatment with lenalidomide for 18 months from the end of R2-B. Estimated enrollment: 42 patients. Sponsor: Fondazione Italiana Linfomi ONLUS, Italy.

'Escalating Doses of Torisel in Combination With Three Chemotherapies Regimens: R-CHOP, R-FC or R-DHA for Patients With Relapsed/Refractory MCL' (NCT01389427), assesses the feasibility, safety and efficacy of temsirolimus in combination with three chemotherapy regimens. Estimated enrollment: 63 patients. Sponsor: Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang GOELAMS, France.

CONCLUSION

Considering the complexities in the treatment of relapsed MCL, these patients should be generally referred to experienced centers to determine the optimal therapeutic strategy and potential inclusion into a clinical trial. In general treatment strategies should depend on the individual risk profile and patients' comorbidities. Our brief practical suggestions how to treat a patient with relapsed MCL are based on the most recent literature, evidence-based guidelines [9^o] and clinical experience (Fig. 1).

For young (<65 years) and fit patients allo-SCT should be considered in all cases after appropriate first-line therapy, due to its curative potential. The salvage regimen should contain cytarabine or bendamustine and rituximab in combination, when possible, with a targeted approach such as bortezomib, lenalidomide or temsirolimus (R-BAC,

R-HADB, BERT, R-2B regimens). The major goal is the achievement of at least a partial response, although a fraction of chemorefractory patients may obtain prolonged remissions, too. For patients not eligible for allo-SCT it is crucial to implement additional consolidation concepts (e.g. rituximab maintenance, RIT consolidation, new molecules within studies) to maintain remission.

For elderly (>65 years) fit patients, young nonfit patients or patients relapsing after allo-SCT a treatment with curative intent is not established. A salvage regimen containing targeted approaches is strongly recommended and the enrollment into a clinical trial is advisable. A tailored therapy should be based on individual risk profile, for example, elevated Ki67 levels [67] may favor a combination of cytarabine and bortezomib (R-HADB) or plus bendamustine (R-BAC) for fit patients, whereas a regimen with bendamustine-rituximab

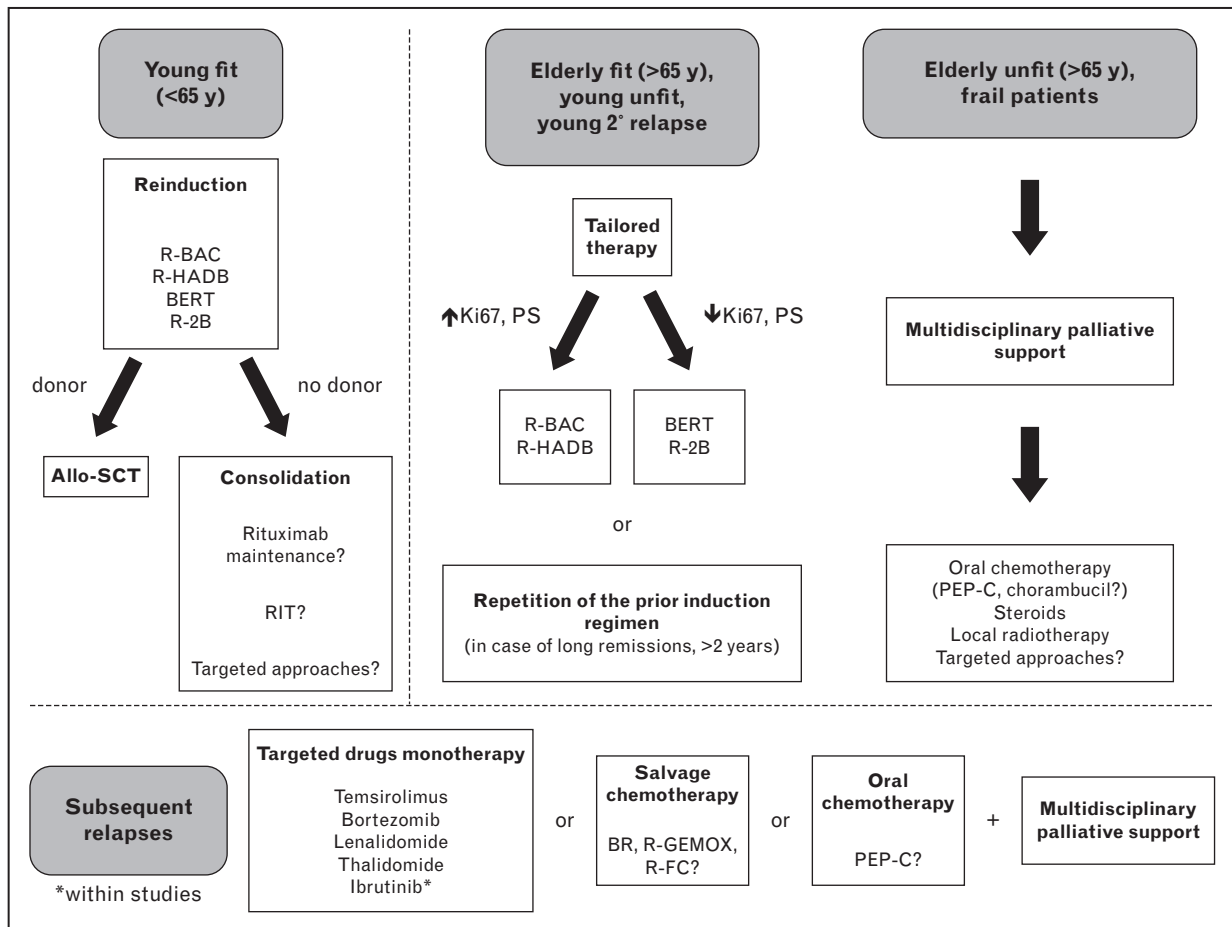


FIGURE 1. A rational therapeutic algorithm for patients with relapsed MCL. allo-SCT, allogeneic stem cell transplantation; auto-SCT, autologous stem cell transplantation; BERT, bendamustine-rituximab-temsirolimus; Ki67, Ki67 proliferative index; PEP-C, metronomic prednisone-etoposide-procarbazine-cyclophosphamide; PS, performance status; R-BAC, rituximab-bendamustine-cytarabine; R-HADB, rituximab high-dose cytarabine-dexamethasone-bortezomib; R-2B, rituximab-lenalidomide-bendamustine; RIT, radioimmunotherapy; BR, bendamustine-rituximab; R-GEMOX, rituximab-gemcitabine-oxaliplatin; R-FC, rituximab-fludarabine-cyclophosphamide; y, years.

in combination with temsirolimus (BERT) or lenalidomide (R-2B) appears more suitable for less fit patients with a lower proliferation index. The repetition of the prior induction regimen could be an appropriate approach, if a longstanding remission (> 2 years) was previously achieved.

For subsequent relapses, along with the deterioration of performance status and QoL, monotherapies with targeted drugs (in particular ibrutinib in the context of a clinical trial, or bortezomib, lenalidomide, thalidomide, temsirolimus) or well tolerated combinations with rituximab, steroids or low-dose chemotherapy should be preferred. Oral palliative combinations, such as the metronomic PEP-C, could be also useful options in this setting. In addition, a multidisciplinary palliative support may be started.

For elderly unfit or frail relapsed patients the preservation of the QoL should be the primary objective of the clinical care. Thus, mild oral chemotherapy combinations, steroids, radiotherapy and in selected cases also molecular approaches represent the standard of care. An adequate palliative support is crucial.

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Conflicts of interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 576–577).

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