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GUIDELINES - CONSENSUS-BASED

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EHA–EU MCL network guidelines for diagnosis and treatment of mantle cell lymphoma

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Abstract

Mantle cell lymphoma (MCL) is a relatively rare B-cell lymphoma subtype, with a higher incidence among males and a median age of 70 years at diagnosis. MCL is characterized by clinically diverse behavior, from indolent disease to extremely aggressive, related to the presence of biological risk factors such as proliferation rate and *TP53* mutations. Most often, patients present with disseminated disease, necessitating systemic treatment. Immunochemotherapy has historically been the mainstay of treatment, but recent data indicate that addition of novel agents, especially covalent Bruton tyrosine kinase inhibitors (cBTKi), may substantially improve outcome in younger and older patients, although a curative approach remains to be shown. In elderly patients, the standard of care is still immuno-chemotherapy such as rituximab-bendamustine, although this may be challenged by non-chemotherapeutic options, such as rituximab plus cBTKi. For patients with relapsed or refractory disease, treatment options are developing rapidly, including CAR-T cell therapy, novel BTK targeting agents, BCL2 inhibitors, and T-cell engagers. In this clinical practice guideline, we present current evidence-based recommendations for diagnosis, staging, treatment, and follow-up of MCL.

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INCIDENCE AND EPIDEMIOLOGY

Mantle cell lymphoma (MCL) is an uncommon type of B-cell lymphoma that comprises around 2%–10% of all lymphomas.[1,2] Its etiology remains incompletely explored. However, environmental factors and infections have been suggested as potential risk factors.[2] The median age at diagnosis is about 70 years with a male predominance, with a ratio of about 3:1.[1,3–5] The average annual age-adjusted incidence in Europe has been estimated at 0.45/100,000 persons/year,[4] but >1/100,000 in Northern Europe.[6] In the United States, the incidence was slightly higher among whites (0.6/100,000) than among blacks and Asians (~0.3/100.000).[2,3] Possibly due to the advent of more effective immunochemotherapy (ICT) regimens, the overall survival rate for MCL has improved significantly during the last couple of decades.[7] For MCL patients treated between 2000 and 2020, the 5- and 10-year survival rates across combined age groups were 58% and 32%, respectively.[8] In recent years, novel targeted agents and T-cell redirecting therapies have led to further development of the therapeutic landscape and their effect on survival trends in population-based studies remains to be demonstrated in the future.

DIAGNOSIS, PATHOLOGY, AND MOLECULAR BIOLOGY

The diagnosis of MCL should be made according to the criteria established by the current lymphoma classifications.[9–11]

Most tumors have a classic morphology of small-medium-sized cells with irregular nuclei and may grow with mantle zone, nodular, or diffuse patterns. However, the malignant lymphocytes may have a spectrum of morphological variants, including small round (resembling chronic lymphocytic leukemia), marginal zone-like, and pleomorphic/blastoid cells. The diagnosis of MCL requires a mature B cell phenotype, often with co-expression of CD5, and the demonstration of cyclin D1 expression and/or *CCND1* rearrangement. SOX11 is expressed in conventional MCL (cMCL). Its detection may also recognize uncommon cyclin D1-negative MCL, which carry *CCND2* or *CCND3* rearrangements.[12] Most cMCL have IGHV with high level of identity with the germline (≥97%).

A leukemic nonnodal MCL (nnMCL) subtype has been recognized with bone marrow involvement and frequent splenomegaly. These cases are SOX11 negative (<10%), carry high levels of IGHV somatic hypermutations (>3%), and usually follow a more indolent clinical course.[13,14] Although in most tumors SOX11 expression and IGHV mutational status distinguished conventional and nonnodal MCL, some cases may have borderline values of these parameters and the distinction between cMCL and nnMCL may be uncertain.

High-risk histological features in MCL are blastoid/pleomorphic morphology and high number of Ki-67-positive cells (≥30%).[15,16] A standardized Ki-67 quantification method has been suggested,[17] and two cutoffs have been proposed. European authors consider ≥30% to confer inferior prognosis, and American ≥50%.[15,18] Assessment of Ki-67 positivity in the bone marrow is less reliable and not recommended for prognostication. *TP53* mutations and 17p deletions are present in 10%–15% of cMCL and 25% of nnMCL.[19,20] Their association with a strongly adverse prognosis supports their study in all patients, preferably at diagnosis.[19,21–23] The type of *TP53* mutation may influence prognosis but has not yet been fully investigated. DNA sequencing is preferable over immunohistochemical detection of p53 overexpression to identify mutations, since up to 30% of mutations are truncating and may not be detectable by immunohistochemistry.[19,20,24,25] In addition, high-proliferative MCL may also overexpress p53 without gene mutations.[20] If only p53 expression by IHC is available, a cutoff of ≥50% should be used to denote positivity.[16] If possible, assessment for *TP53* aberrancy and Ki-67 should be repeated at relapse.

Increased genomic complexity, *CDKN2A* deletions, *MYC* translocations, and other genomic alterations have also been associated with adverse outcome, but this information is not yet well enough defined for routine clinical decision-making.[19,21,26,27] *BTK*, *PLCG2*, *CARD11*, and *BCL2* mutations are recognized resistance mechanisms to specific targeted therapies in some patients.[28]

CCND1 rearrangement and cyclin D1 expression are not exclusive to MCL and may be detected in some cases of multiple myeloma, and in a minority of primary and transformed diffuse large B cell lymphomas (DLBCL). The data favoring the diagnosis of DLBCL with *CCND1* rearrangements over pleomorphic MCL are a prior clonally related small B cell lymphoma, CD5 and SOX11 negativity, concomitant *BCL6*, *BCL2*, *or IRF4* rearrangements, or a mutational profile consistent with DLBCL.[29,30]

The diagnosis of MCL should ideally be based on a surgical specimen, preferably a lymph node excision biopsy. Core biopsies should only be carried out in patients without easily accessible lymph nodes. In patients with solely leukemic disease, the diagnosis may be established in a bone marrow (BM) biopsy or in peripheral blood using additional diagnostic parameters (immunophenotype and translocation *t(11;14)*). Fine needle aspirations are inappropriate. Re-biopsy of relapsed disease is recommended. The diagnosis of MCL should be reviewed by expert hematopathologists. If possible, additional biopsy material should be stored freshly frozen to allow additional molecular analyses.

Recommendations

- A diagnosis of MCL should be based on excision biopsy if feasible [V, A].
- *TP53* mutational analysis should be carried out at diagnosis [IV, A].
- When a new treatment is required, repeat biopsy (Ki-67 and *TP53* mutational analysis is recommended whenever possible; otherwise, p53 expression by IHC should be determined) [IV, B].

STAGING AND RISK ASSESSMENT

MCL most often presents as stage IV disease. Initial workup should include a computed tomography (CT) scan of the neck, thorax, abdomen, and pelvis, a bone marrow aspirate (including flow cytometry), and trephine biopsy. A positron emission tomography (PET)-CT scan provides additional staging information, and is especially recommended in the rare cases of limited stage I/II MCL. In these cases, gastrointestinal endoscopy should also be performed to rule out asymptomatic gastro-intestinal (GI) involvement, present in a significant subset of patients. In contrast to some other types of lymphoma, current evidence suggests that PET-CT is not sufficiently sensitive in identifying bone marrow and GI involvement to obviate the need for biopsy and endoscopy.[31,32] For the bone marrow, highly sensitive molecular techniques for the detection of minimal residual disease (MRD), able to detect bone marrow and/or blood infiltration at levels of 10^{-4} to 10^{-6}, are currently used in clinical trials and are of prognostic significance but have so far not been adopted for routine clinical practice.[33] One exception to consider may be the adoption of MRD for treatment decisions post induction.[34]

Central nervous system (CNS) involvement is rare (<1%) in asymptomatic patients at diagnosis.[35] A routine lumbar puncture at diagnosis in the absence of neurological symptoms is therefore not advised. It is important to perform screening tests for human immunodeficiency virus (HIV) and hepatitis B and C, as a positive test has implications for use of concurrent antiviral therapy. Additional

testing might be needed to assess the risk of treatment-related complications, for example, cardiac evaluation before initiation of BTK-inhibitor therapy or anthracycline-containing regimens.

The standard risk classification for the prognosis of MCL is the MCL International Prognostic Index (MIPI).[36] The MIPI uses four clinical features: age, performance status, serum LDH level, and white blood cell count.[36] The combination of Ki67 with MIPI is known as the 'combined' MIPI (c-MIPI).[15]

Recommendations

- Routine staging for MCL includes computed tomography (CT) scan of the neck, thorax, abdomen, and pelvis, bone marrow aspirate, and biopsy [V, A].
- In suspected limited stage I–II disease, positron emission tomography (PET)-CT scan and gastrointestinal endoscopy are recommended [V, B].

MANAGEMENT OF NEWLY DIAGNOSED DISEASE

Indolent clinical presentations of MCL

Although definitions vary in the literature, "indolent" MCL is often characterized by a leukemic presentation, SOX11 negativity, and low proliferation index (Ki-67), although an indolent "MALT-like" form of mostly extranodal disease, again with low Ki67% and classical morphology, is also recognized.[37,38] Practice over recent years has evolved from treating all patients at diagnosis to characterizing those where active observation may be appropriate. Until recently, clinical trials in MCL did not study subgroups separately.

The recent prospective UK MCL biobank results suggest that over one third (38%, 222/588) of patients at diagnosis can be observed and this group has a median time to initial treatment of approximately 21 months, and over half of these patients observed were not treated within 2 years of follow-up.[39] There was no clear adverse effect on the long-term survival for patients.

Nonrandomized phase II data from the MD Anderson Cancer Centre,[40] the Spanish and Nordic groups,[41,42] and the recent ENRICH phase III study[43] have provided evidence that patients with low-risk disease and often indolent features have excellent disease control and survival outcomes with BTK inhibitor and anti-CD20 monoclonal antibody therapy. Ongoing randomized trials are assessing early intervention of BTK inhibitor and anti-CD20 monoclonal antibody versus observation in indolent MCL (NCT05635162).

Recommendations

- Asymptomatic MCL patients with low-risk features managed by a watch-and-wait strategy should be monitored initially every 3 months, and then every 3–6 months by physical examination, imaging (as clinically required), blood counts, and biochemistry [V, B].
- Early intervention with targeted therapy should be performed only in the context of prospective clinical trials [II, C].
- At clinical progression, treatment will be initiated as for other MCL as below [V, B].

Limited stage disease

Limited stage (stage I–II) MCL is rare, forming 5%–15% of all newly diagnosed cases.[44,45] A thorough staging evaluation, including PET-CT, bone marrow (BM) biopsy, and endoscopy, is typically indicated and becomes especially relevant if localized treatment strategies are planned, since occult BM and gastrointestinal involvement is common.

The first-line treatment is not well defined. In low-risk patients, observation can be considered.[46,47] Involved site radiotherapy (24–36 Gy) is associated with high response rates and remissions may be durable, albeit mostly in stage I disease and low-risk MIPI groups.[44,45,48] In patients with intermediate risk/tumor load, a shortened systemic therapy, followed by radiation, may be considered. For patients with stage II, bulky disease, and/or high-risk MIPI, systemic treatment may lead to better long-term disease control, even if cure remains elusive[44] (Figure 1). Although prospective evidence is scarce, the authors advise that patients with high-risk biology (blastoid morphology, Ki67 > 30%, *TP53* mutations/deletions) should receive systemic treatment as per advanced-stage disease.

Recommendations

- Suspected limited-stage disease should be staged with PET-CT, BM biopsy, and gastroscopy/colonoscopy and gastrointestinal biopsies [II, B].
- In low-risk disease (stage I, without risk factors), observation or ISRT can be offered [II, B].
- In patients with intermediate risk/tumor load, a shortened systemic therapy, followed by radiation, may be considered [IV, B].
- In stage II with high-risk features, systemic treatment as per advanced stage is recommended [IV, B].

Advanced-stage disease

Younger patients

Most trials in this population included patients up to 65 years, but we advise fit patients >65 years also to be treated according to the following (Figure 1). In various randomized phase III studies, a dose-intensified concept of a rituximab- and cytarabine-containing induction, followed by a high-dose consolidation regimen and autologous stem cell transplantation (ASCT), achieved long-lasting remissions, therefore representing the standard of care in young and fit patients until recently (Table 1).[49,50,52–55] In addition, 3 years of rituximab maintenance after ASCT has further improved progression-free survival (PFS) and numerically also overall survival (OS).[53]

However, it is important to note that the relative importance of ASCT was observed before the routine implementation of high-dose cytarabine induction and rituximab maintenance. In a retrospective real-world analysis, there was no significant association between ASCT and time to next treatment (TTNT).[56] In contrast, the addition of rituximab maintenance resulted in a significantly prolonged TTNT and OS. Recently, in a US intergroup trial, ASCT did not improve overall survival rates in patients in PET-defined CR and deep molecular remission ($\times 10^{-6}$) after investigators' choice induction.[34]

The phase III TRIANGLE trial evaluated the remaining value of ASCT in first-line therapy.[54,57] After longer follow-up, a significant improvement of (modified) PFS and OS after the addition of the covalent BTK inhibitor (cBTKi) ibrutinib (delivered with R-CHOP in induction and 2 years of maintenance) was observed. Interestingly, skipping ASCT and adding ibrutinib instead led to a similar benefit, but with much less toxicity. Accordingly, the two ibrutinib arms (+/−ASCT) resulted in similar long-term results in the total study

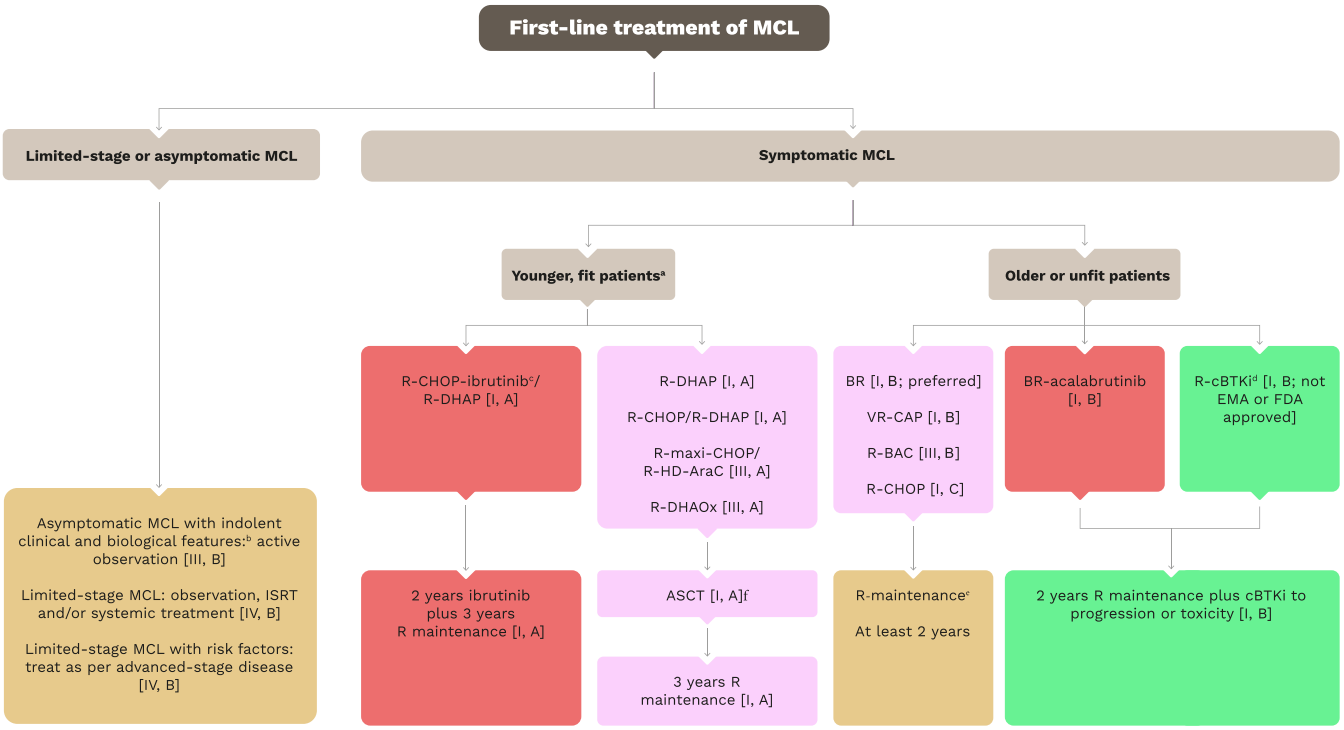

FIGURE 1 **First-line treatment of mantle cell lymphoma**. ASCT, autologous stem cell transplantation; BR, bendamustine–rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; CD, cluster of differentiation; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD, high dose; ISRT, involved-site radiotherapy; LN, lymph node; MCL, mantle cell lymphoma; MRD, minimal residual disease; R, rituximab; R-BAC, rituximab–bendamustine–cytarabine; R-CHOP, rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone; R-DHAOx, rituximab–dexamethasone–high-dose cytarabine–oxaliplatin; R-DHAP, rituximab–dexamethasone–high-dose cytarabine–cisplatin; R-maxi-CHOP, rituximab plus maximum strength cyclophosphamide–doxorubicin–vincristine–prednisone; VR-CAP, bortezomib–rituximab–cyclophosphamide–doxorubicin–prednisone. [a]Patients ≤70 years at the physician's discretion. First-line treatment with a cBTKi-containing regimen is preferred. [b]Typically leukemic or nodal MCL with LNs ≤ 3 cm, Ki67 ≤ 30%, classical or small-cell morphology, no cytopenia, or organ compromise. [c]First-line ibrutinib is not FDA-approved. Other cBTKi considered dependent on availability and preference. [d]Evidence from randomized trials for R–ibrutinib only, although zanubrutinib and acalabrutinib are under investigation alongside anti-CD20 therapy and may represent reasonable alternatives. [e]Not indicated after R-BAC. [f]ASCT should be omitted if MRD assessment by clonoSEQ demonstrates undetectable MRD (10^{-6}) [I, A].

population, although an unplanned subset analysis of biological high-risk patients suggested a possible benefit for the addition of ASCT. The addition of ibrutinib post-ASCT adds considerable infectious toxicity. The addition of rituximab maintenance with or without ibrutinib also resulted in prolonged survival rates in all three arms of the trial.[58]

In this trial, R-CHOP+ibrutinib was administered alternating with R-DHAP (dexamethasone, cytarabine, cisplatin) without ibrutinib or R-DHAOx, where cisplatin was substituted with oxaliplatin. Non-randomized data from the French LyMa trial indicate that outcome with oxaliplatin may be more favorable[59] although very few patients in TRIANGLE received R-DHAOx.

A matched comparison of patients in LyMA and LyMA-101, in which obinutuzumab was used instead of rituximab, showed improved PFS and OS in patients receiving obinutuzumab, indicating that the latter may be a superior CD20 antibody in MCL.[60] However, obinutuzumab is not approved for this indication by EMA or FDA.

Taken together, a cBTKi-containing regimen therefore represents the current gold standard of care in young, fit patients. However, the availability of cBTKi varies across European countries due to regulatory and reimbursement issues. If ibrutinib is unavailable, second-generation cBTKi may be reasonably used if available instead while recognizing the absence of phase III data with acalabrutinib or zanubrutinib.

Recommendations

- Fit younger patients should be treated with R-CHOP-Ibrutinib/R-DHAP or R-DHAOx induction, followed by 2 years of ibrutinib and 3 years of rituximab maintenance [I, A].
- Consider discussing ASCT in selected patients if high-risk features are present [II, C].
- If cBTKi are not available in the first-line treatment, rituximab and high-dose cytarabine-containing induction and ASCT consolidation may be applied, followed by 3 years of rituximab maintenance [I, B].
- In patients in CR with molecular remission by the NGS-based assay postinduction, ASCT can be omitted [II, A].
- Patients unsuitable for dose-intense regimens should be treated according to recommendations for older patients [II, A].

Older and frail patients

Older MCL patients, typically defined as individuals older than 65 years, and younger patients with comorbidities who are unfit for intensive therapies have been treated with conventionally dosed ICT regimens. While R-CHOP, followed by maintenance rituximab induction, leads to a median OS of 6.4 years,[61] a randomized trial suggests an at least comparable PFS for bendamustine-rituximab (BR) induction as compared to rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone (R-CHOP), with a better short-term toxicity

TABLE 1 Dose-intensified immunochemotherapy of mantle cell lymphoma (major phase II/III trials).

Author (year)	Phase	Patients (*n*)	Regimen	ORR% (CR%)	Median PFS (years)	OS (% or years)
Zöllner et al. (2021)[49]	III	93	R-CHOP + ASCT	98 (81)	3.3	7.5 (median)
		81	R-CHOP + IFN	99 (37)	1.4	4.8 (median)
Eskelund et al. (2016)[50]	II	160	R-maxiCHOP/Ara-C + ASCT	96 (54)	8,5	12.7 (median)
Ladetto et al. (2021)[51]	III	300	R-CHOP+HDCy + Ara-C + ASCT	68 (64)	NR	86 (3 years)
			R-CHOP+HDCy + Ara-C + ASCT + Len maintenance		NR	93 (3 years)
Hermine et al. (2023)[52]	III	455	R-CHOP + ASCT	97 (61)	3.9	25 (10 years)
			R-CHOP/DHAP + ASCT	98 (63)	8.4	46 (10 years)
Sarkozy (2024)[53]	III	299	R-DHAP + ASCT	NA	47,7% (7 years)	72.2% (7 years)
			R-DHAP + ASCT + RM	NA	78,5% (7 years)	83.3% (7 years)
Dreyling (2024)[54]	III	288	R-CHOP/DHAP + ASCT ± RM	94% (36%)	70% (4 years)	81% (4 years)
		292	RI-CHOP/DHAP + ASCT ± RIM	98% (45%)	82% (4 years)	88% (4 years)
		290	RI-CHOP/DHAP ± RIM		81% (4 years)	90% (4 years)

Abbreviations: Ara-C, cytarabine; CR, complete response; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; HDCy, high-dose cyclophosphamide; IFN, interferon; Len, lenalidomide; MTX, methotrexate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin.

profile.[62] Rituximab maintenance following BR did not improve outcomes in a single phase II trial,[63] but a large, real-world study showed a significant improvement in time to next treatment (hazard ratio [HR], 1.96; 95% confidence interval [CI], 1.61–2.38) and OS (HR, 1.51; 95% CI, 1.19–1.92),[56] making it a standard option in this setting. Rituximab maintenance following BR has also been utilized within the control arm in large recent randomized trials (SHINE, ECHO, ENRICH), confirming the excellent outcome of this approach.[43,64,65]

Alternative induction regimens include rituximab-bortezomib-cyclophosphamide-doxorubicin-prednisolone, VR-CAP, which improved median PFS and OS over R-CHOP (median 27.7 vs. 14.4 months and 90.7 vs. 55.7 months, respectively).[66] Maintenance rituximab was not applied in this trial, and it was performed in an era prior to routine BTK inhibitor use in relapsed MCL. Although VR-CAP increased hematological toxicity, peripheral neuropathy, and gastrointestinal toxicity, which may be improved by a shortened bortezomib schedule (Days 1 and 4 only),[67] it represents a useful alternative to bendamustine-based regimens by avoiding T-cell immunosuppression in potential future candidates for T-cell-engaging therapies including CAR-T. Thus, VR-CAP, followed by maintenance, may be especially of value for high-risk patients (Figure 1).

The combination of cytarabine with BR (R-BAC) has shown very high response rates and prolonged disease control in a single-arm phase II trial (PFS and OS at 7 years of 56% and 63%, respectively), albeit at the cost of significant hematological toxicity.[57] In contrast, 6 cycles of induction therapy with R-CHOP alternating with intermediate-dose cytarabine without cisplatin did not improve outcomes over 8 cycles of R-CHOP.[68] Attempts to improve maintenance by adding lenalidomide to rituximab improved PFS (76.6 vs. 60.8 months) but not OS in the same randomized phase III trial. Moreover, the combined maintenance increased toxicity and is not routinely recommended in the first-line setting.

The addition of cBTKi to induction and maintenance has also been studied in older populations. The SHINE trial tested the addition of ibrutinib to BR induction and R maintenance in patients over 65 years, leading to improved PFS but increased infectious and cardiac toxicities.[65] The ECHO trial, with a similar design, showed improved PFS with the addition of acalabrutinib to BR and a more tolerable toxicity profile, although with shorter follow-up.[64] The latter combination has recently been FDA- and EMA-approved and is useful in fit patients able to tolerate them. In both SHINE and ECHO, there was no significant improvement in OS by the addition of cBTKi.

Substitution of chemotherapy by cBTKi in patients older than 60 years was recently tested in the phase II/III ENRICH trial. R-Ibrutinib (R-I) improved PFS, the primary endpoint, compared to immunochemotherapy (BR and R-CHOP). The PFS was significantly improved compared to R-CHOP and was similar to BR after a median follow-up of over 4 years. R-I was associated with less hematological toxicity and an improved quality of life, making it an attractive option if available, although not currently approved by EMA or FDA.[43] Other cBTKi (acalabrutinib, zanubrutinib) are currently being tested in phase 2 trials in combination with anti-CD20 moAb +/− venetoclax, with promising efficacy and acceptable toxicity, regardless of age.[42] None of the chemo-free regimens including cBTKi is currently approved in the first-line setting.

In very frail patients, palliative radiotherapy at low doses (2 Gy × 2) may be effective in reducing symptoms, both in newly diagnosed patients and at relapse.[69]

Recommendations

- Patients ≥ 65–70 years unsuitable for intensive therapy should receive one of the following regimens:
  - R-chemotherapy: options include BR, VR-CAP, R-CHOP [I, B], R-BAC [III, B].
  - BR-acalabrutinib [I, B].
  - Continuous cBTKi plus rituximab induction and 2-year rituximab maintenance (not approved by EMA or FDA) [I, B].
- Offer maintenance rituximab for at least 2 years after the following first-line induction regimens:
  - BR [II, B].
  - VR-CAP [IV, B].
  - R-CHOP [I, C].

High-risk disease

Patients with high-risk MCL are typically characterized by either a high-risk MIPI score, high Ki67, blastoid or pleomorphic morphology, and/or a *TP53* mutation or p53 overexpression. Patients with *TP53* mutations are typically, but not exclusively, enriched for other high-risk clinical or morphological features. *TP53* mutations are a more dominant adverse prognostic factor compared to 17p deletions in patients treated with ICT.[22] Outcomes with anti-CD20 plus BTK inhibitor nonchemotherapy combinations in these subgroups are generally poor[42] and the modest numbers of patients in the ENRICH trial with blastoid disease have benefited more from chemotherapy than ibrutinib-rituximab.[43] In a subgroup analysis of the randomized TRIANGLE trial, for patients with high-risk tumors (blastoid, high Ki-67, or p53 overexpression), there was a trend toward improved outcome for patients receiving ibrutinib + ASCT (Arm A + I) versus patients in Arm I (ibrutinib, but no ASCT).[70]

For patients with the *TP53* mutation at diagnosis, recent modest-sized phase II clinical trials suggest that the non-chemotherapy-based triplet approach of anti-CD20, covalent BTK inhibitor, and BCL2 inhibitors may provide numerically improved survival outcomes compared to that of patients receiving only ICT, in whom survival outcomes are very poor (median PFS of approximately 1 year).[22,65] The combination of zanubrutinib, obinutuzumab, and venetoclax (BoVEN) demonstrated a complete response rate of 88% and a 2-year progression-free survival of 72%.[71] Obinutuzumab-ibrutinib-venetoclax has also been studied in a small number of *TP53*-mutated patients and demonstrated encouraging response rates in the OASIS I trial.[72] An alternative approach was adopted by the Italian FIL group, adding venetoclax as consolidation in high-risk MCL after standard R-BAC, showing a 2-year PFS of 58%.[73]

Recommendations

- Fit patients ≤ 70 years with p53 overexpression may be considered for R-CHOP-Ibrutinib/R-DHAP/Ox induction +/−ASCT, followed by 2 years of ibrutinib and 3 years of rituximab maintenance [II, C].
- Consider first-line anti-CD20, BTK inhibitor, and BCL2 inhibitor combinations for patients with *TP53* mutations if available [III, B].
- Patients with *TP53* mutations should be considered for prospective clinical trials of experimental novel agents and/or cellular therapies at all time points of the disease course [IV, B].

MANAGEMENT OF RELAPSED/REFRACTORY MCL

At each MCL disease progression, different aspects have to be evaluated and considered to establish the goal of therapy and individualize the choice of treatment, including disease-risk features (early time to progression, blastoid histology, elevated Ki-67, *TP53* mutational status), patient-specific factors (comorbidities, prior therapies, toxicities, and patient preferences), and treatment-related options (efficacy, time to response, toxicity, oral/iv administration, referral to a CAR-T or transplant center, availability of alternative therapies including experimental clinical trials, reimbursement) (Figure 2).

Relapsed disease after ICT

Covalent BTK inhibitors

cBTKi are the standard of care after progression to first-line ICT,[74–80] and ibrutinib and acalabrutinib are the only cBTKis licensed in Europe for R/R MCL (Table 2). cBTKi are usually administered until disease progression or unacceptable toxicity. Outcomes are heterogenous: approximately one-third of patients do not respond to cBTKi and durable responses are mostly seen in patients reaching complete response (CR). Ibrutinib use has advantages in both early[89] and late relapses[90] compared to ICT, mostly with a higher efficacy when indicated at first MCL relapse.[91] Moreover, ibrutinib is also preferred over other blood–brain-penetrating options in case of CNS involvement.[92] The discontinuation rate of ibrutinib due to toxicity ranges from 10% to 26% in retrospective studies.[93,94] Second-generation cBTKi[74,75,78–80] show higher specificity, resulting in a decreased off-target inhibition and reduced toxicity compared to ibrutinib. Both acalabrutinib and zanubrutinib induce lower rates of atrial fibrillation, hypertension, and bleeding compared to ibrutinib in randomized studies in histologies other than MCL.[95–97] Furthermore, cBTK inhibitor switching can significantly improve most cases of toxicity while maintaining high disease control.[95,98]

cBTKi have also shown efficacy in MCL cases harboring poor-risk biological features, including blastoid/pleomorphic variants, high Ki67, or *TP53* mutated cases, although the duration seems to be shortened to a median of 6 months.[74,77,80,91,93,99] A simple clinical model, the BTKi MIPI,[100] has been proposed to estimate the treatment duration with second-line cBTKi, which facilitates the identification of patients likely to require alternative therapy within a short time frame, thus avoiding abrupt cessation of the cBTKi and tumor flare.[101]

BTKi-based and other chemotherapy-free combinations

To improve the efficacy of ibrutinib, this drug has been explored in combination (Table 2).[1,40,72,82–84,86–88,102,103] Preliminary data from a randomized study[84] of one of the most promising and synergistic combinations, ibrutinib plus venetoclax, are available.[83,84,102,104] Ibrutinib was administered until progression and venetoclax was added only for the first 24 months. The combination led to a significant improvement in PFS compared to single-agent ibrutinib, although it was associated with higher toxicity. So far, no differences in OS between the two arms have been detected. Furthermore, a subgroup analysis of *TP53*-mutated cases suggested promising activity of the combination.[105]

Moreover, other targeted combinations without cBTKi have also been tested. Lenalidomide plus rituximab (R2) is a well-tolerated regimen for patients with relapsed or refractory MCL.[106] The venetoclax–R2 combination showed reasonable activity even in patients previously exposed to BTKi.[87] However, *TP53* mutated cases had a significantly worse outcome compared to wild-type cases.

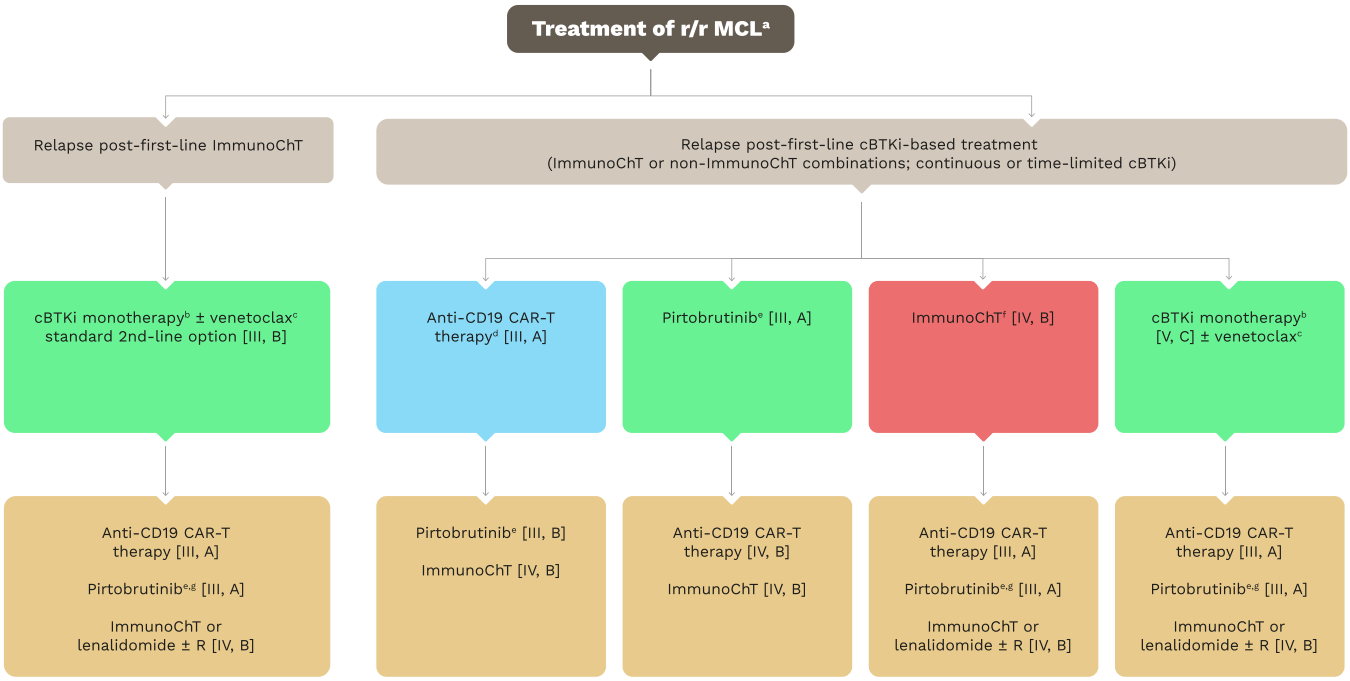

FIGURE 2 **Treatment of relapsed/refractory mantle cell lymphoma.** AlloSCT, allogeneic stem cell transplantation; CAR-T, chimeric antigen receptor T-cell; cBTKi, covalent Bruton tyrosine kinase inhibitor; CNS, central nervous system; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD, high dose; immunoChT, immunochemotherapy; MCL, mantle cell lymphoma; POD, progression of disease; R, rituximab; r/r, relapsed or refractory. [a]AlloSCT can be considered in younger, fit patients with r/r MCL in cases where CAR-T therapy is unavailable or has failed [IV, B]. [b]Ibrutinib: EMA-approved, not FDA-approved; acalabrutinib: FDA- and EMA-approved; zanubrutinib: FDA-approved, not EMA-approved. [c]Ibrutinib–venetoclax is not EMA- or FDA-approved. Consider cBTKi rechallenge if prior intolerance only or prior fixed-duration cBTKi. [d]CAR-T therapy can be considered, if available, second line (brexucabtagene autoleucel: FDA-approved after ≥1 prior lines of therapy, EMA-approved at s ≥ 2. relapse) for patients at high risk of cBTKi failure. Lisocabtagene maraleucel: FDA-approved after ≥2 prior lines including a cBTKi, not EMA-approved. [e]Pirtobrutinib: EMA-approved after ≥1 prior line, FDA-approved after ≥2 prior lines of therapy. [f]The choice of immunochemotherapy is dependent on treatment goals, availability of alternative therapies, prior immunochemotherapy exposure, patient fitness, and choice. Bendamustine should be avoided pre-CAR-T apheresis. [g]The choice between third-line pirtobrutinib and CAR-T therapy should be according to patient fitness, disease kinetics, patient choice, CAR-T therapy suitability, and availability.

It is noteworthy that several phase 2 studies exploring an MRD-driven time-limited treatment of targeted combinations provide initial evidence of the feasibility of this approach in R/R MCL patients, with sustained responses and even the possibility of retreatment.[87,102]

Relapse after cBTKi

The optimal management of patients experiencing a relapse following time-limited cBTKi therapy remains uncertain, although retreatment with a cBTKi may result in reasonable outcomes.[99] Prospective data to guide therapy in this setting in MCL remain absent and should be a focus of future investigation.

In contrast, MCL relapse on continuous cBTKi is an increasingly encountered problem. Until recently, outcomes were poor, with a median OS of around 8 months.[107] Common approaches included chemo-immunotherapy regimens such as R-BAC,[108] the BCL2 inhibitor venetoclax[109], and lenalidomide[110] used with modest efficacy. The first significant improvements for cBTKi-exposed patients were seen with the development of the anti-CD19 chimeric antigen receptor (CAR) T cell therapy brexucabtagene autoleucel. This cellular therapy was evaluated in a predominantly cBTKi-exposed population of MCL patients by the ZUMA-2 investigators in a single-arm phase II study.[111] Among 68 patients with cBTKi-exposed MCL, the ORR was 91%, with a CR rate of 68%, and the median PFS and OS were 25.8 and 46.6 months, respectively.[112] The main toxicity was cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In ZUMA-2, the rate of grade 3 or higher CRS and ICANS were 15% and 31%, respectively, with the latter figure in particular a major issue for patients with MCL, who are often elderly with comorbidities. Lisocabtagene maraleucel is another anti-CD19 CAR T construct that was evaluated by the TRANSCEND NHL001 investigators in 88 patients with MCL (83 cBTKi-exposed).[113] Liso-cel has similar ORR (83%) and CR (72%) but a more favorable toxicity profile, with much lower rates of grade 3 or higher CRS (1%) or ICANS (9%).

Noncovalent, reversible BTK (ncBTK) inhibitors are an alternate means of approaching MCL relapse after cBTKi. The only approved agent in this class is pirtobrutinib, a highly selective agent designed to be active in C481S mutated BTK.[114] The phase II MCL cohort of the BRUIN study included 152 patients with cBTKi-exposed MCL in an older population (median age 70) than in the CAR-T studies.[81] The ORR (49%) and CR rate (16%) were lower than those seen with CAR-T; however, the safety profile is favorable, with low rates of grade 3 or higher adverse events, apart from infections and neutropenia. Pirtobrutinib is an excellent choice for patients unsuitable for, or relapsing after, CAR-T cell therapy, or potentially as a means of bridging to CAR-T in patients with rapid kinetics. Other ncBTKis are in development such as nemtabrutinib, but detailed results in cBTKi-exposed MCL are awaited.[115]

CD20 × CD3 T-cell-engaging antibodies have promising activity in this setting, with glofitamab evaluated in 61 patients with MCL (31

TABLE 2 BTK inhibitors and experimental targeted combinations in R/R mantle cell lymphoma.

Bruton tyrosine kinase inhibitors	N	ORR (%)	CR (%)	DOR (months)	PFS (months)	OS (months)
Ibrutinib[76,77]	111	68	21	17.5	13.9	22.5
Acalabrutinib[75]	124	81	48	28.6	20	59.2
Zanubrutinib[79]	86	83	77	NR	33	36 m 75%
Orelabrutinib[78]	106	81	27	22.9	22	24 m 74%
Pirtobrutinib[81]	90	58	20	24.6	7.4	18 m 59%
Selected experimental cBTKi-based and other targeted combinations						
Ibrutinib, rituximab[40]	50	87	58	46	47	NR
Ibrutinib, bortezomib[82]	55	87.3[#]	41.8[#]	22.7	18.6	NR
Ibrutinib, venetoclax[83]	24	71	62	81	29	32
Ibrutinib, venetoclax (phase 3)[84]	134	82	54[&]	22	31.9[&]	44.9
**R/R TP53 mut (I,V arm)*[43]	45	80	58	26.5	20.9	35
Control arm (single agent Ibrutinib)	133	74	32	17.7	22.1	38.6
Zanubrutinib, sonrotoclax[85]	45	78	62	-	-	-
Ibrutinib, obinutuzumab, venetoclax[72]	24	84	67	NR	2-yr 69%	2-yr 68%
Ibrutinib, lenalidomide, rituximab[86]	50	76	56	NR	16	22
Venetoclax, lenalidomide, rituximab[87]	59	63	49	19 mo in *TP53* mut, others NR	2-yr 49%	2-yr 59%
Ibrutinib, palbociclib[88]	27	67	37	2-yr 69%	2-yr 59%	2-yr 60%

Note: Ibrutinib only EMA-approved (2014); Acalabrutinib FDA- (2017) and EMA-approved (2025), and zanubrutinib only FDA-approved (2019); Orelabrutinib only approved in China (2020). # Best ORR and CR(u) during maintenance; and significant improvement in CR and PFS was observed over the control arm.

Abbreviations: CR, complete response; DOR, duration of response; ORR, overall response; OS, overall survival; PFS, progression-free survival.

cBTKi-exposed). The ORR (74%) and CR rates (71%) are high, with grade 3 + CRS seen in 8%.[116] Glofitamab is logistically easier than CAR-T to deliver; however, the durability of responses also appears to be shorter. Glofitamab is in advanced development in relapsed MCL post cBTKi, with a pivotal ongoing randomized trial enrolling.[117] Another CD20 × CD3 T-cell engager, mosunetuzumab, in combination with polatuzumab vedotin, has also shown promising efficacy post cBTKi.[118]

BTK degraders are heterobifunctional molecules that induce BTK degradation through the ubiquitin proteosome pathway. NX-2127 and NX-5948 are BTK degraders with preliminary activity in MCL, and activity seen in cBTKi-exposed patients across a range of B-cell malignancies.[119] BGB-16673 is another BTK degrader with promising preliminary activity in cBTK-exposed B-cell lymphoma patients, including MCL.[120] More mature results from larger cohorts are awaited.

ROR1 is frequently expressed in MCL and the ROR1 antibody drug conjugate zilovertamab vedotin has demonstrated activity in 17 cBTKi-exposed MCL patients included in the phase I study, with a resultant ORR of 53%.[121]

Role of stem cell transplantation in R/R MCL

At relapse, few recent data supporting a role for ASCT are available. The American Society of Transplantation and Cellular Therapy, the Center for International Blood and Marrow Transplant Research, and the European Society for Blood and Marrow Transplantation jointly published consensus recommendations regarding the role, timing, and sequencing of ASCT.[122] ASCT may be considered among standard-risk MCL patients (e.g., those lacking a *TP53* mutation or biallelic deletion) who have not undergone ASCT in first remission, and in patients with a chemosensitive lymphoma.[122] The role of ASCT after targeted therapy failure is not well documented.

Consolidative allo-SCT remains a critical approach in the management of fit patients with R/R MCL, especially those with the *TP53* mutation. Long-term follow-up in 324 historically treated patients who underwent reduced-intensity allo-SCT showed a 4-year PFS and OS of 31% and 40%, respectively.[123] Another multicenter retrospective study showed 2-year PFS and OS rates of 50% and 53%, respectively.[124] Furthermore, patients with *TP53* aberrations appear to benefit from allo-SCT. The first retrospective analysis, including 42 patients with TP53-mutant R/R MCL, showed a 2-year PFS of 61% and a 2-year OS of 78%.[125] Similar results were reported in another retrospective study, with a 4-year PFS and OS of 51% and 59%, respectively.[126]

With the emergence of new targeted therapies in the R/R setting, the use of allo-SCT should be discussed in patients failing CAR-T on a case-by-case basis, considering the patient's comorbidities, high-risk disease features, and previous treatments. Allo-SCT may also be considered in select younger patients with high-risk features, in CR following CAR-T.

A comparison between a CAR T-cell approach and RIC allo-SCT has not been prospectively investigated, but retrospective data have not documented a clear benefit of one strategy over the other.[127,128]

Recommendations

- For BTKi-naïve patients with relapsed MCL, a cBTKi ± venetoclax (the latter not EMA- or FDA-approved) should be offered as standard post-first-line immunochemotherapy for:
  - Second line rather than later lines in early and late POD [III, B].
  - CNS relapse in BTKi-naive patients [IV, B].
- Treatment options post-cBTKi-containing first-line therapy include
  - Anti-CD19 CAR-T therapy (for patients at high risk of cBTKi failure) [III, A; FDA-approved; EMA approval is after ≥ 2 prior lines of therapy].
  - Pirtobrutinib [III, A; EMA-approved; FDA approval is after ≥ 2 prior lines of therapy].
  - Immunochemotherapy [IV, B].
  - cBTKi rechallenge ± venetoclax (the latter not EMA- or FDA-approved) if prior intolerance or prior fixed duration only of cBTKi therapy [V, C].
- Treatment options post-second-line immunochemotherapy and cBTKi-containing therapy include
  - Anti-CD19 CAR-T therapy [III, A].
  - Pirtobrutinib [III, A].
  - Immunochemotherapy or lenalidomide ± R [IV, B].
- Treatment options post anti-CD19 CAR-T therapy include
  - Pirtobrutinib [III, B].
  - Immunochemotherapy[IV, B].
- Treatment options post-pirtobrutinib include
  - Anti-CD19 CAR-T therapy [IV, B].
  - Immunochemotherapy [IV, B].
- AlloSCT should be considered in younger, fit patients with relapsed MCL in cases where anti-CD19 CAR-T therapy is unavailable or has failed [IV, B].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Asymptomatic patients with clinically indolent, disseminated disease being managed by a watch-and-wait strategy should be monitored by history, including B symptoms, physical examination, blood counts, and biochemistry including LDH, and imaging with abdominal ultrasound or CT neck, chest, abdomen, and pelvis as clinically required, every 3–6 months.

After the first-line systemic treatment, patients should generally be followed permanently, given the continued pattern of relapse with long follow-up. History and physical examination, blood and differential counts, and routine chemistry with LDH should be performed every 3–4 months for 2 years, every 6 months for 3 additional years, and, subsequently, once a year. Annual evaluation of thyroid function (i.e., TSH) should be conducted in patients after irradiation of the neck. Optional CT scan or ultrasound examinations should be conducted every 3–6 months for 2 years, every 6–12 months up to 5 years, and only if progressive disease is suspected thereafter. PET-CT should not be used for surveillance.

Additional monitoring is needed for patients who received CAR-T cell therapy for recurrent/refractory disease.[129,130] The patients are at increased risk of late complications, in particular, infections.[131]

Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with complete remission after anti-CD19 CAR T-cell therapy. Consider Ig replacement therapy 400–500 mg/kg IVIG q 3–4 weeks or 100–200 mg/kg q 1–2 weeks subcutaneous Ig (SCIG) for patients with hypogammaglobulinemia (serum IgG levels <400 mg/dL and severe or recurrent infections, particularly sinopulmonary). Continue Ig replacement therapy until serum IgG levels normalize and infections resolve.[132]

Consider G-CSF until ANC > 500; however, granulocyte-macrophage colony-stimulating factor (GM-CSF) is not recommended early in the setting of CAR T-cell therapy.

For patients with prolonged (>30 days) neutropenia and/or long-term corticosteroid administration, consider bacterial prophylaxis with fluoroquinolones or alternatives as well as fungal prophylaxis with fluconazole or mold-active azole if high risk (prolonged severe neutropenia, recent BMT, prolonged use of steroids, use of BTK inhibitors); continue until resolution of neutropenia and discontinuation of corticosteroids.

After anti-CD19 CAR T-cell therapy, all patients should receive prophylaxis against herpes virus with acyclovir 200-400 mg orally twice a day or valaciclovir 500 mg orally twice a day as well as pneumocystis jirovecii with trimethoprim-sulfamethoxazole orally 2–3 times weekly or alternatives (atovaquone, dapsone, or pentamidine) for a minimum of 6 months and until CD4 count >200 cells/ml.

It is recommended to start COVID-19 and influenza vaccines at 3 months, other inactivated vaccines at 6 months, and live vaccines >1 year from CAR-T.

Laboratory testing should include CBC, LDH at every visit, CRP, fibrinogen, ferritin every visit for the first 12 months after CAR-T, and Ig levels monthly until IgG>400 mg/mL, and then every 3 months in the first 24 months after CAR-T.

CMV, EBV, and HBV in patients known to be seropositive should be tested every 3 months in the first 24 months after CAR-T cell infusion. In the event of detectable viral levels, it is recommended to increase the frequency of monitoring to every 1 to 4 weeks.

Recommendations

- Asymptomatic patients with disseminated MCL managed by a watch-and-wait strategy should be monitored every 3–6 months by physical examination, imaging (as clinically required), blood counts, and biochemistry [V, B].
- After first-line systemic treatment, history and physical examination should be carried out every 3–6 months [V, B]. Follow-up should generally not be discontinued, given the continued pattern of relapse with long follow-up [V, D].
- High-risk patients should be offered more intense monitoring, being candidates for cellular therapies [V, B].
- Adequate prophylaxis (antibiotics and/or IgG supplementation) is required for patients with symptomatic recurrent infections and should take prior treatment into consideration (e.g., CAR-T therapy, bendamustine) [V, B]. COVID-19 and annual seasonal flu vaccination should be considered [V, C].

AUTHOR CONTRIBUTIONS

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