

Mantle Cell Lymphoma

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Table of contents

1 Summary	3
2 Basics	3
2.1 Definition and Basic Information	3
2.2 Epidemiology	4
2.3 Pathogenesis	4
4 Clinical characteristics	4
4.1 Symptoms	4
5 Diagnosis	4
5.1 Diagnostic Approach at Initial Diagnosis	4
5.3 Classification	5
5.3.1 Stages	5
5.4 Risk groups	5
6 Treatment	6
6.1 Treatment structure	6
6.1.1 First-line therapy	6
6.1.2 Relapse / Progression / Refractoriness	7
6.1.3 Consolidation / Maintenance	8
6.2 Treatment modalities	8
6.2.3 Drug therapy	8
6.2.3.1 Acalabrutinib	8
6.2.3.2 Bendamustine	9
6.2.3.3 Bortezomib	9
6.2.3.4 CAR-T cells	9
6.2.3.5 Cyclophosphamide	9
6.2.3.6 Cytarabine	9
6.2.3.7 Dexamethasone	10
6.2.3.8 Doxorubicin	10
6.2.3.9 Ibrutinib	10
6.2.3.10 Lenalidomide	10
6.2.3.11 Prednisone / Prednisolone	10
6.2.3.12 Rituximab	11
6.2.3.13 Temsirolimus	11
6.2.3.14 Venetoclax (off-label)	11
6.2.3.15 Vincristine	11
7 Rehabilitation	12
8 Follow-up and Follow-up	12
8.1 Follow-up	12

9	References	12
14	Links	15
15	Authors' Affiliations	15
16	Disclosures.....	16

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1 Summary

Mantle cell lymphoma is histologically classified as an indolent (cystic) lymphoma, but clinically exhibits a heterogeneous course that is aggressive in some patients. The chromosomal translocation t(11;14) with consequent overexpression of cyclin D1 is pathognomonic.

The vast majority of patients are diagnosed in advanced stages. The prognosis can be estimated using the clinical MCL International Prognostic Index (MIPI) or established biological factors (blastic variant, Ki-67 index, immunohistochemical p53 overexpression, or *TP53* alterations [mutations/deletions]). The MIPI-c combines clinical prognostic assessment with the biological marker Ki-67, allowing for a more differentiated risk assessment; additionally, the current WHO classification requires determination of the TP53 mutation status. The median survival time has historically been approximately 5 years, with significant differences across the various risk groups. The use of BTK inhibitors leads to a significant improvement in prognosis, particularly in younger patients.

The treatment goal for patients with mantle cell lymphoma is to achieve long-term remission with prolonged survival. Treatment is primarily guided by the patient's general condition. Younger patients are treated with alternating cytarabine-containing chemotherapy and R-CHOP/ibrutinib, followed by ibrutinib/rituximab maintenance therapy. (consolidating autologous stem cell transplantation may be used in high-risk patients as part of individualized treatment decisions.) For older patients, immunochemotherapy, e.g., bendamustine-rituximab +/- acalabrutinib followed by rituximab maintenance therapy, is recommended. Alternatively, VR-CAP may also be considered for these patients.

In the event of disease relapse, an individualized assessment of the appropriate therapy is performed, taking into account clinical and biological factors and the course of the disease (POD24). In cases of relapse following first-line chemoimmunotherapy, a BTK inhibitor is preferred over conventional chemotherapy. In the event of BTKi failure, non-covalent BTKis and CAR-T cell therapy are available.

2 Basics

2.1 Definition and Basic Information

Mantle cell lymphoma is formally classified as an indolent lymphoma, but in some cases it has a rapidly progressive course.

2.2 Epidemiology

Five to 7% of malignant lymphomas in Europe are classified as mantle cell lymphomas. The median age at diagnosis is 65 years. Approximately 75% of patients are male.

2.3 Pathogenesis

Mantle cell lymphoma resembles the mature B lymphocytes of the mantle zone [1, 2]. A pathognomonic feature is a chromosomal translocation between the immunoglobulin heavy chain gene on chromosome 14 and the cyclin D1 gene on chromosome 11. The t(11;14) (q13;q32) translocation, found in approximately 95% of all patients, leads to aberrant overexpression of *cyclin D1* and activation of the cell cycle. Additional genetic aberrations influence the clinical course, with TP53 mutations and deletions playing a central role. In patients without Cyclin-D1 overexpression, alterations in *Cyclin-D2* or *-D3* are frequently found.

4 Clinical characteristics

4.1 Symptoms

The clinical characteristics are heterogeneous; usually, the disease is already in the generalized stage at the time of initial diagnosis. In the so-called leukemic, non-nodal, rather indolent (SOX11-negative) mantle cell lymphoma, the leukemic disease with splenomegaly is the primary feature. In the nodal type, lymph node enlargement is common, and splenomegaly and lymphocytosis also occur. Bone marrow infiltration is present in approximately 80–90% of cases, with leukemic phase in 20–30% of cases. Extranodal manifestations (e.g., intestinal involvement) occur more frequently than in other indolent lymphomas [3].

5 Diagnosis

5.1 Diagnostic Approach at Initial Diagnosis

The diagnosis is based on histological examination of the affected lymph node. In the characteristic cytological picture, the cell nucleus appears irregular and indented, the chromatin is dense, and the cytoplasm is sparse. In addition, there is a wide range of variants in which the lymphoma cells appear more lymphocytic (as in CLL), pleomorphic, or blast-like. Examples of microscopic diagnosis can be found in the eLearning Curriculum in Hematology (eLCH), <https://ehaematology.com/>. To distinguish MCL from other lymphomas, immunohistochemical detection of cyclin D1 overexpression or a t(11;14) translocation (*IGH::CCND1* gene fusion) via fluorescence in situ hybridization (FISH) is mandatory. Ki-67 is also mandatory; the current WHO/ICC classification requires p53 immunohistochemistry or mutation analysis [1, 2].

Since the treatment of mantle cell lymphoma depends on the stage of disease, a thorough diagnostic evaluation before starting therapy is essential (staging). This includes (initial examination):

- Medical history, particularly B-symptoms
- Physical examination
- Complete blood count, differential blood count
- LDH, optional: β_2 -microglobulin
- Quantitative immunoglobulins and protein electrophoresis, immunofixation if monoclonal immunoglobulin is suspected

- Hepatitis and HIV serology
- Peripheral blood immunophenotyping (to detect leukemic phase)
- Bone marrow cytology, bone marrow histology, immunophenotyping (BM)
- CT of the neck/thorax/abdomen
- (alternatively: ultrasound for follow-up)
- Fertility counseling (for younger patients)
- Endoscopic diagnosis is recommended only in symptomatic cases

An 18F-FDG positron emission tomography (PET-CT) scan is especially recommended in early stages when local radiation therapy is planned, due to the therapeutic implications (NOTE: A PET-CT scan is not covered by statutory health insurance in Germany).

Depending on the planned therapy, lung function tests (high-dose consolidation) and cardiac function tests (CHOP, ibrutinib) are mandatory prior to the start of therapy.

5.3 Classification

5.3.1 Stages

Staging is classified into stages I through IV according to the Ann Arbor/Lugano classification. However, due to frequent lymph node involvement, most cases present with generalized disease.

I	Involvement of a single lymph node region or presence of a single, localized extranodal focus
II	Involvement of two or more lymph node regions on one side of the diaphragm or the presence of localized extranodal foci and involvement of one or more lymph node regions on one side of the diaphragm
III	Involvement of two or more lymph node regions on both sides of the diaphragm, or involvement of localized extranodal sites and lymph node involvement such that there is involvement on both sides of the diaphragm
IV	Disseminated involvement of one or more extralymphatic organs with or without lymph node involvement

It is also common to add “A” for the absence of, and “B” for the presence of

- unexplained fever >38°C
- unexplained night sweats (requiring a change of clothes)
- unexplained weight loss (>10% of body weight within 6 months)

5.4 Risk groups

The established clinical risk score (MIPI: MCL International Prognostic Index) takes into account the patient’s general condition and age, as well as LDH and white blood cell counts [4]. An online version is also available for calculating the score (<https://german-lymphoma-alliance.de/Scores.html>) [5]. In addition, the proliferation marker Ki-67 (>30%, in combination with the MIPI: MIPI-c) and the presence of TP53 alterations (mutations or overexpression on immunohistochemistry) reliably detects an unfavorable course [6, 7]. The indolent form of MCL cannot be identified based on individual parameters. Anamnestic clues regarding the course of the disease, low proliferation (Ki-67), and a typical pattern of manifestation suggest this variant. SOX11 can be evaluated as a supportive measure [1, 2, 8].

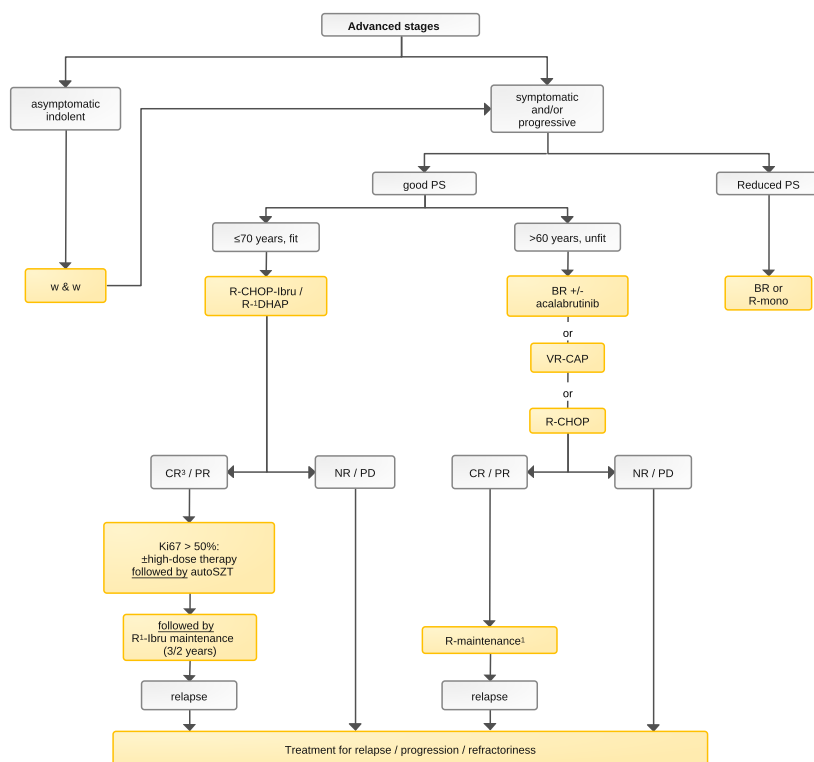
6 Treatment

6.1 Treatment structure

Patients with mantle cell lymphoma should, whenever possible, be treated within clinical trials. The treatment algorithms are shown in [Figures 1 and 2](#).

6.1.1 First-line therapy

Figure 1: Treatment algorithm for first-line therapy



Legend:

PS – performance status; w&w – watch and wait; R-CHOP – Rituximab/Cyclophosphamide/Doxorubicin/Vincristine/Prednisone; Ibru – Ibrutinib; R-DHAP – Dexamethasone/High-dose Cytarabine/Cisplatin; VR-CAP – Rituximab/Cyclophosphamide/Doxorubicin/Bortezomib/Prednisone; BR – Bendamustine/Rituximab; autoSCT – autologous stem cell transplantation; CR – complete remission; NR – no response; PR – partial remission;

¹ R (Rituximab) maintenance off-label

Localized stage

For the minority of patients diagnosed with limited Stage I disease and a low tumor burden, radiation therapy alone or a shortened course of immunochemotherapy followed by consolidation radiation therapy may be considered. Patients with a high tumor burden should be treated in the same manner as patients with advanced-stage diseases.

Advanced stage

- In cases of indolent clinical course with low tumor burden, leukemic presentation (without nodal involvement), or low biological risk (Ki-67 <10%), a close active surveillance strategy may initially be pursued in advanced stages, with therapy initiated only upon progression [8].
- In younger patients (fit, up to 70 years of age), cytarabine-containing induction therapy (R-CHOP/R-DHAP) leads to significantly prolonged progression-free survival and overall survival compared to R-CHOP, each followed by autologous stem cell transplantation [9]. Maintenance therapy with rituximab for 3 years following autologous stem cell transplan-

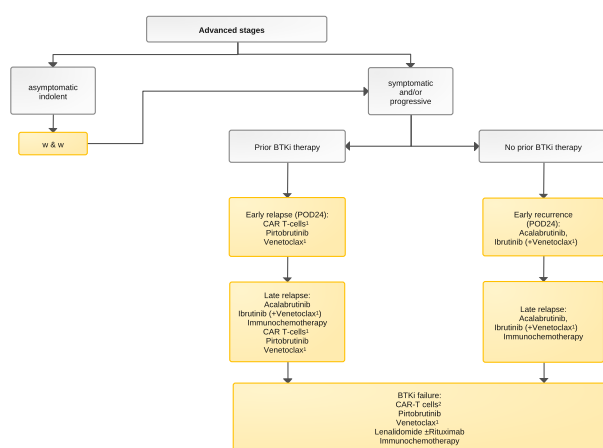
tation prolongs progression-free and overall survival [10]. In a randomized study, the additional administration of ibrutinib during induction (with R-CHOP) and for 2 years in the maintenance phase resulted in significantly improved progression-free survival (PFS) and overall survival (OS) [11]. Autologous SCT in addition to ibrutinib does not improve long-term outcomes in standard-risk cases, but may be considered on an individual basis in high-risk cases (Ki-67 $\geq 50\%$), taking into account the increased toxicity [12].

- For older patients (those who are medically unfit, aged 60 and older), possible combination regimens include R-Bendamustine with or without Acalabrutinib, VR-CAP, or R-CHOP (see Appendix: [Systemic tumor therapy protocols](#)):
 1. R-Bendamustine is relatively well tolerated (no alopecia). It achieves long-lasting remission in more indolent cases. The addition of long-term acalabrutinib therapy improves PFS but not OS [13].
 2. The administration of bortezomib instead of vincristine (VR-CAP) leads to prolonged progression-free and overall survival in patients with more pronounced thrombocytopenia compared to R-CHOP [14].
 3. For very fit patients with a high-risk profile, the R-BAC-500 regimen may be considered [15].
- Maintenance therapy with rituximab following R-CHOP results in a significant prolongation of remission duration and overall survival [16]. The benefit of R-maintenance following R-bendamustine has been demonstrated in retrospective and prospective (non-randomized) analyses [13, 17]. Rituximab maintenance therapy is typically administered for 2 years (+/- long-term BTKi therapy); in younger patients, for 3 years (+ ibrutinib for 2 years).

Information on the approval status is summarized in [Mantle Cell Lymphoma Approval](#).

6.1.2 Relapse / Progression / Refractoriness

Figure 2: Treatment algorithm for relapse, progression, or refractoriness



Legend:

w&w – watch and wait; POD24 – disease progression within 2 years.

² off-label,

³ Allogeneic transplantation should generally only be considered in younger patients after CAR-T cells.

In relapse, BTK inhibitor therapy (ibrutinib/acalabrutinib) is superior to re-chemotherapy in BTKi-naïve patients [18, 19]. In a randomized study, venetoclax in combination with ibrutinib achieved significantly improved PFS (note: off-label). In appropriate cases, this combination is an effective option, particularly in so-called bridging situations [20] leading to CAR-T cell therapy.

Relapses following treatment with a BTK inhibitor (BTKi) often follow an aggressive course:

- Pirtobrutinib achieves, in some cases, long-lasting remissions in approximately half of BTKi failures [21].
- CAR-T cell therapy achieves long-lasting remissions in this patient population, and Liso-cel is better tolerated than Brexu-cel [22, 23].
- venetoclax (which is not approved for MCL) can achieve remission in up to half of cases [24], although the duration of response is limited.
- In previous studies, the bispecific antibody glofitamab also achieves remissions in the majority of BTKi-failure cases following a single pretreatment with obinutuzumab (to reduce the risk of CRS) [25].

In patients with multiple relapses or refractory disease, lenalidomide is also superior to chemotherapy [26]; combination with rituximab leads to higher response rates with comparable tolerability [27]. However, the results are inferior to those of BTK inhibitor therapy, and response rates following BTK therapy are moderate.

The proteasome inhibitor bortezomib also achieves only short remissions in monotherapy; depending on prior therapy, the VR-CAP regimen or R-HAD bortezomib may be considered [15, 28].

The mTOR inhibitor temsirolimus achieves only a short duration of remission (median 2.9 months) in patients with multiple relapses or refractory disease [29]; see [the mantle cell lymphoma indication](#).

6.1.3 Consolidation / Maintenance

Previous studies demonstrated a benefit of rituximab maintenance after chemotherapy in rituximab-naïve patients [30].

In high-risk patients (TP53 alteration, Ki67 > 30%, blastoid MCL), only a short-term remission is expected with a BTK inhibitor, so CAR-T cell therapy should be planned prospectively. In younger patients, allogeneic transplantation should generally only be considered after CAR-T cell therapy has failed [3, 31].

6.2 Treatment modalities

6.2.3 Drug therapy

Information on the approval status of drugs suitable for the treatment of mantle cell lymphoma is listed in [Approval Status](#) for [Mantle Cell Lymphoma](#) in Germany, Austria, and Switzerland.

6.2.3.1 Acalabrutinib

Acalabrutinib is a second-generation inhibitor of Bruton's tyrosine kinase (BTK). This kinase plays a central role in the development, differentiation, signal transduction, and survival of B lymphocytes. Acalabrutinib achieved sustained remissions in several Phase 2 and 3 studies [13, 32]. Compared to ibrutinib, cardiac side effects (atrial fibrillation, hypertension) and (cutaneous) bleeding occur less frequently, while the mild immunosuppressive effect is comparable. Acalabrutinib is administered orally.

6.2.3.2 Bendamustine

Bendamustine is an alkylating agent that also possesses the properties of a purine antimetabolite. The pivotal trial comparing bendamustine versus CHOP, both in combination with rituximab, included 94 patients with MZL. Median progression-free survival was significantly longer in the bendamustine arm (35.1 months) compared to the CHOP control arm (22.1 months). The BRIGHT study included 74 patients with MZL. The remission rate was also high at 94% in the bendamustine/rituximab arm; data on overall survival are not yet available. Grade 3/4 CTCAE adverse effects of bendamustine affect hematopoiesis: neutropenia (23%), thrombocytopenia (12%), and anemia (2.5%). They often require dose adjustments. Other common side effects include fever, nausea/vomiting, and skin rash. Bendamustine is administered intravenously.

6.2.3.3 Bortezomib

The proteasome inhibitor bortezomib was first approved for the treatment of patients with multiple myeloma. Its efficacy in patients with mantle cell lymphoma was demonstrated in Phase II studies in combination with cytostatic agents, steroids, and rituximab. In a Phase III study, bortezomib was more effective than vincristine—when used in place of vincristine as part of an R-CHOP regimen—in terms of remission rate, progression-free survival, and overall survival; see [mantle cell lymphoma Study Results](#) [14]. In this study, bortezomib was administered intravenously; subcutaneous administration is also approved by the EMA. Specific side effects of monotherapy include thrombocytopenia and peripheral neuropathy. The latter occurs less frequently following subcutaneous administration than following intravenous administration. Other side effects include reactivation of the varicella zoster virus (aciclovir prophylaxis recommended) and pulmonary complications such as pneumonitis and interstitial pneumonia.

6.2.3.4 CAR-T cells

Patients with relapsed or refractory mantle cell lymphoma who show disease progression during or after therapy with BTK inhibitors have an especially poor prognosis. As demonstrated in multicenter Phase II studies (ZUMA II and TRANSCEND NHL 001), therapy with CAR-T cells (brexucabtagene autoleucel, lisocabtagene maraleucel) targeting the surface antigen *CD19* achieved high response rates and ongoing remissions in these patients with an unfavorable prognosis. The side effects, some of which were serious and life-threatening, were consistent with those observed in other lymphomas [22, 23].

6.2.3.5 Cyclophosphamide

Cyclophosphamide is effective as a single agent in indolent lymphomas, but in mantle cell lymphoma it is primarily used in combination with doxorubicin, vincristine, prednisone, and rituximab (R-CHOP). The main side effect of cyclophosphamide is hematotoxicity. At higher doses (>1,000 mg), hemorrhagic cystitis may occur, which can be prevented by the prophylactic administration of uromitexan. Cyclophosphamide is administered intravenously in standard lymphoma regimens.

6.2.3.6 Cytarabine

Cytarabine belongs to the nucleoside analogs. It has been the standard of care in induction therapy for patients with acute myeloid leukemia (AML) for more than 40 years. In a Phase III study in younger patients with mantle cell lymphoma, the R-DHAP x 3 regimen (rituximab, dexamethasone, high-dose cytarabine, cisplatin) combined with R-CHOP x 3 was superior to R-

CHOP monotherapy in terms of progression-free and overall survival [10]. Side effects of high-dose cytarabine primarily include hematotoxicity, nausea/vomiting, mucositis, and alopecia. In patients with impaired renal function, the risk of neurotoxicity increases.

6.2.3.7 Dexamethasone

Dexamethasone is a highly potent steroid. In mantle cell lymphoma, it is used in induction therapy for younger patients in the R-DHAP regimen (see chapter 6.2.3.6, Cytarabine). Side effects are similar to those of other steroids (see chapter 6.2.3.11, Prednisone/Prednisolone).

6.2.3.8 Doxorubicin

Doxorubicin belongs to the anthracycline class of drugs. It is primarily used in combination regimens (R-CHOP, VR-CAP) for the treatment of mantle cell lymphoma. In the largest study to date on the treatment of mantle cell lymphoma, therapy with R-CHOP resulted in remission rates of 86%, a median progression-free survival of 28 months, and a significant improvement in overall survival compared to a combination of fludarabine, cyclophosphamide, and rituximab [13]. Two smaller randomized studies have shown that the combination of bendamustine and rituximab is at least as effective as R-CHOP in terms of remission rates and progression-free survival. The main side effects of doxorubicin are nausea/vomiting, alopecia, and hematotoxicity. A critical long-term side effect is cardiomyopathy, particularly above a cumulative dose of 550 mg/m². Grade 3/4 CTCAE side effects of CHOP that occur in more than 5% of patients include neutropenia, anemia, thrombocytopenia, alopecia, and infections. Doxorubicin must be administered strictly intravenously. Extravasation requires immediate intervention.

6.2.3.9 Ibrutinib

Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor. This kinase plays a central role in the development, differentiation, signal transduction, and survival of B lymphocytes. Ibrutinib achieves sustained remissions in multicenter studies [19]. Adverse effects of ibrutinib monotherapy in the MCL3001 study classified as CTCAE Grade 3/4 included neutropenia (13%), thrombocytopenia (9%), anemia (8%), fatigue (4%), diarrhea (3%), and fever (1%). Severe side effects occur significantly less frequently than in the temsirolimus arm. Ibrutinib is administered orally.

6.2.3.10 Lenalidomide

Lenalidomide is an immunomodulatory agent. In patients with relapsed/refractory mantle cell lymphoma, it led in a multicenter, randomized Phase II study to an increase in the remission rate from 11% to 40% and to a prolongation of progression-free survival (hazard ratio 0.61; median 3.5 months) [26]. The most common side effects were neutropenia, anemia, fatigue, thrombocytopenia, diarrhea, and constipation. Severe side effects (CTCAE Grade 3/4) occurring in ≥5% of patients were neutropenia (44%), thrombocytopenia (18%), anemia (8%), and febrile neutropenia (6%). Lenalidomide is administered orally.

6.2.3.11 Prednisone / Prednisolone

Prednisone or prednisolone are commonly used glucocorticoids. They are an integral part of the CHOP regimen and its modifications. Short-term side effects of glucocorticoids include flushing, restlessness, and disturbances in glucose metabolism. Medium- and long-term side effects correspond to the symptoms of Cushing's syndrome, including osteoporosis and changes in body

composition. Critical side effects, particularly in CLL patients, include infections—especially those of viral and fungal origin—due to immunosuppression. Glucocorticoids can be administered orally or intravenously.

6.2.3.12 Rituximab

Rituximab is a chimeric anti-CD20 antibody. Combination with chemotherapy regimens such as CHOP leads to increased remission rates and prolonged progression-free survival compared to chemotherapy alone; see [mantle cell lymphoma Study Results](#). Following successful induction therapy with R-CHOP, rituximab maintenance therapy prolongs progression-free survival and overall survival [13]. (Rituximab maintenance is not formally approved, but is recognized by the GBA as a reimbursable off-label use.) The most common side effects of rituximab are immediate infusion-related reactions with fever, chills, nausea, and a general feeling of illness. Cytokine release syndrome can (especially in cases of pronounced leukemic flushing) lead to severe hypotension with high fever, hypoxia, and the need for intensive care. Rituximab can be administered intravenously or subcutaneously.

6.2.3.13 Temsirolimus

Temsirolimus is an mTOR kinase inhibitor. It was initially approved for the treatment of patients with advanced renal cell carcinoma. Its efficacy in mantle cell lymphoma was demonstrated in a randomized Phase III trial in patients with relapsed or refractory disease, compared with treatment selected by the physician or center [28]. Temsirolimus resulted in a remission rate of 22% and a significant improvement in progression-free survival; see [mantle cell lymphoma Study Results](#). Severe Grade 3/4 adverse effects in more than 5% of patients included thrombocytopenia (59%), anemia (20%), neutropenia (15%), asthenia (11%), infections (9%), diarrhea (7%), rash (7%), dyspnea (7%), and mucositis (6%). A rarer but debilitating side effect of mTOR kinase inhibitors is pneumonitis. Temsirolimus is administered intravenously.

6.2.3.14 Venetoclax (off-label)

Venetoclax is a drug belonging to the class of B-cell lymphoma-2 (Bcl-2) inhibitors. By blocking the anti-apoptotic Bcl-2, it induces programmed cell death. In a Phase I study, monotherapy with venetoclax achieved a promising overall response rate of 75% in the subgroup of patients with relapsed/refractory mantle cell lymphoma, with a CR rate of 21% [24]. In a randomized Phase III study, combination therapy with ibrutinib and venetoclax achieved a significantly prolonged PFS. The most common side effects of venetoclax are neutropenia, diarrhea, nausea, anemia, upper respiratory tract infections, fatigue, and elevated blood phosphate levels. Severe side effects may include febrile neutropenia, pneumonia, and initial tumor lysis syndrome. Venetoclax is administered orally.

6.2.3.15 Vincristine

Vincristine belongs to the vinca alkaloids. In mantle cell lymphoma, it is a part of combination regimens such as R-CHOP. In addition to hematotoxicity, specific side effects is primarily polyneuropathies, beginning as sensory disturbances in the extremities. Vincristine is administered intravenously. Extravasation requires immediate countermeasures.

7 Rehabilitation

Following high-dose therapy, specific rehabilitation measures should be discussed with the patient.

8 Follow-up and Follow-up

8.1 Follow-up

1. During and immediately after therapy (monitoring of treatment, detection of complications and side effects)

- Medical history and physical examination
- White blood cell count, differential blood count, LDH
- Additional laboratory tests as needed for treatment monitoring and complication management

2. Treatment evaluation (cytoreduction, side effects) halfway through the treatment cycles and upon completion of cytostatic therapy, as well as in cases of suspected progression or complications:

- Medical history and physical examination
- Diagnostic imaging (CT, ultrasound)
- Monitoring of treatment complications (laboratory tests; echocardiography and pulmonary function tests as needed)

3. Follow-up examinations after completion of therapy at 3-month intervals, at 3- to 6-month intervals starting in the second year, and at 6- to 12-month intervals starting in the third year as part of follow-up (remission monitoring, detection of long-term toxicity):

- Medical history and physical examination
- White blood cell count, differential blood count
- LDH
- Diagnostic imaging (ultrasound; CT scan) if clinically indicated
- Further diagnostics depending on the findings at baseline and during the course of treatment

4. Determination of 'minimal residual disease' (MRD) only within the context of clinical trials.

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14 Links

A video demonstrating how to perform a bone marrow aspiration was created by the Elisabethinen Hospital in Linz for training and patient use (<https://www.youtube.com/watch?v=3RgGmErO50g>).

Competence Network for Malignant Lymphomas

<http://www.lymphome.de/>

German Leukemia and Lymphoma Aid e. V.

<http://www.leukaemie-hilfe.de/>

German Lymphoma Alliance

<https://www.german-lymphoma-alliance.de/>

European Mantle Cell Lymphoma Network

<http://www.european-mcl.net/>

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16 Disclosures

according to the rules of the responsible Medical Societies.