



# Mantle Cell Lymphoma

## Guideline

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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# Mantle Cell Lymphoma

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## 1 Definition and Basic Information

Mantle cell lymphoma belongs to the indolent lymphomas, despite its aggressive clinical course in most patients.

## 2 Clinical Presentation

The clinical picture is characterized by lymph-node enlargements and splenomegaly. Bone-marrow infiltration occurs in approx. 80-90% of the cases, lymphoma cells are detected in the blood in 20-30% of all patients. Extranodal manifestations (e.g. involvement of the GI tract, meningeosis lymphomatosa) occur more frequently than in follicular lymphomas [1].

## 3 Diagnostics

Diagnosis is based on the histological examination of a suspicious lymph node. Immunohistochemical staining for cyclinD1 overexpression and/or fluorescence in-situ hybridization (FISH) for t(11;14) are mandatory in order to differentiate this lymphoma from other lymphoma subtypes. As the therapy of indolent lymphomas depends on the stage of disease thorough diagnostics are essential prior to onset of therapy (staging).

This includes (initial examination):

- Medical case history, particularly of B symptoms
- Physical examination
- Complete blood cell count, including leukocyte count with differential cell counts, reticulocytes
- ESR, electrophoresis, total protein
- ALT, AST, AP,  $\gamma$ -GT, bilirubin, creatinine, uric acid, blood sugar
- LDH,  $\beta_2$ -microglobulin
- Quick's test, PTT
- Quantitative analysis of immunoglobulins, immune electrophoresis in case of suspected paraproteinemia
- Surface markers based on FACS analysis (only in case of leukemic course)
- Bone-marrow cytology, bone-marrow histology
- CT of the neck/thorax/abdomen

(alternatively: sonography for follow-up purposes)

Positron emission tomography (PET) has no therapeutic consequences and is not recommended.

In order to identify patients with an increased risk for acute and/or late complications, tests of lung function, the heart (ECG, cardiac echo) and renal function are absolutely necessary prior to the onset of therapy.

## 4 Staging

Staging is done by differentiating stages I to IV according to the Ann Arbor Classification, see [Table 1](#). However, the stage will be advanced in most cases due to the frequent bone marrow involvement.

**Table 1: Staging according to Ann Arbor Classification**

Stage	Criteria
I	One single lymph-node area (I/N) affected, or existence of one single or localized extranodal focus (I/E)
II	Two or more lymph-node areas on one side of the diaphragm (II/N) are affected, or existence of extranodal focus (II/E) and one or more lymph-node areas on one side of the diaphragm (II/N/E) affected
III	Two or more lymph-node areas on both sides of the diaphragm (III/N) are affected, or existence of localized extranodal foci and affected lymph nodes, so that both sides of the diaphragm are affected (III/E or III/N/E)
III <sub>1</sub>	Subdiaphragmatic localization, limited to the spleen, celiac and/or portal lymph nodes, either alone or in combination
III <sub>2</sub>	Subdiaphragmatic localization with the involvement of paraaortic, mesenterial, iliac, and/or inguinal lymph nodes, either alone or in combination
IV	Disseminated incidence affecting one or several extralymphatic organs, with or without affected lymph nodes

Lymphatic tissues include: lymph nodes, spleen, thymus gland, Waldeyer's tonsillar ring, appendix. Cervical, axillary, or inguinal lymph-node enlargements as well as enlargements of liver or spleen each count as one area.

Stages are additionally denoted "A" in the absence, and "B" in the presence of

- Fever of unknown origin > 38°C
- Night sweats
- Unintentional weight loss > 10% within a period of 6 months

## 5 Risk Groups

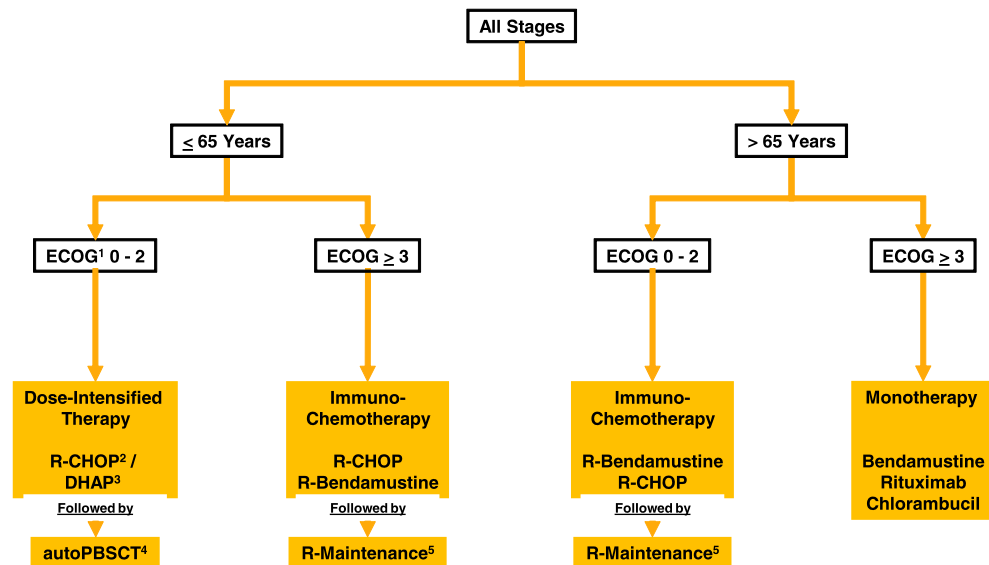
A clinical risk score (MIPI: MCL International Prognostic Index) has been recently established [2]. It takes into account the general health status and the age of the patient, as well as LDH values and WBC counts. An Internet-based version has been made available for its calculation. [3]. The proliferation marker Ki67 also is of high prognostic relevance [4]. Approx. 10-15% of cases display an indolent

course. As yet, these patients are not unequivocally identifiable at first presentation [5].

## 6 Therapy

Patients with indolent lymphomas should be treated, whenever possible, in clinical trials. A therapy algorithm is shown in [Figure 1](#).

**Figure 1: First-Line Therapy**



*Legend:*

1 ECOG - Score acc. to ECOG / WHO / Zubrod on the classification of the general condition;

2 R-CHOP - see [Systemic Therapy - Protocols](#);

3 R-DHAP - see [Systemic Therapy - Protocols](#);

4 autoPBST - autologous stem-cell transplantation; 5 R-Maintenance - Rituximab Maintenance, - see [Systemic Therapy - Protocols](#)

### 6.1 First-Line Therapy

#### 6.1.1 Patients ≤ 65 years

In younger patients (≤65 years) a dose-intensified concept (induction plus high-dose consolidation with autologous stem-cell transplantation, or HyperCVAD) is the standard therapy. It leads to a significant prolongation of progression-free and overall survival [6]. A cytarabine-containing regimen additionally increases progression-free survival [7].

#### 6.1.2 Patients > 65 years

Combination regimens for 'elderly patients' are R-CHOP, R-Bendamustine (cf. Appendix [Systemic Therapy - Protocols](#)), and R-FC especially in exclusively leukemic cases. However, the majority of patients will relapse within the first three years due to the aggressive course of the disease [8]. Maintenance therapy with rituximab after R-CHOP leads to a significant prolongation of remission duration and overall survival [9].

### 6.1.3 Indolent Course

In individual cases a watch & wait strategy with continuous monitoring in short intervals may be pursued if an indolent clinical course is suspected. Treatment in these patients is initiated upon progression of the lymphoma [5].

## 6.2 Relapse

- Immunochemotherapy is the standard therapy in patients with late relapse (remission duration  $\geq 6$  months). Choice of the second line regime depends on the first line therapy.
- In later relapses the mTOR inhibitor temsirolimus is superior to mono-chemotherapy, see Appendix [Systemic Therapy - Protocols](#) [10].
- Other promising agents are proteasome inhibitors (bortezomib) and immunomodulatory substances (thalidomide, lenalidomide). However, no randomized studies are available [11, 12].

## 6.3 Consolidation / Maintenance

- Unless autologous transplantation has already been performed in first line treatment, it should be discussed at the time of the first relapse.
- In case of a relapse after high-dose therapy an allogenic transplantation with reduced conditioning may be discussed for younger patients [1].
- Maintenance therapy with rituximab lead to a significant prolongation of progression-free survival in a small randomized study and can be applied individually.
- Radioimmunotherapy may be an alternative option for consolidation.

## 7 Monitoring and Follow-Up

1. During and immediately after therapy (therapy monitoring, recognition of complications and adverse effects)
  - Medical case history and physical examination
  - Complete blood cell count, including leukocyte count with differential cell counts
  - Functional liver and kidney parameters, if necessary, further laboratory diagnostics for therapy monitoring and diagnosis of complications
2. Therapy assessment (cytoreduction, adverse effects) after completion of one-half of the therapy cycles and after termination of cytostatic therapy, and in case of suspected progression or complication:
  - Medical case history and physical examination
  - Checkup on initial pathological findings, as required for decision-making

- Exclusion of therapy complications (liver and kidney parameters; echocardiography in case of clinical symptoms, chest x-rays, if necessary, pulmonary function)
3. Follow-up examinations after termination of therapy in intervals of three months, after the third year in intervals of 6-12 months, as long-term follow-up (remission surveillance and/or diagnosis of relapse, detection of long-term toxicity):
    - Medical case history and physical examination
    - Complete blood cell count, including leukocyte count with differential cell counts
    - LDH, functional liver and kidney parameters
    - Checkup on initial pathological findings (imaging)
    - Extended diagnostics depending on initial findings and findings compiled in the course of the disease
  4. Analysis of minimal residual disease (MRD) only within clinical trials.

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## 10 Systemic Therapy - Protocols

- [Mantle Cell Lymphoma - Systemic Therapy - Protocols](#)

## 12 Links

### **Malignant Lymphoma Competence Network**

[www.kompetenznetz-leukaemie.de](http://www.kompetenznetz-leukaemie.de)

### **Deutsche Leukämie - und Lymphom - Hilfe e. V.**

[www.leukaemie-hilfe.de](http://www.leukaemie-hilfe.de)

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## **14 Disclosures**

according to the rules of the German Association of Hematology and Oncology (*DGHO, Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie*) and the recommendations of the AWMF (version dated April 23, 2010) and international recommendations.