Mantle Cell Lymphoma

Guideline

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Alexanderplatz 1
D-10178 Berlin

Executive chairman: Prof. Dr. med. Carsten Bokemeyer

Phone: +49 (0)30 27 87 60 89 - 0
Fax: +49 (0)30 27 87 60 89 - 18

info@dgho.de
www.dgho.de

Contact person
Prof. Dr. med. Bernhard Wörmann
Medical superintendent

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Mantle Cell Lymphoma

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Authors: Martin Dreyling, Christian Buske, Johannes Drach, Michael Herold, Mathias J. Rummel

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, γ-GT, bilirubin, creatinine, uric acid, blood sugar
- LDH, β₂-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
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>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>One single lymph-node area (I/N) affected, or existence of one single or localized extranodal focus (I/E)</td>
</tr>
<tr>
<td>II</td>
<td>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</td>
</tr>
<tr>
<td>III</td>
<td>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)</td>
</tr>
<tr>
<td>III₁</td>
<td>Subdiaphragmatic localization, limited to the spleen, celiac and/or portal lymph nodes, either alone or in combination</td>
</tr>
<tr>
<td>III₂</td>
<td>Subdiaphragmatic localization with the involvement of paraaortic, mesenterial, iliac, and/oringuinal lymph nodes, either alone or in combination</td>
</tr>
<tr>
<td>IV</td>
<td>Disseminated incidence affecting one or several extralymphatic organs, with or without affected lymph nodes</td>
</tr>
</tbody>
</table>

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 autoPBSCT – 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 ≥ 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.

8 References


10 Systemic Therapy - Protocols

- Mantle Cell Lymphoma - Systemic Therapy - Protocols

12 Links

Malignant Lymphoma Competence Network
www.kompetenznetz-leukaemie.de

Deutsche Leukämie - und Lymphom - Hilfe e. V.
www.leukaemie-hilfe.de
13 Authors’ Affiliations

Prof. Dr. med. Martin Dreyling
Klinikum der Universität München
Med. Klinik und Poliklinik III Großhadern
Marchioninistr. 15
81377 München
Tel: 089 7095-2202
Fax: 089 7095-2201
martin.dreyling@med.uni-muenchen.de

Prof. Dr. med. Christian Buske
Universitätsklinikum Ulm
Innere Medizin III
Inst. f. Experimentelle Tumorfororschung
Albert-Einstein-Allee 11
89081 Ulm
Tel: 0731 50065801
Fax: 0731 50065802
christian.buske@uni-ulm.de

Ao. Univ. Prof. Dr. Johannes Drach
Allgemeines Krankenhaus Wien
Innere Medizin I
Klinische Abteilung für Onkologie
Währinger Gürtel 18-20
A-1090 Wien
Tel: 0043 1 40400-5457
Fax: 0043 1 40400-4451
johannes.drach@meduniwien.ac.at

Prof. Dr. med. Michael Herold
Helios Klinikum Erfurt GmbH
4. Medizinische Klinik
Hämatologie / internistische Onkologie
Nordhäuser Str. 74
99089 Erfurt
Tel: 0361 781-5298
Fax: 0361 781-5291
michael.herold@helios-kliniken.de
**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.