Mantle Cell Lymphoma: Therapeutic Strategies Are Different from CLL

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Opinion statement

In contrast to the typical course of chronic lymphocytic lymphoma and despite an indolent lymphoma-like presentation, the clinical outcome of mantle cell lymphoma (MCL) is dismal, with a median survival time of 3 years and virtually no long-term survivors. Most patients are diagnosed with advanced stage III/IV disease. Although clinical studies did not prove a clear superiority of anthracyclin-containing combinations, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-like regimens represent the standard therapeutic approach in MCL. Recent randomized studies have shown a benefit of a combined immunochemotherapy strategy (chemotherapy plus rituximab) increasing the complete and overall response rates, whereas further follow-up is pending for evaluation of the progression-free and overall survival. In patients younger than 65 years, a dose-intensive consolidation comprising high-dose radiochemotherapy and subsequent autologous stem cell transplantation after a CHOP-like induction results in an improved progression-free survival. However, despite the benefits of this multimodal approach, most patients relapse even after high-dose therapy. The only curative approach is allogeneic stem cell transplantation, which may be adapted to the elderly MCL patient cohort by modified dose-reduced conditioning regimens. Prospective randomized trials remain critical to further improve the clinical course of MCL with the addition of newer treatment modalities, such as radioactively labeled antibodies and targeted therapies (*eg*, flavopiridol and PS-341).

Introduction

Mantle cell lymphoma (MCL) is characterized by the chromosomal translocation t(11;14)(q13;q32) and the resulting overexpression of the cell cycle regulator cyclin-D1 in virtually all cases [1,2]. The clinical presentation is similar to indolent lymphoma subtypes. The median age is 60 to 65 years with a 3:1 to 4:1 male preponderance. Eighty percent to 85% of patients are diagnosed with advanced stage III/IV disease [3•,4•]. Splenomegaly (35%–55%) and bone marrow involvement is frequent (60%–80%) in patients. Accordingly, leukemic generalization is detectable in approximately 30% to 60% of patients, depending on the method applied. This clinical

chronic lymphocytic lymphoma (CLL) based on cytomorphology alone [5]. Other extranodal presentations include involvement of the gastrointestinal tract (up to 25%; polyposis coli) and the central nervous system (4%–22% of relapsed MCL) [6,7]. Because the cytomorphology of MCL is variable (classic centrocytic cells vs blastoid variants), morphologic diagnosis of MCL may be complex and often difficult. In addition to the coexpression of the T-cell marker CD5 and different B-cell markers (CD19, CD20, CD22, CD79a; higher expression level than CLL), MCL cells lack the CD23 expression frequently detected in CLL [4•]. In contrast to

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clinical course of MCL is aggressive with a low proportion of long-time survivors [3•]. Thus, a wait-and-see strategy similar to classic CLL is not recommended in MCL. Because of the extensive consequences for the therapeutic strategies, the definite diagnosis of MCL should be confirmed by immunophenotyping and optional detection of cyclin-D1 overexpression. The International Prognostic Index may be applied to identify different risk groups [8,9]. However, in various studies, proliferation-derived parameters such as mitoses per high-power field or Ki67 immunostaining were superior to the International Prognostic Index [10,11].

Treatment

Radiotherapy

- Limited stage I/II disease is diagnosed in only 10% to 15% of patients with MCL. In various case reports, regional radiation therapy has been shown to be a potentially curative approach in these rare cases. Extrapolating from other aggressive and indolent lymphomas, a dose of 30 to 40 Gy seems to be reasonable. Based on the limited data published thus far, extended field radiation therapy seems to reduce the rate of local recurrences but not the relapse-free and overall survival in comparison to an involved field therapy [12]. Current study concepts test the additional application of total nodal radiation (German Low-Grade Lymphoma Study Group) or low-dose total body irradiation (European Organization for Research and Treatment of Cancer).
- In advanced stage III/IV disease, the benefit of radiation therapy in addition to systemic chemotherapy is unproven. Thus, local radiation should be reserved for patients with bulky disease not responding to conventional chemotherapy.

Systemic treatments

Conventional chemotherapy

- Eighty percent to 85% of patients with MCL are diagnosed with advanced stage III/IV disease with bone marrow or other extranodal involvement [3•,4•]. In addition, MCL has the lowest long-term survivor rate of all lymphoma subtypes. Therefore, a wait-and-see strategy is not recommended, but treatment should be initiated as soon as diagnostic procedures, including confirmation of histologic diagnosis, are completed. Various systemic chemotherapeutic regimens induce overall response rates of approximately 70% to 80%. However, the rate of complete remissions (CR) is lower than in other lymphoma subtypes (approximately 20%–30%) and there are virtually no long-term survivors. In the largest series presented thus far, different conventional chemotherapy regimens showed only modest differences concerning progression-free and overall survival [3•].

Anthracyclin-containing regimens

- In various studies, the role of anthracyclin-containing regimens, mostly CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like regimens, was investigated in MCL. In a retrospective analysis of 65 patients, Zucca *et al.* [13] reported the superiority of an anthracyclin-containing regimen concerning complete response rate, failure-free survival, and overall survival. In contrast, in the only prospective randomized study of 63 patients with MCL, Meusers *et al.* [14] observed a similar efficacy of anthracyclin-containing CHOP and another standard regimen (cyclophosphamide, vincristine, and prednisone [COP]). CR and overall remission (OR) rates were 58% and 89%, respectively, for patients treated with CHOP and 41% and 84%, respectively, for patients treated with COP. Accordingly, no

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differences were detected for relapse-free and overall survival (CHOP: 10 and 32 months, respectively; COP: 7 and 37 months, respectively) time. Another randomized study also detected no difference in the remission rate between fludarabine monotherapy and an anthracyclin-containing combination with idarubicin [15]. However, the combination regimen achieved a significantly longer progression-free survival.

- Therefore, although the study results are partially inconsistent, most authors accept an anthracyclin-containing (mostly CHOP-like) regimen as a standard approach in MCL, especially as part of a sequential approach with subsequent interferon maintenance or myeloablative consolidation and subsequent autologous stem cell transplantation.
  - CHOP: Cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) on day 1, and prednisone 100 mg on days 1 to 5.
  - COP: Cyclophosphamide 400 mg/m^2 on days 1 to 5, vincristine 1.4 mg/m^2 (maximum 2 mg) on day 1, and prednisone 100 mg on day 1.

Purine analogs

- In contrast to CLL, single-agent fludarabine has only moderate activity in MCL with an overall response rate of 30% to 40% and rare CR [16–18]. However, several clinical studies demonstrated a superior outcome after an anthrachinone or alkylating drug-containing combination implicating a superadditive effect of these cytostatic drugs.
- In a phase II study of 18 newly diagnosed patients with MCL, another purine analog (cladribine) in combination with mitoxantrone achieved a CR and OR rate of 48% and 100%, respectively [19]. In a recent phase III study including 38 patients with MCL, a fludarabine/cyclophosphamide/mitoxantrone regimen (FCM) achieved a 33% remission rate in relapsed MCL [20••]. Cohen *et al.* [21•] reported the efficacy of a fludarabine plus cyclophosphamide (FC) combination in 30 patients with MCL. CR and OR rates were 30% and 63%, respectively. In newly diagnosed MCL, this scheme achieved a CR rate of 70%, implying a remarkably high efficacy in chemotherapy-genuine MCL.
- Fludarabine-containing combinations seem to be the most effective conventional chemotherapy in relapsed MCL. A randomized study has been initiated by the European MCL Network to evaluate the role of an upfront therapy with a fludarabine combination (FC) in comparison to a standard CHOP-like regimen.
  - Fludarabine 25 mg/m^2 on days 1 to 5.
  - FCM: Fludarabine 30 mg/m^2 on days 1 to 3, cyclophosphamide 200 mg/m^2 on days 1 to 3, and mitoxantrone 8 mg/m^2 on day 1.
  - FC: Fludarabine 30 mg/m^2 on days 1 to 3 and cyclophosphamide 600 to 750 mg/m^2 on day 1.
  - F-Ida: Fludarabine 25 mg/m^2 on days 1 to 5 and idarubicine 12 mg/m^2 on day 1.
  - 2-CDA-Mitox: Cladribine 5 mg/m^2 on days 1 to 3 and mitoxantrone 8 mg/m^2 on days 1 to 2.

Other chemotherapeutic regimens

- A new cytostatic approach in the treatment of MCL is the incorporation of high-dose cytarabine. Overall response rates of up to 67% in relapsed MCL have been reported for the DHAP (dexamethasone, Ara-C, and

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cisplatin) regimen [22]. The French group has investigated a sequential CHOP-DHAP hybrid in 28 newly diagnosed patients with MCL [23••]. After four cycles of CHOP, only 7% of patients achieved a CR. In the remaining patients, an additional four cycles of DHAP resulted in a CR rate of 84%. Based on these results, a randomized phase III study of the European MCL network has been initiated.

- Another attempt is the more aggressive treatment strategy presented by Romaguera *et al.* [24••]. In a phase II study of 25 elderly patients with MCL, an alternating regimen (cyclophosphamide, doxorubicin, vincristine, and dexamethasone [Hyper-CVAD] and high-dose methotrexate/cytarabine [MA]) achieved an impressing CR rate of 68% in newly diagnosed patients with MCL. This regimen seems to be also feasible in elderly patients. Promising results have also been reported for the combination of cisplatin, fludarabine, and cytarabine (PFA) [25].
  - DHAP: Dexamethasone 40 mg on days 1 to 4, Ara-C 2 × 2000 mg/m^2 on day 2, and cisplatin 100 mg/m^2 on day 1.
  - Hyper-CVAD: Cyclophosphamide 2 × 300 mg/m^2 every 12 hours on days 1 to 3, doxorubicin 50 mg/m^2 on day 4, vincristine 2 mg on days 4 and 11, and dexamethasone 40 mg on days 1 to 4 and 11 to 14.
  - MA: Methotrexate 1000 mg/m^2 on day 1, cytarabine 2 3000 mg/m^2 every 12 hours on days 2 and 3, methylprednisolone 2 × 50 mg on days 1 to 3.
  - PFA: Cisplatin 25 mg/m^2 on days 1 to 4, fludarabine 30 mg/m^2 on days 3 and 4, and cytarabine 500 mg/m^2 on days 3 and 4.

Biologic modifiers

- In various studies, interferon-α administered as maintenance therapy seems to prolong the progression-free survival in MCL [3•,26]. However, because of the small number of cases, none of the studies achieved a statistically significant result. Based on the moderate efficacy of chemotherapy only, interferon maintenance may be reasonable, especially in patients with relapsed MCL, to extend the achieved remission.

Interferon-α

Standard dosage	Three to 5 million IU subcutaneously three times weekly. Recent data suggest that interferon-α may be substituted by the pegylated substance μg/kg body weight administered once a week based on pharmacokinetic data in patients with hepatitis C [27,28].
Contraindications	Recent history of myocardial infarction, pre-existing liver or central nervous system disorders, and serious psychiatric condition.
Main side effects	Initial fatigue and flu-like symptoms (*eg*, malaise, fevers, chills, and arthralgias) are the most frequent side effects and may lead to a temporary dose reduction. Accordingly, prophylactic antiphlogistic drugs may improve or limit the clinical symptoms. Liver function abnormalities up to fatal hepatotoxicity have been observed. Psychiatric symptoms, especially depression and even suicide, have been associated with interferon therapy. Other potential but rare side effects are nausea, vomiting, and thyroid function abnormalities.
Special points	Besides the observed side effects, approximately 60% of patients tolerate this maintenance therapy for more than 3 to 4 years. In the future, the pegylated substance may improve these side effects (side effects have a similar profile but only once a week).

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Lymphocyte-specific antibodies

- In many studies, monotherapy with the lymphocyte-specific anti-CD20 antibody rituximab showed only moderate activity in MCL with a remission rate of 20% to 40% [29,30]. However, previous in vitro studies have suggested a synergistic effect of the simultaneous application of chemotherapy and rituximab [31]. In a recent phase II study, a combined immunochemotherapy (R-CHOP) achieved a high CR rate of 48% and an OR rate of 96% [32••]. However, the progression-free survival time in this study was only 16 months, emphasizing the aggressive clinical course of MCL.
- In a prospective randomized study, the German Low-Grade Lymphoma Study Group investigated the effect of rituximab in combination with a fludarabine-containing regimen (R-FCM) in 35 patients with relapsed MCL [20••]. CR and OR rates were significantly higher in the immunochemotherapy group (35% and 65%, respectively, vs 0 % and 33%, respectively), confirming the superadditive effect of a combined chemotherapy plus antibody concept (Table 1). In a randomized study of 62 patients with newly diagnosed MCL, a combined immunochemotherapy approach (R-CHOP) achieved a significantly higher remission rate in comparison to standard chemotherapy alone (97% vs 69%) [33•]. Thus, the combined chemotherapy plus rituximab regimens represent the current golden standard in MCL. The role of a rituximab maintenance therapy is being investigated by different study groups.
- Another innovative antibody-based approach is the application of radioactive-labeled lymphocyte-specific antibodies with ^{90}Yttrium or ^{131}Iod in conventional or myeloablative dosage. Recent studies, although based on a limited number of patients, reported impressive survival rates of up to 83% after 2 years in patients with relapsed MCL [34••,35]. Future studies will focus on the combination with conventional or high-dose chemotherapy.

Rituximab

Standard dosage	375 mg/m^2 on days 1, 8, 15, and 22 (monotherapy), and 375 mg/m^2 on day 1 of each cycle (combined immunochemotherapy). Infusion starts at 50 mg/h. The rate will be step-wise increased by 50 mL/h if no side effects occur.
Contraindications	Known hypersensitivity to mouse/humanized antibodies or proteins.
Main side effects	Especially during the first application, anaphylactic reactions with fever, flushes, and rigors occur in up to 15% of patients (12% grade 3/grade 4). If symptoms diminish after infusion has been stopped, infusion may be restarted at a reduced rate.
Special points	Side effects are usually only mild during subsequent courses of rituximab.

Autologous stem cell transplantation

- Since the first report by Stewart *et al.* [36] in 1995, myeloablative therapy with subsequent autologous stem cell transplantation has become an established therapeutic option in patients with MCL. Initial phase II studies showed a wide range of remission and 2-year survival rates (16%–100%), most likely because of the different time of transplantation (first remission vs relapsed disease) and other patient selection criteria. In a retrospective multivariate analysis, total body irradiation was an additional independent prognostic factor [37].
- In 1996, a prospective European Intergroup study was initiated to evaluate the impact of myeloablative radiochemotherapy with subsequent autologous stem cell transplantation in first remission after a CHOP-like regimen

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