Mantle Cell Lymphoma: Biology, Clinical Presentation, and Therapeutic Approaches

Martin Dreyling, MD, on behalf of the European MCL Network

OVERVIEW

Mantle cell lymphoma is molecularly characterized by the chromosomal translocation t(11;14) (q13;q32) that results in a constitutional overexpression of the cell cycle regulator protein cyclin D1. Generally, the disease is characterized by rapid relapses and poor long-term outcome. However, a subset of patients with indolent disease has been identified. Randomized trials have demonstrated the superiority of dose intensified, cytarabine-containing induction with or without autologous stem cell transplantation in younger patients. In elderly patients, a rituximab-based maintenance has significantly prolonged progression-free and overall survival after treatment with rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone (R-CHOP). Unfortunately, the vast majority of patients will eventually relapse. Numerous molecular targeting strategies (bortezomib, lenalidomide, temsirolimus, and especially inhibitors of the B-cell receptor pathway) have achieved high response rates in phase II studies and should be strongly considered in relapsed disease.

The diagnosis of mantle cell lymphoma (MCL) is established according to the criteria of the World Health Organization classification of hematologic neoplasms. In general, histologic confirmation of diagnosis is mandatory and a lymph node biopsy is strongly recommended; in contrast, lymph node fine-needle biopsy is not appropriate. A bone marrow aspiration complemented by flow cytometry are mandatory to quantify the percentage of infiltration and optionally identify the pathognomonic t(11;14) by fluorescence in situ hybridization. Most tumors have a classic morphology of small to medium sized cells with irregular nuclei, dense chromatin, and unapparent nucleoli. In addition, a blastoid variant of the disease has been described, characterized by high mitotic rate and particularly aggressive behavior, which is associated with INK4a/ARF deletions and TP53 mutations (Fig. 1). However, tumor cells may present with a spectrum of morphologic variants, raising some difficulties in the differential diagnosis apart from chronic lymphocytic leukemia, marginal zone lymphomas, large B-cell lymphomas, or blastic hematologic proliferations.

Besides the classical immunophenotype (immunoglobulin M/D, CD19, CD20, CD22, CD43, CD79a, CD5 positive, and CD23, CD10, CD200, BCL6 usually negative), the detection of cyclin D1 overexpression (immunohistochemistry) or the chromosomal translocation t(11;14) by fluorescence in situ hybridization is mandatory, since histomorphologic phenotypes may differ significantly. Nevertheless, rare cases of cyclin D1-negative variant of MCL have been recognized, characterized by the same gene expression profile and secondary genomic alterations as classical MCL. SOX11, a transcription factor expressed in 90% of MCL, might be helpful to identify these cyclin D1-negative variants.

Moreover, Ki67 proliferative index staining is strongly recommended as a powerful prognostic indicator of long-term outcome.

CLINICAL PRESENTATION AND PROGNOSTIC FACTORS

To define the stage of MCL, a computed tomography (CT) scan with iodine contrast of the neck, chest, abdomen, and pelvis is mandatory. PET scan is not included in the consensus recommendations, as a large majority of patients present with an advanced stage III to IV MCL because of frequent bone marrow and/or gastrointestinal involvement. Thus, only in the rare stage I to II patients may PET scan be applied to confirm early-stage disease and guide localized treatment. Similarly, endoscopy, based on up to 60% asymptomatic infiltration of the bowel, is recommended only in limited-stage or symptomatic patients. Cerebrospinal fluid evaluation is not usually required at first presentation, unless neurologic symptoms are present.

A specific prognostic score, the MCL International Prognostic Index (MIPI), allows one to discriminate three prognostic subgroups: the low-risk group with a 5-year median overall survival (OS) of 60%, and the intermediate- and the
high-risk group with a median OS of 51 and 29 months, respectively.4 This score takes into account four parameters (age, performance status, lactate dehydrogenase [LDH], and leukocyte count) was confirmed also in a simplified version. Since MIPI is highly applicable and has been validated in most independent series, its use should be routinely applied in clinical practice.3

TREATMENT

Indolent Mantle Cell Lymphoma

Although most patients with MCL follow an aggressive clinical course associated with rapid progression and a high recurrence rate, a minority of MCL cases (10% to 15%) will have an indolent behavior and may not need therapy for several years; a delayed treatment did not affect the OS in this low-risk group.5 Most of these patients present with normal serum LDH level, splenomegaly, bone marrow and blood involvement, but without major adenopathy. The individual diagnosis of such an indolent subtype is difficult, but a short observation period may be applied in the majority of low-burden patients.

Molecularly, indolent MCLs predominantly display hypermutated immunoglobulin genes, noncomplex karyotypes, and a peculiar gene expression profile. In contrast, the role of transcription factor SOX11 expression alone is not sufficient to predict prognosis.3,6,7

Elderly Patients

Based on a median age of 65 years at first diagnosis, the majority of patients does not qualify for dose-intensified regimens. The standard of care for elderly MCL patients consists of combined immunochemotherapy (rituximab-bendamustine [BR], R-CHOP; Table 1).8 The European MCL Network conducted an international phase III trial comparing R-CHOP with rituximab, fludarabine, and cyclophospham (R-FC) followed by a second maintenance randomization with either IFN-α or rituximab) in elderly patients.9 Unexpectedly, the outcome of the fludarabine-containing regimen was disappointing: although complete response (CR) rates after R-FC and R-CHOP were comparable (40% vs. 34%, p = 0.10), progressive disease was more frequent during R-FC (14% vs. 5%). The median OS was also significantly inferior after R-FC (4-year survival rate, 47% vs. 62%, p = 0.005) and more patients in the fludarabine arm died as a result of relapsed lymphoma or infections. This inferior outcome after R-FC is mostly due to long-lasting hematologic grade 3 to 4 toxicity. Thus, the use of upfront R-FC in elderly MCL patients is discouraged. In contrast, rituximab maintenance reduced the risk of progression or death by 45% (58% patients in remission after 4 years vs. 29% with IFN-α, p = 0.01), almost doubled duration of remission, and significantly improved OS among patients responsive to R-CHOP. Thus, rituximab maintenance (one dose every 2 months) should be offered to all patients responding to R-chemotherapy, especially R-CHOP.3

KEY POINTS

- Detection of cyclin D1 overexpression or t(11;14) is crucial for the correct diagnosis.
- Cell proliferation (Ki-67) and MIPI are established prognostic markers and should be applied in clinical routine.
- Standard of care in younger patients is a cytarabine-containing dose-intensified regimen (R-CHOP/R-DHAP followed by autologous stem cell transplantation and Hyper-CVAD).
- In elderly patients a combined immunochemotherapy (BR, R-CHOP) followed by rituximab maintenance should be applied.
- Molecular approaches (bortezomib, ibrutinib, temsirolimus [an mTOR inhibitor registered in Europe], lenalidomide) should be considered in relapsed disease.

FIG 1. Molecular pathogenesis (modified from Jares et al.43).
consolidation. Four cycles of R-CHOP followed by RIT consolidation compared favorably with historic results of six cycles of R-CHOP.  

Notably, in a randomized first-line trial with 94 MCL patients, the BR schedule was at least as effective as R-CHOP (median PFS 35 vs. 22 months, p ≤ 0.004), and fewer toxic effects (neutropenia, infections, polyneuropathy, and alopecia) were observed, but OS was comparable in both study arms. Thus, specifically in patients with comorbidities, BR may be preferred. 

The combination with cytarabine (R-BAC) has been recently achieved excellent results in primary and relapsed MCL (90% overall response rate (ORR), CR 83%), resulting in an excellent 2-year progression-free survival (PFS) of 70% and 95% in relapsed and first-line patients, respectively. However, a high rate of hematotoxicity has been observed; thus, only very fit patients prequalify for such an approach. 

Based on the excellent results of cytarabine in younger MCL patients, the MCL R2 Elderly trial randomly assigns patients to a standard induction with R-CHOP versus an alternating R-CHOP/R-HAD (rituximab, intermediate age-adjusted dose cytarabine, and dexamethasone) arm.

A rational algorithm for clinical management of MCL patients is presented in Fig. 2. 

### Younger Patients

Although no curative treatment is available for MCL so far, an intensive approach, for example, by an autologous stem cell transplant (SCT) has been demonstrated to induce higher response and survival rates in young and fit patients. Thus, in CHOP-responding patients, a consolidation with total-body irradiation (TBI), high-dose cyclophosphamide, and autologous SCT resulted in longer median PFS (39 vs. 17 months, p = 0.011) compared to a maintenance therapy with IFN-α. In a subsequent meta-analysis OS was also superior in the autologous SCT arm independent of the addition of rituximab. Such high-dose consolidation can be safely delivered in younger fit patients usually up to age 65.

The trials of the last decade established the role of a high-dose cytarabine-containing induction before an autologous SCT (Table 2). Based on several phase II studies, the recent European MCL Younger trial confirmed that an alternating induction of three courses of R-CHOP and rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) followed by myeloablative consolidation and subsequent autologous SCT achieved a significantly improved median time to treatment failure (TTF; 88 vs. 46 months, p = 0.038) and a trend for median OS (not reached vs. 83 months, p = 0.045) in comparison to an R-CHOP only induction followed by autologous SCT.

### TABLE 1. Conventional Immunochemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Features</th>
<th>Evaluable Patients</th>
<th>Therapeutic Regimen</th>
<th>ORR% (CR%)</th>
<th>Median PFS (Months)</th>
<th>2-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenz G et al. 2005</td>
<td>Phase III, randomized</td>
<td>112</td>
<td>CHOP vs. R-CHOP</td>
<td>75 (7) vs. 94 (34)</td>
<td>21 vs. 14 (TTF)</td>
<td>76% vs. 76%</td>
</tr>
<tr>
<td>Herold M et al. 2009</td>
<td>Phase III, randomized</td>
<td>90</td>
<td>MCP vs. R-MCP</td>
<td>63 (15) vs. 71 (32)</td>
<td>18 vs. 20 (TTF)</td>
<td>52% vs. 56% (50 months OS)</td>
</tr>
<tr>
<td>Gressin R et al. 2010</td>
<td>Phase II</td>
<td>113</td>
<td>Rituximab-VADC</td>
<td>73 (46)</td>
<td>16 (no ASCT)</td>
<td>58 (ASCT)**</td>
</tr>
<tr>
<td>Sachanas S et al. 2011</td>
<td>Phase II</td>
<td>20</td>
<td>Rituximab-chlorambucil</td>
<td>95 (90)</td>
<td>89% (3-yr PFS)</td>
<td>95% (3-yr OS)</td>
</tr>
<tr>
<td>Kluin-Nelemans et al. 2012</td>
<td>Phase III, randomized</td>
<td>485</td>
<td>Induction: R-CHOP vs. R-FC</td>
<td>86 (34) vs. 78 (40)</td>
<td>28 vs. 26 (TTF)</td>
<td>62% vs. 47% (4-yr OS)</td>
</tr>
<tr>
<td>Maintenance: rituximab vs. interferon alpha</td>
<td>-</td>
<td>58% vs. 29% (4-yr OS)</td>
<td>79% vs. 67% (4-yr OS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rummel et al. 2013</td>
<td>Phase III, randomized</td>
<td>514 (94 MCL)</td>
<td>R-CHOP vs. rituximab-bendamustine</td>
<td>91 (30)* vs. 93 (40)*</td>
<td>21 vs. 35</td>
<td>“No differences”*</td>
</tr>
<tr>
<td>Combinations with Moleculars</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruan et al. 2011</td>
<td>Phase II</td>
<td>36</td>
<td>R-CHOP + bortezomib</td>
<td>91 (72)</td>
<td>44% (2-yr PFS)</td>
<td>86%</td>
</tr>
<tr>
<td>Houot et al. 2012</td>
<td>Phase II</td>
<td>39</td>
<td>Rituximab, doxorubicin, dexamethasone, chlorambucil, bortezomib</td>
<td>79 (59)</td>
<td>26</td>
<td>69%</td>
</tr>
<tr>
<td>Smith et al. 2012</td>
<td>Phase II</td>
<td>50</td>
<td>R-CHOP + 90Y- ibritumumab tiuxetan</td>
<td>64 (46)</td>
<td>31 (TTF)</td>
<td>73% (5-yr OS)</td>
</tr>
</tbody>
</table>

* Data derived from the overall population of the study, not exclusively from patients with MCL (M. Rummel, personal communication).
** 49 patients received ASCT consolidation.

Abbreviations: ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; TTF, time to treatment failure; TTP, time to progression; DOR, duration of response; R, rituximab; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; BOP, bendamustine/vincristine/prednisone; COP, cyclophosphamide/vincristine/prednisone; VADC, vincristine/doxorubicin/dexamethasone/chlorambucil; FC, fludarabine/cyclophosphamide; ASCT, autologous stem cell transplantation.
Even more impressive, the rate of molecular remission increased from 32% to 73% after induction. In contrast, an induction based on high-dose cytarabine achieves only insufficient response rates. The applied conditioning regimens before autologous SCT are mainly BEAM or TBI-based. A retrospective European Group for Blood and Marrow Transplantation (EBMT) registry study of more than 400 patients suggested that TBI may benefit especially the PR patients after induction. In a retrospective study comparison of the Nordic, HOVON, and MCL Younger protocols, TBI was confirmed to be beneficial only in patients in partial remission. Taken together, these studies suggest that TBI should be strongly considered in patients in PR. In contrast, the benefit of RIT has not been demonstrated in interstudy comparisons.

Allogeneic Stem Cell Transplantation

The approach of allogeneic SCT in MCL emerged in the late 1990s, based on the cure of some relapsed/refractory patients with MCL. Reduced-intensity conditioning regimens (RIC-allo) with lower toxicity and reduced transplant-related mortality provided better long-term results. However, in none of these studies has allogeneic SCT been proven superior to autologous SCT. Thus, the current literature does not support its application in the first-line treatment of MCL. Whether an allogeneic SCT consolidation in first CR could be beneficial in very high-risk patients (blastoid variant, elevated Ki-67) is an intriguing hypothesis that has to be addressed in prospective trials.

### FIG 2. Therapeutic algorithm.

**FIG 2. Therapeutic algorithm.**

- **young patient (<65)**
  - First line treatment
    - dose-intensified immuno-chemotherapy (either sequential: R-CHOP/DHAP => PBSCT or R-Hyper-CVAD)
  - conventional immuno-chemotherapy (e.g. R-CHOP)
  - watch & wait? Rituximab monotherapy
  - R-Chlorambucil
  - BR

- **elderly patient (>65)**
  - conventional immuno-chemotherapy (e.g. R-CHOP)
  - Rituximab maintenance or radioimmunotherapy?

- **compromised patient**
  - high tumor load: immuno-chemotherapy (e.g. R-FC)
  - allo-transplant?
  - radioimmunotherapy?
  - Rituximab maintenance?

### 1. relapse

- immuno-chemotherapy (e.g. BR, R-FC)
  - +/-molecular approaches
  - autologous PBSCT
  - radioimmunotherapy?
  - Rituximab maintenance?

- Immuno-chemotherapy (e.g. BR)
  - molecular approaches

### higher relapse

- molecular approaches (BITL): Bortezomib, Ibrutinib, (Temsirolimus), Lenalidomide
  - (preferable in combination)
  - repeat previous therapy (long remissions)
Patients with Relapsed or Refractory Disease

Among younger patients, an autologous SCT approach should be offered only to those who did not receive an appropriate first-line therapy. On the other hand, allogeneic SCT, despite its high treatment-related mortality and relapse rates, remains the only curative approach in relapsed MCL and should be discussed in young fit patients relapsing after autologous SCT. Specifically, a nonmyeloablative approach without T-depletion is advisable, as this modification is also applicable in older patients.25,26 In younger patients without a human leukocyte antigen–matched donor, a haploidentical transplantation has achieved promising results in recent studies but is still experimental.27

Numerous targeted options in combination with rituximab-supplemented chemotherapy represent highly effective approaches in elderly patients.28 Second-line therapy should be adapted to the age and performance status of the patient. In fit patients non-cross-resistant drugs should be preferred as salvage treatment. Thus, after R-CHOP in first line, regimens containing rituximab, cytarabine, and/or bendamustine—possibly in combination with a molecular approach such as bortezomib, lenalidomide, or temsirolimus (an mTOR inhibitor registered in Europe)—may be considered (Table 3).29-38 Trials combining the proteasome inhibitor with R-CHOP; a doxorubicin, dexamethasone, chlorambucil, and rituximab regimen (RiPAD+C); or high-dose cytarabine regimens showed promising results.29-32 A tailored therapy concept, based on individual risk profile, may favor a cytarabine-based approach plus bortezomib or combined with bendamustine for fit patients with elevated Ki67 levels, whereas a bendamustine-based regimen in combination with temsirolimus or lenalidomide appears more suitable for elderly patients with a more indolent presentation.36,37 However, as these recommendations on tailored therapies are not evidence based, an enrollment of these patients in clinical trials is highly recommended.

On the other hand, in impaired patients or subsequent relapses, monotherapies with targeted drugs (in particular, bortezomib, ibrutinib, temsirolimus, or lenalidomide), as well as well tolerable combinations with rituximab, steroids, or low-dose chemotherapy and palliative radiotherapy should be considered.29,33-35,37,39 Oral palliative combinations, such as the metronomic PEP-C, could be also useful options in this setting.

Unfortunately, survival curves do not display any plateau in patients in relapse, and almost all patients will finally relapse. Limited data are available on rituximab maintenance

### TABLE 2. Dose-Intensified Immunochemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Features</th>
<th>Evaluable Patients</th>
<th>Therapeutic Regimen</th>
<th>ORR% (CR%)</th>
<th>Median PFS (Years)</th>
<th>Median OS (Years)</th>
<th>Dropout Rate</th>
<th>TRM</th>
<th>Secondary Tumors Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCT-Based Regimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dreyling et al. 2005</td>
<td>Phase III, randomized</td>
<td>122</td>
<td>CHOP ± R followed by ASCT vs. interferon-alpha</td>
<td>98 (81)</td>
<td>3.3 vs. 1.4</td>
<td>NR (83%) 3-yr OS vs. NR (77%) 3-yr OS</td>
<td>13% vs. na</td>
<td>5% vs. 0%</td>
<td>5%</td>
</tr>
<tr>
<td>Hermine et al. 2012</td>
<td>Phase III, randomized</td>
<td>455</td>
<td>R-CHOP ± ASCT vs. CHOP/R-DHAP + ASCT</td>
<td>98 (63)</td>
<td>3.8 vs. 7.3</td>
<td>6.8 vs. NR</td>
<td>na</td>
<td>4%</td>
<td>na</td>
</tr>
<tr>
<td>Damon et al. 2009</td>
<td>Phase II</td>
<td>77</td>
<td>R-CHOP + methotrexate + HD-arac/etoposide + ASCT</td>
<td>88 (69)</td>
<td>NR (56%) 5-yr PFS</td>
<td>NR (64%) 5-yr OS</td>
<td>13%</td>
<td>3%</td>
<td>na</td>
</tr>
<tr>
<td>Van't Veer et al. 2009</td>
<td>Phase II</td>
<td>87</td>
<td>R-CHOP + HD-arac + ASCT</td>
<td>70 (64)</td>
<td>NR (36%) 4-yr PFS</td>
<td>NR (66%) 4-yr OS</td>
<td>30%</td>
<td>5%</td>
<td>na</td>
</tr>
<tr>
<td>Geisler et al. 2012</td>
<td>Phase II</td>
<td>160</td>
<td>R-Maxi-CHOP + HD-arac + ASCT</td>
<td>96 (54)</td>
<td>7.4</td>
<td>NR (58%) 10-yr OS</td>
<td>9%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Delarue et al. 2013</td>
<td>Phase II</td>
<td>60</td>
<td>R-CHOP/R-DHAP + ASCT</td>
<td>100 (96)</td>
<td>6.9</td>
<td>NR (75%) 5-yr OS</td>
<td>18%</td>
<td>1.5%</td>
<td>18%</td>
</tr>
<tr>
<td>Touzeau et al. 2013</td>
<td>Retrospective</td>
<td>396</td>
<td>ASCT-based schedules</td>
<td>83 (71)</td>
<td>NR (67%) 3-yr PFS</td>
<td>NR (83%) 3-yr OS</td>
<td>ne</td>
<td>2.5%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-ASCT-Based Regimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romaguera et al. 2010</td>
<td>Phase II, monocentric</td>
<td>97</td>
<td>R-HyperCVAD</td>
<td>97 (87)</td>
<td>4.6</td>
<td>NR (64%) 10-yr OS</td>
<td>29%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Merli et al. 2012</td>
<td>Phase II, multicentric</td>
<td>60</td>
<td>R-HyperCVAD</td>
<td>83 (72)</td>
<td>NR (73%) 5-yr PFS</td>
<td>NR (61%) 5-yr OS</td>
<td>63%</td>
<td>6.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Bernstein et al. 2013</td>
<td>Phase II, multicentric</td>
<td>49</td>
<td>R-HyperCVAD</td>
<td>86 (55)</td>
<td>4.8</td>
<td>6.8</td>
<td>39%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Abbreviations:** ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; R, rituximab; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; TBI, total body irradiation; ASCT, autologous stem cell transplantation; DHAP, dexamethasone/cytarabine/cisplatin; HD-arac, high-dose cytarabine; HyperCVAD, hyperfractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone + methotrexate/cytarabine; NR, not reached; na, not available; ne, not evaluable.
in patients in relapse, and data of RIT consolidation are based on smaller series. The manageable toxicity and oral formulation of lenalidomide, along with its efficacy, make this drug also an attractive option in the context of maintenance regimens, either alone or in combination with rituximab.33-35

In addition, despite some concerns about its cumulative neurotoxicity, bortezomib maintenance is currently tested in young patients after autologous SCT.

### TABLE 3. Targeted Salvage Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Features</th>
<th>Evaluable Patients</th>
<th>Therapeutic Regimen</th>
<th>ORR% (CR%)</th>
<th>Median PFS (Months)</th>
<th>Median OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proteasome Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goy et al. 2009</td>
<td>Phase II</td>
<td>141</td>
<td>Bortezomib</td>
<td>33 (8)</td>
<td>6.7 (TTP)</td>
<td>23.5</td>
</tr>
<tr>
<td>Baiocchi et al. 2011</td>
<td>Phase II</td>
<td>13</td>
<td>Bortezomib, rituximab</td>
<td>29 (29)</td>
<td>1.9</td>
<td>na</td>
</tr>
<tr>
<td>Lamm et al. 2011</td>
<td>Phase II</td>
<td>16</td>
<td>Bortezomib, rituximab, dexamethasone</td>
<td>81 (44)</td>
<td>12.1</td>
<td>38.6</td>
</tr>
<tr>
<td>Weigert et al. 2009</td>
<td>Retrospective</td>
<td>8</td>
<td>Rituximab, high-dose cytarabine, dexamethasone, bortezomib</td>
<td>50 (25)</td>
<td>5</td>
<td>15.5</td>
</tr>
<tr>
<td>Gerecitano et al. 2011</td>
<td>Phase I</td>
<td>10</td>
<td>Rituximab, cyclophosphamide, prednisone, bortezomib</td>
<td>60 (50)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Friedberg et al. 2011</td>
<td>Phase II</td>
<td>7</td>
<td>Bendamustine, rituximab, bortezomib</td>
<td>71 (na)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Kouroukis et al. 2011</td>
<td>Phase II</td>
<td>25</td>
<td>Bortezomib, gemcitabine</td>
<td>60 (11)</td>
<td>11.4</td>
<td>na</td>
</tr>
<tr>
<td>Zinzani et al. 2013</td>
<td>Phase II</td>
<td>57</td>
<td>Lenalidomide</td>
<td>35 (12)</td>
<td>8.8</td>
<td>NR</td>
</tr>
<tr>
<td>Goy et al. 2013</td>
<td>Phase II</td>
<td>134</td>
<td>Lenalidomide</td>
<td>28 (8)</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Wang et al. 2012</td>
<td>Phase II</td>
<td>44</td>
<td>Lenalidomide, rituximab</td>
<td>57 (36)</td>
<td>11.1</td>
<td>24.3</td>
</tr>
<tr>
<td>Zaja et al. 2012</td>
<td>Phase II</td>
<td>33</td>
<td>Lenalidomide, dexamethasone</td>
<td>52 (24)</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Harel et al. 2010</td>
<td>Retrospective</td>
<td>58</td>
<td>Thalidomide ≥ bortezomib ≥ rituximab</td>
<td>50 (21)</td>
<td>NR (1-yr TTF 29%)</td>
<td>NR (1-yr OS 62%)</td>
</tr>
<tr>
<td>Ruan et al. 2010</td>
<td>Phase II</td>
<td>22</td>
<td>Metronomic prednisone, etoposide, procarbazine, cyclophosphamide, rituximab, thalidomide</td>
<td>73 (32)</td>
<td>10</td>
<td>NR (2-yr OS 65%)</td>
</tr>
<tr>
<td><strong>Immunomodulatory Drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witzig et al. 2005</td>
<td>Phase II</td>
<td>34</td>
<td>Temsirolimus</td>
<td>38 (3)</td>
<td>6.5 (TTP)</td>
<td>12</td>
</tr>
<tr>
<td>Ansell et al. 2008</td>
<td>Phase II</td>
<td>27</td>
<td>Temsirolimus</td>
<td>41 (4)</td>
<td>6 (TTP)</td>
<td>14</td>
</tr>
<tr>
<td>Hess et al. 2009</td>
<td>Phase III, randomized</td>
<td>54</td>
<td>Temsirolimus 175 mg/75 mg</td>
<td>22 (2)</td>
<td>4.8</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>54</td>
<td>Temsirolimus 175 mg/25 mg</td>
<td>6 (0)</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>53</td>
<td>Investigator’s choice</td>
<td>2 (2)</td>
<td>1.9</td>
</tr>
<tr>
<td>Ansell et al. 2011</td>
<td>Phase II</td>
<td>69</td>
<td>Temsirolimus, rituximab</td>
<td>59 (19)</td>
<td>9.7</td>
<td>29.5</td>
</tr>
<tr>
<td>Renner et al. 2012</td>
<td>Phase II</td>
<td>35</td>
<td>Everolimus</td>
<td>20 (6)</td>
<td>5.5</td>
<td>na</td>
</tr>
<tr>
<td><strong>mTOR Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. 2013</td>
<td>Phase II</td>
<td>111</td>
<td>Ibrutinib</td>
<td>68 (21)</td>
<td>13.9</td>
<td>NR (1.5-yr OS 58%)</td>
</tr>
<tr>
<td>Kahl et al. 2010</td>
<td>Phase I</td>
<td>16</td>
<td>Cal-101</td>
<td>62 (na)</td>
<td>3 (DOR)</td>
<td>na</td>
</tr>
<tr>
<td>Wang et al. 2009</td>
<td>Phase II</td>
<td>32</td>
<td>90Y-ibritumumab tiuxetan</td>
<td>31 (16)</td>
<td>6 (EFS)</td>
<td>21</td>
</tr>
<tr>
<td>Ferrero et al. 2013</td>
<td>Phase II</td>
<td>15*** +</td>
<td>90Y-ibritumumab tiuxetan</td>
<td>40 (20)</td>
<td>3.7</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30***</td>
<td></td>
<td>72 (38)</td>
<td>8.9</td>
<td>32.2</td>
</tr>
<tr>
<td>Morschhauser et al. 2013</td>
<td>Phase II</td>
<td>40 (15 MCL)</td>
<td>GA-101</td>
<td>27 (13)</td>
<td>2.7*</td>
<td>na</td>
</tr>
<tr>
<td>Viardot et al. 2010</td>
<td>Phase I</td>
<td>7</td>
<td>Blinatumomab</td>
<td>43 (14)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td><strong>BCR Signaling Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. 2009</td>
<td>Phase II</td>
<td>32</td>
<td>90Y-ibritumumab tiuxetan</td>
<td>31 (16)</td>
<td>6 (EFS)</td>
<td>21</td>
</tr>
<tr>
<td>Ferrero et al. 2013</td>
<td>Phase II</td>
<td>15*** +</td>
<td>90Y-ibritumumab tiuxetan</td>
<td>40 (20)</td>
<td>3.7</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30***</td>
<td></td>
<td>72 (38)</td>
<td>8.9</td>
<td>32.2</td>
</tr>
<tr>
<td>Morschhauser et al. 2013</td>
<td>Phase II</td>
<td>40 (15 MCL)</td>
<td>GA-101</td>
<td>27 (13)</td>
<td>2.7*</td>
<td>na</td>
</tr>
<tr>
<td>Viardot et al. 2010</td>
<td>Phase I</td>
<td>7</td>
<td>Blinatumomab</td>
<td>43 (14)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td><strong>Various</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al. 2010</td>
<td>Phase I</td>
<td>10****</td>
<td>Flavopiridol, fludarabine, rituximab</td>
<td>80 (70)</td>
<td>21.9</td>
<td>na</td>
</tr>
<tr>
<td>Holkova et al. 2011</td>
<td>Phase I</td>
<td>6</td>
<td>Flavopiridol, bortezomib</td>
<td>33 (17)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Davids et al. 2013</td>
<td>Phase I</td>
<td>32 (8 MCL)</td>
<td>ABT-199</td>
<td>100 (0)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Evens et al. 2012</td>
<td>Phase II</td>
<td>11</td>
<td>Abexinostat</td>
<td>27 (na)</td>
<td>4</td>
<td>na</td>
</tr>
</tbody>
</table>

*** Fifteen patients received the antibody as relapse monotherapy, 30 patients as consolidation after salvage treatment.

**** Six patients received the schema as first-line therapy.

Abbreviations: ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; TTF, time to treatment failure; TTP, time to progression; DOR, duration of response; EFS, event-free survival; NR, not reached; na, not available.
Innovative Molecular Targeted Approaches

The growing insights into the molecular biology of MCL led to the systematic exploration of targeted approaches.\textsuperscript{28} Many new compounds have been tested in relapsed MCL (Table 3).

Bruton’s tyrosine kinase (BTK) is an essential component of the B-cell–receptor signaling pathway; its covalent oral inhibitor ibrutinib showed durable single-agent efficacy in relapsed or refractory MCL.\textsuperscript{29} The impressive data from an international phase II trial on heavily pretreated MCL patients described great efficacy and excellent tolerability: ORR was 68% (21% CR) with a median duration of response of 17.5 months and a median PFS of 13.9 months. Moreover, the most common adverse events were mild or moderate diarrhea, fatigue, and nausea. Grade 3 or higher hematologic events were infrequent and included neutropenia (16%), thrombocytopenia (11%), and anemia (10%). These impressive results led to its breakthrough designation for relapsed MCL. Results of phase III trials are eagerly awaited comparing ibrutinib versus temsirolimus in patients who relapsed and assessing a BR schedule with or without ibrutinib in first line.

Another inhibitor of the BCR signal cascade, the specific PI3K inhibitor idelalisib achieved also a promising ORR of 62% in relapsed MCL patients, but duration of remission seems to be limited.

New monoclonal anti-CD20 antibodies, such as obinutuzumab and ofatumumab, are currently being investigated in clinical trials, but data in MCL are still limited.\textsuperscript{40} Other intriguing approaches are the bispecific anti-CD19/anti-CD3 mAB, showing a high efficacy particularly in MCL patients.\textsuperscript{41}

Two cell-cycle-targeted drugs, flavopiridol and PD0332991 (direct inhibitors of cyclin-dependent kinase 4 and 6), also showed activity in relapsed MCL alone and in combination with fludarabine, rituximab, or bortezomib. Finally, promising results have been recently reported for an oral second-generation BCL-2 specific BH3 mimetic ABT-199.\textsuperscript{42}

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

Employment or Leadership Position: None. Consultant or Advisory Role: Martin H. Dreyling, Bayer; Celgene; Janssen Oncology; Pfizer. Stock Ownership: None. Honoraria: Martin H. Dreyling, Celgene; Janssen Oncology; Pfizer; Roche. Research Funding: Martin H. Dreyling, Celgene; Janssen Oncology; Mundipharma; Pfizer; Roche. Expert Testimony: None. Other Remuneration: None.

References


vival of mantle cell lymphoma after intensive front-line immunoche-
CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C
Containing Myeloablative Regimen and Autologous Stem Cell Trans-
plantation (ASCT) Increases Overall Survival When Compared to 6
Courses of CHOP Plus Rituximab Followed by Myeloablative Ra-
diochemotherapy and ASCT in Mantle Cell Lymphoma: Final Analysis
of the MCL Younger trial of the European Mantle Cell Lymphoma Net-
rituximab is not enough in first-line treatment of mantle cell lymphoma
with high proliferation: early closure of the Nordic Lymphoma Group
18. Hoster E, Geisler GH, Doorduijn JK, et al. Role Of High-Dose Cytara-
19. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable re-
missions after treatment of newly diagnosed aggressive mantle-cell lym-
alternating with high dose cytarabine and methotrexate for the initial
hyperCVAD MTX/Ara-C and rituximab in patients with previously un-
22. Le Gouill S, Callanan M, Macintyre E, et al. Clinical, Metabolic and Mo-
lecular Responses After 4 Courses of R-DHAP and After Autologous
Stem Cell Transplantation for Untreated Mantle Cell Lymphoma Pa-
ients Included in the LyMa trial, a Lysa Study. Blood. 2012;120 (suppl): 152.
23. Khouri IF, Lee MS, Romaguera J, et al. Allogeneic hematopoietic trans-
plantation for mantle-cell lymphoma: molecular remissions and evi-
allogeneic stem cell transplantation for relapsed/refractory mantle cell
transplantation for chemotherapy-unresponsive mantle cell lymphoma:
a cohort analysis from the center for international blood and mar-
Clofarabine and HLA-Haploidentical Hematopoietic Stem Cell Trans-
28. Pérez-Galán P, Dreiling M, Wiestner A. Mantle cell lymphoma: biol-
ogy, pathogenesis, and the molecular basis of treatment in the genomic
29. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with re-
lapsed or refractory mantle cell lymphoma: updated time-to-event anal-
high dose cytarabine and bortezomib has activity in multiply relapsed and refractory mantle cell lymphoma - long-term results of a multi-
for previously untreated diffuse large B-cell lymphoma and mantle cell
bortezomib, doxorubicin, dexamethasone and chlorambucil (RiPAD +
33. Zinzani PL, Vose JM, Czuczman MS, et al. Long-term follow-up of le-
nalidomide in relapsed/refractory mantle cell lymphoma: subset analy-
tients with mantle-cell lymphoma who relapsed or progressed after or
were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol. 2013;31:3688-3695.
35. Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combina-
tion with rituximab for patients with relapsed or refractory mantle-cell
and Rituximab As First-Line Therapy For Patients > 65 Years With Man-
tle Cell Lymphoma: Results From The Phase I Portion Of The Nordic
tensirolimus compared with investigator’s choice therapy for the treat-
39. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in re-
(GA101) monotherapy in relapsed/refractory diffuse large B-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN
Inhibitor ABT-199 (GDC-0199) In Patients With Relapsed/Refractory
(R/R) Non-Hodgkin Lymphoma (NHL): Responses Observed In All