REVIEW ARTICLE

Drugs 2007; 67 (12): 1689-1702
0012-6667/07/0012-1689/$49.95/0

Current Management of Mantle Cell Lymphoma

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Contents

Abstract

Mantle cell lymphoma is a rare yet well defined subtype of B-cell non-Hodgkin's lymphoma. The correct histological diagnosis of this lymphoma subtype is of the utmost importance; however, it is also a very difficult diagnosis. Clinical management is often complex, and despite the successful introduction of monoclonal antibodies and dose-intensified regimens, including autologous and allogeneic stem cell transplantation strategies, the prognosis remains particularly poor. Recently gained insights into the underlying biology and pathogenesis have unravelled numerous promising molecular targeting strategies; however, their introduction into clinical practice and current treatment algorithms remains a challenge. This article addresses these issues providing relevant information for current state-of-the-art management of patients with mantle cell lymphoma and giving a perspective of upcoming treatment strategies.

Mantle cell lymphoma (MCL) is a well defined, clinicopathological subtype of B-cell non-Hodgkin's lymphoma within the WHO classification[1]

and accounts for 5–10% of all lymphoid malignancies with an incidence of 2–3/100 000.[2]

The abbreviation MCL may also denote 'most challenging lymphoma' because of several specific and unique features of this particular lymphoma. The correct histological diagnosis is demanding to make, often requiring an expert haematopathologist. Clinical management is often complex with no worldwide accepted standard of care. Despite the successful introduction of monoclonal antibodies and dose-intensified regimens, prognosis remains particularly poor with a median overall survival (OS) of only 3–4 years and fewer than 10% long-term survivors.[3] Recently gained insights into the underlying biology and pathogenesis have unravelled numerous promising molecular targeting strategies; however, their introduction into clinical practice and current treatment algorithms remains a challenge.

This review addresses these issues, providing relevant information for decision making in clinical practice and a perspective on upcoming management strategies.

1. Histopathology, Immunophenotype, Cyto- and Molecular Genetics

MCL presents with a broad cytological and histological spectrum, which may hamper the diagnosis based on morphology alone. The growth pattern of MCL may be diffuse, nodular or mantle zone, commonly composed of small- to medium-sized lymphoid cells, with irregular or 'cleaved' nuclei. Recently, the European MCL Network reviewed 304 cases of MCL: in addition to the known cytological subtypes of classical (87.5%), small cell (3.6%), pleomorphic (5.9%) and blastic (2.6%), new pleomorphic subgroups were identified with mixtures of cells (classical + pleomorphic type; 1.6%) or transitions (classical/pleomorphic type; 1.6%); however, in contrast to previous reports, the morphological appearance does not seem to be a valid prognostic or predictive factor.[4]

The immunophenotype of MCL resembles that of a mature B cell (CD10−, CD19+, CD20+, CD22+, CD79a+) with coexpression of the T-cell antigen CD5; in contrast to chronic lymphocytic leukaemia (CLL), cells typically do not express CD23.

The genetic hallmark of MCL is the translocation t[11;14](q13;q32), which can be detected by classical cytogenetics or fluorescence *in situ* hybridisation (FISH) analysis, with most of the breakpoints occurring at the major translocation cluster. The gene of cyclin D1 (*bcl-1*) on chromosome 11q13 is brought under the control of the enhancer of the immunoglobulin heavy chain locus on 14q32. Resultant overexpression of this cell-cycle regulator protein may be detected by cyclin D1 staining in the large majority of patients, which led to the general acceptance of this lymphoma entity.[1]

It is still under debate whether cases of atypical CLL with t[11;14] represent a different disease entity. On the other hand, cases of t[11;14]-negative MCL have been reported, which display a similar clinical course to classical MCL.[5]

2. Underlying Biology and Pathogenesis

Although still not completely understood, increasing insights into the underlying biology and pathogenesis of MCL have been gained recently. Considering upcoming molecular targeted strategies, this issue will be of increasing interest in the near future.

Increased levels of cyclin D1 assembled with cyclin-dependent kinase 4 and 6 dysregulate the cell cycle by phosphorylation of the retinoblastoma protein, thereby promoting G1→S phase transition. Furthermore, this complex sequesters p27, thereby disinhibiting the cyclin E/cyclin-dependent kinase (CDK)2 complex, also resulting in acceleration of cell-cycle progression. In a substantial proportion of MCL patients, decreased levels of inhibitors of CDK4 and 6, such as $p16^{INK4a}$, can be detected. The gene for $p16^{INK4a}$ is located on chromosome 9p21 and about 20% of MCL patients carry homogenous deletions of this region. Typically, those patients have MCL, which is characterised by blastoid morphology and an even more aggressive clinical behaviour. Interestingly, the gene locus on 9p21 not only encodes for p16 but also for another protein, p14, which is involved in the DNA damage response. Decreased levels of p14 results in increased MDM2 (mouse double minute 2 homologue)-mediated p53 degradation. Furthermore, the *ATM* (ataxia telangiectasia mutated) gene on chromosome 11q22–23 is mutated in up to 75% of patients also resulting in

impaired p53-mediated cell-cycle arrest, DNA repair and apoptosis. Taken together, the pathogenesis of MCL is characterised by simultaneous disruption of cell-cycle regulation and DNA damage response.[6]

3. Clinical Presentation, Making the Diagnosis and Prognostic Factors

MCL is a rare disease with an incidence of about 2–3/100 000, accounting for 5–10% of non-Hodgkin's lymphomas. It is typically a disease of the elderly with a male predominance (male-to-female ratio 3–4 **:** 1). The majority of patients present with advanced-stage disease (Ann Arbor stage III/IV) at initial diagnosis. MCL is characterised by a relatively steep, continuously declining survival curve, with a median survival of about 4 years and with fewer than 15% long-term survivors,[3] rendering it a lymphoma subtype of particularly poor prognosis.

As with other malignant lymphomas, diagnosis of MCL requires tissue diagnosis, preferably by excisional lymph node biopsy, ideally evaluated by an expert haematopathologist. In addition to typical morphology and immunophenotype, staining for cyclin D1 is frequently helpful to confirm the diagnosis and further cytogenetics (either classical or FISH) is rarely required in routine clinical practice.[7] More than 90% of patients present with extranodal manifestations, thus bone marrow aspiration and biopsy is mandatory. A substantial proportion (up to 77%) of patients will have evidence of circulating MCL cells detected either by peripheral blood smear or flow cytometry.[8] For initial staging of advanced-stage disease we usually recommend endoscopy only if clinical symptoms are suggestive for infiltration. In a prospective trial, 26% of patients with MCL presented with gastrointestinal (GI) symptoms at the time of diagnosis; however, MCL infiltration was present histologically in the lower GI tract in 88% of patients and in the upper GI tract in 43% of patients.[9] As the use of aggressive staging evaluation of the GI tract was found to have little impact on patient management, we normally recommend a further invasive diagnostic work-up only for confirmation of early-stage disease or control of remission after therapy. CNS involvement has only been rarely described (4% of cases),[10] and was usually associated with advanced, often leukaemic, disease and neurological symptoms.[11] Considering the limited efficacy of prophylactic[12] as well as therapeutic treatment,[10] we commonly recommend examination of cerebrospinal fluid (CSF) only in patients with neurological abnormalities.

Clinical features associated with adverse prognosis are advanced-stage disease, occurrence of B symptoms (such as fever >38°C; unintentional weight loss of >10% of normal bodyweight over a period of ≤6 months; drenching sweats, especially at night) and poor performance status.[13] In contrast, younger age (<65 years), normal serum lactic dehydrogenase levels as well as normal β2-microglobulin levels seem to be associated with a better outcome.[14] The value of the International Prognostic Index seems to be only of limited additional impact.[15] In contrast, minimal residual disease seems to be a strong prognostic factor in patients with MCL following high-dose therapy and autologous haematopoietic stem cell transplantation (HSCT).[16] However, data on combined immunochemotherapy are contradictory.[17]

Highly interesting data have been obtained by gene expression analysis. Certain proliferation signatures identified patient subsets that differed by >5 years in OS.[5] The prognostic role of cell proliferation was verified by a large clinicopathological study of prospective clinical trials performed by the European MCL Network: a high mitotic index and a high Ki-67 were associated with a poor survival probability. Multivariate analysis confirmed the central prognostic role of cell proliferation and its superiority to all other histomorphological and clinical criteria.[4]

4. Treatment Strategies

Considering the aggressive clinical course in the majority of patients and the poor OS prognosis, a watch-and-wait strategy should not usually be pursued.

4.1 Limited-Stage Disease

As expected, the small subgroup of patients presenting with limited-stage disease has a better OS (median 6.8 years).[18] Interestingly, MCL cells *in vitro* are characterised by high radiosensitivity.[19] The available data suggest an important role for

radiotherapy in patients with limited-stage disease. In a retrospective analysis including patients with stage IA or IIA non-bulky MCL, the initial use of radiotherapy (mostly involved field) with or without cytostatic chemotherapy significantly improved progression-free survival (PFS) [5-year PFS 68% vs 11%]. While results for OS did not reach statistical significance, there was a plateau in the PFS curve at 60% and 6 of 17 patients were alive without progression at >5 years.[18]

However, as the vast majority of patients present with advanced-stage disease, systemic therapy is usually warranted.

4.2 Conventional Cytostatic Chemotherapy

Conventional mono- or polychemotherapy does not provide long-term control of the disease and remains a non-curative approach. In the only randomised trial, no advantage of the anthracycline-containing CHOP regimen (cyclophosphamide, vincristine, doxorubicin, prednisone) in comparison to a non-anthracycline combination (COP) [cyclophosphamide, vincristine, prednisone] was detectable.[20] In contrast, a retrospective study suggested superiority of anthracycline-containing regimens in patients with a low and low-intermediate risk profile according to the International Prognostic Index.[21] However, because of the aggressive clinical course of MCL, many clinicians favour CHOP-like or even more intensive regimens.

In recent years the purine analogues such as fludarabine[22] and cladribine[23] have been recognised as highly active and possibly less toxic compounds. While fludarabine monotherapy demonstrated only moderate efficacy in MCL, fludarabine-containing regimens with either alkylating agents or anthracyclines have been successfully applied in the first-line setting[24,25] or for relapsed disease;[26,27] the addition of rituximab yielded improved treatment results in the first randomised trials [27,28] (table I). However, haematological toxicity and even stem cell toxicity have to be considered, especially for patients who are potential candidates for autologous stem cell harvest.

Another highly interesting agent is the nitrogen mustard compound bendamustine, which is chemically related to the alkylating agents chlorambucil and cyclophosphamide. By replacing the benzene ring in the chlorambucil molecule with a benzimidazole ring, bendamustine may also act as a purine analogue, yielding a unique activity profile. While bendamustine was available in the German Demo-

Table I. Efficacy of fludarabine-containing regimens for mantle cell lymphoma

Study (year)	Regimen	No. of pts	Disease status	OR (CR) [%]
Flinn et al.[29] (2000)	Fludarabine 20 mg/m^2/d × 5	10	First-line	80 (40)
	Cyclophosphamide 600 mg/m^2/d × 1			
Zinzani et al.[25] (2000)	Fludarabine 25 mg/m^2/d × 3	18	First-line	61 (33)
	Idarubicin 12 mg/m^2/d × 1			
Cohen et al.[30] (2001)	Fludarabine 20–25 mg/m^2/d × 3	30	First-line and	63 (30)
	Cyclophosphamide 600 mg/m^2/d × 1		relapsed	
Seymour et al.[26] (2002)	Fludarabine 30 mg/m^2/d × 2	8	Relapsed	88[a]
	Cisplatin 25 mg/m^2/d × 4			
	Cytarabine 500 mg/m^2/d × 2			
Forstpointner et al.[28] (2004)	Fludarabine 25 mg/m^2/d × 3	50	Relapsed	46 vs 58 (0 vs 29)
	Cyclophosphamide 200 mg/m^2/d × 3			
	Mitoxantrone 8 mg/m^2/d × 1			
	± Rituximab 375 mg/m^2/d × 1			
Thomas et al.[27] (2005)	Fludarabine 25 mg/m^2/d × 3 (or fludarabine 40 mg/m/d orally)	16	Relapsed	75 (56)
	Cyclophosphamide 250 mg/m^2/d × 3			
	± Rituximab 375 mg/m^2/d × 1			

a CR not reported, data from subgroup analysis.

CR = complete response rate; **OR** = overall response rate; **pts** = patients.

cratic Republic for decades, it is now recognised as a highly active and well tolerated agent in the treatment of a variety of lymphoid malignancies, including MCL. A randomised phase III trial in patients with indolent Non-Hodgkin's lymphoma and MCL demonstrated that bendamustin can efficaciously and safely replace cyclophosphamide in combination with vincristine and prednisone (BOP vs COP).[31] In an initial phase II trial, bendamustin in combination with rituximab showed an overall response rate (OR) of 75% with a complete response rate (CR) of 50% in 16 patients with relapsed or refractory MCL.[32] In addition, preliminary data from the German Low Grade Lymphoma Study Group (GLSG) indicate, that even in rituximab pretreated patients with relapsed and refractory lymphoma including 14 with MCL, bendamustine in combination with mitoxantrone and rituximab was well tolerated and highly effective with an OR of 93% and a CR of 40%.[33]

4.3 Dose-Intensified Regimens

Various study groups have reported promising results for high-dose, cytarabine-containing regimens. In a French trial, the DHAP regimen (dexamethasone, high-dose cytarabine, cisplatin) was given as salvage therapy for patients who did not achieve a CR after four cycles of CHOP. Of 25 patients, all but two responded, the CR was 84%.[34] Another even more dose-intensified regimen of HyperCVAD/MA (fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone; alternated with high-dose methotrexate and cytarabine) was introduced by the M.D. Anderson group and demonstrated a CR of 38% and a partial response of 55.5% after four cycles in 45 patients with previously untreated as well as relapsed or refractory MCL.[35] Originally, both DHAP and HyperCVAD protocols were applied as cytoreduction before consolidating myeloablative therapy followed by autologous HSCT. Meanwhile, even more impressive results have been reported when rituximab was combined with either the DHAP regimen[36] or the HyperCVAD/MA regimen[37] without autologous HSCT.

4.4 Autologous Stem Cell Transplantation

Myeloablative regimens followed by mandatory autologous stem cell rescue were initially investigated in small phase II trials.[38-43] In summary, these results suggested that patients in their first remission[44] gained the most benefit from this approach.

Thus, the European MCL Network conducted the first randomised trial to address the value of consolidating myeloablative radiochemotherapy (total body irradiation plus high-dose cyclophosphamide) followed by autologous HSCT versus interferon (IFN)-α maintenance therapy after initial CHOP-like induction therapy. Of the 122 patients, 62 proceeded to autologous HSCT and 60 received IFNα. Patients in the autologous HSCT arm experienced a significantly longer PFS with a median of 39 months compared with 17 months ($p = 0.0108$) [figure 1]. However, a longer follow-up is needed to determine the effect on OS (3-year OS was 83% vs 77%).[45] Thus, myeloablative radiochemotherapy followed by autologous HSCT represents one of the standard therapeutic options in the first-line treatment of younger patients without significant co-morbidity.

4.5 Monoclonal Antibodies

Rituximab targets CD20, which is expressed on virtually all B-cell lymphomas and is absent on plasma and haematopoietic stem cells. Rituximab is a chimeric IgG_1 antibody that induces antibody-

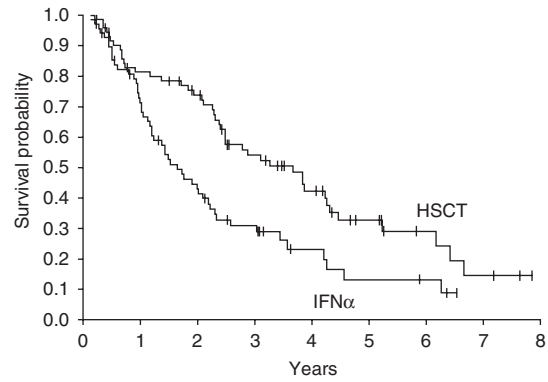


Fig. 1. Progression-free survival for patients with advanced-stage mantle cell lymphoma treated with autologous haemoatopoietic stem cell transplantation (HSCT) vs interferon (IFN)-α maintenance therapy after initial CHOP-like (cyclophosphamide, vincristine, doxorubicin, prednisone) induction therapy (update of Dreyling et al.[45]).

Table II. Important clinical trials evaluating cytostatic chemotherapy combined with rituximab in mantle cell lymphoma (MCL)

Study (year)	Phase, disease status	Regimen	No. of pts	Results
Howard et al.[17] (2002)	II, newly diagnosed MCL	CHOP + rituximab	40	CR/CRu: 40% PR: 48% Median PFS: 16.6mo
Lenz et al.[53] (2005)	III, newly diagnosed MCL	CHOP ± rituximab (followed by IFNα maintenance vs autologous HSCT)	122	CR: 34% vs 7% PR: 60% vs 68% No significant difference in PFS Median TTF: 21 vs 14mo
Forstpointner et al.[28] (2004)	III, relapsed or refractory MCL	FCM ± rituximab (followed by observation vs rituximab maintenance)	40	CR: 29% vs 0% PR: 29% vs 46% Median PFS: 8 vs 4mo Median OS: NR vs 11mo
Romaguera et al.[37] (2005)	II, newly diagnosed MCL	HyperCVAD/MA + rituximab	97	CR/CRu: 87% PR: 10% 3y FFS: 64% 3y OS: 82%
de Guibert et al.[36] (2006)	II, newly diagnosed MCL	DHAP + rituximab (followed by autologous HSCT)	24	CR/CRu: 92% PR: 4% 3y EFS: 65% 3y OS: 63%

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; **CR** = complete response rate; **CRu** = complete response unconfirmed rate; **DHAP** = dexamethasone, high-dose cytarabine, cisplatin; **EFS** = event-free survival; **FCM** = fludarabine, cyclophosphamide, mitoxantrone; **FFS** = failure-free survival; **HSCT** = haematopoietic stem cell transplantation; **HyperCVAD/MA** = fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone; alternated with high-dose methotrexate and cytarabine; **IFNα** = interferon-α; **NR** = not reported; **OS** = overall survival; **PFS** = progression-free survival; **PR** = partial response rate; **pts** = patients; **TTF** = time to treatment failure.

dependent cellular cytotoxicity and complement-dependent cytotoxicity. In addition, intracellular signalling may contribute to its efficacy; however, the exact *in vivo* function of CD20 is still unknown.[46]

Several trials have confirmed that single-agent rituximab has only moderate activity in MCL. In a relatively large trial, patients were treated with standard rituximab induction (375 mg/m^2/week × 4 weeks) at initial diagnosis or in relapse; the OR was 27% and the CR was 2%. In responders, rituximab maintenance failed to demonstrate a statistically significant benefit compared with observation only.[47] Despite its moderate efficacy, rituximab monotherapy remains a valuable therapeutic option for patients with strict contraindications for systemic chemotherapy or significant co-morbidity, because of its excellent toxicity profile.

Other monoclonal antibodies, either chimeric or even fully humanised, targeting a variety of epitopes in addition to CD20,[48] such as CD22,[49,50] CD80[51] or human leukocyte antigen (HLA)-DR,[52] are currently being investigated in preclinical and clinical trials; however, data for MCL are still scarce.

4.6 Immunochemotherapy

After promising results from phase II trials,[17] rituximab in combination with polychemotherapy has been investigated in several phase II and III clinical trials (table II). The European MCL Network conducted a randomised trial comparing the combination of CHOP and rituximab (R-CHOP) with CHOP alone enrolling 126 patients with previously untreated advanced-stage MCL. R-CHOP was significantly superior to CHOP in terms of OR (94% vs 75%; p = 0.0054), CR (34% vs 7%; p = 0.00024), and time to treatment failure (median, 21 vs 14 months; p = 0.0131); however, a longer follow-up is needed to evaluate the impact on OS.[53] Importantly, there was no clinically significant additional toxicity. Similar results have been reported in a smaller clinical phase III trial.[54]

Immunochemotherapy as salvage therapy has also been addressed in a randomised trial. Patients with relapsed or refractory MCL were assigned to

the fludarabine-containing regimen FCM (fludarabine, cyclophosphamide, mitoxantrone) alone or combined with rituximab (R-FCM). The addition of rituximab not only improved the OR (58% vs 46%) and the CR (29% vs 0%), but, even more importantly, significantly prolonged OS (p = 0.0042).[28] Interestingly, in this trial, the addition of rituximab as maintenance therapy also improved the 3-year PFS from 9% to 45%.[55] It has been shown that rituximab maintenance is effective after salvage with rituximab chemotherapy and prolongs response duration in patients with relapsed or refractory MCL.[56]

Rituximab, in addition to the dose-intensified regimen HyperCVAD/MA, was investigated in a large but non-randomised trial in patients with previously untreated MCL. Of 97 assessable patients, 97% responded and 87% achieved a CR or an unconfirmed CR. With a median follow-up time of 40 months, the 3-year failure-free survival (FFS) and OS were 64% and 82%, respectively,[37] and none of the patients received consolidating autologous HSCT. These results are undoubtedly impressive and comparable to an autologous HSCT approach, not only considering efficacy but also toxicity. A total of 8% treatment-related deaths occurred and because of the shorter FFS concurrent with significant toxicity in patients aged >65 years, this regimen should not be recommended for this age subgroup. In summary, HyperCVAD/MA plus rituximab represents a promising treatment option for younger patients without significant co-morbidity, as is consolidating myeloablative radiochemotherapy followed by autologous HSCT.

4.7 Maintenance Therapy

Analysis of phase III trials investigating the value of IFNα maintenance following conventional induction therapy suggested a tendency towards a prolonged PFS. However, the number of patients was too low to exactly define the benefit of IFNα.[53]

While rituximab maintenance failed to demonstrate a statistically significant benefit compared with observation only in patients with MCL responding to rituximab induction therapy,[47] it improved the 3-year PFS from 9% to 45% after the salvage regimen rituximab ± FCM in a randomised trial.[55] A recent phase II trial also reported a remarkable PFS of 37 months after a modified HyperCVAD regimen followed by similar rituximab maintenance therapy.[57]

4.8 CNS Involvement

The presence of meningosis lymphomatosa in patients with MCL is rare (<5%) but, if present, is associated with a dismal prognosis: in one report, survival time ranged from 18 to 55 days after diagnosis of CNS involvement with no patient responding to intrathecal chemotherapy.[10] While some authors recommend intrathecal prophylaxis in high-risk patients, no approach has yet proven efficacy[12] and the identification of risk factors and results from clinical trials are eagerly awaited.

4.9 Summary

The standard therapeutic approach to patients with MCL may be summarised as follows:

- Rituximab plus chemotherapy should be considered the standard of care for patients with advanced-stage disease treated front-line or at relapse. Most recently, a meta-analysis of the Cochrane Hematologic Malignancies Group has demonstrated a benefit in terms of response rate, FFS and OS favouring immunochemotherapy with rituximab when compared with chemotherapy alone.[58]
- Younger patients without significant co-morbidity should be treated aggressively, either with dose-intensified regimens such as HyperCVAD plus rituximab without high-dose consolidation or with myeloablative regimens followed by autologous HSCT after initial CHOP- or DHAP-like induction therapy. Whether the addition of rituximab to myeloablative regimens further improves treatment needs to be determined from randomised trials. However, promising results have been reported in phase II trials (rituximab after autologous HSCT, during induction or mobilisation treatment, i.e. '*in vivo* purging'[59-61]).
- Patients who are not considered candidates for aggressive regimens may be treated with either anthracycline- or fludarabine-containing regimens; a randomised trial of the European MCL Network is currently addressing this issue.[62]

In general, clinical trials should be considered, especially in relapsed or refractory patients, for maintenance therapy and for innovative approaches including radioimmunotherapy, molecular targeted therapeutic options or allogeneic transplantation, which is briefly discussed in sections 5.1–5.3.

5. Perspective on Novel Treatment Strategies

5.1 Radioimmunotherapy

Radioimmunotherapy represents a novel therapeutic approach that combines the tumour-targeting attributes of lymphocyte-specific monoclonal antibodies with therapeutic radioisotopes to be delivered to sites of disseminated disease. This treatment modality is particularly appealing in advanced-stage malignant lymphoma, which is commonly considered to be inherently radiosensitive.[63,64] The most extensively studied and, to date, the only approved radioimmunoconjugates in the US and the EU, ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab, are both directed against CD20. This B-cell-specific epitope represents an excellent target antigen,[65] as it is expressed on virtually all B-cell lymphomas,[66] does not internalise or shed from the surface in response to antibody binding[67] and is absent on haematopoietic stem cells.[68] Although no comparative clinical trial has been performed between ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab, published results suggest that the two agents have similar response rates and response durations.[69] In contrast to the ^{131}I-labelled antibodies, no protracted inpatient admission is required for the pure β emitter ^{90}Y-ibritumomab tiuxetan. However, neither radioimmunoconjugate is currently approved for the treatment of MCL.

Single-agent radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan in relapsed and refractory MCL has been investigated in two ongoing phase II trials.[70,71] Efficacy is limited with an OR of about 30–40% and the duration of response is disappointingly short. Hence, there might be a role for radioimmunotherapy in multimodal approaches. Radioimmunotherapy may be applied as part of the induction therapy,[72] as consolidation therapy[73] or as part of a high-dose regimen followed by autologous or even allogeneic transplantation.[74,75] Preliminary data suggest that these approaches are feasible and safely used; however, evaluation of duration of response needs a longer follow-up.

Gopal et al.[76] pioneered the highly interesting concept of applying high-dose radioimmunotherapy (^{131}I-tositumomab) as part of the myeloablative regimen, followed by high-dose etoposide and cyclophosphamide before autologous HSCT. This phase II trial enrolled 16 patients with relapsed or refractory MCL, the median dose of ^{131}I was 510 mCi (18.87 GBq). While there were no treatment-related deaths, an impressive response rate of 100% and a CR of 91% were reported. The 3-year OS was 93% and the 3-year PFS was 61%.

5.2 Molecular Targeted Approaches

The growing insights into the underlying biology and pathogenesis of MCL form the basis for the introduction of molecular targeted therapeutic approaches.

Gene profiling studies demonstrate overexpression of nuclear factor kappa B (NFκB)-dependent gene products in MCL indicating constitutive activation of the NFκB signalling pathway.[77] NFκB has been implicated in blocking apoptosis, promoting cell proliferation and mediating treatment resistance.[78] Activation of NFκB requires phosphorylation of its inhibitor IκB leading to polyubiquitinylation and degradation by the proteasome. The ubiquitin-proteasome pathway is essential for maintaining intracellular protein homeostasis and represents a valid target for the treatment of malignant disease.[79] Apart from IκB, various other regulatory proteins for cell-cycle progression and apoptosis as well as oncogenes are processed by this pathway,[80] which are of particular importance in MCL, including p53, p27, p21, CDKs and cyclins, members of the Bcl-2 family, Mcl-1, BH3 only protein Noxa, and reactive oxygen species.

Bortezomib is a potent, selective and reversible inhibitor of the 26S proteasome with demonstrated efficacy in relapsed multiple myeloma.[81,82] Single-agent bortezomib has demonstrated clinical activity in several haematological malignancies,[83] with especially encouraging results in relapsed or refractory MCL.[84-87] Objective response is achieved in up

Table III. Efficacy of bortezomib in relapsed or refractory mantle cell lymphoma (MCL) in important phase II clinical trials

Study (year)	Phase, disease status	Regimen	No. of pts	Response rates (%)
Strauss et al.[86] (2006)	II, relapsed or refractory MCL	Bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11	24	OR: 29 CR: 2
O'Connor et al.[84] (2005)	II, relapsed or refractory MCL	Bortezomib 1.5 mg/m^2 on days 1, 4, 8, 11	11	OR: 45 CR/CRu: 9
Goy et al.[85] (2005)	II, relapsed or refractory MCL	Bortezomib 1.5 mg/m^2 on days 1, 4, 8, 11	29	OR: 41 CR: 21
Fisher et al.[87] (2006)	II, relapsed or refractory MCL	Bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11	141	OR: 33 CR/CRu: 8

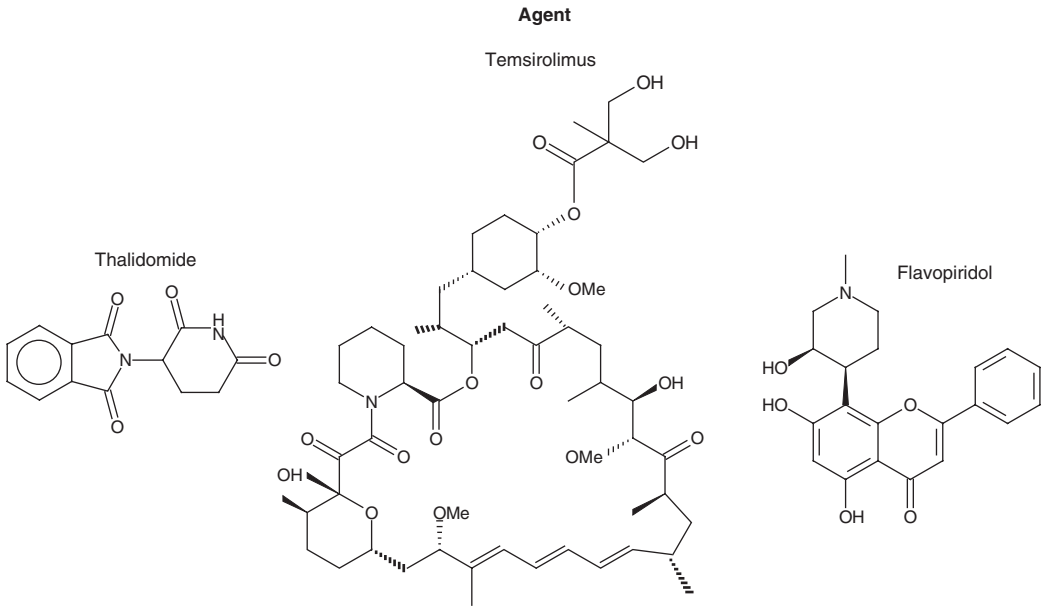
CR = complete response rate; **CRu** = complete response unconfirmed rate; **OR** = overall response rate; **pts** = patients.

to 45% of patients with MCL; however, CRs are low (table III) and median duration of response relatively short. In the largest trial enrolling 141 patients a median duration of response of 9.2 months and a median time to progression of 6.2 months were observed.[87] Considering the abundant presence and requirement of proteasome activity in eukaryotic cells, bortezomib displays surprisingly little toxicity in clinical practice with mild thrombocytopenia, neuropathy and diarrhoea being most common.[83] Thus, combination therapy of bortezomib with conventional chemotherapy is a highly attractive option[88-90] and feasibility has been demonstrated for the combination of bortezomib with liposomal doxorubicin.[91] Preliminary preclinical and clinical data[92] suggest synergistic efficacy for bortezomib in combination with cytarabine representing the rationale of currently ongoing randomised trials.

Figure 2 offers a selection of other promising small molecules that have already entered clinical trials for relapsed or refractory disease. Thalidomide is known to interfere with angiogenesis and the microenvironment. In a small phase II trial the combination with rituximab yielded an OR of 81% and a CR of 31%.[93] The mechanism of action of temsirolimus is complex: translation of cyclin D1 messenger RNA is inhibited by interfering with the mammalian target of rapamycin. In a phase II trial, single-agent treatment yielded an OR of 38%, while the CR was low (3%) and the median time to progression and duration of response short (6.5 and 6.9 months, respectively).[94] Furthermore, haematological toxicity was considerably high, and so different dose levels are currently being evaluated in clinical trials in an effort to reduce cumulative myelotoxicity.[95] Interestingly, alvocidib (flavopiridol) directly inhibits CDK4 and 6, leading to downregulation of cyclin D1; but, an initial phase II trial failed to demonstrate any relevant activity.[96] However, recently, after pharmacokinetic improvement of the administration schedule, significant activity has been reported in patients with refractory CLL, even those with tumour lysis syndrome occurring as a result of alvocidib treatment, justifying further studies in patients with high-risk CLL and other diseases, such as MCL.[97]

5.3 Allogeneic Stem Cell Transplantation

It is generally accepted that allogeneic stem cell transplantation is the only curative therapeutic option for advanced-stage MCL[98] and there is evidence for a graft-versus-lymphoma effect.[99] However, only a minority of patients are suitable candidates for such an approach, and conventional conditioning is still associated with considerable morbidity and mortality.[100] A recent improvement has been made with the introduction of reduced intensity conditioning pioneered by Khouri et al.[99] in a small phase II trial of patients with relapsed and refractory, mostly chemosensitive MCL. The CR was impressively high at 94%, and no patient died during the first 100 days. While no severe acute graft-versus-host disease was observed, every third patient had significant chronic graft-versus-host disease. After a follow-up of 28 months, the estimated 3-year PFS and OS were 82% and 85%, respectively. Of note, one patient with relapsed disease was successfully treated with donor lymphocyte infusion resulting in a durable CR, providing evidence for a graft-versus-lymphoma effect. In contrast, results in chemorefractory disease are still sobering with an OS of <2 years.[100]



Agent	Mode of action	Efficacy	Remarks
Thalidomide	Affects angiogenesis and microenvironment	Thalidomide + rituximab for relapsed/refractory MCL OR 81%, CR 31%	• n = 16[1] • phase II trial • well tolerated: infusion reaction, fatigue, neuropathy
Temsirolimus	Inhibitor of mTOR → inhibition of cyclin D1 translation	Single agent temsirolimus for relapsed/refractory MCL OR 38%, CR 3% median TTP 6.5mo	• n = 34[2] • phase II trial • haematological toxicity (grade 3/4 in 82%)
Alvocidib (flavopiridol)	Inhibition of CDKs and downregulation of cyclin D1	Single agent flavopiridol for relapsed/refractory MCL OR 11%, CR 0%, median DR 3.4mo	• n = 30[3] • phase II trial • but: increased efficacy using a pharmacologically derived schedule

Fig. 2. Selection of small molecules other than bortezomib currently in clinical evaluation for molecular targeted therapy for relapsed or refractory mantle cell lymphoma (MCL). **1** Kaufmann et al.[93] (2004); **2** Witzig et al.[94] (2005); **3** Kouroukis et al.[96] (2003). **CDK** = cyclin-dependent kinase; **CR =** complete response rate; **DR =** duration of response; **mTOR** = mammalian target of rapamycin; **OR** = overall response rate; **TTP** = time to progression.

5.4 Summary

It is preferable that targeted therapies be administered in clinical trials. Promising results have been reported for rituximab and some molecular targeted agents in patients with relapsed or refractory MCL, and are likely to be incorporated in multimodal approaches in the near future. Allogeneic transplantation should be considered only in suitable patients with relapsed disease after appropriate first-line therapy. The concept of reduced intensity conditioning is highly attractive and incorporation of investigational strategies into the preparative regimen is likely to further improve treatment results without necessarily increasing treatment toxicity.

6. Conclusion

Despite its rarity, MCL is of particular clinical and scientific interest for several reasons. Owing to improved diagnostic possibilities, MCL is now recognised as a unique lymphoma subtype that, despite its indolent morphology, typically presents with advanced stage disease, often with extranodal dissemination, and typically pursues an aggressive clinical course. Although in advanced-stage disease, conventional chemotherapy remains a non-curative approach, significant improvement has been achieved by the successful introduction of immunochemotherapy and dose-intensified approaches, including autologous HSCT, as demonstrated in randomised clinical trials. For further advancement of treatment results, it is of utmost importance to continue recruiting patients into high-quality clinical trials whenever possible, especially considering upcoming molecluar-targeted approaches and innovative treatment options, including allogeneic transplantation strategies, which are still considered the only curative therapy for a carefully selected patient population. As a result of recently gained and still evolving insights in underlying biology and pathogenesis, MCL provides a paradigm for neoplasms with dysregulated control of cell cycle machinery and impaired apoptotic pathways.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. Dr Unterhalt has no conflicts of interest that are directly relevant to the content of this review. Dr Weigert has received speaker's honoraria from Roche and Schering. Dr Hiddemann has acted as a consultant and provided expert testimony for Roche, received speaker's honoraria from Roche and Schering, and received financial support for investigator initiated clinical trials from Roche, Schering and Millenium. Dr Dreyling has acted as a consultant for Millenium, received speaker's honoraria from Roche and Schering, and received financial support for clinical trials from Roche, Schering and OrthoBiotech.

References

1. Jaffe ES, Harris NL, Stein H. Tumours of the haemopoitic and lymphoid tissues. Lyon: IARC Press, 2001
2. Meusers P, Hense J, Brittinger G. Mantle cell lymphoma: diagnostic criteria, clinical aspects and therapeutic problems. Leukemia 1997; 11 Suppl. 2: S60-4
3. Lenz G, Dreyling M, Hiddemann W. Mantle cell lymphoma: established therapeutic options and future directions. Ann Hematol 2004; 83 (2): 71-7
4. Tiemann M, Schrader C, Klapper W, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol 2005; 131 (1): 29-38
5. Rosenwald A, Wright G, Wiestner A, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell 2003; 3 (2): 185-97
6. Fernandez V, Hartmann E, Ott G, et al. Pathogenesis of mantle-cell lymphoma: all oncogenic roads lead to dysregulation of cell cycle and DNA damage response pathways. J Clin Oncol 2005; 23 (26): 6364-9
7. Witzig TE. Current treatment approaches for mantle-cell lymphoma. J Clin Oncol 2005; 23 (26): 6409-14
8. Cohen PL, Kurtin PJ, Donovan KA, et al. Bone marrow and peripheral blood involvement in mantle cell lymphoma. Br J Haematol 1998; 101 (2): 302-10
9. Romaguera JE, Medeiros LJ, Hagemeister FB, et al. Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. Cancer 2003; 97 (3): 586-91
10. Oinonen R, Franssila K, Elonen E. Central nervous system involvement in patients with mantle cell lymphoma. Ann Hematol 1999; 78 (3): 145-9
11. Montserrat E, Bosch F, Lopez-Guillermo A, et al. CNS involvement in mantle-cell lymphoma. J Clin Oncol 1996; 14 (3): 941-4
12. Chua SL, Seymour JF, Streater J, et al. Intrathecal chemotherapy alone is inadequate central nervous system prophylaxis in patients with intermediate-grade non-Hodgkin's lymphoma. Leuk Lymphoma 2002; 43 (9): 1783-8
13. Weisenburger DD, Vose JM, Greiner TC, et al. Mantle cell lymphoma: a clinicopathologic study of 68 cases from the Nebraska Lymphoma Study Group. Am J Hematol 2000; 64 (3): 190-6
14. Khouri IF, Saliba RM, Okoroji GJ, et al. Long-term follow-up of autologous stem cell transplantation in patients with diffuse mantle cell lymphoma in first disease remission: the prognostic value of beta2-microglobulin and the tumor score. Cancer 2003; 98 (12): 2630-5
15. Raty R, Franssila K, Joensuu H, et al. Ki-67 expression level, histological subtype, and the International Prognostic Index as outcome predictors in mantle cell lymphoma. Eur J Haematol 2002; 69 (1): 11-20
16. Pott C, Schrader C, Gesk S, et al. Quantitative assessment of molecular remission after high-dose therapy with autologous stem cell transplantation predicts long-term remission in mantle cell lymphoma. Blood 2006; 107 (6): 2271-8
17. Howard OM, Gribben JG, Neuberg DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. J Clin Oncol 2002; 20 (5): 1288-94
18. Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. Ann Oncol 2003; 14 (10): 1555-61
19. M'Kacher R, Bennaceur A, Farace F, et al. Multiple molecular mechanisms contribute to radiation sensitivity in mantle cell lymphoma. Oncogene 2003; 22 (39): 7905-12
20. Meusers P, Engelhard M, Bartels H, et al. Multicentre randomized therapeutic trial for advanced centrocytic lymphoma: anthracycline does not improve the prognosis. Hematol Oncol 1989; 7 (5): 365-80
21. Zucca E, Roggero E, Pinotti G, et al. Patterns of survival in mantle cell lymphoma. Ann Oncol 1995; 6 (3): 257-62
22. Lenz G, Hiddemann W, Dreyling M. The role of fludarabine in the treatment of follicular and mantle cell lymphoma. Cancer 2004; 101 (5): 883-93
23. Rummel MJ, Chow KU, Karakas T, et al. Reduced-dose cladribine (2-CdA) plus mitoxantrone is effective in the treat-

ment of mantle-cell and low-grade non-Hodgkin's lymphoma. Eur J Cancer 2002; 38 (13): 1739-46
24. Zinzani PL, Magagnoli M, Moretti L, et al. Fludarabine-based chemotherapy in untreated mantle cell lymphomas: an encouraging experience in 29 patients. Haematologica 1999; 84 (11): 1002-6
25. Zinzani PL, Magagnoli M, Moretti L, et al. Randomized trial of fludarabine versus fludarabine and idarubicin as frontline treatment in patients with indolent or mantle-cell lymphoma. J Clin Oncol 2000; 18 (4): 773-9
26. Seymour JF, Grigg AP, Szer J, et al. Cisplatin, fludarabine, and cytarabine: a novel, pharmacologically designed salvage therapy for patients with refractory, histologically aggressive or mantle cell non-Hodgkin's lymphoma. Cancer 2002; 94 (3): 585-93
27. Thomas DW, Owen RG, Johnson SA, et al. Superior quality and duration of responses among patients with mantle-cell lymphoma treated with fludarabine and cyclophosphamide with or without rituximab compared with prior responses to CHOP. Leuk Lymphoma 2005; 46 (4): 549-52
28. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004; 104 (10): 3064-71
29. Flinn IW, Byrd JC, Morrison C, et al. Fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated indolent lymphoid malignancies. Blood 2000; 96 (1): 71-5
30. Cohen BJ, Moskowitz C, Straus D, et al. Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 2001; 42 (5): 1015-22
31. Herold M, Schulze A, Niederwieser D, et al. Bendamustine, vincristine and prednisone (BOP) versus cyclophosphamide, vincristine and prednisone (COP) in advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma: results of a randomised phase III trial (OSHO#19). J Cancer Res Clin Oncol 2006; 132 (2): 105-12
32. Rummel MJ, Al-Batran SE, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol 2005; 23 (15): 3383-9
33. Weide R, Heymanns J, Thomalla J, et al. Bendamustine/mitoxantrone/rituximab (BMR): a very effective and well tolerated immuno-chemotherapy for relapsed and refractory indolent lymphomas: high response rate in patients pretreated with rituximab. Results of a multicentre phase-II-study of the German Low Grade Lymphoma Study Group (GLSG) [abstract no. 6616]. 41st Annual Meeting of the American Society of Clinical Oncology; 2005 May 13-17; Orlando (FL). Proc Annu Meet Am Soc Clin Oncol 2005; 23 (16s): 589s
34. Lefrere F, Delmer A, Suzan F, et al. Sequential chemotherapy by CHOP and DHAP regimens followed by high-dose therapy with stem cell transplantation induces a high rate of complete response and improves event-free survival in mantle cell lymphoma: a prospective study. Leukemia 2002; 16 (4): 587-93
35. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: an active regimen for aggressive mantle-cell lymphoma. J Clin Oncol 1998; 16 (12): 3803-9
36. de Guibert S, Jaccard A, Bernard M, et al. Rituximab and DHAP followed by intensive therapy with autologous stem-cell transplantation as first-line therapy for mantle cell lymphoma. Haematologica 2006; 91 (3): 425-6
37. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005; 23 (28): 7013-23
38. Ketterer N, Salles G, Espinouse D, et al. Intensive therapy with peripheral stem cell transplantation in 16 patients with mantle cell lymphoma. Ann Oncol 1997; 8 (7): 701-4
39. Stewart DA, Vose JM, Weisenburger DD, et al. The role of high-dose therapy and autologous hematopoietic stem cell transplantation for mantle cell lymphoma. Ann Oncol 1995; 6 (3): 263-6
40. Freedman AS, Neuberg D, Gribben JG, et al. High-dose chemoradiotherapy and anti-B-cell monoclonal antibody-purged autologous bone marrow transplantation in mantle-cell lymphoma: no evidence for long-term remission. J Clin Oncol 1998; 16 (1): 13-8
41. Haas R, Brittinger G, Meusers P, et al. Myeloablative therapy with blood stem cell transplantation is effective in mantle cell lymphoma. Leukemia 1996; 10 (12): 1975-9
42. Blay JY, Sebban C, Surbiguet C, et al. High-dose chemotherapy with hematopoietic stem cell transplantation in patients with mantle cell or diffuse centrocytic non-Hodgkin's lymphomas: a single center experience on 18 patients. Bone Marrow Transplant 1998; 21 (1): 51-4
43. Kroger N, Hoffknecht M, Dreger P, et al. Long-term disease-free survival of patients with advanced mantle-cell lymphoma following high-dose chemotherapy. Bone Marrow Transplant 1998; 21 (1): 55-7
44. Dreger P, Martin S, Kuse R, et al. The impact of autologous stem cell transplantation on the prognosis of mantle cell lymphoma: a joint analysis of two prospective studies with 46 patients. Hematol J 2000; 1 (2): 87-94
45. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005; 105 (7): 2677-84
46. Buske C, Weigert O, Dreyling M, et al. Current status and perspective of antibody therapy in follicular lymphoma. Haematologica 2006; 91 (1): 104-12
47. Ghielmini M, Schmitz SF, Cogliatti S, et al. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). J Clin Oncol 2005; 23 (4): 705-11
48. Morschhauser F, Leonard J, Coiffier B, et al. Initial safety and efficacy results of a second-generation humanized anti-CD20 antibody, IMMU-106 (hA20), in non-Hodgkin's lymphoma [abstract]. Blood 2005; 106 (11): 683a
49. Leonard JP, Coleman M, Ketas J, et al. Combination antibody therapy with epratuzumab and rituximab in relapsed or refractory non-Hodgkin's lymphoma. J Clin Oncol 2005; 23 (22): 5044-51
50. DiJoseph JF, Armellino DC, Boghaert ER, et al. Antibody-targeted chemotherapy with CMC-544: a CD22-targeted immunoconjugate of calicheamicin for the treatment of B-lymphoid malignancies. Blood 2004; 103 (5): 1807-14
51. Younes A, Hariharan K, Allen RS, et al. Initial trials of anti-CD80 monoclonal antibody (Galiximab) therapy for patients with relapsed or refractory follicular lymphoma. Clin Lymphoma 2003; 3 (4): 257-9
52. Nagy ZA, Hubner B, Lohning C, et al. Fully human, HLA-DR-specific monoclonal antibodies efficiently induce programmed death of malignant lymphoid cells. Nat Med 2002; 8 (8): 801-7
53. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincris-

tine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005; 23 (9): 1984-92
54. Herold M, Dolken G, Fiedler F, et al. Randomized phase III study for the treatment of advanced indolent non-Hodgkin's lymphomas (NHL) and mantle cell lymphoma: chemotherapy versus chemotherapy plus rituximab. Ann Hematol 2003; 82 (2): 77-9
55. Hiddemann W, Forstpointner R, Dreyling M, et al. Rituximab maintenance prolongs response duration after salvage therapy with R-FCM in patients with relapsed follicular lymphomas and mantle cell lymphomas: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG) [abstract]. Blood (ASH Annual Meeting Abstracts) 2005; 106 (11): 920
56. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide and mitoxantrone (R-FCM) in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006; 108 (13): 4003-8
57. Kahl B, Longo W, Eickhoff J, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network. Ann Oncol 2006; 17 (9): 1418-23
58. Schulz H, Bohlius J, Skoetz N, et al. Combined immunochemotherapy with rituximab improves overall survival in patients with follicular and mantle cell lymphoma: updated meta-analysis results. Blood 2006; 106 (11): 106-7a
59. Gianni AM, Magni M, Martelli M, et al. Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen). Blood 2003; 102 (2): 749-55
60. Mangel J, Leitch HA, Connors JM, et al. Intensive chemotherapy and autologous stem-cell transplantation plus rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis. Ann Oncol 2004; 15 (2): 283-90
61. Thieblemont C, Antal D, Lacotte-Thierry L, et al. Chemotherapy with rituximab followed by high-dose therapy and autologous stem cell transplantation in patients with mantle cell lymphoma. Cancer 2005; 104 (7): 1434-41
62. European MCL Network [online]. Available from URL: http://www.European-MCL.net [Accessed 2007 May 30]
63. Johansson L, Carlsson J, Nilsson K. Radiosensitivity of human B-lymphocytic lymphomas in vitro. Int J Radiat Biol Relat Stud Phys Chem Med 1982; 41 (4): 411-20
64. Safwat A. The role of low-dose total body irradiation in treatment of non-Hodgkin's lymphoma: a new look at an old method. Radiother Oncol 2000; 56 (1): 1-8
65. Press OW. Radioimmunotherapy for non-Hodgkin's lymphomas: a historical perspective. Semin Oncol 2003; 30 (2 Suppl. 4): 10-21
66. Anderson KC, Bates MP, Slaughenhoupt BL, et al. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. Blood 1984; 63 (6): 1424-33
67. Press OW, Appelbaum F, Ledbetter JA, et al. Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas. Blood 1987; 69 (2): 584-91
68. Tedder TF, Boyd AW, Freedman AS, et al. The B cell surface molecule B1 is functionally linked with B cell activation and differentiation. J Immunol 1985; 135 (2): 973-9
69. Rao AV, Akabani G, Rizzieri DA. Radioimmunotherapy for non-Hodgkin's lymphoma. Clin Med Res 2005; 3 (3): 157-65
70. Younes A, Pro B, Rodriguez MA, et al. Activity of yttrium 90 (90Y) ibritumomab tiuxetan (Zevalin®) in 22 patients with relapsed and refractory mantle cell lymphoma (MCL) [abstract no. 2452]. Blood 2005; 106 (11): 689a
71. Weigert O, Schilling C, Rummel MJ, et al. Efficacy and safety of a single-course of yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin®) in patients with relapsed or refractory mantle cell lymphoma (MCL) after/not appropriate for autologous stem cell transplantation (ASCT): a phase II trial of the European MCL Network [abstract no. 4786]. Blood 2005; 106 (11): 277b
72. Zelenetz A, Noy A, Pandit-Taskar N, et al. Sequential radioimmunotherapy with tositumomab/iodine I131 tositumomab followed by CHOP for mantle cell lymphoma demonstrates RIT can induce molecular remissions [abstract]. Proc Am Soc Clin Oncol 2006; 24 (18S): 436s
73. Weigert O, Jurczak W, Schilling C, et al. Efficacy of radioimmunotherapy with (90Y) ibritumomab tiuxetan is superior as consolidation in relapsed or refractory mantle cell lymphoma: results of two phase II trials of the European MCL Network and the PLRG [abstract]. Proc Am Soc Clin Oncol 2006; 24 (18S): 430s
74. Devizzi L, Seregni E, Guidetti A, et al. High-dose myeloablative Zevalin radioimmunotherapy with tandem stem-cell autografting has minimal toxicity and full feasibility in an outpatient setting [abstract]. Blood 2005; 106 (11): 768a
75. Shimoni A, Zwas T, Oksman Y, et al. Ibritumomab tiuxetan (Zevalin) in the conditioning regimen for autologous and reduced-intensity allogeneic stem-cell transplantation in patients with chemo-refractory non-Hodgkin's lymphoma [abstract no. 1131]. Blood 2005; 106 (11): 329a
76. Gopal AK, Rajendran JG, Petersdorf SH, et al. High-dose chemo-radioimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma. Blood 2002; 99 (9): 3158-62
77. Martinez N, Camacho FI, Algara P, et al. The molecular signature of mantle cell lymphoma reveals multiple signals favoring cell survival. Cancer Res 2003; 63 (23): 8226-32
78. Nakanishi C, Toi M. Nuclear factor-kappaB inhibitors as sensitizers to anticancer drugs. Nat Rev Cancer 2005; 5 (4): 297-309
79. Ciechanover A. The ubiquitin-proteasome proteolytic pathway. Cell 1994; 79: 13-21
80. Adams J. The proteasome: a suitable antineoplastic target. Nat Rev Cancer 2004; 4 (5): 349-60
81. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003; 348 (26): 2609-17
82. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005; 352 (24): 2487-98
83. Orlowski RZ, Stinchcombe TE, Mitchell BS, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. J Clin Oncol 2002; 20 (22): 4420-7
84. O'Connor OA, Wright J, Moskowitz C, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. J Clin Oncol 2005; 23 (4): 676-84
85. Goy A, Younes A, McLaughlin P, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 2005; 23 (4): 667-75
86. Strauss SJ, Maharaj L, Hoare S, et al. Bortezomib therapy in patients with relapsed or refractory lymphoma: potential correlation of in vitro sensitivity and tumor necrosis factor alpha response with clinical activity. J Clin Oncol 2006; 24 (13): 2105-12

87. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006; 24 (30): 4867-74
88. Jeremias I, Kupatt C, Baumann B, et al. Inhibition of nuclear factor kappaB activation attenuates apoptosis resistance in lymphoid cells. Blood 1998; 91 (12): 4624-31
89. Mitsiades N, Mitsiades CS, Richardson PG, et al. The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. Blood 2003; 101 (6): 2377-80
90. Leonard J, Furman R, Cheung Y-K, et al. Phase I/II trial of bortezomib + CHOP-rituximab in diffuse large B cell (DLBCL) and mantle cell lymphoma (MCL): phase I results [abstract]. Blood 2005; 106 (11): 147a
91. Orlowski RZ, Voorhees PM, Garcia RA, et al. Phase 1 trial of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with advanced hematologic malignancies. Blood 2005; 105 (8): 3058-65
92. Weigert O, Pastore A, Rieken M, et al. Sequence-dependent synergy of the proteasome inhibitor bortezomib and cytarabine in mantle cell lymphoma. Leukemia 2007; 21 (3): 524-8
93. Kaufmann H, Raderer M, Wohrer S, et al. Antitumor activity of rituximab plus thalidomide in patients with relapsed/refractory mantle cell lymphoma. Blood 2004; 104 (8): 2269-71
94. Witzig TE, Geyer SM, Ghobrial I, et al. Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. J Clin Oncol 2005; 23 (23): 5347-56
95. Ansell SM, Geyer SM, Kurtin P, et al. Anti-tumor activity of mTOR inhibitor temsirolimus for relapsed mantle cell lymphoma: a phase II trial in the North Central Cancer Treatment Group [abstract]. Proc Am Soc Clin Oncol 2006; 24 (18s): 430s
96. Kouroukis CT, Belch A, Crump M, et al. Flavopiridol in untreated or relapsed mantle-cell lymphoma: results of a phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2003; 21 (9): 1740-5
97. Byrd JC, Lin TS, Dalton JT, et al. Flavopiridol administered using a pharmacologically derived schedule is associated with marked clinical efficacy in refractory, genetically high-risk chronic lymphocytic leukemia. Blood 2007; 109 (2): 399-404
98. Kroger N, Hoffknecht M, Kruger W, et al. Allogeneic bone marrow transplantation for refractory mantle cell lymphoma. Ann Hematol 2000; 79 (10): 578-80
99. Khouri IF, Lee MS, Saliba RM, et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. J Clin Oncol 2003; 21 (23): 4407-12
100. Robinson SP, Goldstone AH, Mackinnon S, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood 2002; 100 (13): 4310-6

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