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Lymphoma (LI Gordon, Section Editor)

Current and Emerging Therapies in Mantle Cell Lymphoma

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Opinion statement

Mantle Cell Lymphoma, characterized by the t(11;14)(q13; q32) chromosomal translocation and cyclin D1 expression, remains one of the most challenging lymphoma subtypes to treat. Therapy can be divided into treatment modalities for younger, stem cell transplant (SCT)-eligible patients vs older, SCT-ineligible patients. For clinically fit patients younger than 60–65 years of age we recommend cytarabine-containing induction and conditioning regimens such as Rituximab (R)-CHOP alternating with R-DHAP followed by autologous SCT consolidation. Elderly patients benefit from R-bendamustine or R-CHOP with maintenance rituximab following induction therapy, especially after R-CHOP. While standard chemoimmunotherapy provides high overall response rates, the responses are not durable and sequential therapies are thus necessary. MCL is proving to be sensitive to novel therapies that may in the near future become useful adjuncts to standard regimens. For example, bortezomib, lenalidomide, and temsirolimus each have single-agent efficacy in relapsed and refractory disease. Several targeted agents are emerging that likewise may transform management of MCL. The B-cell receptor pathway appears to be critical in the pathogenesis of MCL, and novel agents such as ibrutinib and idelalisib that target this signaling pathway are highly active in relapsed and refractory MCL. Similarly, cell cycle inhibitors targeting cyclin dependent kinases as well as HDAC inhibitors have shown promise in early studies.

Introduction

Mantle Cell lymphoma (MCL), characterized by the t(11;14)(q13;q32) chromosomal translocation and cyclin D1 expression, comprises about 6 % of all non-Hodgkin lymphomas (NHL) [1–4]. MCL is more common in elderly men, with 74 % of cases being male and an average age at presentation of 63 years [5]. It typically presents in advanced stages, with bone marrow and extranodal involvement being quite common. Gastrointestinal involvement in particular is present in the majority of cases, with some showing colonic lymphomatous

polyposis [6]. Diagnostic workup is similar to other NHL, with standard blood counts and chemistry panels, LDH, bone marrow biopsy and aspirate with flow cytometry and cytogenetics, and CT or PET imaging of the neck, chest, abdomen, and pelvis. Some centers perform routine staging colonoscopy, while others limit this only to those patients with relevant symptoms.

Histopathologically, MCL typically presents with a diffuse pattern, however mantle zone and nodular variants are recognized. The cells appear small to medium sized with scant cytoplasm, condensed chromatin, and small nucleoli, but may present initially or at relapse with blastoid morphology [1]. Immunophenotypically MCL exhibits CD5, CD20, Bcl-2 and FMC7 positivity, and is CD10, CD23, and CD25 negative. Documentation of nuclear cyclin D1 expression and/or the t(11;14) by fluorescent in situ hybridization (FISH) or standard cytogenetics is necessary to distinguish MCL from other NHL.

In addition to cell cycle dysregulation, the B-cell receptor (BCR) pathway appears critical to MCL pathogenesis. Once activated, BCR induces downstream phosphorylation of kinases such as phosphotidylinositol-3-kinase (PI3K), Bruton tyrosine kinase (BTK), and mammalian target of rapamycin (mTOR), ultimately leading to the activation of NF-kappa-B and transcription of genes involved in B-cell survival, proliferation and apoptosis [4]. Preclinical studies have shown this to be a targetable pathway in MCL. For example, the PI3K inhibitor BEZ235 inhibits MCL cells in vitro and is synergistic with conventional agents and overcomes bortezomib resistance in vitro [7]. Recent clinical trials have confirmed efficacy in relapsed and refractory MCL, as described below.

The Mantle Cell International Prognostic Index (MIPI) is a clinical scoring system specifically that uses age, LDH, total white blood count, and performance status to predict 5-year overall survival (OS) [8•]. MIPI divides MCL patients into low- (LR), intermediate- (IR) and high-risk (HR). In a retrospective analysis of 455 patients with advanced MCL, median OS in the LR group was not reached, whereas it was 51 months in the IR group and 29 months for the HR patients. MIPI has also been shown to predict OS after chemotherapy followed by autologous SCT [9]. Other prognostic tools include percentage of Ki-67 positive cells, or Ki-67 index, as a measure of cellular proliferation. Ki-67 has been shown to predict OS in MCL patients, specifically MCL patients exposed to rituximab [10]. A modification of the MIPI incorporating the Ki-67 index score has also been shown to predict OS [11]. Detection of minimal residual disease (MRD) in peripheral blood and bone marrow after autologous SCT was shown to independently predict time to treatment failure (TTF) in a phase III MCL trial [12•, 13]. Going forward, the use of MRD-negativity as a treatment goal may become standard.

Treatment

As Mantle Cell Lymphoma nearly always presents in advanced stages, there is usually no role for radiation therapy and chemoimmunotherapy remains the mainstay of treatment. Generally, treatment options are chosen based on patient's performance status and candidacy for transplant. A summary of recent sentinel therapeutic trials in MCL is detailed in Table 1. While high partial (PR) and complete response (CR) rates are obtained with initial therapy, relapse 1 to 3 years after treatment is expected. Fortunately, the increasing number of treatment options has improved OS from the historical 3 years to 5 to 7 years presently; especially for those with lower-risk IPI scores [6].

Watchful Waiting

A subset of MCL patients with an indolent course has been characterized. Comprising about 20 % of patients, these individuals often have a CLL-like presentation with leukemic phase and splenomegaly or may have had slowly progressing and relatively low tumor burden lymphadenopathy. Biologically these cases show hypermutated immunoglobulin heavy chain genes, noncomplex karyotypes, and lack expression of SOX11 [23]. For asymptomatic patients

Table 1. Recent key articles

Regimen	Population assessed	Type of study	Outcomes assessed	Key findings	Reference
R-CHOP alternating with R-DHAP → auto-SCT	Stage III–IV MCL	Phase II	EFS, 5 y OS	60 Patients, ORR 95 % 5 y, median EFS 83.9 m, 5 y EFS 64 %, median DFS 78 m, PFS 84 m, median OS not reached, OS 75 %. 49 patients underwent SCT. Of patients who underwent SCT, 96 % had CR.	Delarue et al [15••]
R-CHOP vs R-CHOP alternating with R-DHAP →HD ara-c myeloablative chemo and auto-SCT	Previously untreated stage II–IV MCL up to 65 yoa	Phase III	CR, DR, TTF, 3 y OS	497 Patients, CR/Cru 41 % arm A vs 60 % arm B (P=0.0003), OR after transplant 97 % in both arms, TTF 49 m arm A vs NR arm B (P=0.0384), RD after ASCT 51 m arm A vs NR arm (P=0.077), 3 y OS 79 % arm A vs 80 % arm B.	Hermine et al [14]
Bendamustine + R vs R-CHOP	Upfront indolent and MCL	Phase III	PFS, OS	514 Patients, B-R improved PFS vs R-CHOP, median 69.5 m vs 31.2 m (P<0.001), no difference in OS between 2 groups.	Rummel et al [16••]
R-FC or R-CHOP, with either R maintenance or IFN-α	MCL age ≥60, ineligible for high dose therapy	Phase III	OS, DR	532 In intention-to-treat analysis. Similar CR for R-FC and R-CHOP (40 % vs 34 %), increased PD with R-FC (14 % vs 5 %). OS better with RCHOP (62 % 4 yr OS vs 47 % P=0.005), 316 received maintenance R, RRR of progression or death of 45 % (P=0.01), maintenance R improved OS in R-CHOP group: 4 y OS 87 % vs 63 % with IFN-α (P=0.005).	Kluin-Nelemans et al [40••]
Modified R-hyper-CVAD with bortezomib with maintenance rituximab	Previously untreated MCL	Phase II	OR, CR, 3 y PFS and OS	75 Patients with MCL, ORR 97 %, CR 68 %, PR 29 %. If SD, PR or CR, patients received MR weekly × 5 every 6 months × 2 y; 3 y PFS 74 %; 3 y OS was 88 % for MR vs SCT.	Chang et al [17] Kahl et al [18, 19•]
R-CHOP → Yttrium-^{90} -ibritumomab	Previously untreated MCL	Phase II	ORR, TTF, 5 y OS	56 Patients ORR 82 %, TTF 34.2 m, median OS NR, 5 y OS 73 % (79 % if age ≤65 y).	Smith et al [20]
R-CHOP with bortezomib	Previously untreated MCL and DLBCL	Phase I/II	ORR, PFS, 2 y OS	36 Patients with MCL, 2/3 MCL patients had medium or high MIPI, average age 66 y, ORR 81 %, 2 y PFS 44 %, 2 y OS 86 %.	Ruan et al [21]

observation is a reasonable approach as a retrospective analysis of 97 patients demonstrated improved OS in the observation arm (OS not reached vs 64 months in the treatment arm; P=0.004) [24]. Observed patients had better performance status and lower IPI stage. As this was a retrospective study, however, it is not possible to ascertain that the higher OS found in this cohort is due to their having been observed vs features of their disease or performance status that led them to be good candidates for observation in the first place.

We recommend following observed patients closely during the early months after diagnosis to gauge the pace of disease progression, and subsequently scaling back frequency of visits as deemed appropriate for each patient. Indications for initiation of treatment include symptomatic or bulky lymphadenopathy or splenomegaly, constitutional symptoms or transfusion requirement for cytopenias related to MCL.

Pharmacologic Treatment

Aggressive Therapy with Transplant

For younger patients (<65 yr) with good performance status, the incorporation of high-dose cytarabine with first treatment induction regimen is important. Autologous SCT (auto-SCT) should be strongly considered as consolidation following induction, although as yet phase III data for SCT consolidation vs observation or other consolidation approach is lacking. While auto-SCT is considered a standard of care in patients who are eligible, there is as yet no

proven OS benefit [25].

One retrospective analysis investigated the efficacy of R-CHOP alone vs R-CHOP followed by auto-SCT vs the R-hyper-CVAD/methotrexate-cytarabine regimen alone [26]. 156 patients with untreated MCL were assessed. Patients receiving the latter regimen or auto-SCT after R-CHOP had a higher PFS vs R-CHOP alone (P=0.001). Overall, median progression-free survival (PFS) was only 3 years with the 2 aggressive regimens.

A phase III study examined the effect of cytarabine-containing treatment and preparative regimens in patients with MCL undergoing auto-SCT [13, 27•]. Four hundred ninety-seven patients were randomized to receive either standard R-CHOP for 6 cycles followed by myeloablative radiochemotherapy and auto-SCT (arm A), or alternating R-CHOP and R-DHAP for 6 total cycles followed by cytarabine-based myeloablation and auto-SCT (arm B). Patients had previously untreated stage II–IV MCL, and were up to 65 years old. The cytarabine-containing regimen had higher CR/CRu rates (54 % vs 40 %; P=0.0003), with improved TTF (88 months in arm B vs 46 months in arm A; P=0.0382). Three-year OS was superior in arm B (NR vs 82 months; P=0.045). Arm B did have increased grade 3–4 hematologic toxicity; however this was not clinically significant. Additionally, MRD was measured by real- time quantitative PCR (RQ-PCR), which was found to strongly prognosticate early clinical outcome, more so than clinical or morphological assessment [14]. A smaller phase III trial (LyMa) confirmed the benefit of cytarabine, showing a 76 % CR/CRu in 152 newly diagnosed MCL patients who received R-DHAP alone for 4 cycles [28].

These results were corroborated in a phase II study evaluating the effect of CHOP and DHAP with rituximab followed by auto-SCT [16••]. Sixty patients with stage III–IV MCL received 3 cycles of CHOP followed by 3 cycles of DHAP, with rituximab given with the final 4 cycles. Responders received auto-SCT. ORR was 95 % at 5 years, with median event-free survival (EFS) of 83.9 months. The median OS was not reached, with an OS of 75 % at 5 years. Of the 49 patients who underwent auto-SCT, 96 % had CR, 11 study participants developed secondary malignancies.

Alternative high-dose cytarabine approaches include use in an intensification regimen rather than upfront chemotherapy or pre-transplant conditioning regimens. This was investigated in a phase II CALGB study [12•, 29]. Seventy-eight patients were treated with R-M-CHOP (R-CHOP with high-dose methotrexate) followed by high-dose cytarabine, etoposide, and rituximab intensification. Patients then underwent myeloablative conditioning prior to auto-SCT. Two-year PFS was 76 %, 5-year PFS was 56 %, and 5-year OS was 64 % in this group, with the regimen found to be reasonably well-tolerated.

In summary, these studies demonstrate that cytarabine-containing chemotherapy and preparative regimens followed by auto-SCT are a safe and effective therapy in younger patients MCL, and represent a standard of care pending confirmatory phase III trials of auto-SCT vs observation or alternative consolidation and maintenance therapies. When administering cytarabine, renal function and urine output must be monitored. Cerebellar toxicity is an uncommon but potentially devastating treatment complication, and cerebellar function should be monitored closely prior to each dose. Patients should receive prophylaxis for chemical conjunctivitis with either saline or dexamethasone eye drops.

Aggressive Therapy Without Transplant Consolidation

An alternate regimen utilizing high-dose cytarabine and high-dose methotrexate in the absence of transplant has been investigated. In a single-center phase II study, 97 patients with previously untreated MCL received R-hyper-CVAD alternating with R-MA (rituximab, high dose methotrexate, and cytarabine) [30•, 31]. In a 10-year follow-up analysis, the initial CR rate was 87 % and the median OS had not been reached. Median TTF was 4.6 years. Elevated beta-2 microglobulin and poor-risk IPI and MIPI were found to predict OS. Patients older than 65 years had significantly poorer OS and TTF, with worse hematologic toxicity. A subsequent multicenter study of the same regimen prior to auto-SCT demonstrated worse toxicity than the single center study with lower response rates [32]. Other studies have also shown unacceptable degrees of myelosuppression and toxicity-related deaths when using modified R-hyper-CVAD in elderly population [33]. This regimen can be considered in younger patients able to tolerate aggressive therapy but are otherwise unwilling or unable to undergo auto-SCT.

The benefit of high-dose methotrexate is uncertain and probably not required in therapeutic regimens for MCL. High-dose cytarabine appears to be the more relevant agent in treating MCL, however methotrexate may be considered if CNS disease is suspected (this is uncommon). High-dose methotrexate should only be given in a center that has experience with its administration and is able to provide on-site measurement of serum methotrexate levels. Renal function, urine output, and urine pH must be very closely monitored, and patients should receive leucovorin rescue per protocol to prevent extreme myelosuppression and mucositis which can lead to fatal infections.

Elderly/transplant Ineligible

MCL most commonly presents in elderly patients, many of whom are not eligible for transplant. In elderly patients, or younger patients with a poor performance status or other comorbidities, less aggressive treatment regimens should be utilized.

Bendamustine

Bendamustine has been used in Germany for decades, but has only recently been approved in other European countries and the United States. It is a nitrogen mustard-type alkylator and has been shown to be effective in the management of CLL and myeloma as well as NHL. Bendamustine and rituximab (BR) have been shown to have efficacy in relapsed MCL in a small (n=12) phase II study that showed an ORR of 92 % [34]. Given these promising results, a phase III study (StiL) was undertaken to examine BR vs R-CHOP in the upfront treatment of indolent lymphomas and MCL [16••]. Five hundred and fifteen patients received either BR (bendamustine 90 mg/m^2 d1-2 and rituximab d1 every 28 days) or standard R-CHOP every 21 days for a maximum of 6 cycles. Patients who received BR had improved PFS (69.5 months vs 31.2 months; P<0.001), with no difference in OS between the 2 groups (43 and 45 deaths

in the 2 groups, respectively). The BR group had less hematologic toxicity did the R-CHOP, with equivalent or superior efficacy. A similar study looked at the ORR of BR vs R-CVP or R-CHOP. Four hundred and nineteen patients with either newly diagnosed NHL or MCL were assessed. Among the MCL patients, BR showed a higher CR rate (51 % vs 24 %) although hematologic toxicities were more common; 6 patients in the BR arm died while on study [35].

We recommend BR as upfront therapy in elderly patients or any patient who may not be able to tolerate more aggressive therapy. If bendamustine is considered in relapsed disease in patients who have had prior cytotoxic chemotherapy exposure, we recommend a dose reduction to 70 mg/m^2 d1-2 every 28 days to decrease the risk of severe myelosuppression.

Maintenance Rituximab

Adding rituximab to the chemotherapy and preparative regimens prior to transplant has been shown to improve OS and PFS in MCL patients [36–39]. The use of rituximab as maintenance therapy has shown benefit in follicular and other indolent lymphomas, however data for maintenance rituximab (MR) in MCL has been lacking until recently. A phase III study enrolled 560 previously untreated MCL patients who were randomized to either R-CHOP vs R-FC (rituximab, fludarabine, cyclophosphamide) followed by either MR or interferon (IFN)-alpha [40••]. The study population was composed of transplant ineligible and elderly patients (median age 70 years). R-CHOP was shown to have superior ORR vs R-FC (87 % vs 78 %; P=0.0508), as well as superior OS (64 months vs 40 months; P=0.0072) and superior 4-year OS (62 % vs 47 %; P=0.005). The frequency of grade 3–4 hematologic toxicity was higher in the R-FC arm. The 316 patients receiving MR showed improved disease-free survival (DFS) vs IFN-alfa (58 % vs 29 %; P=0.01). MR improved the 4-year OS in patients who responded to R-CHOP (87 % vs 63 %, P=0.005).

The utility of MR was further investigated in a phase II study that administered maintenance rituximab following modified R- hyper-CVAD with bortezomib (VcR-CVAD) in 22 patients with MCL, demonstrating a CR/CRu of 77 % with a median PFS of 37 months [17]. The median OS was not reached. While this study showed promising results using MR, the VcR-CVAD regimen had to be modified by eliminating the second dose of vincristine and dexamethasone due to unacceptable toxicity.

MR has been shown to increase the percentage of patients with prolonged remission, but not DR in a phase III study of 56 MCL patients receiving R-FCM (fludarabine, cyclophosphamide, mitoxantrone, and rituximab) [41]. Similarly, a regimen of VcR-CVAD followed by MR in a phase II study of 75 patients with MCL has shown a 3-year PFS of 73 % and 3-year OS of 88 %, comparable with a control arm that underwent auto-SCT off-study [18, 19•]. An ECOG/Intergroup trial is ongoing testing MR with or without lenalidomide (see below).

R-CHOP followed by MR is a preferred regimen in elderly, transplant ineligible patients with MCL and was far superior to R-FC, which should not be used in MCL due to toxicity and poorer outcomes. The question of whether MR is beneficial following treatment with BR has yet to be answered (see below). Overall, we recommend the use of MR following R-CHOP in elderly and transplant-ineligible patients. MR following BR can be considered, recognizing that the confirmatory studies supporting this regimen are still pending.

Radioimmunotherapy

The use of ^{90}Y-ibritumomab tiuxetan, a radioimmunotherapeutic used in conjunction with rituximab as consolidation therapy after induction with R-CHOP has been investigated in a recent phase II study [20]. ^{90}Y-ibritumomab was given after 4 cycles of R-CHOP to patients with previously untreated MCL. Among the 56 patients analyzed, ORR was 82 % with a TTF of 34.2 months and 5-year OS of 73 % (median OS not reached). This regimen can be considered after R-CHOP however it has not been compared in a randomized study vs no consolidation therapy or MR.

Relapsed/refractory Disease

For patients with relapsed or refractory (R/R) MCL, there are numerous newer therapeutic agents that can be considered.

Bortezomib

Bortezomib, a proteasome inhibitor, is FDA approved for the treatment of R/R MCL. We recommend subcutaneous rather than IV administration, as a phase III study in multiple myeloma demonstrated comparable efficacy of bortezomib with less neuropathy when administered subcutaneously [41]. The multicenter, phase II PINNACLE study looked at bortezomib (1.3 mg/m^2 on d1, 4, 8, 11 q21d) in R/R MCL [22]. The median OS was 23.5 months, and was 35.4 months in responding patients. The 12-month OS was 69 % in all patients, and 91 % in responders.

A Phase I-II study looked at R-CHOP with concurrent bortezomib in 36 patients with MCL [21]. Most patients had an intermediate- or high-risk MIPI, with an average age of 66 years. ORR was 81 %, with a 2 year PFS of 44 %, and 2 year OS of 86 %. Taken together, these studies led to the approval of bortezomib for relapsed/refractory MCL. Patients must be monitored for thrombocytopenia and peripheral neuropathy when on bortezomib.

Lenalidomide

Lenalidomide, a derivative of thalidomide that works via several mechanisms including altering the tumor microenvironment and modulating immune response, has also been studied in MCL.

Two phase II studies have looked at single-agent oral lenalidomide in R/R MCL [42]. Both gave oral lenalidomide (25 mg d1-21 q28d). The NHL-003 trial found an ORR of 35 % in 57 MCL patients, with PFS of 5.7 months, and OS NR [43]. The ORR was higher in patients who had

received prior bortezomib and had a prior stem cell transplant. A more recent phase II multicenter study (EMERGE) in 134 patients with heavily pretreated R/R MCL showed an ORR of 28 % with median PFS of 4 months and median OS of 19 months [44].

Preclinical data demonstrates synergy for combined rituximab plus lenalidomide and led to a Phase I-II study of the combination in R/R MCL. Fifty-two patients received oral lenalidomide (20 mg d1-21 q28d) and weekly rituximab [45, 46]. OS was 24.3 months with PFS of 11 months. Most patients had prior exposure to rituximab.

mTOR Inhibitors

Temsirolimus inhibits the mammalian target of rapamycin, ultimately resulting in cell death. In a phase III study it was administered to 162 patients with R/R MCL and was compared with investigator's choice of therapy [47]. Temsirolimus was superior in median PFS (3.4–4.8 months vs 1.9 months; $P=0.0009$) as well as in ORR (22 % vs 2 %; $P=0.0019$) with no difference in median OS. Importantly, the duration of treatment was significantly longer in the temsirolimus arm. This study is limited in that it was compared against substandard treatment regimens for MCL (most patients received fludarabine or gemcitabine). 89 % of patients who received temsirolimus had grade 3 or 4 hematologic complications and asthenia. This study supports the use of temsirolimus in the treatment of R/R MCL; while it is approved in Europe, it is not yet FDA approved for this indication.

Other

Several older regimens have demonstrated efficacy in the treatment of MCL but have fallen out of favor as upfront therapy as the newer agents detailed above have emerged. These regimens are detailed in Supplemental Table 1.

Novel Agents

As we better understand the pathogenesis of MCL, unique cellular processes are revealed as potential therapeutic targets. A summary of key studies involving novel agents is listed in Table 2.

B-cell Receptor Pathway Inhibition

Detailed understanding of the B-cell receptor pathway has revealed some of the most promising therapeutic targets in MCL. Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, blocks B-cell activation and has been shown to be effective in mouse models of B cell malignancies [54]. A recent Phase II study of ibrutinib in 56 patients with R/R B-cell malignancies, 9 of whom had MCL, found an ORR of 54 % (78 % in MCL) with a 13.5 months PFS [49•]. In addition, a Phase II study of the BTK inhibitor ibrutinib (560 mg qday) in 115 MCL patients showed an ORR of 66 % [48•]. A study for patients who have relapsed after bortezomib has completed accrual, with results pending.

The PI3K inhibitor GS-1101 (CAL-101) has demonstrated efficacy in B-cell NHL as well as CLL [50]. In a Phase I trial of patients with R/R NHL, GS-1101 was given to 55 patients, 18 with MCL [55]. The ORR in the

Table 2. Novel agents

Drug class	Drugs	Mechanism of action	Study design	Dosing and schedule	Key Findings	Reference
B cell receptor antagonists	Ibrutinib (PCI-32765)	Bruton tyrosine kinase inhibitor, blocking product phosphorylation leading to subsequent inactivation of MAP kinase and NF-kappa B pathways.	Phase II ibrutinib in R/R MCL	Ibrutinib daily at 560 mg in continuous 28-d cycles until disease progression.	48 Patients, ORR 67 %, ORR 75 % in bortezomib-exposed cohort, 58 % in bortezomib-naïve cohort.	Wang et al [48•]
			Phase I/II ibrutinib in R/R B cell malignancies	Escalating dose of ibrutinib, 2 schedules.	56 Patients, ORR 54 %, 78 % in MCL patients (7/9), 13.5 m PFS.	Advani et al [49•]
	Idelalisib, NVP-BEZ235, perifosine, ON1910.Na	Phosphatidylinositol 3-kinase inhibitor, leading to subsequent inactivation of downstream pathways and cellular apoptosis.	Phase I idelalisib in R/R/NHL	Idelalisib orally daily or bid continuously in 28-d cycles for up to 12 cycles.	18 Patients with MCL, 55 patients total, 62 % ORR in MCL, median DR 3 m in MCL, MTD 150 mg bid.	Kahl et al [50]
			MCL tissue and cell samples exposed to BEZ235	Inhibition with BEZ235 inhibited MCL cell growth, was synergistic with conventional agents.	Inhibition with BEZ235 inhibited MCL cell growth, was synergistic with conventional agents.	Kin et al [5]
CDK inhibitors	PD 0332991, flavopiridol, seliciclib, SNS-032	CDK complexes with cyclin D1, promoting cell proliferation. Inhibition blocks retinoblastoma protein phosphorylation, resulting in cell cycle arrest.	Phase Ib PD 0332991 in R/R MCL	PD 0332991 125 mg daily.	17 Patients, 5 achieved PFS >1 y, 18 % ORR, with reduction in FDG uptake on PET.	Leonard et al [51]
Bcl2 inhibitors	AT-101, ABT-263, obatoclax	Dampens antiapoptotic effects of Bcl-2.			AT-101 was synergistic with carfilzomib, etoposide, doxorubicin, and 4-hydrocyclophosphamide in MCL.	Paoluzzi et al [52]
HDAC inhibitors	Vorinostat, abexinostat, panobinostat	Inhibits histone deacetylase.	Phase II abexinostat in R/R FL or NHL	Abexinostat (PCI-24781) 45 mg/m^2 PO BID × 7 d every other wk.	14 MCL patients; ORR 27 %, PFS 4 m.	Evens et al [53]

MCL cohort was 62 %, with a median DR of 3 months; the maximum tolerated dose (MTD) was 150 mg bid.

Other Targets

Cyclin Dependent Kinase (CDK) is an enzyme that complexes with cyclin D1, ultimately promoting cellular proliferation. Inhibition of this kinase has been shown to block retinoblastoma protein phosphorylation, resulting in cell cycle arrest. In R/R CLL, flavopiridol, a CDK-inhibitor, has efficacy, even in high-risk patient groups [56]. A Phase Ib study of the CDK inhibitor PD 0332991 in R/R MCL demonstrated a PFS greater than 1 year in 5 of the 17 patients enrolled [50]. ORR was only 18 % in this small study. Grade 3–4 neutropenia and thrombocytopenia were common, occurring in about a third and half of study patients, respectively.

The B-cell lymphoma-2 (Bcl-2) protein is present in most B-cell lymphomas and has anti-apoptotic effects. AT-101, a Bcl-2 inhibitor, has been shown to promote apoptosis by dampening Bcl-2 function, ultimately potentiating the effect of standard chemotherapeutic agents in an in vivo model of B cell lymphoma [52]. Studies involving Bcl2-inhibitors such as obatoclax, AT-101, and ABT-737 are ongoing.

Additional larger studies are needed to confirm safety and further quantitate efficacy of these novel agents vs current standard therapies. As results emerge from ongoing Phase II and Phase III trials it is likely that some of these agents, especially those targeting the BCR pathway, will transform our management of MCL and other lymphomas. Whether these agents will function independently of or in addition to standard therapies remains to be seen.

Ongoing Studies

While bendamustine has shown excellent efficacy and safety in elderly MCL patients, it has not been compared against aggressive regimens in younger patients. The Southwest Oncology Group/Intergroup 1106 trial seeks to answer this question by comparing R-bendamustine vs R-hyper-CVAD/methotrexate-cytarabine induction regimens. Both arms will be followed by autologous stem cell transplant in de novo MCL [57]. While the benefit of MR after R-CHOP has been shown, its utility after R-bendamustine has not been proven. Furthermore, the role of newer agents such as bortezomib and lenalidomide in conjunction with bendamustine has not been fully studied. To that end, the Eastern Cooperative Oncology Group/Intergroup is currently enrolling patients to receive induction BR with or without bortezomib followed by rituximab maintenance with or without lenalidomide [58].

Conclusions

Dramatic advances have been achieved during the past decade in the molecular and cellular biology of MCL, and toward improved outcomes and survival for MCL patients. Given the number of highly promising new

agents and therapeutic regimens, patients and oncologists have reason to be optimistic that the pace of progress will continue and, indeed, accelerate. Durable remission and potential cure, once considered unrealistic in MCL, should now become the priority for translational and clinical research.

Conflicts of Interest

L. Kyle Brett declares that she has no conflicts of interest.
Michael E. Williams is a consultant to Celgene, Millennium, Genentech, Pharmacyclics, has grants/grants pending with Allos, Astra Zeneca, Celgene, Genentech, Gilead, Janssen, Millennium, Novartis, and Pharmacyclics, and has had travel/accommodations expenses covered or reimbursed by Celgene, Genentech, and Novartis.

Electronic Supplementary Material

The online version of this article (doi:10.1007/s11864-013-0230-z) contains supplementary material, which is available to authorized users.

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