Published in final edited form as:

Cancer Control. 2012 July ; 19(3): 227–235.

MANTLE CELL LYMPHOMA: A CLINICALLY HETEROGENEOUS DISEASE IN NEED OF TAILORED APPROACHES

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Introduction

Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma considered incurable using conventional chemotherapeutic approaches. Emerging clinical data suggest considerable clinical heterogeneity, with some patients showing chronic/indolent course, while others may have a more fulminant course and very short survival akin to the acute leukemias. In the following review, we will attempt to highlight the epidemiology, prognosis, and management of this protean and challenging condition.

Diagnosis

MCL cells are typically described as being slightly increased in size with an indented nucleus lacking nucleoli. The classic immunophenotype includes positivity for CD5, CD19, CD20, and sIgM [Fig 1a]. Differentiating from marginal zone lymphoma and chronic lymphocytic leukemia may be challenging, though MCL is more likely to have higher expression of CD20, is typically negative for CD11c. Although CD23 is also typically negative, positive cases may be seen in up to 25% of cases^{1,2}. MCL is more specifically identified by the presence of the translocation t(11;14)(q13;q32), which juxtaposes the cyclin D1 gene to the immunoglobulin locus. Rare cyclin D1 negative variants do exist, which may be characterized by increased expression of cyclin D2. However, additional confirmatory testing is needed in such situations, as the specificity for cyclin D2 immunostaining in MCL is low. Although methodology continues to be refined, dual color FISH remains the most sensitive method for detection at this time [Fig 1b].^{1,3}

Epidemiology and Etiology

MCL accounts for 2–10% of the non-Hodgkin lymphomas, with a recently reported incidence rate of 0.51–0.55 per 100,000 persons. In general, patients are typically Caucasian (~2:1), male (~2.5:1), elderly (median age of onset: 68 years), and usually present with extensive disease, including widespread lymphadenopathy, bone marrow involvement, splenomegaly, circulating tumor cells, and bowel infiltration.⁴ US cancer registry data

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suggest an increase in the incidence of MCL between 1992 and 2007^{5,6}. Interestingly, this is coupled with a decrease in the number of cases of CLL, suggesting that improvements in diagnosis have facilitated better differentiation between these two entities⁷. This may similarly help to explain improvements in survival if patients are being diagnosed in earlier more indolent phases.

While some non-Hodgkin lymphomas have been found to be related to specific inherited, environmental, or infectious exposures, no strong and consistent relationship has been made for MCL. Weaker associations have been noted with exposure to European strains of *Borellia burgdoferi* (OR 3.5, 95% CI 1.8–7.4)⁸, family history of hematologic malignancy (OR 2.0, 95% CI 1.2–3.0)⁹, and genetic polymorphisms in the pro-inflammatory cytokine IL-10 (OR 1.3 per allele, *p* for trend=.04)¹⁰. Never-the-less, observed restrictions in immunoglobulin diversity suggest there may be as yet unidentified exposures that play a critical role in the development, and potentially maintenance, of this malignancy^{11,12}.

Indolent MCL

Retrospective data demonstrate that up to 30% of patients with MCL may have an indolent presentation, with no acute indication for therapy^{13,14}. These patients were identified by studying time to treatment, with indolent patients showing a delay of approximately one year before initiation of therapy. Notably, once patients require therapy, their outcome does not appear to be appreciably different from those with more classic presentations of disease^{13,14}. This may suggest a progression from indolent to aggressive disease akin to what is seen in multiple myeloma, where patients may progress from an indolent asymptomatic stage (smoldering myeloma) to more fulminant disease.

It is important to distinguish indolent MCL from ‘in situ’ MCL. The natural history of in situ MCL is not clearly delineated. Most series, including our own [Kubal T, unpublished observations], have only identified cases of in situ MCL retrospectively after patients’ present with more aggressive disease^{15,16,17}. This may suggest that a cohort of patients with in situ disease may exist that do not ultimately develop disease. Among those who do progress to aggressive disease, latency periods of up to 12 years have been noted, suggesting that these patients may be closely monitored without introduction of therapy¹⁸.

Attempts to prospectively identify patients with indolent MCL have proven difficult. Clinically, such patients often present with mild lymphocytosis and splenomegaly, with bone marrow and/or gastrointestinal involvement. However, some patients will also present with slowly progressive lymphadenopathy¹⁴. The use of PET-CT has helped to identify highly proliferative, so called blastoid variants, of MCL, which will typically show maximum standard uptake values in excess of 14. However, PET-CT has not been shown to reliably facilitate identification of indolent variants¹⁹. Ki-67, an obligate marker of proliferation, has been shown to correlate with prognosis, but is limited by significant inter-observer variability in measurement^{20,21}. Current research using quantitative image analysis to account for this is ongoing, but is not yet routinely available.

Molecular exploration has identified two potential candidates for discrimination of indolent cases: SOX11 and HDAC11. SOX11, a DNA binding protein important in cell ontogeny, is

commonly and aberrantly expressed in MCL. Emerging data suggest that indolent cases may lack expression of this protein²². Mechanistically, however, enforced suppression of SOX11 in cell culture increased proliferative rates, suggesting that further confirmation by other groups will be needed before any definitive conclusions can be reached in this regards²³. Finally, work by our group suggests that expression of the histone deacetylase, HDAC11, may correlate with prognosis. Specifically, blastoid MCL demonstrated very high expression of this enzyme (~15–20 fold), while classic MCL had an intermediate level of expression (~10 fold), and indolent MCL had only a minimal elevation (~2–3 fold)^{24,25}. Further work to better clarify the role and mechanism of HDAC11's influence on proliferation is ongoing.

Prognosis

The prognosis in MCL appears to be improving. This is likely a reflection of both earlier identification of more indolent cases, as well as the application of modern therapeutic modalities, including rituximab and autologous transplantation^{26,27}. Characterization of prognosis using algorithms tailored to either indolent lymphomas (the Follicular Lymphoma International Prognostic Index) or aggressive lymphomas (the International Prognostic Index) fail to effectively stratify patients into distinct subgroups. This has culminated in the development of a MCL specific algorithm – the Mantle Cell Lymphoma International Prognostic Index, or MIPI. This algorithm relies both on measures of chemotherapy tolerance (age, performance status) and indirect measures of disease activity (white blood cell count, LDH) to stratify patients into low, intermediate, and high risk groups. With a median followup of 32 months, those in the low risk group an estimated 5 year survival of 60%, while those in the intermediate and high risk groups had a median survival of 51 and 29 months, respectively^{28,29,30}.

Importantly, the MIPI is prognostic for overall survival, not chemotherapy response or progression free survival. Further, the MIPI has only been validated when calculated prior to first therapy. Ki-67, when 30% may be associated with inferior progression free survival, though, as mentioned above is limited by poor inter-observer agreement, particularly around this threshold²¹. A study by the GOELAMS found that PET-CT might predict for worse event free survival when using a cut-off of SUV values of 6, but sample size was small, and these data await confirmation³¹. Further, as with Ki-67, PET-CT is also limited by inter-observer variability³².

First Line Treatment

Therapeutic strategies in MCL have evolved over the past decade in an effort to improve the depth and duration of remission. These approaches can be thought of in two broad contexts: treatment of the young/fit individual and treatment of the old and/or infirm individual. Among young patients with limited comorbidity, the emphasis has been on increased treatment intensity, coupling targeted agents to aggressive chemotherapeutic regimens to improve the depth of response in anticipation of autologous stem cell transplantation. Alternatively, in older and infirm patients, an emphasis has been placed on de-intensification

of therapy, using targeted agents to either replace high dose therapy, and/or as a form of maintenance to prolong remission duration. These approaches are described further below.

Treatment of Indolent Disease

MCL in its indolent phases can be observed without therapy without any apparent detriment to survival. One clinical presentation includes asymptomatic lymphocytosis, splenomegaly without lymphadenopathy. Alternatively, some patients might present with asymptomatic, slowly progressive, non-bulky adenopathy^{33,34}. Either group of patients can be followed clinically without introduction of therapy until development of symptoms, rapidly growing lymphadenopathy, cytopenias due to splenomegaly or progression in bone marrow. However, some patients may be uncomfortable with watchful waiting and/or present with fatigue related to disease. In such cases rituximab can be administered as a single agent, given once weekly for four weeks, and followed with maintenance dosing once every two months for two years, akin to follicular lymphoma^{35,36,37,38,39}. While rare infections, as well as infusion reactions, have been reported in conjunction with rituximab, overall there would appear to be a favorable benefit to toxicity ratio with this approach³⁹.

Some patients with similar presentation may progress to a leukemic form of disease, with marked elevation in the white blood cell count (>100 k/ μ l), high LDH, progressive splenomegaly, and decline in the hemoglobin and/or platelet count. Leukemic MCL is frequently associated with p53 mutation and/or MDM2 overexpression (which binds active p53), and accordingly shows low response to standard chemotherapies. Such patients may benefit from palliative splenectomy, which has been shown to forestall the introduction of chemotherapy for as long as four years^{40,41,42}.

Treatment of Limited Stage Disease

Up to 6–8% of patients with MCL may present with stage I or II disease, with limited data on treatment outcome⁶. The largest retrospective analysis in this regards included 26 patients with nonbulky stage I and IIA disease treated with chemotherapy with or without involved field radiotherapy. Receipt of radiation was associated with a significant improvement in progression free survival (5 year PFS 68% vs 11%), with no patients demonstrating progression beyond six years⁴³. For stage I MCL, our practice has been to recommend involved field radiation in accordance to NCCN guidelines recommendation.⁴⁴

Evolution of Treatment for Advanced Disease

Formal randomized comparisons of chemotherapeutic approaches are uncommon given relative infrequency of MCL relative to other non-Hodgkin lymphomas. One of the earliest trials conducted by the EORTC retrospectively compared two highly aggressive regimens, CHVmp-VB (cyclophosphamide, doxorubicin, teniposide, prednisone, vincristine, and bleomycin) with ProMACE-MOPP (doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, procarbazine, and prednisone) in intermediate and high grade MCL. While CHMmp-VB demonstrated a slight improvement in CR rate (57%) and PFS (21 months) compared to ProMACE-MOPP, other trials using CHOP alone demonstrated

lower toxicity and similar time to treatment failure (~2 years) despite lower CR rates (15%)^{45,46,47}.

The introduction of rituximab to the therapeutic armamentarium was explored in several phase 2 studies, and ultimately in a pivotal randomized comparison of R-CHOP with CHOP^{36,37,38,48,49}. This trial demonstrated a significant improvement in response rates (94% vs 75%, $p=.0054$) and CR rate (34% v 7%, $P=.00024$) in the R-CHOP arm. Interestingly, median time to treatment failure was also improved in the R-CHOP arm (21 months v 14 months, $p=.0131$), while progression free survival and overall survival were not improved. In this respect, it is important to mention that time to treatment failure was measured from the time of treatment initiation, while progression free survival was measured from the time of treatment completion among responders only (those with CR or PR). This may suggest that the primary benefit for rituximab was in improving chemotherapy response in otherwise refractory patients.

Evolution of therapy for the Young

Cytarabine was the next drug to be incorporated into the therapeutic paradigm for MCL. Initial data came from a small French trial in which patients without CR after four cycles of CHOP were subsequently treated with DHAP (dexamethasone, high-dose cytarabine, and cisplatin). Among 25 patients who failed to obtain CR, DHAP was able to produce CR in 84% and median progression free survival of 51 months⁵⁰. This culminated in the development of regimens alternating cycles of CHOP-like chemotherapy with high-dose cytarabine given together with rituximab. Indeed, a recent comparison of R-CHOP (six cycles) versus R-CHOP/R-DHAP (given sequentially for 3 cycles each), demonstrated that the cytarabine containing arm was able to produce a higher rate of complete molecular response. Interestingly, while molecular response did not correlate with radiologic response, those with molecular response demonstrated an improved progression free survival⁵¹. One regimen in particular, R-HyperCVAD/MA has shown significant promise in MCL^{52,53}. Although this regimen was complicated by significant toxicity, particularly for those over age 65, the CR rate was 87% with and overall response rate 97%. Unlike early applications of high dose multi-agent chemotherapy, this approach was associated with a prolonged time to treatment failure (median 4.6 years) and overall survival when compared to historical controls (64% at 10 years with median followup duration of 8.3 years). Notably, time to treatment failure was far worse among those over 65y, with only 16% still in remission, and 33% alive at 8 years (versus 46% and 68%, respectively, among those under 65y, $p<.05$). This may be attributed to decreased compliance with prescribed therapy related to increased toxicity in this subgroup.

Early data with R-CHOP based inductions suggested that remission data could be prolonged using consolidation with high dose therapy and autologous stem cell transplantation^{49,54}. Further, outcomes appeared to be best among those transplanted in first complete remission^{55,56}. These data prompted further study of high dose cytarabine containing regimens administered in conjunction with autologous stem cell transplant⁵⁷. Pivotal phase II data were reported by the Nordic group in 2008, in which patients were treated with alternating cycles of Maxi-CHOP (similar to HyperCVAD) and high dose cytarabine for a

total of six cycles, followed by high dose conditioning using either BEAM or BEAC and autologous transplant. Rituximab was also administered during cycles 4–6, and in the event of molecular relapse post-transplantation. This approach yielded a CR rate of 54% with an overall response rate of 96%. With median followup duration of 3.8 years, the 4 year event free survival rate was 63%⁵⁸. A similar approach was explored by the CALGB, utilizing an induction of R-CHOP and methotrexate for 2–3 cycles, followed by one cycle of rituximab, high dose cytarabine, and etoposide, BEC conditioning and autologous transplant. All patients went on to receive an additional two doses of rituximab at weeks 6 and 7 after transplantation. With a median followup of 4.7 years, this study demonstrated a 5 year PFS of 56% (95% CI, 43% to 68%), and 5 year OS of 64% (95% CI, 50% to 75%). Unlike the Nordic study, which was limited to those age 65 and under, this study allowed patients up to age 69 to be enrolled (median age 57 years). Although responses were not stratified by age, those with high risk MIPI had a significantly lower survival than those with low or intermediate risk disease (33% vs 75%, $p < .03$)⁵⁹. Indeed, significant grade 3–4 toxicity was observed in both trials, largely related to neutropenic fever and infection^{58,59}.

This has prompted further study of alternative approaches to induction, as well as additional retrospective evaluation of high-dose cytarabine containing regimens. One alternative approach utilized a sequential regimen of R-CHOP for 4 cycles, followed by R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) for 2–3 cycles, and autologous transplant with BEAM conditioning. With 4.8 years of median followup, the authors observed a median PFS of 5 years and 5 year OS of 76%. Toxicity data were not presented in detail, however, despite inclusion of patients over the age of 60y (29% of cohort), this variable did not correlate with survival. Rather, proliferative index, as measured by Ki-67, was the only variable to be associated with this outcome.²¹ A more recent retrospective analysis from National Cancer Center Network's (NCCN) Non-Hodgkin Lymphoma Database reviewed outcomes among patients receiving R-CHOP or R-HyperCVAD/MA with or without autologous stem cell transplant. With a median followup of 33 months, this study demonstrated similar 3 year PFS for the R-HyperCVAD/MA (58%, 95% CI: 44–69%), R-HyperCVAD/MA+transplant (55%, 95% CI: 22–79%), and R-CHOP+transplant (56%, 95% CI: 33–74%) arms, while the R-CHOP arm was the only to demonstrate inferior 3 year PFS (18%, 95% CI: 6–36%). Three year OS data were also compared, and showed no significant differences between R-CHOP (69%, 95% CI: 46–83%), R-CHOP+transplant (87%, 95% CI: 64–95%), and R-HyperCVAD/MA (85%, 95% CI: 74–92%). Data were not mature enough to allow comparison with R-HyperCVAD/MA+transplant. Also confirmed was a higher rate of complications and an decreased ability to tolerate all six prescribed cycles among those receiving R-HyperCVAD/MA +/- transplant.⁶⁰ Together these data suggest that it may be possible to achieve a prolonged remission with less intensive therapy when coupled to autologous transplant.⁵¹ This may, in fact, be related to increasing depth of response, as measured by molecular response, when transplant is coupled to a less intensive induction. Alternatively, it may be premature to withhold autologous transplant even after more intensive therapy, as further differences may emerge with time.⁶¹

Evolution of therapy for the Elderly

While intensification of therapy to improve remission depth/duration has been the paradigm for young and fit patients, the approach in elderly patients has instead emphasized the addition, and increasingly the substitution, of novel agents with prolonged maintenance approaches to improve outcomes.

Important in this regards are seminal data presented at 2009 American Society of Hematology annual meeting comparing R-CHOP with R-bendamustine. Among 93 patients with MCL (with a median age of 70), R-bendamustine was shown to improve CR rates (39.6% v 30%, $p < .05$) as well as progression free survival (33 v 23 months, $p < .05$). Perhaps more relevant to this population, R-bendamustine was also associated with significantly less toxicity, including hematologic/infectious toxicity, alopecia, stomatitis, and paresthesias⁶². Although final published data are still pending, the significance of these findings has propelled R-bendamustine to the front-line in many patients (including younger patients). Ongoing cooperative group trials in older and younger patients are further evaluating the role of R-bendamustine.

Another promising approach includes the combination of cladribine and rituximab. This was initially explored by the North Central Cancer Treatment Group in an elderly cohort of 29 patients with untreated MCL (median age 70). This regimen was associated with an overall response rate of 66% (52% CR). The median PFS for all patients was ~1 year. However, among those who obtained CR the duration of response was prolonged, with only 20% relapsing after a median followup of 21.5 months. Further, this regimen was associated with a 2 year survival of 78%, despite a lack of autologous transplant consolidation⁶³. Given the strength of these data, a followup trial was performed with cladribine and rituximab. Importantly, this trial administered rituximab once per week for the first cycle, after which rituximab was given once with each additional cycle. Additionally, rituximab was continued in the majority of responders as a maintenance therapy. In this study of 31 untreated patients, an improved overall response rate (87%) and complete response rate (61%) were observed. After a median followup of 32.5 months, the median PFS and OS were 37.5 and 85 months, respectively. Among those who obtained a complete response, only 1 has relapsed after median followup of 23 months⁶⁴.

Given the importance of rituximab in the induction setting, current studies are attempting to address the importance of this agent when administered as maintenance following chemotherapy, in lieu of autologous stem cell transplantation. Two trials recently examined this approach. The first trial explored the role of rituximab maintenance administered for two years to those with a CR or PR following modified R-HyperCVAD (in which high-dose cytarabine and methotrexate were omitted). Among 22 patients with newly diagnosed MCL, the median age was 63, and ranged from 40–81 years. Despite omission of high dose cytarabine, the overall response rate after induction was 77% (64% CR). With a median followup of 62 months, the median progression free survival in this cohort was 38 months, and the median overall survival 70 months⁶⁵. This is surprisingly similar to the aforementioned data using rituximab and cladribine with rituximab maintenance⁶⁴. A subsequent trial was recently performed by the European MCL Network and presented at the

2011 annual meeting of the American Society of Hematology. This trial recruited only patients over the age of 60 considered ineligible for more intensive approaches. In this trial, rituximab or interferon alpha maintenance was administered until progression in those with either a CR or PR following standard R-CHOP or R-FC induction. The overall response rate following R-CHOP was 87% (CR 50%). With a median followup of 38 months, the median remission duration in those randomized to rituximab maintenance is 56 months, compared to 26 months with interferon ($p=.01$). In addition rituximab maintenance resulted in an overall survival benefit in those patients that were initially treated with R-CHOP (4 year OS 87% vs 57%, $p<.01$)⁶⁶. These outcome data are surprisingly similar to the more intensive approaches described for younger patients.

Relapsed Disease

Unfortunately, despite intensive and/or prolonged chemotherapeutic approaches, MCL remains incurable in the absence of allogeneic transplantation. This approach, however, is encumbered by significant toxicity, and is likely best tailored to young, fit patients with chemo-sensitive disease.⁶⁷ Although a complete review of treatment approaches in this setting is beyond the scope of this review, a few are worthy of mention.

Lenalidomide, a second generation immunomodulatory agent derived from thalidomide is showing increasing promise in this malignancy. Lenalidomide as a single agent appears to show response rates as high as 53% with a median progression free survival of nearly six months⁶⁸. Perhaps reflective of its immune-potentiating effects, when coupled to rituximab, the median progression free survival increases to approximately 14 months^{69,70}. This is quite a dramatic response in the relapsed and refractory setting, and has prompted the development of phase II studies to study the role of this combination as a front-line regimen for patients considered ineligible for more intensive approaches (clinicaltrials.gov identifier NCT01472562).

Bortezomib has similarly shown promise in the relapsed and refractory patients, and was FDA approved for use in this setting. Response rates and median progression free survival mirror that seen with single agent lenalidomide, hovering around 50% and 6 months, respectively^{71,72,73,74}. Interestingly, however, among responding patients, the median progression free survival is quite prolonged (10–24 months). These data have fueled numerous phase 1 and 2 studies in which bortezomib has been coupled to cytotoxic backbones – including bendamustine⁷⁵, gemcitabine⁷⁶, CHOP^{77,78}, and HyperCVAD⁷⁹, among others. Perhaps the most compelling data in this regards comes from a small phase II trial investigating the combination of bortezomib with rituximab and dexamethasone in 16 heavily pretreated patients. This combination produced an overall response of 81.3% with a CR rate of 43.8% with median progression free and overall survival of 12.1 and 38.6 months, respectively. Further, of the seven patients who obtained a CR, five sustained this response beyond 48 months in absence of further therapy⁸⁰.

Several preclinical studies have suggested aberrant signaling via the AKT-MTOR pathway might play a dominant role in driving proliferation in MCL⁸¹. Attempts to inhibit this pathway with Temsirolimus, an inhibitor of the MTORC1 complex, however, have proven

only moderately successful with response rates of approximately 20%, and a corresponding progression free survival of approximately 5 months⁸².

Several malignancies have shown significant disruption of gene expression as a consequence of aberrant epigenetic modification. Histone deacetylases, in particular, appear to play an important role in immunological escape, proliferation, and autocrine cytokine signaling which may be important in maintaining the microenvironmental niche and facilitating drug resistance^{83,84,85,86,87}. As a single agent, the nonspecific histone deacetylase inhibitor vorinostat failed to show significant response in relapsed/refractory MCL, however, one of the nine treated patients maintained stable disease for over 2 years⁸⁸. Building on this approach is an ongoing study evaluating the efficacy of vorinostat given in conjunction with velcade in relapsed/refractory MCL, with early data showing a 47% overall response rate⁸⁹. Of particular interest are isotype specific HDAC inhibitors, including those targeting HDAC6, which may contribute significantly the malignant phenotype of MCL⁸⁶.

Emerging Agents

Several drugs currently being explored in phase I and II studies are showing exquisite promise in MCL. One particularly promising approach has focused on disruption of B-cell receptor downstream signaling. Two agents are notable in this regards: PCI37625 and CAL-101. Administration of PCI37625 leads to targeted inhibition of Bruton's Tyrosine Kinase, and so far is showing an overall response rate of 67%⁹⁰. CAL-101 is targeted to the specific isoform of Phosphatidylinositol 3-kinase delta, and has shown an overall response rate of 62%⁹¹. Interestingly, both agents are associated with lymphocytosis, suggesting that inhibition of this pathway may be associated with disruption of microenvironment, perhaps via secondary influences on CXCR4 signaling^{92,93}.

The failure of temsirolimus to produce dramatic responses has fostered further preclinical study showing that MCL may escape MTORC1 inhibition via increasing signaling through MTORC2 and phosphorylation of AKT, a survival pathway⁹⁴. This has led to the development of several dual MTORC inhibitors, including OSI-027 and PP242, both of which are currently in phase I clinical testing.

Given that over-expression cyclinD1 is central to pathogenesis of mantle cell lymphoma, current studies are also underway to inhibit this molecule. Interestingly targeted disruption of cyclinD1 was associated with increased signaling via cyclinD2 and cyclinD3 in preclinical models⁹⁵. Therefore research has been focused on inhibiting downstream targets of cyclinD1. One such novel agent is PD0332991, which targets cyclin dependent kinases 4 and 6 to effectively inhibit proliferation in MCL. Clinical studies using this as a single agent have shown an overall response rate of 18% in relapsed cases. Although this response rate was lower than expected, subsequent pharmacodynamic studies demonstrated significant inhibition of cell cycling⁹⁶. This has fueled an alternative approach, currently under study, in which PD0332991 is administered to coordinate cell cycling to facilitate enhanced sensitivity to the agent bortezomib⁹⁷.

Conclusions

MCL is a protean disease with both indolent and highly aggressive presentations, which must be reconciled with host factors, including patient age and comorbid conditions, to appropriately tailor therapy. Although increases in treatment intensity and duration have yielded significant benefit for many with MCL, the disease continues to be characterized by a pattern of continuous relapse. Novel approaches are beginning to show promise in these settings, with many exciting agents currently poised to make significant additional impact.

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Fig 1.

(a): Classical immunophenotype for MCL shows high CD20 expression in conjunction with CD5. CD23 is typically negative, though can be dimly positive in up to 25% of cases.

CD11c is very seldom positive, and may provide better diagnostic utility than CD23.^{1,2} (b)

The translocation between 11q13 and 14q32 defines the vast majority of cases, and is best identified by dual color FISH techniques.^{3,98,99,100}

Fig 2.

Treatment approaches in MCL. Treatment in the young has steadily progressed with regards to intensity with the goal of molecular eradication of disease. Treatment in the elderly, alternatively has stressed treatment tolerance with the application of novel agents for maintenance and in relapsed settings.