Mantle cell lymphoma: observation to transplantation

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Ther Adv Hematol

2015, Vol. 6(1) 37–48

DOI: 10.1177/
2040620714561579

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Abstract: Mantle cell lymphoma as a rare non-Hodgkin B-cell lymphoma can present in different clinical presentations such as an aggressive form or a more indolent picture. Treatment modality is based on multiple factors including age, presence or absence of symptoms, and comorbidities. Watchful waiting is a reasonable approach for asymptomatic patients especially in elderly. In symptomatic patients, treatment is chemo-immunotherapy followed by maintenance immunotherapy or autologous bone marrow transplant. Allogeneic bone marrow transplant has a potential benefit of cure for relapsed/refractory cases, but it has a high mortality rate. Novel treatment with agents such as ibrutinib, a Bruton tyrosine kinase inhibitor, has shown promising results in relapse/refractory cases. We extensively review the most recent data on diagnostic and therapeutic management of mantle cell lymphoma through presenting two extreme clinical scenarios.

Keywords: chemo-immunotherapy, ibrutinib, mantle cell lymphoma, transplantation

Introduction

Mantle cell lymphoma (MCL) represents about 6–8% of all non-Hodgkin lymphomas. The median age at presentation is in the 60s and there is a male to female predominance of 2:1. MCL patients usually present with stage III/IV disease with bone marrow involvement, extensive lymphadenopathy and splenomegaly. They can present with leukocytosis or pancytopenia, and involvement of extranodal sites such as the gastrointestinal (GI) tract or Waldeyer's ring is also common. Four histological subtypes have been defined, although with the exception of the blastic type, the clinical significance of morphological differences is uncertain. The chromosomal abnormality, t(11, 14)(q13, q32) between the IGH and CyclinD1 genes, resulting in overexpression of cyclinD1 (bcl-1) is seen in up to 99% of MCL patients. Despite new aggressive therapeutic approaches, the median overall survival for MCL patients is in the range of only 5–7 years. Here we review the most recent literature on the management of this type of lymphoma along with two different clinical scenarios typical of patients with MCL.

Case A

A 39-year-old man with a history of chronic abdominal pain underwent a CT scan of abdomen and pelvis which showed splenomegaly and multiple masses in the cecum with pericecal lymphadenopathy. A colonoscopy confirmed nonobstructing masses in the cecum and a biopsy was taken which showed lymphoma. A diagnosis of MCL was confirmed by flow cytometry which showed a monoclonal B-cell population expressing CD5+ and CD20+, cyclin D1+, but was negative for CD10 and CD23. Immunohistochemistry on the biopsy specimen showed SOX11 overexpression. The proliferative index, using staining for the Ki-67 antigen, was estimated as 47%. His white blood cell count (WBC) was 22,000 with 68% lymphocytes, 23% granulocytes and 8% monocytes. His hemoglobin was 9.2 and his serum lactate dehydrogenase (LDH) was 323 (upper limit of normal 150). For further staging evaluation a bone marrow biopsy as well as whole body positron emission tomography-computer tomography (PET-CT) scan was obtained. His bone marrow biopsy was positive for involvement with MCL; a PET-CT scan revealed no intrathoracic lymphadenopathy. The hepatitis panel and HIV serology was negative. Since the

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patient did not have any GI symptoms, no colonoscopy was done. The patient was neurologically asymptomatic. The patient's ECOG performance status was 2. Based on the simplified Mantle cell lymphoma International Prognostic Index (MIPI) risk stratification he was considered a high risk patient and his estimated 5-year overall survival (OS) was considered about 29 months.

The patient was treated with the R-HyperCVAD (rituximab plus hyperfractionated cyclophosphamide, vincristine doxorubicin, and dexamethasone alternating with cycles of methotrexate and cytarabine) regimen. He achieved complete response (CR) after the 4th cycle, completing a full eight cycles of chemo-immunotherapy without any serious acute event. His treatment was then consolidated with autologous stem-cell transplantation (AutoSCT). The patient achieved a complete remission. At 17 months post-transplant he developed shortness of breath and a cough. PET-CT showed left hilar and mediastinal lymphadenopathy with a small left pleural effusion. A bronchoscopy and biopsy confirmed the disease relapse. He then underwent salvage chemotherapy with three cycles of the rituximab plus ifosfamide, carboplatin and etoposide (R-ICE) regimen and a restaging workup then showed minimal disease. Thereafter he was consolidated with a reduced intensity preparative chemotherapy followed by allogeneic stem-cell transplantation (AlloSCT). The patient has been disease free for about 36 months.

Case B

A 68-year-old man with splenomegaly found on a routine physical exam underwent a CT scan of the abdomen and pelvis which showed moderate splenomegaly and multiple enlarged retroperitoneal lymph nodes. PET-CT did not reveal any thoracic lymphadenopathy but confirmed the presence of retroperitoneal lymph nodes with a maximum standardized uptake value (SUV) of 3.2 in a left midparaaortocaval lymph node. Biopsy of that lymph node confirmed classic MCL with no SOX-11 overexpression and a Ki-67 percentage of 9%. The patient denied weight loss, fevers or night sweats or any other symptoms. His performance status (PS) was 1 and his bone marrow biopsy was positive for involvement with lymphoma. His WBC was 6200 with a normal differential. His hemoglobin was 12.3 and his lactate dehydrogenase (LDH) was 203. A 'watch and wait' strategy was chosen for this patient until about 10 months later when

he came back with complaints of back pain as well as weight loss of 15 lb in 2 months. A new CT scan revealed progressively enlarging retroperitoneal lymph nodes. His PS was 2 and his WBC was 8600 with 81% lymphocytes. His hemoglobin was 11.1 and his LDH was 375.

He was treated with R-Bendamustine for six cycles, achieving a CR. He then continued his rituximab as a maintenance therapy for 2 years. He was in remission for 18 months after completion of maintenance but then returns with night sweats for 1 month and a PS of 3 and multiple enlarged cervical lymph nodes. Lymph node biopsy again confirmed disease relapse. His WBC was 15,300 with 75% lymphocytes. His hemoglobin was 9.0 and his LDH was 410. He was then offered participation in a phase II clinical trial with GS-9973 (Entospletinib), an investigational oral inhibitor of spleen tyrosine kinase. He is under treatment currently.

Discussion

MCL patients typically have stage III or IV disease at the time of diagnosis, with extensive lymphadenopathy, splenomegaly and blood and bone marrow involvement [Tiemann *et al.* 2005]. It is imperative to perform a full staging workup before starting treatment. This should include a complete blood count (CBC), chemistry profile, bone marrow biopsy with flow cytometry and also imaging of the thorax, abdomen and pelvis. As with other lymphomas, the use of fluoro-deoxyglucose positron emission tomography (FDG-PET) is increasing for patients with MCL. Studies in several lymphoma subtypes have suggested that the use of FDG-PET CT compared with conventional CT scanning is associated with higher sensitivity and frequently 'upstages' patients because of its ability to detect metabolically active areas of disease not apparent on routine radiology. Since the majority of patients with MCL have stage III or IV disease at presentation, this is unlikely to have a significant impact on the choice of therapy. At present, there are very few prospective data to support the use FDG-PET CT for staging, during therapy and after therapy outside of a clinical trial [Brepoels *et al.* 2008; Gill *et al.* 2008a, 2008b]. However, in the context of relatively intensive chemotherapy regimens, FDG-PET CT has shown to have prognostic value, with higher progression-free survival (PFS) and OS rates reported in MCL patients who are FDG-PET-negative at the completion

Table 1. Simplified Mantle cell International Prognostic Index (MIPI).

Points	Age (years)	WBC ($10^9/L$)	LDH/ULN LDH	ECOG PS
0	Less than 50	Less than 6,700	Less than 0.67	0–1
1	50–59	6,700–9,999	0.67–0.99	–
2	60–69	10,0–14,999	1.00–1.49	2–4
3	70	15,000	1.500	–

PS, performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal; WBC, white blood cell count

of chemotherapy [Karam *et al.* 2009; Schaffel *et al.* 2009; Mato *et al.* 2012].

Symptomatic involvement of the GI tract by MCL has been reported in 15–30% of patients at the time of presentation [Norton *et al.* 1995; Majlis *et al.* 1997; Romaguera *et al.* 2000]. In a study by Romaguera and colleagues, the use of routine staging with colonoscopy in all patients regardless of symptom status detected GI involvement in 88% of patients, many of whom had macroscopically normal GI mucosa [Romaguera *et al.* 2003]. The incidence of lower GI tract involvement is higher than in the upper GI tract. In general, knowledge of GI tract involvement has only a minor, if any impacts on management since most patients have advanced disease involving other known sites. However, colonoscopy and/or upper GI endoscopy is recommended for patients with GI symptoms including abdominal pain, changes in bowel habit and bleeding.

Central nervous system (CNS) involvement at the time of diagnosis of MCL is rare (<5%); this incidence is increased up to 26% over 5 years of clinical progression in the setting of relapsed/refractory disease [Ferrer *et al.* 2008; Gill *et al.* 2009]. MRI imaging of CNS and cerebrospinal fluid (CSF) examination for staging is indicated in neurologically symptomatic MCL patients. Some reports suggest a higher incidence of CNS involvement for patients with the blastoid variant of MCL. Routine CSF cytologic examination in asymptomatic patients is generally not recommended.

The transcription factor SRY (sex determining region Y) -11 (SOX11), is overexpressed in 90–95% of MCL patients and has been shown to have diagnostic utility in rare cases of cyclin D1 negative MCL, and in the distinction between MCL and diffuse large B-cell lymphoma (DLBCL) [Mozos *et al.* 2009]. Several studies have suggested that the absence of SOX11 by immunohistochemistry or gene expression

profiling is associated with a more indolent clinical course, characterized by a lower frequency of nodal involvement and higher frequency of leukemic presentation [Ek *et al.* 2008; Dictor *et al.* 2009; Fernandez *et al.* 2010]. However, results from recent studies have failed to confirm this finding [Nygren *et al.* 2012]. Therefore, although SOX11 overexpression has diagnostic utility in MCL, its role as a prognostic factor remains unclear. Emerging data has suggested a possible role for histone deacetylase expression as a prognostic factor in MCL, although this requires confirmation [Hoster *et al.* 2008].

Most trials in MCL have reported a median duration of response to conventional chemotherapy of 1.5–3 years and a median OS of 5–7 years. The MIPI, described by the European Mantle Cell Lymphoma Network, has been widely used for prognostication and risk-adapted therapy of MCL patients [Hoster *et al.* 2008; Geisler *et al.* 2010; Romaguera *et al.* 2010]. The independent prognostic factors incorporated in this index include patient's age, performance status, LDH level and WBC at the time of diagnosis (Table 1). In the simplified MIPI (s-MIPI) each prognostic factor has a score of 0–3. Patients with a total score of 0–3 are considered as low risk, 4–5 intermediate risk and 6–11 are defined to be high risk. Case A has s-MIPI score of 8 which categorizes him in the high-risk group.

The proliferative index, determined by Ki-67 percentage, which correlates with the level of cyclin D1 mRNA, was identified by the European MCL Network as an important prognostic marker [Rosenwald *et al.* 2003; Katzenberger *et al.* 2006; Determann *et al.* 2008; Klapper *et al.* 2009]. It is generally considered low when reported below 30% on immunostaining and high when it is more than or equal to 30%. The blastoid subtype typically has a high index, usually over 40%. Ki-67 percentage has been included in the MIPI scoring system to produce a modified MIPI known as the

biological MIPI (MIPIb) [Hoster *et al.* 2008]. A high Ki-67 can be added as one score to the total s-MIPI score for calculating the risk level. For selected patients with indolent disease and low MIPI scores, especially if older, initial observation may be appropriate. For patients with intermediate- or high-risk scores a definitive therapeutic approach is warranted which varies mainly based on the patient's age and presence or absence of comorbidities (see below).

At present, no standard of care exists for the first-line management of patients with MCL. Optimal first-line therapy is controversial and prospective, randomized trials of intensive chemo-immunotherapy regimens compared with more 'standard' NHL regimens are still in progress or only recently reported. Current approaches are therefore based primarily on results from phase II studies, results of which are likely to be influenced by selection bias. In early studies, CHOP was widely used as a first-line regimen and after the introduction of rituximab, a prospective, randomized trial compared CHOP with R-CHOP for initial therapy of MCL. This trial demonstrated higher overall response and CR rates for R-CHOP compared with CHOP, as well as improved time to treatment failure (21 months *versus* 14 months for R-CHOP and CHOP, respectively, $p=0.0131$), although no difference in PFS or OS was observed [Lenz *et al.* 2005].

In view of the relatively poor time to treatment failure and PFS rates reported for R-CHOP and similar regimens, several groups have explored more intensive induction regimens for younger patients with MCL. The HyperCVAD regimen (hyperfractionated cyclophosphamide, vincristine, adriamycin and dexamethasone alternating with high-dose cytarabine and methotrexate), initially developed at the MD Anderson Cancer center for the treatment of adult patients with acute lymphoblastic leukemia was evaluated in patients with MCL. In the initial description of this regimen, responding patients underwent consolidative therapy with AutoSCT or AlloSCT. For previously untreated patients, the overall response rate was 93% and the 3-year OS and event-free survival (EFS) were 92% and 73%, respectively [Khouri *et al.* 1998]. In a subsequent phase II study, the same group added rituximab to the HyperCVAD regimen and omitted stem-cell transplantation for patients in CR at completion of induction therapy. An overall response rate of 97% was reported (87% CR)

and with median follow up at 8.3 years, the 10-year OS was 64% [Romaguera *et al.* 2005; Bernstein *et al.* 2010]. The R-HyperCVAD regimen is associated with significant toxicity, particularly myelosuppression and immune compromise, limiting its applicability to unselected patient populations and to older patients. A phase II study of the R-HyperCVAD regimen in an unselected patient population in the context of a multicenter study reported inferior results and marked toxicity of this regimen [Bernstein *et al.* 2013]. Subsequent studies have confirmed the high myelotoxicity of this regimen, reflected in the high rate of failure to mobilize hematopoietic progenitor cells for subsequent autologous transplantation [Hill *et al.* 2011].

Other intensive approaches to treatment of younger patients with MCL have exploited the apparently high activity of high-dose cytarabine in this disease. Sequential studies from the Nordic Lymphoma Group have culminated in the MCL2 study, in which patients aged less than 65 years were treated with alternating cycles of an intensified CHOP regimen ('maxi-CHOP') with high-dose cytarabine for total of six cycles, with the addition of rituximab. This induction therapy was followed by high-dose therapy and AutoSCT as remission consolidation therapy. An overall response rate of 96% was reported, with a 4-year EFS rate of 63% [Geisler *et al.* 2008]. In a subsequent update, although some late relapses were reported, the median EFS was 7.4 years and the median OS and RFS exceeded 10 years [Geisler *et al.* 2012]. Comparable results have recently been reported from the Group D'Etude des Lymphomes de l'Adulte (GELA), from a phase II study of the use of CHOP for three cycles, followed by DHAP for three cycles, with the inclusion of rituximab and consolidation with high-dose therapy and AutoSCT [Delarue *et al.* 2013]. With median follow up at 67 months, the median EFS was 83 months, median OS had not been reached and 5-year OS was 75%. The apparent benefit of an intensive approach in younger patients has recently been confirmed in a large, prospective randomized study from the European Mantle Cell Lymphoma Network in which patients less than 65 years old with MCL were randomized between six cycles of R-CHOP followed by AutoSCT or alternating cycles of R-CHOP $\times$ 3 and R-DHAP (dexamethasone, high-dose cytarabine and cisplatin) $\times$ 3 followed by AutoSCT. Although response rates were comparable in both arms of the study, remission

duration was superior in the R-DHAP containing arm (49 months *versus* 84 months, $p = 0.0001$), as was median OS (82 months *versus* not reached, $p = 0.045$) [Hermine *et al.* 2012].

Based on these observations, current evidence favors the use of intensive induction therapy including high-dose cytarabine for younger patients with advanced MCL. The optimal regimen has not yet been defined, and is likely to evolve with the introduction of new agents into front-line therapy, including bendamustine and bortezomib (see below). At present, most centers include consolidative high-dose therapy, using a regimen including cytarabine, and AutoSCT for responding patient after intensive induction therapy. Several studies have demonstrated the use of consolidation therapy with AutoSCT after myeloablative chemotherapy in MCL patients younger than age 65 especially when in first CR [Tam *et al.* 2000; Andersen *et al.* 2003; Vandenberghe *et al.* 2003; Lefrere *et al.* 2004; Dreyling *et al.* 2005; Evens *et al.* 2008; Geisler *et al.* 2008, 2012; Hermine *et al.* 2012; Delarue *et al.* 2013].

In a multi-institutional retrospective cohort study LeCase and colleagues compared outcomes for patients with MCL who had received R-CHOP or R-HyperCVAD induction, with or without AutoSCT [LeCase *et al.* 2012]. Three year PFS rates were 58% for R-HyperCVAD, 55% for R-HyperCVAD followed by AutoSCT, 56% for R-CHOP followed by AutoSCT and 18% for R-CHOP only. No significant differences in overall survival were observed for any of these approaches, although follow up for those receiving R-HyperCVAD followed by AutoSCT was very short.

Based on these observations and the results of the trials summarized in the preceding section, it is now widely accepted that R-CHOP alone is inadequate therapy for younger patients with MCL and that if this regimen is chosen, consolidative AutoSCT should be used in first remission, achieving results comparable with those achieved with intensive induction therapy. Current phase II data as well as the results of a single randomized trial suggest a benefit for AutoSCT after high-dose cytarabine-based induction therapy (see the previous section). The benefit of consolidative AutoSCT after the R-HyperCVAD regimen has not been confirmed in a prospective setting but is widely used based on experience with other intensive

regimens. The applicability of AutoSCT after this regimen is, however, limited by the difficulty in stem cell harvesting after R-HyperCVAD. Because of this, many centers collect peripheral blood progenitor cells after four cycles of therapy, and some centers give a total of only four cycles prior to transplant, although there are few prospective data to support this approach. Although limited data have been reported for the use of AlloSCT in first remission for younger patients with MCL with a suitable donor, the high regimen related toxicity and mortality associated with AlloSCT have largely precluded its use in first remission [Tam *et al.* 2000; Evens *et al.* 2008]. Although AlloSCT is being used increasingly in the relapse setting (see below) it is not currently recommended for consolidation of first remission.

No standard of care exists for the management of relapsed and refractory MCL in younger patients. Reports of the use of AutoSCT in the relapsed and refractory setting have been disappointing, with only around 25–30% patients remaining disease free after 2–3 years of follow up [Ketterer *et al.* 1997; Vose *et al.* 2000]. As a result of this, and based on observations of an apparent graft *versus* lymphoma effect in MCL, AlloSCT has been evaluated extensively in younger patients with relapsed disease. As with other subtypes of lymphoma, the benefit of stem-cell transplantation for relapsed or refractory disease appears to be related to the responsiveness of the disease to cytoreductive therapy given prior to transplantation.

Multiple single institution and registry studies have investigated the use of AlloSCT in relapsed and refractory disease, including patients who have previously undergone AutoSCT [Goy *et al.* 2000; O'Connor *et al.* 2005; Fisher *et al.* 2006; Hertzberg *et al.* 2006; Kane *et al.* 2007; Cook *et al.* 2010; Le Gouill *et al.* 2012; Hamadani *et al.* 2013]. Results from these studies have been variable, probably in part because of the effect of selection bias in single institution and registry-based studies, but most of these studies suggest that a proportion of patients with relapsed and refractory MCL achieve long-term DFS and potentially are cured by this approach. Typically, around 25% of patients undergoing AlloSCT achieve durable remissions if their disease is demonstrated to be chemosensitive prior to transplant. In most series, the use of AlloSCT in this population has been associated with high nonrelapse mortality, mostly due to graft *versus* host disease and its complications and typically

affecting 30–40% of patients. In view of this, uncertainty exists regarding the optimal conditioning regimens.

Reduced-intensity conditioning regimens were developed to provide sufficient immunosuppression to allow engraftment and graft-versus-lymphoma effect while avoiding the toxicities associated with the myeloablative regimens. The reported 1-year treatment-related mortality (TRM) has typically been lower in RI-AlloSCT regimens, usually less than 30%, when compared with MA-AlloSCT regimens, where TRM has typically been in the 40–50% range [Khouri *et al.* 2003; Maris *et al.* 2004; Hertzberg *et al.* 2006; Corradini *et al.* 2007; Armand *et al.* 2008; Cook *et al.* 2010; Le Gouill *et al.* 2012; Hamadani *et al.* 2013]. However, recent comparative studies have demonstrated comparable outcomes for both types of regimen. For example, a recent report from the CIBMTR included 202 patients with MCL, 74 of who received myeloablative regimens, the remainder undergoing RI-AlloSCT. At 3 years, no differences were observed in relapse or progression (33% for MA *versus* 32% for RI, $p=0.89$), nonrelapse mortality (47% for MA *versus* 45% for RI, $p=0.68$), PFS (20% for MA *versus* 25% for RI, $p=0.53$) or OS (25% for MA *versus* 30% for RI, $p=0.45$). These authors concluded that the intensity of the conditioning regimen did not affect outcome.

Current evidence suggests that AlloSCT is a curative option for about 25% of younger patients with relapsed and refractory MCL who respond to pretransplant therapy. There are no prospective data which support the use of myeloablative over reduced intensity conditioning although many transplant centers currently favor the latter approach. Patients with relapsed disease who are not eligible for transplantation should be offered participation in clinical trials in the absence of a current standard of care.

Although many centers have evaluated 'standard' cytoreductive regimens such as R-DHAP or R-ICE (rituximab, ifosfamide, carboplatin, etoposide) in this context, there is increasing interest in the role of newer agents such as bortezomib in the pretransplant setting. Single-agent bortezomib has been evaluated in several studies for patients with relapsed and refractory MCL and is currently licensed for this indication [Goy *et al.* 2000; Fisher *et al.* 2006; Kane *et al.* 2007; O'Connor *et al.* 2005]. In phase II studies, reported response

rates have been around 50%, with typical response duration being approximately 6 months. Long-term follow up of one of these studies has reported median response duration of 9.2 months, with an OS of around 2 years [Kane *et al.* 2007]. In this study, results were similar for patients who had received intensive compared with relatively non-intensive first-line therapy. Currently, there are very few data regarding the role of single-agent bortezomib as a pretransplant, cytoreductive therapy. As other new agents are identified with activity in MCL (see below) it is likely that these will also be considered as pretransplant therapies for patients with relapsed and refractory disease.

Although no standard of care has been identified in asymptomatic MCL patients, it is now recognized that up to 30% of patients have a relatively indolent clinical presentation, characterized by splenomegaly, bone marrow and/or GI involvement, often also with mild peripheral blood lymphocytosis and slowly progressive lymphadenopathy, but without systemic symptoms. Pathology in these patients typically shows low Ki-67 expression and although some reports suggest that absence of SOX11 overexpression is a common feature of this entity, recent data have not supported this [Dictor *et al.* 2009; Nygren *et al.* 2012].

Asymptomatic elderly patients with this disease presentation, especially those with low MIPI scores can be observed until disease progression in a manner similar to that commonly used in other indolent lymphomas. Retrospective studies suggest that such patients can be managed by a 'watch and wait' approach for a median of approximately 1 year and that this delay in initiation of therapy does not appear to have a negative impact on their survival [Eve *et al.* 2009; Martin *et al.* 2009, Martin and Leonard, 2011].

It is important to distinguish indolent MCL from 'in situ' MCL. 'In situ' MCL is a rare entity which is usually diagnosed incidentally on lymph node biopsies and is characterized by the presence of scattered clonal B cells that bear all of the characteristics of MCL, including cyclin D1 expression, occurring in the mantle zone of the lymph node, but without disruption of the normal follicular architecture [Richard *et al.* 2006; Carvajal-Cuenca *et al.* 2012]. The natural history of this entity is not fully understood although some studies have shown that this entity has potential to transform into an overt aggressive MCL, although this may take many years.

In summary, case B with asymptomatic disease and a presentation characteristic of indolent MCL can be safely observed initially. By contrast, symptomatic patients, those with high MIPI scores, and all patients with blastoid pathology and/or Ki-67 percentage over 30% should be considered for immediate treatment.

When the patient B became symptomatic, he then required treatment. At 68 years of age, he might be eligible for an intensive approach such as R-HyperCVAD or R-CHOP induction followed by AutoSCT. However, age over 65 has been shown to be associated with inferior outcome with R-HyperCVAD, primarily because of a high rate of infectious complications and frequent dose reductions and delays because of toxicity [Romaguera *et al.* 2010]. Similarly, depending upon comorbidities, he may be at increased risk of regimen related toxicity and mortality from high-dose therapy and AutoSCT. R-CHOP been compared with a combination of rituximab, fludarabine and cyclophosphamide (R-FC) in older patients with MCL in a randomized European study which included a second randomization to interferon or rituximab maintenance. A total of 532 eligible patients were included in the intent to treat analysis, which showed equivalent response rates in both arms (34% for R-CHOP *versus* 40% for R-FC) [Kluin-Nelemans *et al.* 2012]. However, 4-year OS favored the use of R-CHOP (62% for R-CHOP *versus* 47% for R-FC). These data have established R-CHOP as an acceptable induction regimen for older patients, especially those with adequate cardiac function and no other significant comorbidities.

The introduction of bendamustine has also resulted in studies assessing the utility of this agent in the first-line setting [Rummel *et al.* 2005]. Based on encouraging phase III data Rummel and colleagues have reported results from a randomized study comparing R-bendamustine with R-CHOP as initial therapy for patients with various subtypes of indolent non-Hodgkin lymphoma including MCL [Rummel *et al.* 2013]. A total of 549 patients were randomized on this study, of whom 93 had MCL. In an unplanned subset analysis of this group, the median progression free survival was 35 months for the BR arm compared with 22 months for the R-CHOP arm ($p=0.0061$). No OS difference has been observed, although significantly less toxicity was seen in the BR arm. Based on these data,

which are yet to be fully published, the combination of bendamustine and rituximab is now widely accepted as an option for first line therapy in MCL, particularly for older patients and those with significant comorbidities.

Based on the known efficacy of bortezomib in the salvage setting, current US intergroup studies are investigating the addition of bortezomib to the BR combination for the first-line therapy of older patients with MCL. These studies are ongoing.

The potential benefit of maintenance therapy with rituximab was initially evaluated in phase II studies, including those from The German Low Grade Lymphoma Study Group in relapsed MCL patients, showing apparently improved duration of remission [Forstpointner *et al.* 2006]. The apparent benefit of maintenance rituximab was also reported after bortezomib, rituximab and a modified hyper-CVAD regimen by the Wisconsin Oncology Group [Chang *et al.* 2011; Kenkre *et al.* 2011]. The previously cited European study of R-CHOP *versus* R-FC also included a second randomization for responding patients to rituximab maintenance or interferon maintenance. In this study, the use of rituximab maintenance was superior to interferon maintenance with 4-year OS rates of 87% and 63%, respectively ($p=0.005$).

Based on these data, R maintenance after R-CHOP should be considered in lieu of AutoSCT in the elderly and other patients who are not eligible for transplantation. The role of rituximab maintenance after other induction regimens including bendamustine is not yet established. However, based on the experience with R-CHOP, the use of rituximab maintenance in MCL is now being widely adopted for patients receiving R-bendamustine induction and has also been included as a standard component of the next generation of US intergroup randomized trials.

Treatment with bortezomib is a common approach for relapse/refractory MCL with reasonable response rates as documented above, confirmed in the PINNACLE trial [Armand *et al.* 2008]. Bortezomib has been evaluated in combination with bendamustine and rituximab in the relapsed setting, producing an overall response rate of 83% and 2-year PFS of 47%. Based on these data, the combination is now being evaluated by several groups in the first-line setting [Friedberg *et al.* 2011].

Cladribine and rituximab have also been studied in this patient population, with comparable results [Inwards *et al.* 2008; Spurgeon *et al.* 2011]. The mTOR (mammalian target of rapamycin) inhibitor, temsirolimus, has demonstrated moderate activity in relapsed and refractory MCL patients [Ansell *et al.* 2008; Hess *et al.* 2009]. Interestingly the recently FDA-approved immunomodulatory agent lenalidomide, either as monotherapy or in combination with rituximab has shown significant activity, with response rates of around 30% and median PFS rates of approximately 6 months in this subset of patients [Habermann *et al.* 2009; Eve *et al.* 2012; Wang *et al.* 2012; Goy *et al.* 2013]. Lenalidomide is now being evaluated in prospective studies as a component of first-line therapy and as a potential maintenance therapy.

Most recently, ibrutinib, the Bruton's tyrosine Kinase inhibitor as a single-agent oral medication for MCL patients who had received at least one prior therapy was approved by the FDA [Wang *et al.* 2013a]. In the PCYC-1104 trial, the overall response rate was observed in 65.8% of 111 patients with the CR rate in 17.1% of patients; the PFS was prolonged to 13.9 months. Ongoing phase I/II studies are evaluating the combination of ibrutinib and rituximab, CHOP and bendamustine [Younes *et al.* 2014; Wang *et al.* 2013b].

In view of the poor outcome for patients with relapsed disease, clinical trial participation should be the preferred option. Several new targeted agents have emerged and shown activity in patients with relapsed MCL. These include the agents directed at downstream targets of cyclin D1 as well as the PI3 (phosphatidylinositol-3) kinase inhibitor directing at B-cell receptors [Leonard *et al.* 2012; Gopal *et al.* 2014; Kahl *et al.* 2014]. There are emerging data for the oral agent idelalisib (formerly CAL-101 or GS-1101) as an inhibitor of PI3 kinase provides impressive response rates in relapsed/refractory MCL patients.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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