Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology December 2013

Integrating Emerging Treatment Options in Mantle Cell Lymphoma

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Abstract: Mantle cell lymphoma is an uncommon lymphoma subtype that is currently considered incurable and lacks a single standard of care. Choice of treatment is complicated by the disease's clinical heterogeneity. The course of the disease may be indolent, moderately aggressive, or aggressive. A translocation between chromosomes 11 and 14 is observed in the majority of mantle cell lymphoma patients, and the diseased cells may develop a variety of other genetic aberrations. Although the disease tends to respond well to treatment, patients almost invariably relapse, with many becoming chemotherapy refractory over time. The development of new treatment strategies has improved the prognosis for these patients. Novel approaches include intensive chemotherapy, often in combination with stem cell transplantation; maintenance therapy with extended duration; and new targeted treatments such as ibrutinib, bendamustine, bortezomib, lenalidomide, and idelalisib. Many of these new agents have shown promising activity, both as single agents and in combination regimens.

Supported through funding from Pharmacyclics Inc.

Integrating Emerging Treatment Options in Mantle Cell Lymphoma: Introduction

Brad S. Kahl, MD

Mantle cell lymphoma (MCL) is a unique subtype of non-Hodgkin lymphoma (NHL). MCL accounts for approximately 6% of new lymphoma cases each year.[1] Because it is a relatively uncommon form of lymphoma, it is more difficult to study than other lymphoma subtypes. There are many single-arm, phase 2 trials in the MCL literature, but there is a relative paucity of large, randomized, phase 3 trials. As a result, comparisons are often made across trials, and observations are based on extrapolation.

Mantle Cell Lymphoma Biology

The biology of MCL is unique. Virtually all cases of MCL are characterized by a translocation between chromosomes 11 and 14 t(11;14), which juxtaposes the BCL-1 oncogene on chromosome 11 behind the immunoglobulin gene heavy chain promoter on chromosome 14.[2] This translocation results in overexpression of the protein cyclin D-1, which in turn leads to cell cycle deregulation and abnormal progression of these cells through normal cell cycle checkpoints (Figure 1). It is believed that t(11;14) is a very early event in the lymphomagenesis of MCL.

By the time patients present for diagnosis in the clinic, the biology of the disease has evolved considerably and is far more complicated than a simple t(11;14) translocation. Fairly good drugs have been developed against cyclin D1 protein expression, but these drugs have shown only modest clinical activity in MCL. Therefore, targeting cyclin D1 by itself is probably insufficient as an antitumor strategy in MCL. As MCL progresses, some of the other genetic abnormalities that seem to be acquired include mutations in genes such as ataxia telangiectasia mutated (ATM), TEK2, INK4, retinoblastoma, MDM2, and p53. As more of these genetic abnormalities accumulate, patients tend to develop a more aggressive version of MCL that may have a higher proliferative rate and more generalized resistance to therapy.

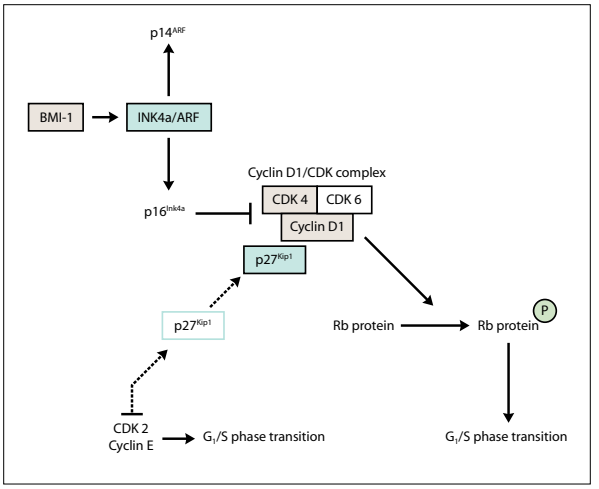

Figure 1. In mantle cell lymphoma, overexpression of the protein cyclin D-1 leads to cell cycle deregulation and abnormal progression of these cells through normal cell cycle checkpoints. Adapted from Benn HAN. *The Molecular Oncology Report*. 2006;1(1).[8]

Diagnosis and Clinical Features

The diagnosis of MCL is straightforward. The cell of origin is a pre–germinal center lymphocyte. The cell arises from the mantle zone just outside the germinal center follicle. The immunophenotype is unique. Patients tend to be CD5-positive and CD23-negative, and they tend to have bright CD20. They should be nuclear cyclin D-1 positive by immunohistochemistry. They should be FMC-7 positive as well, although not

all institutions stain for this marker. Genetic testing should show a t(11;14) detectable by fluorescence in situ hybridization. The morphology of MCL cells can vary. The cells are typically small-to-medium–sized with irregular nuclei. Sometimes the nuclei are round, mimicking small lymphocytic lymphoma. Occasionally, the cells are larger and can be confused with large cell lymphoma. There is also a blastic variant of MCL, in which the disease may initially resemble acute lymphoblastic leukemia.

Within the lymph node, the growth pattern can show a somewhat vague nodular pattern that is usually diffuse but can also resemble follicular lymphoma. Occasionally, patients have a mantle zone growth pattern in which the mantle outside the follicle is expanded. There is some evidence that these patients have a slightly more indolent course.

The clinical features for MCL are also unique compared with other types of NHL.[3] For example, MCL is much more common in men than in women, with a ratio of approximately 4:1. The median age for MCL patients is 64 years, which is older than for other NHL subtypes. Most patients present at an advanced stage, and 30% of patients will present in a leukemic phase. Bone marrow involvement is also common. As shown by researchers at MD Anderson, involvement of the gastrointestinal tract is common.[4] Biopsies of normal-appearing mucosa indicate that 80% of patients have gastrointestinal involvement. Some patients will present with lymphomatous polyposis, such that the colon with MCL may contain dozens of small polyps. Elevated lactate dehydrogenase occurs in approximately a quarter of patients, and elevated β2-microglobulin is observed in a majority.

Clinical Course and Prognosis

The clinical course of MCL is moderately aggressive. It tends to progress more slowly than diffuse large B-cell lymphoma, Burkitt's lymphoma, and some of the fast-moving T-cell lymphomas, but it usually progresses more quickly than the indolent lymphomas, such as follicular lymphoma or small lymphocytic lymphoma. Unfortunately, MCL lacks the curative potential seen with some of the aggressive lymphomas, and there is no plateau in progression-free survival (PFS). Some patients will enjoy very long remissions lasting more than 10 years. The natural history is such that late relapses can occur, and it is difficult to know if anyone is ever truly cured of this disease.

Fortunately, the prognosis seems to be improving for MCL. In a 2009 European study that compared MCL cases from the late 1970s and early 1980s with cases from the late 1990s and early 2000s, the median overall survival (OS) improved from 3 years to 5 years.[5] Prognosis for individual patients can be based on biologic and clinical factors. Rosenwald and coauthors used gene expression profiling and the resultant proliferation index to divide an MCL population into 4 quartiles.[6] They found that 25% of patients had a very high proliferation index and a poor prognosis, with a median survival of less than 18 months. Approximately half of the patients had a median survival of 3 to 4 years. The remaining 25% of patients had a median survival of 7 to 8 years. Unfortunately, gene expression profiling cannot currently be used in the clinic. Ki-67 staining can be used as a surrogate but is less reliable and provides less discriminatory power. Proliferation index cut points—of less than 10%, 10% to 30%, and greater than 30%—can provide an estimate of the patient's risk. Patients with a high proliferation rate tend to have a worse prognosis.

The MCL International Prognostic Index (MIPI) can be used to help estimate prognosis based on clinical features. The following factors have a negative impact on prognosis: age older than 60 years; poor performance status; high lactate dehydrogenase; and high white blood cell count. A web-based tool incorporates a logarithm to calculate a patient's MIPI.[7] The MIPI separates newly diagnosed MCL patients into 3 risk categories. Approximately 40% to 50% of new patients are low risk, 35% of patients are intermediate risk, and 20% of patients are high risk. This knowledge can be useful at diagnosis, when estimating a patient's prognosis and considering therapeutic options.

Acknowledgment

Dr Kahl is a consultant for Genentech, Celgene, Millennium, Infinity, and Gilead.

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Frontline Management Strategies for Younger, Fit Patients With Mantle Cell Lymphoma

Nathan H. Fowler, MD

The treatment of MCL in 2013 remains a challenge. In patients who are younger and fit, there is not yet a standard of care. Despite intensive approaches, such as combination anthracycline therapy followed by autologous stem cell transplantation (ASCT), most patients are still not cured of their disease. Several prospective studies suggest that most intensive regimens result in a PFS of approximately 5 years.[1]

Many patients who relapse can quickly become chemorefractory, and rates of OS following first relapse are not prolonged. When patients are seen initially in the clinic, a careful review of the pathology and clinical presentation is critical to identify those who may have the so-called indolent variant of MCL. Unfortunately, an indolent presentation in observed in only a minority (10%-20%) of cases, and most patients will present with aggressive disease, including significant nodal involvement and splenomegaly. Gastrointestinal involvement and even intestinal obstruction can also occur.

As mentioned, a minority of patients present with a slow clinical course. Often this is characterized by adenopathy that has been present for several months to years, accompanied by asymptomatic lymphocytosis. In addition, patients with the indolent variant can have low volume adenopathy, with occult involvement in the large bowel. These patients are often diagnosed incidentally by their primary care physician following routine blood work or surveillance colonoscopy. Unfortunately, there are no commonly accepted criteria on how to identify patients with "indolent" MCL. In our practice, a normal LDH and a low level of Ki-67 expression has been used as an identifying factor; generally, a Ki-67 of less than 20% is considered predictive of patients who could have a slow clinical course. However, there is still an evolving understanding as to how to identify the pathologic differences between patients with classic vs indolent variants. When patients with a slow clinical course, a low Ki-67, and no significant adenopathy present to the clinic, I generally recommend close surveillance with restaging computed tomography (CT) scans every 3 months for 6 to 9 months to ensure that the disease is not progressing rapidly.

When patients with indolent MCL require treatment—in the absence of a change in their clinical course—they are often managed like patients with other low-grade indolent lymphomas. Treatment can involve single-agent rituximab or less intense combination regimens with monoclonal antibodies. As mentioned, these patients are in the minority.

Most patients present with adenopathy—as well as disease that can involve the colon, spleen, and bone marrow—and will require therapy soon after diagnosis. The most common approach in fit patients is an intensive strategy. The immunochemotherapy combination of rituximab plus hyperfractionated cyclophosphamide, plus vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine (R-hyper-CVD) is the most common regimen used at my institution. Other effective upfront regimens include rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or R-CHOP alternating with dexamethasone, cytarabine, and cisplatin (R-DHAP), followed by autologous transplant. Despite these intensive approaches, most patients still progress within 5 to 6 years.

At MD Anderson, R-hyper-CVAD is commonly used in patients with classic MCL that requires treatment. In general, we attempt to give patients 6 to 8 cycles of therapy, and obtain restaging studies, including CT scans and colonoscopies, if the patient has bowel involvement following cycles 3 and 6. In prospective, single-institution studies, we have reported response rates approaching 80% to 90%, with most patients attaining a complete response (CR).[2] OS in most of the patients, especially those older than 65 years, has been better than 5 years, although there has been no plateau in PFS. Although effective, this strategy has been associated with toxicity, especially in patients older than 65 years. Close oversight and supportive care are essential to minimize side effects and optimize patient outcomes. Extended follow-up has shown that a small minority of patients can develop myelodysplasia, and some have succumbed to acute myeloid leukemia.

Several alternative management approaches have been reported, such as the Nordic regimen, which is R-CHOP alternating with rituximab plus high-dose cytarabine.[3] The Cancer and Leukemia Group B has also published augmented R-CHOP–like regimens followed by stem cell transplant, and others have shown that alternating R-CHOP with rituximab plus ifosfamide, carboplatin, etoposide (R-ICE) or rituximab plus cytosine, arabino-

side, cisplatin, and dexamethasone (R-DHAP) followed by transplant is a reasonable approach for patients who require treatment (Figure 2).[4,5] Similar to our experience, these approaches are also associated with significant myelosuppression and non-hematologic side effects. In most of these single-arm studies, rates of 3-year event-free survival are approximately 60% to 70%.

Recent Clinical Data and Agents in Development

The European MCL Network conducted a randomized study of younger patients with MCL who could tolerate aggressive therapy.[6] This study compared 6 courses of R-CHOP followed by myeloablative radiochemotherapy and ASCT vs alternating courses of 3 × CHOP and 3 × R-DHAP followed by a high-dose Ara-C–containing myeloablative regimen and ASCT.[6] This study appeared to show an improvement in time to treatment failure in patients who had received high-dose Ara-C in addition to R-CHOP followed by ASCT, which suggests that the improved outcomes could have been secondary to cytarabine exposure, even though the conditioning regimens were slightly different.

The phase 3 STiL (Study Group Indolent Lymphomas) trial recently provided some intriguing data.[7] This study compared bendamustine and rituximab vs R-CHOP in newly diagnosed patients who had indolent lymphoma or MCL. Patients were randomized 1:1 to receive 6 cycles of either regimen. The primary objective was to prove noninferiority of bendamustine plus rituximab vs R-CHOP. The study enrolled nearly 550 patients, 93 of which had MCL. Newly diagnosed patients with MCL showed a benefit from treatment with bendamustine plus rituximab, with a median PFS of 35 months vs 22 months in the R-CHOP arm. Although impressive, these results should be interpreted with caution, and bendamustine plus rituximab cannot be considered superior to an intensive approach without further randomized trials.

In the near future, we may also see rituximab maintenance move into frontline treatment, or at least into frontline clinical trials. A recent study in elderly patients with MCL suggested that rituximab maintenance following R-CHOP or rituximab plus fludarabine resulted in not only an improvement in remission duration but also in OS.[8] The study excluded younger, fit patients, and it is unknown whether rituximab maintenance would also be beneficial in this population, which generally receives intensive therapy. In elderly patients, however, there was clearly a survival benefit. Prospective studies in younger and fit patients are needed and may show an improvement using a similar approach.

There are several exciting agents in clinical trials. Bortezomib has been shown to be active in patients with relapsed

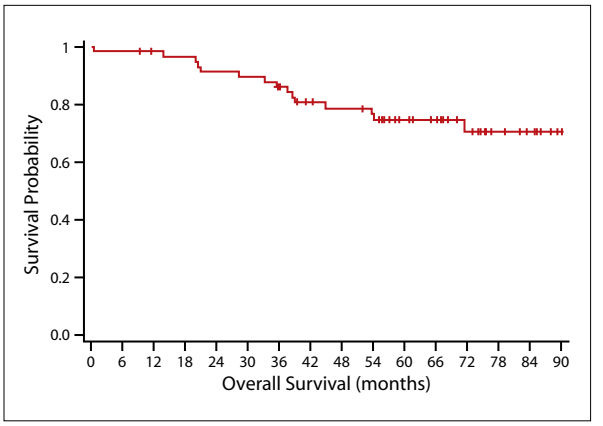

Figure 2. Overall survival in a phase 2 study of CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DHAP, dexamethasone, cytarabine, and cisplatin. Adapted from Delarue R et al. *Blood*. 2013;121(1):48-53.[5]

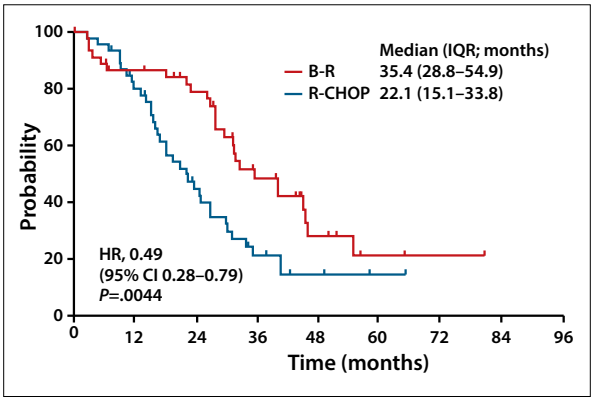

Figure 3. Progression-free survival among patients with mantle cell lymphoma in a trial from the German Study Group of Indolent Lymphomas, which compared rituximab plus bendamustine versus R-CHOP. B-R, bendamustine, rituximab; HR, hazard ratio; IQR, interquartile range; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. Adapted from Rummel MJ et al. *Lancet*. 2013;381(9873):1203-1210.[7]

MCL.[9] Innovative randomized cooperative group studies are under way that are integrating bortezomib with bendamustine into therapy for newly diagnosed patients. Lenalidomide was recently approved for MCL in the relapsed setting in patients who have received 2 prior therapies, including bortezomib.[10] At MD Anderson, we have shown that the combination of rituximab and lenalidomide is also active in relapsed MCL,[11] and lenalidomide will likely be integrated into frontline regimens in studies in the near future.[12] B-cell receptor inhibitors are clearly quite active in this disease and show great promise both as single- agent therapy and as a way by which to augment response to traditional chemotherapeutics. Studies in patients with relapsed disease have shown high

response rates to agents such as ibrutinib,[13] idelalisib,[14] and IPI-145.[15] BCL-2 inhibitors are also active, as are new, next-generation conjugated and nascent monoclonal antibodies. Frontline studies are yet to be launched, but in the coming years, we will likely see integration of these active biologic agents into frontline therapy, and I strongly believe that they will be part of the treatment approach in younger, fit patients.

Acknowledgment

Dr Fowler has served on scientific advisory boards for Pharmacyclics, Janssen, Infinity, Celgene, and Roche. He currently receives research funding or serves as principal investigator for studies from Pharmacyclics, Janssen, Roche, Celgene, and Gilead.

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Frontline Management Strategies for Older MCL Patients

Brad S. Kahl, MD

Treatment Goals and Management Challenges

When a new patient presents with a diagnosis of MCL, I first try to determine whether he or she is better suited to an intensive approach (such as stem cell transplant) or a less-intensive strategy. A more intensive strategy may be considered for fit patients. Although intensive treatment is associated with more short-term side effects and toxicities, it appears to produce more durable initial remissions. Whether initial treatment with intensive regimens improves OS is unclear.

The first consideration is the patient's age. In general, a patient aged 60 years or younger is a good candidate for an intensive strategy, and a patient aged 70 years or older would more likely benefit from a less intensive strategy. Younger patients occasionally prefer a less intensive strategy, and this approach is reasonable, particularly with the newer agents becoming available and the improved strategies for relapsed and refractory disease.

Recent Clinical Data and Evolving Treatment Options

R-CHOP has been somewhat disappointing in MCL, owing to a relatively short median PFS. The response rates are high; 90% of patients achieve a remission, including 30% to 40% CRs. The median PFS is only 18 months to 2 years. The STiL study compared rituximab plus bendamustine vs R-CHOP for patients with indolent lymphoma.[1] The study included almost 50 MCL patients

in each arm. The median age of these MCL patients was 70 years, so it was an older population. In this small study, the Kaplan-Meier curves for PFS showed that the bendamustine-plus-rituximab regimen performed better than the R-CHOP regimen (35 months vs 22 months, respectively). This subset analysis suggests that bendamustine plus rituximab might be a better induction regimen than R-CHOP for older MCL patients.

The North American BRIGHT (First-Line Bendamustine-Rituximab [BR] Compared With Standard R-CHOP/R-CVP for Patients With Advanced Indolent Non-Hodgkin Lymphoma [NHL] or Mantle Cell Lymphoma [MCL]) study attempted to confirm the results of the STiL trial.[2-4] Results of the BRIGHT study have not yet been published, but they were presented at the 2012 American Society of Hematology meeting and elsewhere.[2-4] Approximately 20 MCL patients were enrolled in each arm. The overall response rates were identical for rituximab plus bendamustine and R-CHOP. The rituximab plus bendamustine regimen was more successful at achieving CRs (Figure 4). The CR rate for rituximab plus bendamustine was nearly 50%, whereas it was closer to 30% for R-CHOP. These 2 treatments have different safety profiles. The R-CHOP regimen includes vincristine, as well as prednisone and an anthracycline, which can be problematic for older patients. More data are needed, and several large trials are under way that use rituximab plus bendamustine as the chemotherapy backbone for older patients with MCL.

In MCL, the real challenge is maintaining remission. A large, randomized clinical trial from Europe provided valuable data in this area. This study included 560 patients aged 60 years and older.[5] Using a 2-by-2 randomization, the trial compared 2 different induction strategies and 2 different maintenance strategies. Induction was either 8 cycles of R-CHOP or 6 cycles of fludarabine, cyclophosphamide, and rituximab (FCR). The goal was to discern how well purine nucleotide analogues perform in MCL. After induction, both treatments achieved similar results, with CR rates of 40% with FCR and 34% with R-CHOP. The median time to treatment failure was 28 months for FCR and 26 months for R-CHOP. The OS curves showed an advantage for R-CHOP, and the data suggest that the FCR regimen was associated with a toxicity profile that negatively impacted OS. This trial indicates that R-CHOP is superior to FCR.

The second randomization in this trial was to maintenance therapy with rituximab or interferon-α. Rituximab was administered every 2 months until disease progression; interestingly, there was no stop date on the maintenance rituximab. The trial showed a fairly substantial remission duration benefit for maintenance rituximab over interferon-α (Figure 5). Maintenance

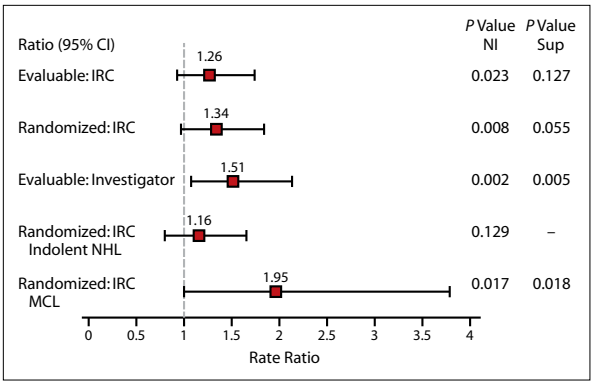

Figure 4. Among patients with mantle cell lymphoma in the BRIGHT study, the complete response rate ratio of 1.95 significantly favored bendamustine/rituximab over R-CHOP/R-CVP. BRIGHT, First-Line Bendamustine-Rituximab [BR] Compared With Standard R-CHOP/R-CVP for Patients With Advanced Indolent Non-Hodgkin Lymphoma [NHL] or Mantle Cell Lymphoma [MCL]; IRC, independent review committee; NHL, non-Hodgkin lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone. Adapted from Flinn I et al. *J Clin Oncol*. 2013;31(15S).[2]

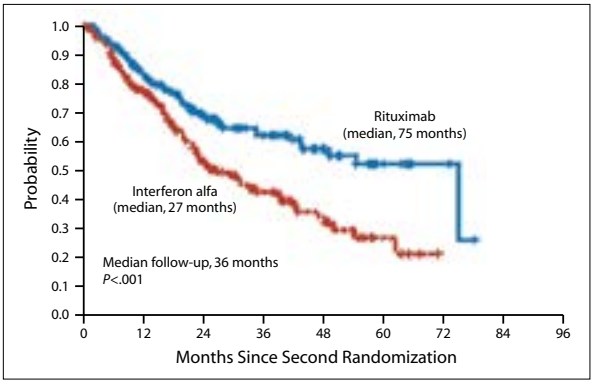

Figure 5. Duration of remission among older mantle cell lymphoma patients who were randomly assigned to maintenance therapy with rituximab or interferon alfa. Adapted from Kluin-Nelemans HC et al. *N Engl J Med.* 2012;367(6):520-531.[5]

rituximab delivered most of its benefits to the patients who received R-CHOP; in fact, the magnitude of that difference was great enough to yield an OS advantage to these patients. Thus, among the patients who responded to R-CHOP, maintenance therapy with rituximab yielded a significantly higher 4-year survival rate of 87% vs 63% with interferon-α.

As mentioned, there are data supporting the use of rituximab plus bendamustine as an induction platform rather than R-CHOP. An approach I will often utilize for older patients is rituximab plus bendamustine for 6 cycles followed by maintenance rituximab.

The optimal duration of rituximab maintenance remains undefined. In the European study, rituximab maintenance was continued indefinitely, but the follow-up was limited. My institution has performed studies with prolonged maintenance in MCL. In one study, maintenance rituximab was continued for 5 years.[6] Approximately one-third of patients were unable to complete 5 years of maintenance because of immunoglobulin depletion and recurrent infections. For the time being, my approach is to give the traditional 2 years of maintenance. Some physicians recommend that patients continue to receive maintenance rituximab until immunoglobulin levels become low and infections occur. At this point, human intravenous immunoglobulin replacement therapy can be initiated while continuing the rituximab. Further study is needed to determine the optimal duration of maintenance rituximab.

E1411 is a US intergroup trial under way for older, newly diagnosed MCL patients. All patients will receive bendamustine plus rituximab for 6 cycles plus 2 years of rituximab maintenance.[7] Patients are randomized to have bortezomib added to the induction regimen. Bortezomib is an active drug in MCL, and bortezomib added to bendamustine plus rituximab has shown excellent activity in a small trial.[8] The goal of E1411 is to determine what bortezomib adds to the bendamustine-plus-rituximab backbone in a randomized clinical trial. In the maintenance portion of the trial, patients can receive either single-agent rituximab or a combination of rituximab and lenalidomide. Rituximab and lenalidomide together appeared to be a promising combination.[9]

Acknowledgment

Dr Kahl is a consultant for Genentech, Celgene, Millennium, Infinity, and Gilead.

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Management Strategies for Relapsed/Refractory MCL

Myron S. Czuczman, MD

Relapsed or Refractory Disease

There is no standard definition for relapsed or refractory disease in MCL. In a recent international trial, patients with relapsed disease were those who had achieved a CR with a previous therapy, but then lost the CR after more than 6 months following the last dose of treatment.[1] Refractory disease was defined as either a lack of CR with previous treatment, or the loss of a CR within 6 months after the last dose of treatment. (This trial, which is currently under review, administered a combination of bendamustine and rituximab.)

Many MCL patients respond to treatment, but there are concerns regarding duration of response and PFS. Unfortunately, the majority of patients who have a response will relapse. Historically, median survival after relapse has been approximately 2 years, and duration of response has been approximately 9 months.[2] There are now novel agents that show promise in extending these benefits.

Options for Second-Line Therapy

There has been no consensus regarding the optimal sequencing of second-line therapies. Second-line therapies listed

in guidelines from the National Comprehensive Cancer Network include bendamustine, bortezomib, and lenalidomide, with or without rituximab.[3] Most physicians do add rituximab to these agents. Other options listed include cladribine, as well as fludarabine-based combination regimens such as rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM). A phase 3 German study showed that rituximab plus FCM was superior to FCM alone.[4] Patients with relapsed disease received second-line FCM with or without rituximab and were then randomized to maintenance rituximab or observation. The patients who received rituximab did significantly better, with the median response duration not yet reached vs 16 months for the observation arm at the time of publication. It is currently unknown whether patients who receive rituximab maintenance as part of first-line therapy will benefit from receiving subsequent maintenance therapy with rituximab.

As mentioned earlier, the phase 3 STiL trial compared bendamustine plus rituximab vs R-CHOP in patients who had both follicular lymphoma and MCL.[5] Twenty percent of the enrolled patients had MCL. It was impressive that overall response, CR, and PFS were better in the bendamustine-plus-rituximab arm. There was no difference, however, in OS.

When deciding on treatment, it is important to consider several factors, such as the patient's age, performance status, comorbidities, tumor biology and histologic subtype, agents used in first-line therapy, and duration of response to first-line therapy. ASCT is used in a number of these patients upfront, and it is important to consider the patient's level of bone marrow reserve. Several agents utilized in second-line therapy will cause significant myelosuppression, and it is necessary to consider not only whether the regimen will be effective, but also whether an adequate number of cycles can be administered to control the disease. It is important to discuss treatment options with patients, and to understand their preferences with regard to toxicity profiles.

The NCCN guidelines still include the use of an antimetabolite, pentostatin, with cyclophosphamide and rituximab. Purine analogues can have activity in older patients or those with poor performance status who receive upfront bendamustine plus rituximab. The guidelines also include metronomic therapy, or PEP-C, which was piloted by Coleman and colleagues.[6] This oral regimen uses prednisone, etoposide, procarbazine, and cyclophosphamide, with or without rituximab.

The combination of bendamustine and rituximab in the relapsed setting is associated with an impressive overall response rate of approximately 80%, even in those patients who did not receive the same combination upfront. Median PFS was approximately 2 years to 2.5 years. In the previously mentioned recently completed

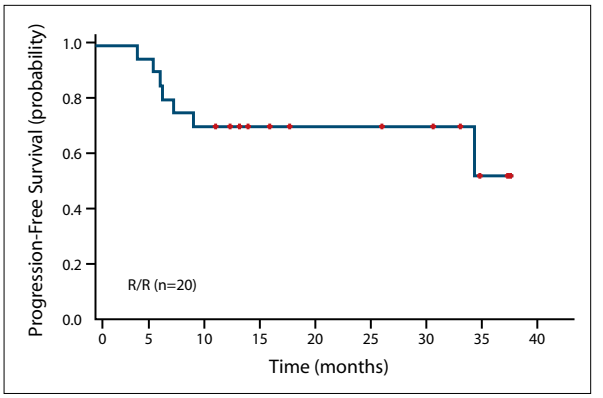

Figure 6. In a small study that examined rituximab plus bendamustine with the addition of cytarabine in mantle cell lymphoma, progression-free survival at 2 years was 70% in relapsed or refractory patients. Visco C et al. *J Clin Oncol.* 2013;31(11):1442-1449.[7]

international phase 2 trial of bendamustine and rituximab in relapsed/refractory MCL, 45 of 47 patients were evaluable.[1] The study enrolled elderly patients (median age, 71 years). Most patients were male, and 82% had stage IV disease. The overall response rate was 82%, with a 40% CR rate. The CR rate was higher in patients with relapsed disease than refractory disease, which is not surprising. Positron emission tomography (PET) scanning was performed before and after treatment. The fluorodeoxyglucose-PET conversion rate from positive to negative was 75%. Although it is too early to draw conclusions, the PFS was 62% at 1 year and is continuing to be monitored.

Also of interest was a small study that examined rituximab plus bendamustine with the addition of cytarabine.[7] In 20 relapsed or refractory patients, there was an 80% objective response rate with a 70% CR rate, and 70% of patients were progression-free at 2 years (Figure 6). These results were from a small number of relapsed patients, so it is not clear whether this combination of rituximab plus bendamustine and cytarabine might have the same activity when used as first-line treatment. The challenge is that there is no set schedule for these patients.

Bortezomib is approved by the US Food and Drug Administration (FDA) for relapsed or refractory MCL after at least 1 prior treatment. The approval was based on a pivotal phase 2 clinical trial, PINNACLE (Multicenter Phase II Study of Bortezomib in Patients With Relapsed or Refractory Mantle Cell Lymphoma).[8] Among 141 evaluable patients, the overall response rate was 32% with 8% CR, and the median duration of response was 9.2 months. The median PFS was 6 months for all patients. The median OS was approximately 2 years in all patients, but it increased to 35 months in patients who responded to the treatment. The impact of grade 3/4 adverse events in elderly patients should be kept in mind. Peripheral

Table 1. Best Response to Ibrutinib in a Phase 2 Trial*

	No Prior Treatment With Bortezomib (n=63)	Prior Treatment With Bortezomib (n=48)	All Patients (N=111)
Response, n (%)			
Overall	43 (68)	32 (67)	75 (68)
Complete	12 (19)	11 (23)	23 (21)
Partial	31 (49)	21 (44)	52 (47)
None†	20 (32)	15 (31)	35 (32)
Response duration, months			
Median	15.8	NR	17.5
95% CI	5.6-NR	NR-NR	15.8-NR
Progression-free survival, months			
Median	7.4	16.6	13.9
95% CI	5.3-19.2	8.3-NR	7.0-NR
Overall survival, months			
Median	NR	NR	NR
95% CI	10.0-NR	11.9-NR	13.2-NR

*Response data included only those patients who received ibrutinib and were assessed for efficacy at least once after baseline.
†Defined as disease that was stable or progressive.
NR, not reached.
Data from Wang ML et al. *N Engl J Med*. 2013;369(6):507-516.[15]

neuropathy can be a concern, especially when these agents are combined with other drugs, such as vinca alkaloids. Peripheral neuropathy was the most common non-hematologic, grade 3 adverse event in the PINNACLE trial, occurring in 13% of patients. Fewer than 15% of patients experienced fatigue or thrombocytopenia.

Bortezomib is being studied with other agents, including rituximab. One study is looking at the combination of bortezomib or hyper-CVAD with or without rituximab maintenance. Bortezomib resistance has been seen in some patients. Gene expression profiling studies showed that bortezomib-resistant MCL showed some differentiation to partial plasmacytic differentiation, consistent with genetic changes.[9] It is unclear whether resistance will be seen when these drugs are used as first-line therapy. There are now several novel, targeted agents that may help circumvent issues of resistance.

Lenalidomide, which belongs to the class of immunomodulatory drugs, was approved by the FDA in 2013 for patients with MCL whose disease relapsed or progressed after 2 prior treatments, one of which included bortezomib.[10] Approval was based on the phase 2, multicentered, single-arm, open-label, MCL-001 study.[11] The study enrolled 134 MCL patients who had received prior treatment with an anthracycline or mitoxantrone, cyclophosphamide, rituximab, and bortezomib, alone or in combination. The primary endpoint was objective response rate, and the independent review committee found a 26% objective response rate with 7% CRs. Median duration of response was 16.6 months, and median OS was 19.0 months. Lenalidomide is also being studied in combination with rituximab and has shown excellent responses.[12]

Maintenance lenalidomide has also been investigated. There was a small phase 2 study that indicated a potential improvement in PFS.[13] Studies must be done to determine whether lenalidomide alone or in combination with other agents may provide a benefit after induction or salvage therapy.

Another combination of interest is thalidomide plus rituximab. In a 2004 study, this regimen had activity in relapsed or refractory MCL.[14]

Agents in Development

Exciting results have been seen in trials of ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor that inhibits the B-cell receptor signaling pathway. Ibrutinib was granted breakthrough therapy status by the FDA in early 2013. Wang and colleagues published results from a large, international, phase 2 trial in which patients received 560 mg of ibrutinib orally, once daily until progression or toxicity.[15] The study included 111 patients with relapsed or refractory MCL. A separate analysis was performed for patients who had completed fewer than 2 cycles of bortezomib vs those who had received 2 or more cycles of bortezomib. The primary endpoint was overall

response rate. The median age of the study population was 68 years, and patients had received a median of 3 prior therapies. The most common treatment-related adverse events were mild or moderate diarrhea, fatigue, and nausea. The trial yielded an impressive 68% objective response rate with 21% CRs (Table 1). Prior use of bortezomib did not affect the objective response rate. Of interest, at a median follow-up of 15.3 months, the estimated median duration of response was 17.5 months, with an estimated median PFS of 13.9 months. OS was not reached, but the estimated OS at 18 months was 58%. At the time of reporting, among the 111 evaluable patients, 46 were still receiving ibrutinib. Sixty-five patients discontinued treatment (50 because of disease progression, 7 based on a decision from the physician or patient, and 8 because of adverse events).

Clearly, ibrutinib has durable single-agent activity. There is an interesting phenomenon concerning inhibitors of the B-cell receptor pathway. In the study by Wang and colleagues, 34% of patients demonstrated an increase in peripheral lymphoma cells in the circulation.[15] The peak occurred after approximately 4 weeks of treatment and was caused not by progression but by mobilization of MCL cells within nodal regions or mobilization of the bone marrow into the blood stream. The peripheral lymphoma cell count subsequently decreased. The response did not vary on the basis of baseline characteristics that are typically applied to patients who are resistant to chemotherapy. This pattern of lymphocytosis reflects a unique mechanism of action and accompanies some very exciting data.

Additionally, patient responses have improved with longer time on treatment, as presented by Wang at the 2012 American Society of Hematology meeting.[16] After a median time on study treatment of 3.8 months, the CR rate was 16%. The CR rate increased in patients who continued on therapy. Final trial results were published in the *New England Journal of Medicine* earlier this year.[15] An overall response rate of 68% was achieved (21% CR, 47% partial response), with an estimated median duration of response of 17.5 months and median progression-free survival of 13.9 months (Figure 7). OS was not reached after a median follow-up of 15.3 months (Figure 8). There were some grade 3 toxicities, but the agent was very well tolerated, including in elderly patients. Based on these results, the FDA granted accelerated approval to ibrutinib on November 13, 2013 for the treatment of MCL following at least 1 prior therapy.

Temsirolimus is an mTOR pathway inhibitor that decreases cyclin D1 transcription and protein expression of the cyclin D-1. It was approved by European authorities based on a phase 3 trial that enrolled 162 patients who had received as many as 3 prior treatments.[17] Temsi-

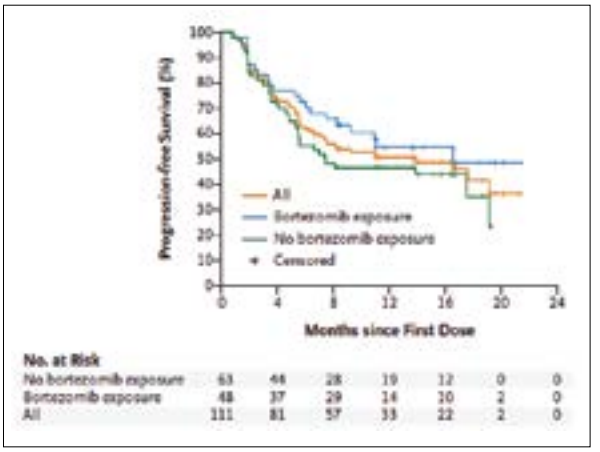

Figure 7. Progression-free survival achieved with single-agent ibrutinib in a phase 2 trial in patients with relapsed/refractory mantle cell lymphoma. Adapted from Wang ML et al. *N Engl J Med*. 2013;369(6):507-516.[15]

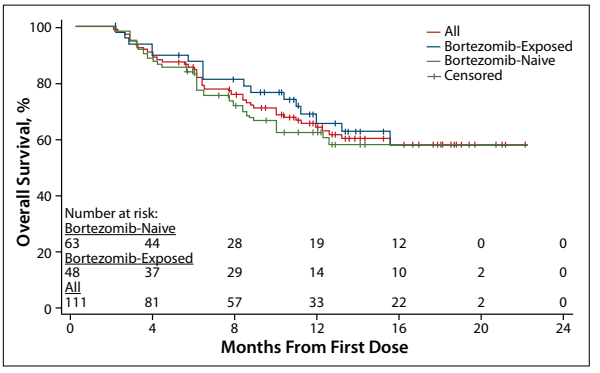

Figure 8. Overall survival achieved with single-agent ibrutinib in a phase 2 trial in patients with relapsed/refractory mantle cell lymphoma. Adapted from Wang ML et al. *N Engl J Med*. 2013;369(6):507-516.[15]

rolimus was initially given at 175 mg weekly for 3 weeks; then patients received either 75 mg weekly or 25 mg weekly until progression. Alternatively, patients received maintenance treatment of physician's choice. The patients who received maintenance with 75 mg of temsirolimus weekly had a 22% response rate, with PFS of approximately 5 months. Those who received the lower maintenance dose had only a 6% response rate, and patients who were treated with the investigator's choice had a 2% objective response rate with PFS of less than 2 months.

In phase 2 trials, the oral agent everolimus, another mTOR pathway inhibitor, has shown a response rate of 12% to 32%.[18,19] The combination of temsirolimus and rituximab has achieved objective responses of 50% to 60% in rituximab-sensitive and rituximab-resistant patients.[20] Additional trials are under way examining different temsirolimus regimens.

Idelalisib is a phosphatidylinositol-3-kinase-δ (PI3Kδ) inhibitor also known as *CAL-101* or *GS-1101*. It has lim-

ited data in MCL. A phase 1 study in 16 MCL patients indicated that it may have activity.[21] For patients who received at least 100 mg twice daily, the objective response rate was 52%. There are no significant data yet on the duration of response, but additional study of PI3Kδ inhibitors in MCL is expected.

Histone deacetylase inhibitors are being evaluated. In addition, the oral agent ABT-199 is a B-cell inhibitor that is being studied in both indolent lymphoma and CLL. It may prove to have significant activity in MCL. Components of the *Jak/STAT* pathway may also present reasonable targets.[22]

Antibodies

Preliminary data have shown that obinutuzumab, the second-generation anti-CD20 antibody, was active in a small number of patients. In one study, it achieved a response in 4 of 15 MCL patients.[23] Ofatumumab has been combined with bendamustine or lenalidomide. At Roswell Park, we found that ofatumumab has significant in vitro activity compared with rituximab in MCL cells, and we have a trial under way with ofatumumab and hyper-CVAD. Blinatumomab, a bifunctional antibody that binds to CD19 as well as to CD3, may have activity.[24] Some preclinical data suggest that perhaps drug immunoconjugates, such as the anti-CD79b combined with monomethyl auristatin E, may hold potential for treatment of MCL.

Conclusion

There is an array of exciting novel therapies in MCL. When selecting treatment for MCL, it is important to keep in mind whether patients have responded to initial or previous treatments, the durability of the response, and toxicity profiles. New combination studies are in progress. Immunotherapy will likely not be used alone. It will probably be necessary to combine some of these novel agents or to use them in combination with older agents to achieve the maximum response. It is also necessary to consider whether these agents will be given concurrently or sequentially. The duration of maintenance therapy, or consolidation treatments, may be shorter. For consolidation, a potential option may be to rotate some of these drugs to avoid resistance. The focus then for the relapsed or refractory patient is the rational design of less toxic, more effective targeted treatments that maintain quality of life.

Data suggest that ASCT may be better in patients who are in the frontline setting, but it should also be considered for relapsed or refractory patients. Nonmyeloablative allogeneic stem cell transplantation may be considered as well based on data suggesting that patients can have prolonged response, and a small proportion may even be cured. With allogeneic stem cell transplantation, it is necessary to consider the age of the patient and whether a suitable match can be found.

Acknowledgment

Dr Czuczman has served as an advisor or consultant for Genentech, Inc.; Onyx Pharmaceuticals, Inc.; Celgene Corporation; Mundipharma; Teva Pharmaceuticals USA; and Seattle Genetics, Inc.

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Integrating Emerging Treatment Options in Mantle Cell Lymphoma: General Discussion

Brad S. Kahl, MD Dr Czuczman, you just discussed many different options for relapsed/refractory MCL. Of all those strategies, which are you must excited about?

Myron S. Czuczman, MD The data from ibrutinib are, of course, very exciting, especially because the toxicity profile shows that it is well tolerated. I believe that this drug may be effective not only in the relapsed setting but also perhaps in the frontline setting. Some of the novel targeted agents available may allow us to avoid ASCT. I am also excited about lenalidomide based on its single-agent activity. With its unique mechanisms of action, lenalidomide may prove to be valuable with respect to minimal residual disease, which can lead to relapse after primary therapy. By randomizing patients to observation or maintenance with agents such as ibrutinib, lenalidomide, rituximab, or the second-generation antibodies, we may see a significant improvement, not only in the upfront setting but also in the second-line or later settings.

Brad S. Kahl, MD Dr Fowler, at MD Anderson, the standard approach for younger patients is the traditional hyper-CVAD regimen. Are you incorporating stem cell transplant into the frontline approach of your MCL patients, or do you tend to use 6 to 8 cycles of conventional hyper-CVAD without the stem cell transplant?

Nathan H. Fowler, MD Nonrandomized, retrospective studies from other centers suggest that cytarabine-containing intensive regimens, such as hyper-CVAD, likely have similar long-term outcomes as ASCT and, therefore, we do not routinely use ASCT in patients in the frontline setting. We believe that patients who did not obtain a complete remission with hyper-CVAD in the frontline setting would potentially benefit from either autologous or allogeneic transplant as a salvage option.

Brad S. Kahl, MD What kind of off-study strategy is recommended for an older patient who is not a candidate for an intensive approach?

Nathan H. Fowler, MD In elderly patients who are not candidates for intensive therapy, such as hyper-CVAD, our general approach has been to move toward off-label use of bendamustine and rituximab with or without rituximab maintenance.

Brad S. Kahl, MD Dr Czuczman, at Roswell Park, how do you approach the older mantle cell patients at frontline?

Myron S. Czuczman, MD We see a number of elderly patients. A patient in her 80s presented with disease throughout her colon as well as in her gastric mucosa; she had significant bleeding and was fragile. After 2 cycles of bendamustine and rituximab, her bleeding stopped, and she did not perforate. Her CT scans dramatically improved. At the end of therapy, colonoscopy and upper endoscopy were completely negative, as were blind biopsies. She achieved a CR.

Another interesting case was an elderly man, approximately 80 years old, with comorbidities. He had received prior treatment with R-CHOP. After treatment with bendamustine plus rituximab, he developed an enormous fungating mass in the upper palate. The patient under-

went field radiation therapy, and this tumor resolved. The patient then began treatment with 20 mg of lenalidomide, which he has been tolerating well, and he has remained in remission for several months at this time. It is necessary to remain alert for adverse events associated with novel regimens. Dose decreases may be called for if patients experience a significant amount of myelosuppression.

Nathan H. Fowler, MD Data with indolent lymphomas have shown that intensive therapies can only get us so far in the frontline setting. For several years, we used very intensive regimens for frontline patients with follicular lymphoma. Similar to other incurable lymphomas, there is a percentage of patients who will obtain durable, long-term remissions. However, the majority of patients still relapse, and I believe the only way to move the field forward in MCL is to integrate some of these new biologic approaches into conventional chemotherapy.

Myron S. Czuczman, MD I agree. I also think that it is critical for everyone in the field, especially researchers and those involved in clinical trials, to search for biomarkers. It is a requirement, not just an option. For all of these novel drugs, correlative studies are necessary and should be incorporated into current and future clinical trials.

Acknowledgments

Dr Kahl is a consultant for Genentech, Celgene, Millennium, Infinity, and Gilead. Dr Czuczman has served as an advisor or consultant for Genentech, Inc.; Onyx Pharmaceuticals, Inc.; Celgene Corporation; Mundipharma; Teva Pharmaceuticals USA; and Seattle Genetics, Inc. Dr Fowler has served on scientific advisory boards for Pharmacyclics, Janssen, Infinity, Celgene, and Roche. He currently receives research funding or serves as principal investigator for studies from Pharmacyclics, Janssen, Roche, Celgene, and Gilead.

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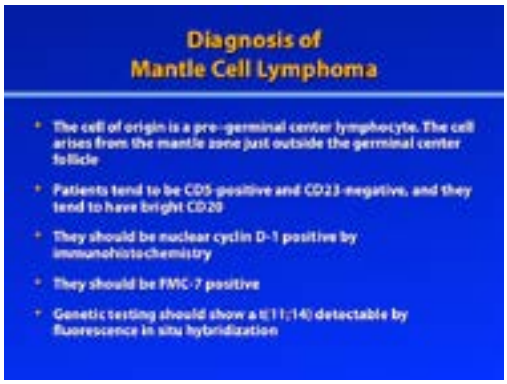

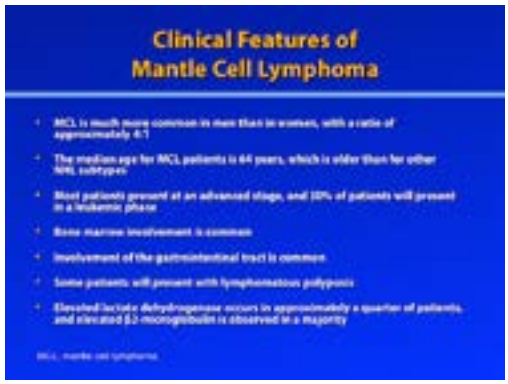

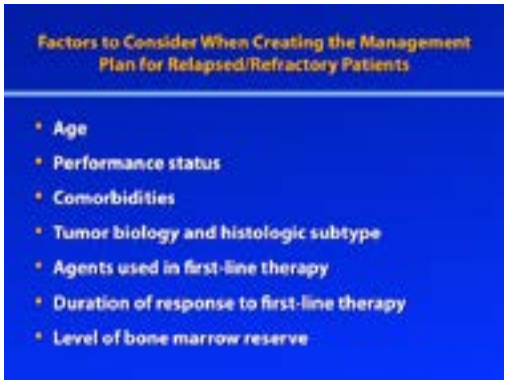

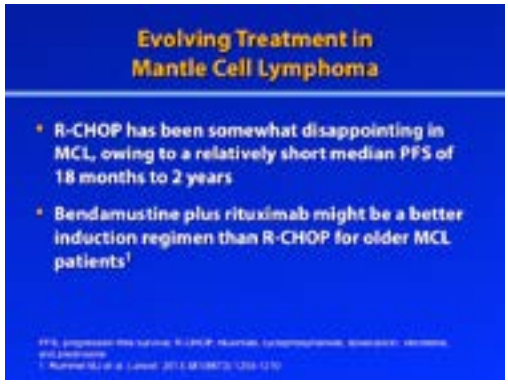

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