Payer Implications of the 2014 Clinical Updates on Hematologic Malignancies for Hematology/Oncology and Managed Care Professionals

Expert Insights on Data Presented at the 2014 NCCN Annual Congress on Hematologic Malignancies

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ABSTRACT

Multiple myeloma (MM) represents the second most common hematologic malignancy in the United States, trailing only lymphoma—and more specifically non-Hodgkin lymphoma (NHL)—in terms of prevalence. Approximately 24,050 new cases of MM were expected to be diagnosed in 2014, with an estimated excess of 11,000 deaths attributed to the disease. Meanwhile, the most common blood cancer in the United States and a top-10 cancer overall, lymphoma accounts for more than half of all new hematologic malignancies. Lymphoma is broadly categorized as either Hodgkin disease or NHL, with more than 88% of lymphoma cases (~70,800) attributed to the latter form of the disease and nearly 19,000 deaths due to NHL predicted for 2014. Beyond the general Hodgkin disease/NHL designation, there is a myriad of types and subtypes of lymphoma, typically described according to cancer cell appearance and/or growth patterns. In NHL, B-cell lymphomas account for approximately 85% of cases, with other forms such as chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) accounting for approximately 5% of cases each.

Although MM remains incurable, promising advances in therapy have significantly improved survival rates among patients with the disease, particularly in the past decade. The 5-year relative survival rate for patients with MM was only 25% between 1975 and 1977 but increased to 43% between 2002 and 2008. Likewise, the 5-year relative survival rate for patients with all forms of NHL has improved drastically over the past several decades, increasing by approximately 20% since 1990.

Although there are minimal nationwide survival data available for CLL and MCL, improvements may likewise be anticipated with increased research focus on these disease subtypes and advancements in therapeutic options. Overall, mortality rates for NHL declined by an average of 2.6% each year between 2002 and 2011.

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While MM and the NHL subtypes of CLL and MCL specifically do not rank among leading cancers in terms of incidence or annual medical expenditures, managed care stakeholders are nevertheless aware of their significant clinical and economic impact. In the wake of approvals of a host of new agents costing more than $100,000 per member per year, the economic burden associated with specific hematologic malignancies is evident regardless of their incidence. This trend is certainly not exclusive to hematologic cancers; all 13 drugs approved by the Food and Drug Administration (FDA) in 2012 for various cancer indications were priced in excess of nearly $6,000 per month. Cancer drug prices in general have nearly doubled from a decade ago.

The trend of exponentially rising costs of hematologic malignancies is further driven in part by prolonged survival among patients receiving appropriate therapy. In fact, while most of the aforementioned agents approved in 2012 for the treatment of other cancers offer little in the way of an extended survival benefit—only 1 of the 13 drugs may extend survival by more than a median of 6 months—prolonged survival in patients with MM and NHL appears to be the direct result of these recent advances in therapy. Specifically, the advent of immunomodulatory agents, proteasome inhibitors, and tyrosine kinase inhibitors has had a remarkable influence on treatment outcomes for patients with these 2 hematologic malignancies, as well
as how the diseases are approached by clinicians and payers alike. Furthermore, as a result of this recently attainable prolonged survival in patients with MM and NHL, corresponding increased costs are inevitable.

As a means of keeping oncologists and hematologists informed regarding treatment advances and emerging data in the increasingly complex landscape of hematologic malignancies, the National Comprehensive Cancer Network (NCCN) hosts an annual congress featuring scientific sessions on current topics relevant to practicing clinicians. On September 19 and 20, 2014, NCCN hosted the 9th Annual Congress: Hematologic Malignancies in New York City. The congress was moderated by Andrew D. Zelenetz, MD, PhD, Memorial Sloan-Kettering Cancer Center, chair of the NCCN Guidelines panel for NHL. The congress focused on new approaches to patient management and updates that have been incorporated into the NCCN Clinical Practice Guidelines for hematologic malignancies.

In light of the rapidly escalating therapeutic armamentarium and the pertinence of effectively managing these hematologic malignancies in the payer space, a subsequent roundtable discussion was held among leading clinicians and managed care executives to foster insightful discourse on viewpoints presented in the scientific sessions. Roundtable participants included Jeffrey D. Dunn, PharmD, MBA, Senior Vice President and Chief Clinical Officer, VRx Pharmacy Services; Michael J. Fine, MD, Medical Director, Health Net of California; and Sergio A. Giralt, MD, Hematologist, Memorial Sloan-Kettering Cancer Center.

EXPERT ROUNDTABLE DISCUSSION

Introduction

Lisa A. Raedler, PhD, RPh (Moderator): Our goals are to understand our panel’s opinions and insights regarding changes in treatment approaches for hematologic malignancies and to learn about how these changes are affecting or will affect both clinical practice and payer strategies. Our discussion will include top-line summaries of data presented at the 2014 NCCN Hematology Congress, as well as the impact of these data and treatment trends on hematology practice and on managed care decision making, elucidated by each of our roundtable experts.

Joining us is Jeffrey D. Dunn, PharmD, MBA, who is Senior Vice President and Chief Clinical Officer at VRx Pharmacy Services. VRx Pharmacy Services incorporates pharmacy benefit manager functions, pharmacy and therapeutics formulary management, medication therapy management, integrated care management, and government functions for commercial and Medicare Part D employer groups and health plans. Also joining our roundtable discussion is Michael J. Fine, MD, who is Medical Director of Health Net of California and is responsible for commercial and Medicare products in California. Finally, our resident clinician is Sergio A. Giralt, MD, who is Chief of the Adult Bone Marrow Transplant Service and the Melvin Berlin Family Chair in Multiple Myeloma at Memorial Sloan-Kettering Cancer Center. He is a board-certified hematologist/oncologist with clinical activity and research focusing on stem cell transplantation for patients with blood disorders.
Insights on the Management of Multiple Myeloma

Lisa A. Raedler, PhD, RPh: MM represents a continuum in terms of disease activity. It begins with a very indolent course with a smoldering designation and can move into fully active MM. At the NCCN meeting, there was discussion about smoldering multiple myeloma (sMM), what that designation means, and how it is diagnosed. Should sMM be treated? If so, how should it be treated?

Sergio A. Giralt, MD: The first thing that should be recognized is that the definition of sMM has changed, largely because the definition of symptomatic MM has changed (Table 1). According to the updated International Myeloma Working Group criteria for the diagnosis of MM, patients with abnormal findings on magnetic resonance imaging, those with a free light chain ratio of 100, or those whose bone marrow features more than 60% plasma cells are now considered to be at high risk for progression within 2 years and should be treated. According to the traditional CRAB criteria—specific parameters surrounding calcium elevation, renal insufficiency, anemia, and bone lesions—these patients would not be considered symptomatic, but that has changed as of November 2014.

Based on the modern criteria, patients with sMM should not be treated outside of the context of a clinical trial and should continue to be observed. These patients should also be encouraged to participate in national clinical trials, such as the sMM trial sponsored by the Eastern Cooperative Oncology Group (ECOG).

It is important to understand that, because the definition of symptomatic MM has changed, we now are treating patients who we would not have treated previously. Once a patient starts treatment outside of a clinical trial, by definition, they are no longer considered to have sMM; they are considered to have asymptomatic MM. Although these patients may not qualify specifically for the traditional criteria of symptomatic MM, the intention of the physician is not to treat a patient with sMM but instead to treat a patient with early symptomatic disease.

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Lisa A. Raedler, PhD, RPh: From your perspectives as representatives of payers and specialty pharmacies, does this kind of diagnosis, this level of granularity, hit your radar? If so, help me understand how and why.

Jeffrey D. Dunn, PharmD, MBA: From the pharmacy perspective, this is not on our radar yet. Our prior authorization (PA) criteria are typically derived from the FDA-labeled indications of the various agents. Looking at bortezomib, for example, the package insert states that the agent is indicated for MM or MCL, and that is reflected in our PA criteria. If, for example, a drug also had a second-line or alternate indication, then that could be built into the PA as well. Payers do not get involved in the actual diagnosis of MM.

If you have moved beyond straightforward drug utilization management into a pathways type of program, then you can build some of these diagnostic
criteria into your pathways. A pathways-based program is essentially a care process model, where you have information around diagnosis, treatment, screening, follow-up, and even end of life decisions, including when to stop treatment. Payers differ in how these types of programs are rolled out; some are purely educational while others tie incentives to pathway adherence. These incentives and how they ultimately shape clinical practice among network oncologists and hematologists really determine if a pathways program is worthwhile.

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In a pathways program, payers give oncologists a catalog of therapies and a preferred sequence of agents. However, there are ways around a specific pathway if a physician asks the review committee to consider a specific patient’s unique clinical needs. Generally, as long as adequate evidence supports the recommended treatment, it is allowed.

Michael J. Fine, MD: I agree with Jeff that most plans do not get down to the detail of when to start therapy, when to end it, or when to switch to another drug. If the patient has a diagnosis of MM, we leave it to the hematologist to decide when to start treatment and when to discontinue it. I think that is pretty universal.

Our plan does not use pathways. We share the same views as Jeff. Often they are not evidence-based, but rely on consensus treatment at a local level. The consensus regarding how to treat patients is established among the oncologists and hematologists in the group. These clinicians present their proposed pathways to plans and say, “We are going to make care consistent and that will save you money.” It is not clear to me that claims about cost savings are valid, but the oncology groups argue exactly that. What follows is, “Because we are going to make treatment more consistent across all providers, you should pay us more.” I personally think that approach is fraught with problems.

On the other hand, the NCCN and American Society of Clinical Oncology (ASCO) guidelines could be used as the basis of pathways programs, but this is not how most plans are creating pathways.

Jeffrey D. Dunn, PharmD, MBA: I completely agree. A lot of this is oncologist driven. We do not get involved in starting and stopping rules for treatment right now. While we would love to have those kinds of management interventions in place, oncology has really been a hands-off category for the most part. We have focused more on the reimbursement side with
oncologists, such as fee schedules. We are also using some site-of-care and channel management initiatives, including specialty pharmacy interventions and some other tools. This has been more of the focus, rather than getting into rules regarding initiation and termination of treatment.

While we could build specific requirements for initiating therapy into our own PA criteria, we have never done so, and NCCN does not provide any guidance along those lines. I think the NCCN guidelines are most helpful for a minority of plans that use pathways. For us, the NCCN guidelines are most valuable when considering off-label requests. We look for levels of evidence there, as well as in Micromedex and some other resources. The NCCN guidelines do not really don’t help when it comes to formulary decisions per se, because they generally do not indicate that one drug should be used before another in specific situations.

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Lisa A. Raedler, PhD, RPh: If you were to treat a patient with sMM, what regimens or treatments are viable alternatives? Do you consider standard MM regimens of bortezomib, lenalidomide, and dexamethasone (VRd); cyclophosphamide, bortezomib, and dexamethasone (CyBORD); or other combinations? According to Mateos et al, the combination of lenalidomide and dexamethasone (Rd) increases time to progression and OS in patients with sMM. At the American Society of Hematology (ASH) 2013 annual meeting, Landgren et al showed that carfilzomib, lenalidomide, and dexamethasone (KRd) elicited very high response rates, with 100% of sMM patients achieving a very good partial response or better, in a small phase 2 study. At ASH 2014, positive minimal residual disease data were presented from this study. What are your thoughts on these findings?

Sergio A. Giralt, MD: If a patient has true sMM—for example, over 1 year, the paraprotein peak has not moved and hemoglobin level is 12 g/dL and has not changed—he or she should not be treated outside of a clinical trial. The patient should be observed or treated in the context of a clinical trial but not in a standard practice setting.

The data from Mateos et al are interesting, although the control group did extremely poorly and never received lenalidomide. That particular trial will not answer the question of whether sMM patients should undergo lenalidomide therapy. The ongoing ECOG trial is answering this question by evaluating lenalidomide at diagnosis versus lenalidomide at progression in patients with sMM.

Data from Landgren et al were derived from the concept of eliminating the malignant clone before it causes serious problems. There are 2 philosophies regarding lenalidomide: it is either a minimally-effective approach with minimal toxicity that can delay progression, or, according to Landgren’s philosophy, it can eliminate the malignant clone and potentially elicit a cure. Both of these approaches are valid for patients with true sMM, but only in the context of a clinical trial.

Lisa A. Raedler, PhD, RPh: From a payer perspective, have these findings influenced any aspect of the utilization management interventions or other various approaches you’ve put in place?
Michael J. Fine, MD: This question has been asked for decades: what is the best way to manage “early” hematologic malignancies? Do you hit them hard upfront, or do you assume patients have a chronic disease and treat them to ensure that progression occurs as slowly as possible? Until there are definitive answers, managed care plans are not going to get involved in how best to treat these patients. We actually don’t even manage many drugs in terms of line of therapy. It’s not worth the effort from a financial perspective.

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Lisa A. Raedler, PhD, RPh: Panobinostat was approved for relapsed MM in February 2014. Results from the PANORAMA-1 trial show that 61% of patients with relapsed MM who were treated with panobinostat, bortezomib, and dexamethasone (PVD) achieved an objective response compared with 55% among those treated with bortezomib and dexamethasone (Vd). The rates of complete response and near-complete response were significantly higher among patients treated with PVD versus Vd (28% vs 16%, respectively). Furthermore, the addition of panobinostat to Vd improved PFS by 4 months (12 months vs 8.1 months, respectively). An interim analysis showed that median OS was slightly longer in patients treated with PVD at 34 months versus Vd at 30 months, although this difference was not statistically significant. Of note, the rate of severe adverse events (AEs) was higher when panobinostat was added to the treatment regimen. The most common severe AEs included low platelet counts (67% vs 31%), low lymphocyte counts (53% vs 41%), low neutrophil counts (35% vs 11%), and diarrhea (26% vs 8%). Cardiac toxicities were also associated with panobinostat. In all, twice as many patients receiving PVD discontinued treatment due to AEs than patients receiving Vd. Can you weigh in on the implications of these findings?

Sergio A. Giralt, MD: Panobinostat showed a significant PFS benefit, albeit around 6 months, with an insignificant OS benefit and significant gastrointestinal toxicity. Some clinicians will tell you that any drug that works is a good drug and that it should be up to physicians and patients to decide whether the risk-benefit ratio of a drug is one that merits its use. The Oncologic Drugs Advisory Committee should be there just to ensure that all drugs available are effective and can be administered by a trained physician in a risk-benefit appropriate manner. Having said that, I think panobinostat barely crosses that threshold. The patient advocates say it the best: more people died on the control arm than the panobinostat arm.

Jeffrey D. Dunn, PharmD, MBA: Payers default to the language approved by the FDA. If a drug is approved, has a label, is available, and is used, then that’s how we’ll cover it. If we have multiple regimens or combinations, the next logical progression would be to start looking at differences in OS and PFS. Without head-to-head studies, however, we have to be careful about potentially going down the road of preferring one drug or regimen over another. Unless you are using pathways, most plans are not involved in that kind of management right now. If the drug is out and approved, it's covered.
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Sergio A. Giralt, MD: The first MM relapse space features carfilzomib, lenalidomide, and dexamethasone (KRd) versus Rd, with KRd showing superiority (Table 2). The most commonly used regimens for patients who experience a relapse are probably VRd and CyBorD, with KRd entering the arena. Panobinostat’s label is understandably more restrictive. Will payers look at this and tell hematologists when they can consider panobinostat beyond the specifications in the label?

Michael J. Fine, MD: No. Perhaps, down the road, if we can work with oncology groups and potentially move in the direction of more formulary management in oncology, my answer may change. Because our current decisions are based primarily on approved labeling, we hope FDA will start looking at things a bit more critically. We see many drugs approved with a 2- to 3-month OS and 4- to 6-month PFS benefit. Eventually, we are hopeful that, as we get more choices, we can start applying cost-effectiveness analyses and making decisions based on cost-effectiveness.

Jeffrey D. Dunn, PharmD, MBA: While cost plays a significant role in virtually every other disease state, it weighs less heavily in oncology-based decision making for us. If anyone is going to push back on manufacturers regarding cost, it is going to be oncologists, oncology groups, and their Pharmacy & Therapeutics committees, not ours. If oncologists do not support an agent due to its excessive cost and lack of benefit, then it’s easy for payers to follow suit. However, payers will not exclude an agent without that level of support from clinicians who prescribe the drugs.

Lisa A. Raedler, PhD, RPh: Dr. Giralt, you pointed to the fact that relapsed MM is a very crowded space. What is your advice to hematologists who do not specialize in MM? How should they juggle all of these agents and combinations? When should they select one over the other?

Sergio A. Giralt, MD: In the frontline setting, you segregate transplant-eligible and non–transplant-eligible MM patients. The transplant-eligible patients are now primarily getting triple therapy, so if you trained at Mayo, you prescribe CyBorD. If you are influenced by Harvard training, you prescribe VRd. Emerging data indicate that VRd may be better than CyBorD, such that, despite the lack of randomized trials, this trend may result in more use of VRd upfront.

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At the point of MM relapse, we focus more on individualized therapy. For example, if a patient has severe diabetes, hematologists want to minimize use of corticosteroids. In patients with neuropathy,
hematologists want to avoid using bortezomib. In those with a history of clots or bleeding, hematologists avoid immunomodulatory drugs because of the associated need for anticoagulation supportive therapy.

Additionally, some clinicians prefer to “stack” therapies in the relapsed MM setting; they start with one agent and add onto it until a sustainable response is achieved. So, while most hematologists have a preferred induction therapy for MM with the goal of the deepest response possible, in the relapse setting things become a “free for all.”

In the event of a symptomatic relapse, we do believe that treatment should be more aggressive. This setting is now becoming better defined; we have 2 randomized trials indicating that intensive therapy enhances depth of response. The mindset with salvage therapy has been to manage the disease and minimize AEs. That will change over the next 5 years, such that we will take a more varied and aggressive stance toward relapsing MM. We are already performing more salvage transplants in the relapsed setting.

Overall, this space is going through a lot of flux. Payers’ hands will be tied as an increasing number of expensive agents are approved for use in the relapse setting. As these agents are combined in various regimens, monthly drugs costs approaching $30,000 are imminent.

Jeffrey D. Dunn, PharmD, MBA: I have seen estimates indicating that 25% of Americans who are diagnosed with cancer will end up declaring bankruptcy. We are concerned about these trends, and we have employers’ interests to worry about as well. With the patient stuck in the middle, and knowing that we’ve put caps on everything else, we’re quite literally running out of money.

Michael J. Fine, MD: When we think about risk, there are 4 main stakeholders: the patient, the payer, the provider, and pharmaceutical manufacturers. Who holds the risk in the arrangement? Right now, it’s the payer and the patient. We’re working on approaches with providers that share this risk. This gets quite complex with oncology, especially because there are therapies for MM that are covered under both the medical and pharmacy benefit. No one has yet been able to figure out how best to manage the pharma component of risk sharing. Until somebody—whether it’s the Centers for Medicare & Medicaid Services (CMS) or FDA—starts including cost and value in this discussion, we are heading in a scary direction.

**Insights on the Management of Chronic Lymphocytic Leukemia**

Lisa A. Raedler, PhD, RPh: In CLL, we have somewhat similar challenges to those in MM. Many new products are jockeying for space in both upfront regimens and in the relapsed setting. At the NCCN Hematology Congress, Dr. Jennifer Brown of the Dana-Farber/Brigham and Women’s Cancer Center highlighted the potential clinical implications of mutations in NOTCH1, SF3B1, and BIRC3 genes. What is your take on the significance of these prognostic factors? Should therapy change accordingly?

Sergio A. Giralt, MD: The big question here is which patients with CLL should undergo a mutational analysis upfront. The obvious answer would be anybody in whom mutational analysis will make a difference for frontline treatment. But, other than conventional cytogenetic testing for markers such as deletion 17p, I don’t think these new analyses are ready for prime time. Eventually they will guide treatment, but until that time comes, they should be considered investigational tools. In the relapsed CLL setting, however, mutational analysis testing is valid because results can guide
treatment. Of course, when trying to ascertain the best course of therapy for a patient with relapsed CLL, enrollment in a clinical trial is always a viable option. I hope we can convince community oncologists of the importance of clinical trials, such that they are inspired to demand access.

Michael J. Fine, MD: Mutational analysis tests present a significant challenge for payers; gene expression testing and analyses of other biomarkers are rapidly expanding. We are trying to keep up with all of it. Which tests really affect treatment decisions and hopefully improve outcomes? The big issue is that oncologists want to perform all of this molecular testing with the hope that it will help guide treatment, despite the absence of clear direction or evidence. It’s been a challenge; if we deny a test, the oncologist counters with the fact that it may eventually influence treatment.

In these scenarios, we cover the cost of the test if a patient is being considered for a clinical trial and one of the requirements for that trial is the presence of a certain mutation or marker. If it’s going to affect whether the patient is accepted into a clinical trial or receive specific care, we will cover it. We will cover patients who want to participate in any clinical trial, not just phase 3 trials. Essentially, any patient with cancer who’s not eligible for standard treatment can participate in a clinical trial.

I agree with Sergio that this information should be disseminated and encouraged. There’s no excuse for patients who are good candidates in rural communities to not be placed in clinical trials.

Sergio A. Giralt, MD: We know that some of these mutations and abnormalities may make a difference. If you think about frontline treatment for CLL, it is probably going to a bendamustine- or ibrutinib-based regimen. Ideally, phase 3 trials of frontline treatment will clearly define optimal therapy, especially as we depart further from fludarabine, cyclophosphamide, and rituximab (FCR) (Table 3).7

Jeffrey D. Dunn, PharmD, MBA: From a pharmacy perspective, if any mutation and associated test is specified in product labeling, then it is built into our PA criteria. Analysis of the test and determination of which tests will be paid generally go through our medical technology group on the medical director’s side rather than pharmacy.

We like tests that lead to a yes/no decision. Related to the ongoing theme of cost and pricing, knowing that a patient is going to have a better likelihood of responding to treatment because of a diagnostic test provides definitive value. At the same time, the cynical part of me predicts that an increased response rate to a drug as a result of testing will inevitably lead to higher pricing and additional costs to payers.

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Sergio A. Giralt, MD: Deletion 17p is the paradigm in CLL. Ibrutinib is not going to be cheap, but for 17p deleted patients, it’s the definitive first-line choice. It’s similar to imatinib for chronic myeloid leukemia and trastuzumab for HER2-positive breast cancer. This will be automatic.

Michael J. Fine, MD: In the situation with CLL, deletion 17p is pretty straightforward. When the answer is clear, use of the test is not only encouraged, it is actually mandated. Most plans require that the patients for whom initial use of ibrutinib is requested undergo 17p deletion testing before the drug is authorized.

Lisa A. Raedler, PhD, RPh: You indicated that, for patients with CLL who have a 17p deletion, ibrutinib is an almost automatic choice. But from conversations that we have had with community-based hematologists, there appears to be some confusion. In the case of a healthy, younger patient who can tolerate aggressive treatment, is FCR an option? Should a patient with a 17p deletion receive ibrutinib initially, regardless of age and performance status, or should the drug be used after FCR?

Sergio A. Giralt, MD: I predict that, in the frontline setting, the easier regimen will be chosen. Unless there are issues surrounding reimbursement, ibrutinib will be the most common choice. Use of FCR in this setting will eventually phase out, largely because bendamustine and rituximab (BR) is a lot easier than FCR, despite its higher cost. Unfortunately, the more expensive regimen also happens to be better in this case.

That said, for patients with deletion 17p, ibrutinib is recommended as first-line therapy. In those patients without deletion 11p or 17p, the preference is BR or a fludarabine-based regimen. Interestingly, for patients who are under 70 years old, the NCCN guidelines list a whole menu of options, including FCR and FR. For patients with deletion 17p, the options are ibrutinib, alemtuzumab and rituximab, or FCR.

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If I were treating a young, healthy person today, I would still use FCR because it has a lengthy track record. However, if I were treating a patient in whom FCR might be difficult, I would have no reservations about prescribing ibrutinib if the patient had the 17p deletion.

Lisa A. Raedler, PhD, RPh: In 2014, FDA approved ibrutinib and idelalisib (with rituximab) for relapsed/refractory (r/r) CLL. How will these options alter management of r/r CLL?

Sergio A. Giralt, MD: We now have all these drugs in this setting that are eventually going to have to be compared and managed based on their cost. The initial push is going to come from the European Medicines Agency (EMA). The EMA will likely start head-to-head comparisons of the newer agents with other traditional therapies that are less expensive. Based on those comparisons, organizations will start adapting guidelines in the United States. Today, we have a “dealer’s choice” situation. You use what you want, and then you use the next one. Eventually, every patient with CLL is going to get every drug.

Lisa A. Raedler, PhD, RPh: In keeping with the recurring theme of a crowded space in terms of treatment options, the FDA recently approved obinutuzumab (OB) with chlorambucil for previously-untreated CLL. How will this option alter management of CLL?
Sergio A. Giralt, MD: Based on all of these recent approvals and a wealth of treatment options available, risk-stratified therapy for CLL has certainly come of age. Now, clinicians need to know whether patients have deletion 17p. We will divide patients into high-risk CLL and standard-risk CLL. Some high-risk CLL patients will have deletion 17p, and for them, ibrutinib should be considered as treatment.

For other high-risk patients who are symptomatic and need treatment, the decision is based on age and overall health. For younger patients without the 17p deletion, the top choices are going to be FCR or bendamustine plus an antibody. OB can be used upfront in Europe, but it hasn’t been approved in combination with anything else other than chlorambucil in the United States.

The emergence of a biosimilar rituximab will further alter all of these considerations, because clinicians already feel very comfortable using rituximab with its proven track record. A phase 3 trial showing a significant survival benefit when replacing rituximab with OB will be needed for the newer antibody to gain traction.

Jeffrey D. Dunn, PharmD, MBA: From a pharmacy payer perspective, the reality is that, as more drugs are approved and shift lines of therapy, the only thing we do is change the PA form. It really comes down to a management priority for us: we look at the number of patients, cost, and available treatment options. To date, our focus has been breast, colon, lung, and prostate cancer. However, as the population ages, there might be an opportunity to manage hematologic malignancies more rigorously.

The biosimilar issue is a significant one. When a biosimilar rituximab is available, presuming its cost is different, it opens the door for many new discussions. We may divide populations like CLL patients out further. For example, we might only allow other monoclonal antibodies to be used first-line in certain specific populations based on age, renal function, comorbidities, or mutations. The goal would be to promote use of rituximab first for most people.

Also important is the way in which biosimilars will affect benefit design. Payers are unprepared right now to deal with biosimilar drugs; most have one specialty tier that is capped. There is no incentive for a provider or a member to use a less expensive medication when they are paying the same for it as the brand name. We also think that some providers will consider biosimilars to be new and potentially inferior agents. As a result, there will be a bit of a disconnect between providers and payers on the uptake on those drugs, which will influence overall cost. For biosimilars to have a beneficial impact on the health care budget, we have to figure out how we as payers can somehow incentivize other stakeholders to use them.

Sergio A. Giralt, MD: Another factor to consider is that—amid all of these new drug approvals—referral to transplant is significantly delayed, particularly in indolent lymphoma and CLL. Many of these new drugs can be an effective bridge to transplant, but they are often used in lieu of transplant, despite the fact that transplant can be a less costly option in appropriate patients. Has this raised any concerns among payers that a potentially curative treatment modality is being overlooked?

Michael J. Fine, MD: Our perspective as a payer is that it’s the responsibility of the provider community and the specialty societies to educate physicians on when a transplant is appropriate. As Jeff pointed out, we’re not allowed to practice medicine. All we can do is determine if a patient meets the criteria when his or her physician requests a transplant. I don’t disagree with your position, but I think that is really the responsibility of the specialty societies.

That said, the criteria regarding who should undergo transplantation and when this should occur could benefit from a little more objectivity. We have our own
criteria, but what we have found is that centers operating in California have different criteria, often with little evidence-based reason for it. The most concerning component of all this is the difference in age that is allowed among transplant centers, despite the fact that there seems to be solid evidence of significantly poorer outcomes in older patients. This is an area where there really needs to be a registry or some other data collection method to identify when patients should undergo transplantation and who is really a reasonable candidate.

“...the criteria surrounding who should undergo transplantation and when this should occur could benefit from a little more objectivity....The most concerning component of all this is the difference in age that is allowed among transplant centers, despite the fact that there seems to be solid evidence of significantly poorer outcomes in older patients.”

- Dr. Michael Fine

Sergio A. Giralt, MD: From a medical society perspective, we are trying to do just that. The problem is not that too many people are undergoing transplantation; it’s that too few are undergoing transplantation, and when they do, they are in later disease stages.

We’re currently 3 years into the Stem Cell Transplant Outcomes Database. Any payer, or patient for that matter, can go to BetheMatch.org and see the results for a given transplant center. This should eventually lead to the identification of centers of excellence, as well as outliers, as their individual results are compared in a head-to-head manner. In the Stem Cell Therapeutic Outcomes Database, you’ll be able to see whether or not a particular center is meeting the mark. Our medical society is now charged with addressing centers that are underperformers to get them up to speed. As a result, when clinicians make poor choices regarding which patients they refer for transplant, they are going to see the consequences.

“...any payer, or any patient for that matter, can go to BetheMatch.org and see the results for a given transplant center. This should eventually result in the identification of centers of excellence, as well as outliers, as their individual results are compared in a head-to-head manner.”

- Dr. Sergio Giralt

Insights on the Management of Mantle Cell Lymphoma

Lisa A. Raedler, PhD, RPh: MCL obviously features a smaller subset of patients than the other hematologic malignancies that we have discussed. However, similar to MM and CLL, there are several new therapeutic options available for clinicians and their patients. The FDA approved bortezomib in October 2014 for patients with previously untreated MCL, in addition to its existing approval for patients with r/r MCL.

Furthermore, ibrutinib has been approved since November 2013 for patients with r/r MCL. How has the availability of these new options altered the management of MCL on the clinical and payer sides?

Sergio A. Giralt, MD: In the majority of patients with MCL, standard care should be similar to the therapies used in the Nordic trials. More often than not, for
patients who are transplant eligible, the choice of therapy should be high-dose cytarabine and methotrexate regimens that will eventually lead to an autologous transplant.

We all know that the data for ibrutinib in MCL look great. I think this agent should be considered first in the context of salvage therapy. The question is, “What do we do with ibrutinib and bortezomib in the context of frontline treatment?” To learn if either of these drugs could replace the need for an autologous transplant consolidation is a valid research question. But, my concern is that we’re seeing more and more hematologists opting for drug therapy in lieu of transplant upfront. These clinicians are losing the opportunity to perform the transplant at the appropriate time in appropriate patients. For patients with MCL who are not transplant eligible, I think BR should continue to be the standard. I believe BR is a better choice than cyclophosphamide, doxorubicin, vincristine, and predisone (CHOP) in terms of toxicity.

The NCCN guidelines are fairly specific about what we should be doing now in MCL; the advent of ibrutinib and bortezomib should not change the current first-line treatment of patients who are transplant eligible. These recently-approved agents provide options for people who are not transplant eligible, but the preponderance of data still supports the use of BR.

In r/r MCL, the clinician’s options are rituximab, bortezomib, ibrutinib, and lenalidomide. Again, the data for ibrutinib in this setting are very promising, but with no head-to-head trials comparing any of the agents, it’s really a “dealer’s choice” scenario. What do you feel comfortable with? Does the patient have neuropathy? Does the patient want to receive oral treatment alone? For me, rituximab is a top-line choice.

Michael J. Fine, MD: From a payer perspective, MCL is pretty far off the radar. The one question I would raise regarding the regimens cited in the NCCN guidelines is whether anyone should still be prescribing CHOP. While this regimen is very appealing to payers due to its relatively low cost, it is rarely used due to extreme toxicity. However, as long as it is still in the guidelines as a first-line therapy option, some will argue it is just as effective as other more tolerable regimens. I predict that if a clinical pathway were developed for MCL, CHOP would be excluded completely. My personal impression is that both NCCN and ASCO have been slow to remove some of the older therapies that are effective but have much higher toxicity. As long as they remain in the published guidelines, it creates a tempting opportunity for plans to try to occasionally move patients toward them. This temptation exists not only for plans, but also in integrated delivery networks, accountable care organizations (ACOs), or other organizations where the payer and provider are the same, and there is a desire and financial incentive to keep costs low. If these drugs really do not belong in the guidelines anymore, they should go. These treatment settings are crowded enough.

Summary

Lisa A. Raedler, PhD, RPh: We have discussed and debated specific challenges surrounding the management of hematologic malignancies of key importance to providers and payers alike. Although our discussion centered on specific cancers, many of the key takeaways can be applied to the management of other tumor types and to issues surrounding orally-administered cancer medications. To truly advance evidence-based, cost-effective cancer care in the future, steps must be taken to foster positive interaction among key health care stakeholders. What are your perspectives on the current relationship between payers and providers as they pertain to the
management of hematologic malignancies? What can be done to facilitate further productive discourse?

**Sergio A. Giralt, MD:** This must be a 2-way street. At least in the transplant space, we have seen that nothing gets accomplished with a confrontational relationship. Only by working together will everyone be able to benefit in a way that is meaningful to their own position. Our interests are analogous, but we are often approaching a given situation from opposite angles.

We have worked with payers for many years through the medical society, focusing on access and reimbursement as well as other key components of managed health care. Although costly, transplantation in the context of hematologic malignancies has the benefit of carrying a more manageable budget compared with high-profile tumor types such as breast cancer. Breast cancer is an excellent example of cooperation between payers and providers who agree to judicious prescribing and fair reimbursement of high-cost therapies, such as HER2 targeted agents. Even pharma has been doing its part to price some targeted therapies competitively to not break the bank.

“I believe that, as much as possible, we need to sit together, recognize the problems, and strategize a common solution. If we can’t come to agreement, we need an honest broker to facilitate the process. In the transplant space, that honest broker has been—to an extent—the government, because they also pay for a significant number of procedures.”

- Dr. Sergio Giralt

I believe that, as much as possible, we need to sit together, recognize the problems, and strategize a common solution. If we can’t come to agreement, we need an honest broker to facilitate the process. In the transplant space, that honest broker has been—to an extent—the government, because they also pay for a significant number of procedures.

**Michael J. Fine, MD:** I agree on this latter point. The government provides the only viable solution in this particular scenario for several reasons. They make decisions regarding what the FDA considers in clinical trials. They make decisions regarding what CMS is going to cover and not cover; this, in turn, drives a lot of commercial decisions. Perhaps most significantly, the government is increasingly becoming the majority payer for health care in this country. In this sense, we have to all be hopeful that they can serve in the role of an honest broker.

The “pie-in-the-sky” belief that somehow the marketplace is going to address this issue and equalize itself is nonsense. The only way this will happen with the marketplace righting itself is along the lines of what Jeff described earlier: if left unchecked, the marketplace will essentially price enough patients out of their ability to afford care and ultimately reduce overall costs. Obviously that would present an even bigger problem rather than a solution. The government has to make decisions about controlling costs of these new agents, which ultimately translates into some degree of regulation. Payers are not in a position to control these costs in a sustainable manner, other than by transferring more of the economic burden onto the patient. Again, this results in the conundrum of patients being unable to afford health care.

**Jeffrey D. Dunn, PharmD, MBA:** It would be nice to have some kind of value-based and cost-effectiveness oriented approach in the United States to provide the easy answer. Politically, I don’t know if this country is ever going to move in that direction, but that would be ideal.

As far as the payer-provider relationship goes, there seems to be more understanding in oncology than in other specialties, such as neurology and rheumatology.
Oncologists seem much more cognizant of the impact of these high costs on their patients, our members. Having said that, I think the relationship between oncologists and payers falls somewhere along the spectrum between “adversarial” and “collaborative” in nature. We are seeing a lot of consolidation, and there is a balance between the oncology group needing the payer and vice versa. As such, we’ve addressed a lot of the reimbursement and related issues. Still, at the end of the day, we would all love to be involved in the discussions taking place on both sides and collaborate to a greater extent. In the short term, I think the oncologist has to take the public face.

“...the relationship between oncologists and payers falls somewhere along the spectrum between “adversarial” and “collaborative” in nature. We are seeing a lot of consolidation, and there’s a balance between the oncology group needing the payer and vice versa.”

- Dr. Jeffrey Dunn

Sergio A. Giralt, MD: This is something that ASCO and ASH need to do at a granular level rather than just taking a general approach. In other words, for each individual hematologic malignancy, outline exactly what needs to be covered and at what level. When we have one-fourth of Americans with cancer going bankrupt, that is clearly not a sustainable model.

Jeffrey D. Dunn, PharmD, MBA: Again, the stance that Sloan-Kettering took against unsustainable drug costs in oncology was something that only group providers could see through to fruition. Payers are not in the position to execute such a “coup” against exponentially-rising costs. We recognize that we need to work with oncologists to get to the point where we have preferred regimens. We need to include costs in these discussions and look at what is in the best interests of our patients. If providers publicly front that effort, it would make the process a whole lot easier.

Michael J. Fine, MD: We also need research to be funded by parties other than the manufacturers. When pharma designs their trials, they are understandably doing so with maximum revenue in mind. The result is more and more studies demonstrating that expensive combinations of targeted agents are better than monotherapy. No one is answering the question of whether combination therapy is better than monotherapy used sequentially. No one is answering whether this is really a cost-effective way to treat the disease. We need some independent funding sources to conduct important trials that will answer these relevant clinical questions. Unfortunately, I think the National Clinical Trials Network—where the government is funding the research—is very limited in terms of resources and not moving nimblly enough. To a certain degree, it's also limited in its access to research drugs. In seeking to answer questions regarding head-to-head comparative efficacy and optimal sequencing for salvage therapy, how likely is it that the manufacturer will provide the study drugs free of charge?

Jeffrey D. Dunn, PharmD, MBA: Speaking to the concept of researching salvage therapy, I think payers are going to be less likely to go there, too. We are more concerned with first- and second-line therapies because the salvage populations are much smaller and our attempts to manage them are different. However, having said that, a huge unmet need in this space is to learn when enough is enough. When do you say “no,” and when do you stop?

Michael J. Fine, MD: We have a lot of problems but no solutions. Perhaps the EMA will be our salvation, as Sergio suggested. Maybe they will do all of the things that we're not going to do here, and we can use that information.
Lisa A. Raedler, PhD, RPh: There was quite a great deal of discussion surrounding these unsustainable costs and who is going to bear the burden at recent national meetings. It seems that we cannot expect government or pharma to strategize groundbreaking solutions any time soon. The provider community seems to bridge the gap between payers and pharma, linking all of the stakeholders together and putting them in a position to enact more immediate change. There was mention of ASCO and ASH taking steps, but could you provide an example of what that could look like from the provider side?

Sergio A. Giralt, MD: I don’t think anyone really knows. On the payer side, we have a lot of problems with no solutions. That same notion holds true in the provider space. I don’t know if anybody has come up with a potential pathway—forget about solution—to bring in all the stakeholders and come up with a plan.

Michael J. Fine, MD: Maybe that’s the first step, then. Figure out how the specialty societies can work together to lobby the government to at least start to conduct some of the research that will answer these questions.

Sergio A. Giralt, MD: The reality is you’d probably need a full-time person to take on that task. You have to bring in the presidents of pharma and the societies and then sit down and discuss the problems: the high cost of targeted agents, inappropriate use, and a paucity of comparative effectiveness data and data that’s transferrable to an evidence-based hierarchy of therapies. From there, you start working on a formula that we can use to move forward.

Lisa A. Raedler, PhD, RPh: I thank you all for your participation; this has been a stimulating discussion. To summarize, it appears that the approval of new agents or new indications for existing agents has generally complicated an already overcrowded treatment armamentarium. While data surrounding newly available agents are promising, there seems to be a growing trend for clinicians to prescribe drug therapy instead of potentially curative transplant. Furthermore, despite the potential of novel mechanisms of action and identification of clinical markers of disease activity, oncologists and hematologists may tend to continue prescribing agents with which they are more familiar. The current guidelines allow for significant freedom of choice in this respect. Until comparative data are available, guidelines will remain open to interpretation.

From the payer perspective, drug utilization management is based primarily on FDA-approved labeling. Clinical pathways programs may represent more nuanced drug management, but these remain in their infancy. By and large, payers do not overextend their influence in the oncology space; they allow network providers significant freedom in terms of reimbursement for products and services that are FDA indicated or at least evidence based. The eventual introduction of biosimilars presents a challenge in that, although they offer potentially lower costs, they will require innovative thinking on the part of payers in terms of benefit design.

Overall, payers and providers are both cognizant of the unsustainable costs associated with available therapies, leaving both groups of stakeholders searching for solutions. Providers may be in a better position to take the first step toward addressing this issue, considering that they seem to hold the most leverage for pushback against pharmaceutical manufacturers. Although no concrete solutions are imminent, both parties recognize the need for solutions and are willing to collaborate. Stakeholders remain optimistic that these unified efforts can impart some level of meaningful change in the future.
REFERENCES


**Table 1. Revised International Myeloma Working Group criteria for MM and sMM.**

### Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- **Myeloma defining events:**
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal of >2.75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

### Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10-60%
- Absence of myeloma defining events or amyloidosis

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*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
†Measured or estimated by validated equations. ‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.
Table 2. Synopsis of the NCCN guidelines for drug therapy of MM for (A) primary treatment and (B) previously treated patients.\(^6\)

### NCCN Guidelines Version 2.2015

**Multiple Myeloma**

**MYELOMA THERAPY\(^1\)\(^-\)\(^3\)**

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
</table>
| **Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)** | • Bortezomib/dexamethasone (category 1)  
• Bortezomib/cyclophosphamide/dexamethasone  
• Bortezomib/doxorubicin/dexamethasone (category 1)  
• Bortezomib/lenalidomide\(^4\)/dexamethasone  
• Bortezomib/thalidomide/dexamethasone (category 1)  
• Lenalidomide\(^4\)/dexamethasone (category 1) | • Carfilzomib\(^7\)/lenalidomide\(^5\)/dexamethasone  
• Dexamethasone (category 2B)  
• Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)  
• Thalidomide/dexamethasone (category 2B) |
| **Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)** | • Bortezomib/dexamethasone  
• Lenalidomide/low-dose dexamethasone (category 1)\(^5\)  
• Melphalan/prednisone/bortezomib (MPB) (category 1)  
• Melphalan/prednisone/lenalidomide (MPL) (category 1)  
• Melphalan/prednisone/thalidomide (MPT) (category 1) | • Dexamethasone (category 2B)  
• Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)  
• Melphalan/prednisone (MP)  
• Thalidomide/dexamethasone (category 2B)  
• Vincristine/doxorubicin/dexamethasone (VAD) (category 2B) |
| **Maintenance Therapy** | • Bortezomib  
• Lenalidomide\(^6\) (category 1)  
• Thalidomide (category 1) | • Bortezomib + prednisone (category 2B)  
• Bortezomib + thalidomide (category 2B)  
• Interferon (category 2B)  
• Steroids (category 2B)  
• Thalidomide + prednisone (category 2B) |

1. Selected, but not inclusive of all regimens.
2. Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
3. Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
4. Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
6. There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.
7. Optimal dosing in this regimen has not been defined.

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Exposure to myelotoxic agents (including alkylating agents and nitrosourea) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

**Preferred Regimens**

<table>
<thead>
<tr>
<th>Therapy for Previously Treated Multiple Myeloma</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Repeat primary induction therapy (if relapse at &gt;6 mo)</em></td>
<td>• Bendamustine</td>
</tr>
<tr>
<td>• Bortezomib (category 1)</td>
<td>• Bortezomib/vorinostat</td>
</tr>
<tr>
<td>• Bortezomib/dexamethasone</td>
<td>• Lenalidomide/ bendamustine/ dexamethasone</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide/dexamethasone</td>
<td></td>
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<tr>
<td>• Bortezomib/liposomal doxorubicin (category 1)</td>
<td></td>
</tr>
<tr>
<td>• Bortezomib/thalidomide/dexamethasone</td>
<td></td>
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<tr>
<td>• Carfilzomib&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>• Cyclophosphamide/bortezomib/dexamethasone</td>
<td></td>
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<tr>
<td>• Cyclophosphamide/lenalidomide/dexamethasone</td>
<td></td>
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<tr>
<td>• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)</td>
<td></td>
</tr>
<tr>
<td>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)</td>
<td></td>
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<tr>
<td>• High-dose cyclophosphamide</td>
<td></td>
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<tr>
<td>• Lenalidomide/dexamethasone&lt;sup&gt;10&lt;/sup&gt; (category 1)</td>
<td></td>
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<tr>
<td>• Pomalidomide&lt;sup&gt;9&lt;/sup&gt;/dexamethasone&lt;sup&gt;10&lt;/sup&gt;</td>
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<tr>
<td>• Thalidomide/dexamethasone&lt;sup&gt;10&lt;/sup&gt;</td>
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</table>

1. Selected, but not inclusive of all regimens.
2. Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
3. Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
4. Consideration for appropriate regimen is based on the context of clinical relapse.
5. Indicated for patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.
6. Consider single-agent lenalidomide, pomalidomide, or thalidomide for steroid-intolerant individuals.

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**Table 3. Synopsis of NCCN guidelines for drug therapy of CLL in (A) first-line therapy and (B) relapsed/refractory disease.**

**NCCN Guidelines Version 1.2015
CLL/SLL**

**SUGGESTED TREATMENT REGIMENS**\(^a\)

*(in order of preference)*

**CLL without del (11q) or del (17p)**

**Frail patient, significant comorbidity**

<table>
<thead>
<tr>
<th>(not able to tolerate purine analogs)</th>
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<tbody>
<tr>
<td>• Obinutuzumab + chlorambucil (category 1)</td>
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<tr>
<td>• Ofatumumab + chlorambucil</td>
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<tr>
<td>• Rituximab + chlorambucil</td>
</tr>
<tr>
<td>• Obinutuzumab (category 2B)</td>
</tr>
<tr>
<td>• Rituximab (category 2B)</td>
</tr>
<tr>
<td>• Chlorambucil (category 2B)</td>
</tr>
<tr>
<td>• Pulse corticosteroids (category 3)</td>
</tr>
</tbody>
</table>

**First-line therapy**\(^b\)

- **Age ≥70 y and younger patients with significant comorbidities**
  - Obinutuzumab + chlorambucil (category 1)
  - Ofatumumab + chlorambucil
  - Rituximab + chlorambucil
  - Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) ± rituximab
  - Obinutuzumab (category 2B)
  - Fludarabine\(^c,d,e\) ± rituximab (category 2B)
  - Chlorambucil (category 2B)
  - Rituximab (category 3)
  - Cladribine (category 3)\(^f\)

- **Age <70 y without significant comorbidities**
  - Chemoimmunotherapy
    - FCR\(^c\) (fludarabine,\(^e\) cyclophosphamide, rituximab) (category 1)
    - FR\(^c\) (fludarabine,\(^e\) rituximab)
    - PCR (pentostatin, cyclophosphamide, rituximab)
    - Bendamustine ± rituximab

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\(^a\) See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
\(^b\) See Supportive Care for Patients with CLL (CSLL-C).
\(^c\) Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
\(^d\) In patients ≥70 y, fludarabine does not have a benefit for first-line therapy over other therapies including chlorambucil.
\(^e\) See Discussion for further information on oral fludarabine.
\(^f\) In rare circumstances of CNS disease, cladribine is potentially useful.

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NCCN Guidelines Version 1.2015
CLL/SLL

SUGGESTED TREATMENT REGIMENS\(^a\)
(in order of preference)

CLL without del (11q) or del (17p)

**Relapsed/Refractory therapy\(^b\)**

<table>
<thead>
<tr>
<th>Age ≥70 y and younger patients with significant comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ibrutinib(^g) (category 1)</td>
</tr>
<tr>
<td>• Idelalisib ± rituximab(^g,h)</td>
</tr>
<tr>
<td>• Chemoimmunotherapy</td>
</tr>
<tr>
<td>o Reduced-dose FCR(^c,e)</td>
</tr>
<tr>
<td>o Reduced-dose PCR</td>
</tr>
<tr>
<td>o Bendamustine ± rituximab</td>
</tr>
<tr>
<td>o High-dose methylprednisolone (HDMP) + rituximab</td>
</tr>
<tr>
<td>o Rituximab + chlorambucil</td>
</tr>
<tr>
<td>• Ofatumumab</td>
</tr>
<tr>
<td>• Obinutuzumab</td>
</tr>
<tr>
<td>• Lenalidomide(^l) ± rituximab</td>
</tr>
<tr>
<td>• Alemtuzumab(^l) ± rituximab</td>
</tr>
<tr>
<td>• Dose-dense rituximab (category 2B)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Age &lt;70 y without significant comorbidities</th>
</tr>
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<tbody>
<tr>
<td>• Ibrutinib(^g) (category 1)</td>
</tr>
<tr>
<td>• Idelalisib ± rituximab(^g,h)</td>
</tr>
<tr>
<td>• Chemoimmunotherapy</td>
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<tr>
<td>o FCR(^c,e)</td>
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<tr>
<td>o PCR</td>
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<tr>
<td>o Bendamustine ± rituximab</td>
</tr>
<tr>
<td>o Fludarabine(^c,e) + alemtuzumab</td>
</tr>
<tr>
<td>o RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)</td>
</tr>
<tr>
<td>o OFAR(^e) (oxaliplatin, fludarabine,(^e) cytarabine, rituximab)</td>
</tr>
<tr>
<td>• Ofatumumab</td>
</tr>
<tr>
<td>• Obinutuzumab</td>
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<tr>
<td>• Lenalidomide(^l) ± rituximab</td>
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<tr>
<td>• Alemtuzumab(^l) ± rituximab</td>
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<tr>
<td>• HDMP + rituximab</td>
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</tbody>
</table>

\(^a\) See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
\(^b\) See Supportive Care for Patients with CLL (CSLL-C).
\(^c\) Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
\(^d\) See Discussion for further information on oral fludarabine.
\(^e\) See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).

\(^g\) Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)


\(^h\) While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.
METHOD OF PARTICIPATION

There are no fees for participating in and receiving credit for this activity. During the period March 2015 through September 30, 2016, participants must 1) read the learning objectives and faculty disclosures, 2) study the educational activity, 3) complete the posttest by recording the best answer to each question and obtaining a score of 70% or higher, 4) complete the evaluation form.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better.

For Pharmacists: Upon receipt of the completed activity evaluation form, transcript information will be available at www.mycpemonitor.com within 4 weeks.

To access the posttest and evaluation for this activity, please visit www.impactedu.net/NCCN/