Practical Clinical Considerations in Sequencing CLL Therapies

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Overview
This activity is designed to inform physicians about the current and emerging treatment landscape in chronic lymphocytic leukemia (CLL) and factors that influence the sequencing of CLL therapies.

Target Audience
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with hematologic malignancies. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers with an interest in the current topic are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:

- Identify the factors that guide individualized treatment decision making in patients with newly diagnosed and relapsed/refractory CLL
- Summarize key clinical trial findings demonstrating the safety and efficacy of recently approved CLL therapies
- Utilize evidence-based data to appropriately implement new CLL therapies into clinical practice
- Recognize the advantages and limitations of allogeneic hematopoietic stem cell transplantation in patients with CLL
- Discuss novel agents that are currently under investigation as monotherapy or in combination with other agents in the treatment of patients with CLL

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries.[1-6] In the United States, an estimated 18,960 people will be diagnosed with CLL and an estimated 4660 people will die of the disease in 2016.[7,8] The average age at the time of CLL diagnosis is about 71 years; the risk of developing CLL is slightly greater in men than in women.[7]

The clinical course of CLL is highly heterogeneous, with substantial variation in disease progression, response to therapy, and survival.[1,2,9,10] Some patients present with indolent disease that can be managed for decades with a watch-and-wait strategy, whereas others present with a progressive disease that does not respond well to therapy.[1,9-11] Front-line treatment decisions should be based on patient age, fitness, comorbidity burden (especially liver and renal function), concomitant medication use, and genetic aberrations.[12] Additional factors, such as the intensity and toxicity of prior therapies and the quality and duration of response, must be considered in patients with relapsed/refractory CLL.[12]

Historically, patients with CLL were treated with alkylating agents that did not affect the natural history of the disease.[4,13] Chlorambucil monotherapy was the standard of care in CLL for several decades.[5] In recent years, the CLL treatment landscape has been expanded to include several new agents, including three CD20-directed monoclonal antibodies (rituximab, ofatumumab, and obinutuzumab), two kinase inhibitors (ibrutinib and idelalisib), and the BCL-2 inhibitor venetoclax.[6] Despite the clinical benefits associated with the use of these agents, disease progression and drug resistance are frequent.[13] At present, allogeneic hematopoietic stem cell transplantation (HSCT) remains a potentially curative option for CLL[1,14,15]; however, patients who undergo the procedure face a substantial risk of treatment-associated morbidity and mortality.[1] Furthermore, allogeneic HSCT is feasible in only a minority of younger, fit patients who have a matching donor.[1,15]

Rituximab was approved by the U.S. Food and Drug Administration (FDA) in February 2010 for use in combination with fludarabine and cyclophosphamide (FC) in the treatment of previously untreated and previously treated patients with CLL.[16,17] The fludarabine/cyclophosphamide/rituximab (FCR) regimen was initially investigated at the University of Texas MD Anderson Cancer Center as front-line therapy in 224 patients with progressive or advanced CLL.[18] In the study, the overall response rate (ORR) was 95% (complete remission, 70%; nodular partial remission, 10%; and partial remission, 15%), and an analysis of time to treatment failure showed that 69% of patients were projected to be failure free at 4 years.[18] Grade 3/4 neutropenia was reported during 52% of treatment courses, and major and minor infections were observed in 2.6% and 10% of treatment courses, respectively.[18]

The approval of rituximab was based on data showing that rituximab in combination with FC chemotherapy improved survival compared with FC chemotherapy alone in treatment-naïve patients with CLL and patients with relapsed/refractory disease. In the randomized, open-label, phase 3 CLL8 study in 817 treatment-naïve, fit patients (median age, 61 years) with CD20-positive CLL, treatment with FCR versus FC was shown to improve progression-free survival (PFS) and overall survival (OS).[19] At 3 years post randomization, 65% of patients receiving FCR were free of progression compared with 45% of patients receiving FC, and the OS rate was 87% versus 83%, respectively.[19] Grade 3/4 neutropenia and leukocytopenia occurred more often in patients receiving FCR than FC, but other adverse events (AEs), including severe infection, were not increased in patients receiving FCR.[19] Updated data from the CLL8 study (published in 2016) showed that at median follow-up of 5.9 years, median PFS was 56.8 and 32.9 months in patients receiving FCR and FC, respectively; median OS was not reached versus 86.0 months, respectively.[14] Long-term safety analysis showed that patients receiving FCR had a higher rate of prolonged neutropenia during the first year post treatment than did those receiving FC (16.6% vs 8.8%, respectively).[14] Data from the REACH study in 546 previously treated assessable patients with CLL showed that median PFS was 30.6 versus 20.6 months with FCR and FC, respectively, at median follow-up of 25 months.[20] Additionally, the response rate, complete response rate, duration of response, event-free survival, and time to new CLL treatment or death were also significantly improved in the FCR versus FC group.[20] Grade 3/4 AEs occurred in 80% of patients receiving FCR and 74% of those receiving FC, and serious AEs were also slightly higher in the FCR than FC arm (50% vs 48%, respectively).[20]

At present, FCR is considered the standard of care in previously untreated patients with CLL who are fit and do not have severe comorbidities or high-risk genetics.[1,21] Utilization of a reduced-dose FCR regimen or bendamustine in combination with rituximab (BR) may be appropriate in some patients to reduce toxicity.[1,21] Data from the international, open-label, randomized, phase 3, noninferiority CLL10 trial in 561 treatment-naïve, fit patients (median age, 61 years) with advanced CLL showed that treatment with FCR was associated with longer median PFS than was treatment with BR (55.2 vs 41.7 months, respectively); however, severe neutropenia occurred more often in those treated with FCR than BR (84% vs 59%, respectively), as did severe infection (39% vs 25%, respectively).[22]

Ofatumumab received FDA approval for 4 indications in CLL between October 2009 and August 2016: (1) in combination with chlorambucil for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate; (2) in combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL; (3) for extended

treatment of patients who are in complete or partial response after ≥2 lines of therapy for recurrent or progressive CLL; and (4) for the treatment of patients with CLL that is refractory to fludarabine and alemtuzumab.[23-25] The use of single-agent ofatumumab has demonstrated efficacy in the treatment of patients with fludarabine- and alemtuzumab-refractory CLL,[26,27] and adding ofatumumab to chlorambucil in the front-line CLL setting has been shown to improve PFS.[28] In COMPLEMENT-1, a randomized, multicenter, open-label, phase 3 trial investigating chlorambucil in combination with versus chlorambucil alone in 447 previously untreated patients (median age, 69 years) with CLL, median PFS was 22.4 and 13.1 months, respectively.[28] Grade ≥3 AEs occurred more often in patients receiving chlorambucil plus ofatumumab than chlorambucil alone (50% vs 43%, respectively); the most common AE was neutropenia (26% vs 14%, respectively).[28]

In October 2013, the CD20-directed cytolytic antibody obinutuzumab was approved by the FDA in combination with chlorambucil for the treatment of patients with previously untreated CLL.[29,30] FDA approval was based on primary findings from the 3-arm, randomized, phase 3 CLL11 study comparing the efficacy and safety of chlorambucil, obinutuzumab/chlorambucil, and rituximab/chlorambucil in 781 previously untreated patients (median age, 73 years) with CLL and comorbid conditions.[30,31] In the study, median PFS was 11.1, 16.3, and 26.7 months with chlorambucil alone, rituximab/chlorambucil, and obinutuzumab/chlorambucil, respectively; the rate of death was 20%, 15%, and 9%, respectively.[31] Neutropenia and infusion-related reactions were reported more often in patients treated with obinutuzumab/chlorambucil than in those treated with rituximab/chlorambucil; however, the risk of infection was not increased in the obinutuzumab/chlorambucil group.[31] Updated data from the CLL11 study (published in 2015) showed that PFS was substantially longer in patients receiving obinutuzumab/chlorambucil than rituximab/chlorambucil (29.2 vs 15.4 months, respectively).[32] A statistically significant OS benefit was not demonstrated for obinutuzumab/chlorambucil over rituximab/chlorambucil, but the OS finding remains immature due to the small number of deaths in the antibody treatment arms.[32] No new safety findings were reported in the CLL11 update.[32]

Patients with CLL who have a 17p deletion and/or mutation of the TP53 gene often have an aggressive disease course and poor response to treatment.[1,12] Until recently, the anti-CD52 antibody alemtuzumab was the only effective agent available for patients with these genetic aberrations, but its use was associated with a high risk of serious infections.[1] The introduction of 2 kinase inhibitors—the Bruton tyrosine kinase ibrutinib and the phosphatidylinositol 3-kinase delta inhibitor idelalisib—marked another milestone in the treatment of CLL, especially in patients with del(17p)/TP53 mutations.[1]

Ibrutinib is currently approved for the treatment of previously treated and previously untreated patients with CLL/small lymphocytic lymphoma (SLL), including those with a 17p deletion.[33-35] Initially, ibrutinib was granted accelerated approval by the FDA in February 2014 for the treatment of patients with CLL/SLL who have received ≥1 therapy.[34] In July 2014, the FDA expanded its approval of ibrutinib to include patients with CLL/SLL who had a 17p deletion.[35] The latter approval was based on data from the multicenter, open-label, phase 3 RESONATE study comparing the efficacy and safety of ibrutinib versus ofatumumab in 391 previously treated patients (median age, 67 years) with relapsed/refractory CLL or SLL.[35,36] In RESONATE, ibrutinib significantly improved median PFS compared with ofatumumab (not reached vs 8.1 months, respectively) at median follow-up of 9.4 months.[37] The OS rate was 90% and 81% in the ibrutinib and ofatumumab groups, respectively, and the ORR was significantly higher in the former than latter group (42.6% vs 4.1%, respectively).[37] Furthermore, 83% vs 49% of patients with a deletion in 17p who were treated with ibrutinib and ofatumumab, respectively, were alive (with no disease progression) at 6 months.[37] The most commonly reported nonhematologic AEs were diarrhea, fatigue, pyrexia, and nausea in patients treated with ibrutinib versus fatigue, infusion-related reactions, and cough in those treated with ofatumumab.[37]

In March 2016, ibrutinib was approved by the FDA for use as front-line therapy in patients with CLL/SLL based on data from RESONATE-2, an international, open-label, randomized phase 3 trial in 269 previously untreated patients (median age, 73 years) with CLL or SLL who received ibrutinib or chlorambucil.[3,38] In the study, treatment with ibrutinib versus chlorambucil produced a significantly longer median PFS (not reached and 18.9 months, respectively) and a higher ORR (86% and 35%, respectively).[3] Furthermore, ibrutinib was associated with significantly prolonged OS compared with chlorambucil.[3] At 24 months, the estimated survival rate was 98% in patients receiving ibrutinib versus 85% in those receiving chlorambucil; the relative risk of death was 84% lower in the former than latter group.[3] The rate of sustained improvement in hematologic variables was also significantly higher with ibrutinib than chlorambucil.[3] The most common grade ≥3 AEs were neutropenia, which occurred in 10% of patients receiving ibrutinib vs 18% of those receiving chlorambucil, and anemia, which occurred in 6% and 8% of patients, respectively.[3]

Ibrutinib also demonstrated efficacy in RESONATE-17, a multicenter, international, open-label, single-arm study in 144 patients (median age, 64 years) with del(17p)-relapsed/refractory CLL or SLL.[39] At median follow-up of 27.6 months, investigator-assessed overall response was 83%, and 24-month PFS and OS were 63% and 75%, respectively.[39] Grade 3/4 bleeding was reported in 8% of patients, and grade ≥3 infections were reported in 30% of patients.[39] The addition of ibrutinib to bendamustine/rituximab has also been shown to be an effective strategy in previously treated

patients with CLL.[40] In the HELIOS trial, a randomized, double-blind, phase 3 study in 578 patients (median age, 64 years) with previously treated CLL/SLL comparing ibrutinib/bendamustine/rituximab with placebo/bendamustine/rituximab, PFS at median follow-up of 17 months was significantly improved in the ibrutinib group compared with the placebo group (not reached vs 13.3 months, respectively).[40] PFS assessed by an independent review committee at 18 months was 79% versus 24% in patients receiving ibrutinib and placebo, respectively.[40] Grade 3/4 AEs occurred in 77% of patients in the ibrutinib group versus 74% of those in the placebo group; the most common grade 3/4 AEs in both groups were neutropenia (54% vs 51%, respectively) and thrombocytopenia (15% in each group).[40]

In July 2014, idelalisib was approved by the FDA in combination with rituximab for the treatment of patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy due to other comorbidities and for the treatment of patients with relapsed SLL who have received ≥2 prior systemic therapies.[41,42] Several phase 1/2 studies have shown that idelalisib is clinically active in CLL, especially in patients with relapsed/refractory disease; the ORRs in these studies have ranged between 70% and 82%.[43] For example, in a phase 1 study evaluating idelalisib in 54 patients with relapsed/refractory CLL and adverse characteristics, median PFS was 15.8 months, nodal response was 81%, and the ORR was 72%.[44] The most commonly reported grade ≥3 AEs were pneumonia (20%), neutropenic fever (11%), and diarrhea (6%).[44] FDA approval was based on data from a multicenter, randomized, double-blind, placebo-controlled, phase 3 study in 220 patients with relapsed CLL and major comorbid conditions.[45] In the study, idelalisib/rituximab versus placebo/rituximab significantly improved median PFS (not reached and 5.5 months, respectively), OS at 12 months (92% and 80%, respectively), and overall response (81% and 13%, respectively).[45] Serious AEs were reported in 40% and 35% of patients receiving idelalisib/rituximab versus placebo/rituximab, respectively.[45]

Venetoclax, a pro-apoptotic small molecule inhibitor of Bcl-2, was approved by the FDA in April 2016 for the treatment of patients with CLL who have been treated with ≥1 prior therapy and have a 17p deletion, as detected by an FDA-approved test.[46,47] In a single-arm, multicenter, phase 2 study in 107 patients with relapsed/refractory CLL with del(17p) who received venetoclax, the ORR was 79.4% at median follow-up of 12.1 months; the most common grade 3/4 AEs were neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%).[48] Data from a phase 1 dose escalation study of daily oral venetoclax in 116 patients (dose escalation phase, N=56; expansion phase, N=60) with relapsed/refractory CLL or SLL showed that venetoclax was active at dose levels ranging from 150 to 1200 mg/day; a maximum tolerated dose was not identified.[49] The response rate was 79%, and 20% of patients achieved complete remission.[49] Clinical tumor lysis syndrome occurred in 3 of 56 patients in the dose escalation phase, but in none of the 60 patients in the expansion cohort after adjustment was made to the dose escalation schedule.[49]

In summary, the treatment landscape in CLL is currently undergoing rapid and dramatic change brought about by the development and use of novel agents that have produced impressive response rates with acceptable toxicity.[5,50] Many other agents (eg, duvelisib, acalabrutinib, and pembrolizumab) are also being investigated and may someday represent further expansion of the CLL treatment armamentarium.[6,15,51] Nonetheless, much remains to be elucidated about the long-term safety and efficacy of these new agents and how best to implement them into treatment paradigms to optimize patient care.[51]

Susan M. O'Brien, MD, Associate Director for Clinical Science at the Chao Family Comprehensive Cancer Center, and Medical Director for the Sue and Ralph Stern Center for Cancer Clinical Trials and Research at UC Irvine Health (Irvine, CA), offered her insights on the current and emerging treatment landscape in CLL and the practical clinical considerations that should be taken into account in the sequencing of CLL therapies.

Moderator: Would you discuss the CLL patient populations in which the use of ibrutinib would be a reasonable option as front-line therapy?

Dr. O'Brien: Ibrutinib was approved by the FDA based on data from a randomized trial in which it was compared with chlorambucil. It is important to note that the population in that trial was relatively older, and in an older population, I would not hesitate to use ibrutinib. Arguably, chlorambucil would not be an acceptable standard in a younger fit population. In younger fit patients, my decision would depend on mutation status, and the reason for that is that there have been three publications in the past year—one from Germany, one from Italy, and one from MD Anderson—that all show very consistent results. The MD Anderson data represent the longest follow-up of the three publications, partly because the fludarabine/cyclophosphamide/rituximab (FCR) regimen was designed there. But what these publications show is that in patients with a mutated immunoglobulin variable region heavy chain (*IGVH*) gene, there seems to be a plateau on the PFS curve, and it is likely that some of these patients may be cured. If you look at the MD Anderson data 12 to 16 years out, about 60% of the mutated patients are represented on the plateau, whereas unmutated patients, for the most part, are not. So, in the unmutated patients, I would be willing to use ibrutinib, although my first choice is always a clinical trial. In the mutated patients, I would have—and have had—longer discussions with them in terms of the pros and cons of using FCR versus ibrutinib.

Moderator: What are some reasonable front-line treatment options for the following CLL patient populations: (1) patients aged <70 years without significant comorbidities who do not have del(11q) or del(17p)/TP53 mutations and (2) patients aged ≥70 years and younger patients with significant comorbidities who do not have del(11q) or del(17p)/TP53 mutations?

Dr. O'Brien: If a patient has del(17p), I would never use chemotherapy because we know that it is not very effective. So, I would go straight to ibrutinib. I would probably do the same in a patient with del(11q)—not so much because of the 11q deletion alone—but because about 90% of patients with this deletion have an unmutated *IGVH* gene. It is extremely rare to have a del(11q) and be mutated. So, for practical purposes, patients with del(11q) are essentially all unmutated. Therefore, I would be willing to use ibrutinib in patients with del(17p)/TP53 mutations and del(11q) mutations, even in those who are younger. In patients over the age of 70, I would go straight to ibrutinib. In these patients, mutation status is not as important because of life expectancy considerations and also because chemotherapy is much more toxic than in younger patients.

Moderator: Numerous new therapies are being investigated as front-line treatment for CLL in phase 3 clinical trials. Which ongoing trials are of most interest to you? Do you anticipate any major additions to the CLL front-line treatment armamentarium in the near future?

Dr. O'Brien: I think that a very interesting potential front-line regimen currently being investigated in several places is the combination of venetoclax and obinutuzumab. I'm particularly interested in a trial sponsored by AbbVie comparing chlorambucil and obinutuzumab because the Germans have presented data that the run-ins to the large randomized trial they are conducting show that many of these patients are becoming minimal residual disease (MRD)-negative. A similar finding has also been observed with venetoclax in the relapsed setting. In fact, data presented at the American Society of Hematology (ASH) meeting for rituximab and venetoclax showed that the MRD negativity rate in relapse is about 50%. If you can get MRD negativity in relapse, one would presume that it would be significantly higher in the front-line setting.

Now, the question is: Will obinutuzumab be a better partner with venetoclax than rituximab? I believe that, right now, it's not clear. We know that obinutuzumab is better with chlorambucil because of the three-arm randomized trial that the Germans conducted in which they compared chlorambucil with both chlorambucil plus rituximab and chlorambucil plus obinutuzumab. In that trial, chlorambucil plus obinutuzumab was clearly better than chlorambucil plus rituximab, and both of these regimens were better than chlorambucil alone. But, chlorambucil is a very weak chemotherapy, so it is possible that the antibody contributed more to the combination in this case.

There was also some recent data comparing the R-CHOP regimen (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) versus CHOP and obinutuzumab in lymphoma that showed no difference in progression-free survival (PFS). Why would that be the case when obinutuzumab combined with chlorambucil showed such a big difference? Well, CHOP is a much stronger backbone of chemotherapy, and so the antibody may not have added as much there. The point I'm making is the same with venetoclax: We don't know. We don't have any data about which antibody would be better. But if I extrapolate from the relapsed data, where the combination causes about 50% MRD-negativity, it would not at all surprise me if it were around 80% in the front-line setting, which would be very striking. For these reasons, I think that the combination of venetoclax and obinutuzumab is one of the most interesting front-line- regimens currently under investigation.

Moderator: The phase 3 HELIOS trial investigated the use of ibrutinib in combination with bendamustine and rituximab (BR) in patients with relapsed/refractory CLL. Would you comment on the efficacy and safety findings in this trial?

Dr. O'Brien: First, let me say that my opinions about the HELIOS trial, which investigated BR with and without ibrutinib, are evolving. When the data were first presented at ASH, I don't think that it was surprising to anyone that ibrutinib, given concomitantly with BR and then continuously as a single agent (as it would normally be administered if one used it as a single agent), was found to be significantly better than BR alone. I don't think that this finding surprised anyone, partly because the combination arm had built-in maintenance with ibrutinib, which was not the case in the other arm of the trial. When these findings were presented at ASCO, Lloyd Damon from the University of California-San Francisco, who was the discussant at the oral session, raised an interesting question: We know that ibrutinib adds to BR, but is the reverse true (ie, does BR add anything to what you have gotten with ibrutinib alone)? To make the point, he presented the phase 2 data that have the longest follow-up with ibrutinib in the relapse setting and suggested that, thus far, the outcomes look quite similar.

So, I was somewhat skeptical about using the BR plus ibrutinib combination: Why not just go straight to ibrutinib? The reason I say that my thoughts may be changing is that the complete response (CR) rate in the BR plus ibrutinib arm, as the data have been updated, has increased very substantially. In contrast, the CR rate has not really increased at all in the BR arm. The latter is not surprising given that once patients completed treatment with BR, they didn't receive anything else and CR didn't increase. But if one asks about the comparison with single-agent ibrutinib, the picture starts to look different. Again, if you consider the phase 2 data with single-agent ibrutinib, which is the longest follow-up data available, the CR rates in the relapsed setting are still very low—single digits, even with longer follow-up, which is probably now around 4 years. Yet, CR was achieved in about one-third of the patients who were treated with

BR and then with ibrutinib. So, it might well be the case that with longer-term follow-up, we will see a benefit to using a combination as opposed to just single-agent ibrutinib. Certainly, if I was going to use chemotherapy, I would want to use it with ibrutinib. I think that the flip question still exists: Do I want to undertake the toxicity of the chemotherapy? Is it going to add that much more than if I just put the patient on ibrutinib? And, now, the data with longer follow-up is suggesting that maybe it would, but I'd like to see still more follow-up data.

Moderator: Venetoclax, a highly selective inhibitor of BCL2, is approved for the treatment of patients with CLL who have a 17p deletion and have received ≥1 prior therapy. In recent clinical trials, the use of venetoclax has been associated with a high incidence of tumor lysis syndrome. Would you discuss prophylactic measures that can be undertaken to minimize the risk of tumor lysis syndrome in patients receiving treatment with venetoclax?

Dr. O'Brien: The main risk associated with venetoclax, of course, is tumor lysis. The precautions that were undertaken when the clinical trials were amended are shown in a very simple table in the package insert. Essentially, patients with an elevated lymphocyte count and bulky nodes are considered to be at the highest risk of tumor lysis and need to be hospitalized to initiate venetoclax. The package insert also recommends that patients with intermediate risk for tumor lysis be hospitalized if they have reduced renal function, which will probably include a lot of the older patients. In addition, typical tumor lysis prophylaxis—hydration and very careful monitoring—should also be implemented. Several other strategies help to reduce the occurrence of tumor lysis. The trials were adapted to slow down the stepped-up dosing of venetoclax. Also, it is important to start with a very low dose of 20 mg and then gradually go up to the full target dose of 400 mg. It takes about 4 weeks to actually reach the target dose. We found that once appropriate measures were implemented, no significant tumor lysis was observed in the trials.

Other people have discussed the concept of debulking, but there is currently no debulking regimen approved with venetoclax. Nonetheless, people have thought about ways to minimize the risk of tumor lysis going forward that would potentially perhaps not even require hospitalization. Obviously, one could use different strategies for debulking, such as short-course chemotherapy or antibody, and trials are underway for both options. One of the advantages of, let's say, using antibody alone would be that patients would not experience the side effects of chemotherapy. And, we all think of antibody as being relatively well tolerated, with infusion reactions being the main issue, predominantly with the first dose

One strategy that is currently being investigated in clinical trials is front-loading with antibodies to debulk the patient to minimize monitoring and make hospitalization unnecessary. Again, that's not the standard right now, but it's something that's being looked at in clinical trials. Additionally, it would be an interesting strategy if we think that when venetoclax receives a broader label in the relapse setting that it will be in combination with obinutuzumab (which is very likely based on the Murano trial). At present, we still must do stepped up-dosing, hospitalization in high-risk patients, and very careful tumor lysis prophylaxis and monitoring of labs.

Moderator: Several novel agents, including duvelisib, acalabrutinib, and pembrolizumab, are currently being investigated as monotherapy or in combination with other agents in CLL. What is the status of these agents?

Dr. O'Brien: Duvelisib is PI3-delta-gamma inhibitor. Idelalisib inhibits only delta, but duvelisib also inhibits gamma and clearly shows some good activity in CLL. Duvelisib is currently in a potential pivotal trial in a randomized comparison with ofatumumab in relapsed CLL. The trial design is essentially the same as the one that led to the full approval of ibrutinib after accelerated approval was given based on phase 2 data. The duvelisib trial has reached accrual, so that drug is the farthest along in terms of potentially getting an FDA registration in CLL—assuming that the randomized comparison with ofatumumab is positive—which I would guess it would be, and that there are no flaws in the study that would make the FDA not consider it an acceptable registration study.

Acalabrutinib is a next-generation Bruton tyrosine kinase (BTK) inhibitor. One of the putative advantages of this drug compared with ibrutinib is that the toxicity profile may be better. We know that ibrutinib inhibits other kinases in addition to BTK, as does, to some extent, acalabrutinib. It is also believed that the inhibition of some of these other kinases is actually responsible for some of the side effects of ibrutinib, as opposed to the direct binding to BTK. For example, atrial fibrillation, bleeding, and the inhibition of platelet aggregation are not thought to be mediated through the actual binding to BTK.

Also, if you consider the IC50 for acalabrutinib against some of the other kinases, it is, in some cases, higher. In fact, acalabrutinib has a 10-fold or even higher IC50 than ibrutinib for some of the other kinases. The reason is that you may not be targeting these other kinases as well and therefore would be sparing the patients atrial fibrillation or bleeding problems. The efficacy of acalabrutinib also looked quite good in the phase 1 trial, the results of which were recently published in the *New England Journal of Medicine*. Acalabrutinib is also in a few registration trials. There is a randomized comparison directly of acalabrutinib versus ibrutinib in relapsed patients with high-risk disease, defined as del(17p) or del(11q). A three-arm front-line trial investigating chlorambucil/obinutuzumab versus acalabrutinib versus acalabrutinib/obinutuzumab is also underway, and that could potentially lead to a front-line indication. These trials are ongoing, but are not as far along as the duvelisib trial. If approved, duvelisib would be the first B-cell receptor inhibitor since ibrutinib and idelalisib were approved.

Pembrolizumab, of course, is a checkpoint inhibitor. Mayo Clinic investigators presented their data at ASH last year pertaining to patients they enrolled with refractory CLL, including those with Richter's transformation or transformation to large-cell lymphoma, who received pembrolizumab. By the way, when patients with CLL develop Richter's or transform to large-cell lymphoma, they are usually considered to have end-stage disease. The standard chemotherapy regimens that we use for large-cell lymphoma are not effective, probably because this is an evolved clone in a heavily pretreated patient with CLL. And, survival is generally less than 1 year. So, this is a really difficult group of patients; in fact, there is no approved drug specifically for Richter's syndrome. Again, usually we use the same sorts of regimens that we would use in large-cell lymphoma, like R-CHOP, for example. But if a response is achieved, it generally tends to be partial and very transient.

What is fascinating about the Mayo Clinic data is that pembrolizumab was actually resulting in complete remission in the large-cell lymphoma component in several patients, although it had very little effect on the CLL component. I know that there is also substantial interest in potentially using checkpoint inhibitors in combination with other agents. There are currently several trials using checkpoint inhibitors—not just pembrolizumab, but others—in combination with ibrutinib, for example. But, there is also substantial interest in using pembrolizumab in the Richter's transformation setting because it is a very dire disease state for which there are no FDA-approved treatments.

Moderator: What data support referring high-risk patients with relapsed CLL for allogeneic hematopoietic stem cell transplantation assessment? What are your thoughts on using reduced-intensity conditioning?

Dr. O'Brien: Historically, patients with del(17p) would be the only group for whom most CLL physicians would recommend transplant in first remission. Obviously, transplant has a potential for cure, but it can be associated with significant morbidities and death. In general, transplant would not be used in the front-line CLL setting because a regimen like FCR can result in a remission that lasts for years. And, if a patient who had a decent remission does relapse after a long remission, it would be possible for them to re-respond to chemotherapy, which would send them into a second remission.

But, patients with 17p deletions are difficult to get into remission with chemotherapy. Furthermore, if they do achieve remission, you cannot rely on trying to get them in again if they recur, which they all do. Now that that is evolving, I would actually say that there is not a role in the front-line setting for stem cell transplant based on National Institutes of Health (NIH) data from Adrian Weistner, where they have front-line data with ibrutinib in 17p. It was interesting because the label for front-line treatment with ibrutinib in 17p was actually based on very little front-line data. I believe that the thinking was that ibrutinib was so much better than chemotherapy in the relapsed setting that it did not make sense to treat patients with chemotherapy when the responses were so transient. But there was actually not a lot of data at that time. So, when the NIH data came out, we saw that about 85% of patients with a del(17p) or TP53 mutation who got ibrutinib up front were still in remission 2 years later. The point is that now we've gone from very transient remissions with chemotherapy to what appears to be reasonably durable remissions. The other point is that we now have venetoclax, which was recently approved by the FDA for relapsed patients with del(17p). So, when these patients do relapse, and it looks like the average is going to be years as opposed to months with chemotherapy, there is now another drug that we can give them. The dire circumstances with chemotherapy in patients with 17p deletions are not necessarily there now in terms of front-line therapy.

In the relapsed setting, most patients with del(17p) nowadays would have been treated with chemotherapy, because 2, 3, or 4 years ago, ibrutinib was not approved for front-line del(17p). I do discuss stem cell transplant with most of the patients I see today with del(17p) who were treated with ibrutinib as a relapsed therapy. Again, I would say that it is moving back in the algorithm because of the availability of venetoclax, but we do have data on median PFS in del(17p)-relapsed patients who get ibrutinib, and it is about 3 years. Three years is fantastic for relapsed del(17p) because the best front-line data for PFS with chemotherapy prior to the front-line was only 12 months. So, to get 3 years in the relapsed setting really shows that ibrutinib is a major advantage. Of course, we don't know what the median PFS is in the front-line setting, but it looks like it's going to be longer than that.

The point I'm making now about relapse is that 3 years is great in this high-risk population, but we're not talking about 5 years or 10 years. Therefore, in relatively young, fit patients with del(17p) who have received chemotherapy and have relapsed, even if they received ibrutinib, the average duration of remission is a couple of years. I still think that it is worth having a discussion with these patients, but it may be pushed back actually even further now with the approval of venetoclax for that patient population just in the past few months.

Regarding reduced-intensity conditioning, it is important to keep in mind that the average age of CLL patients is around 70 years, and even younger patients with CLL are in their 60s. Because myeloablative therapy is too toxic in older patients, with rare exceptions, unless you have a very young patient with CLL, reduced-intensity conditioning transplants are performed in nearly all patients because of age.

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