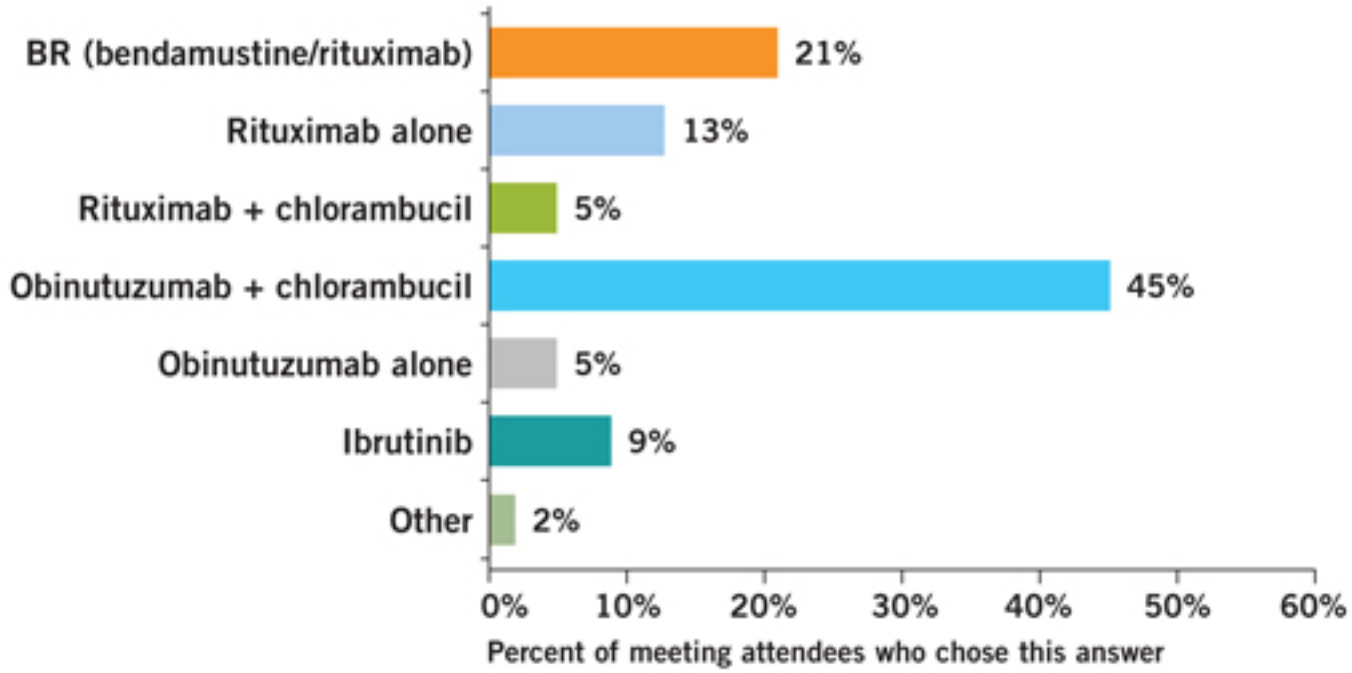
Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Chronic Lymphocytic Leukemia — Michael E Williams, MD, ScM

In general, what initial therapy would you recommend for an otherwise healthy 81-year-old patient with chronic lymphocytic leukemia (CLL) and normal-risk cytogenetics who requires treatment?



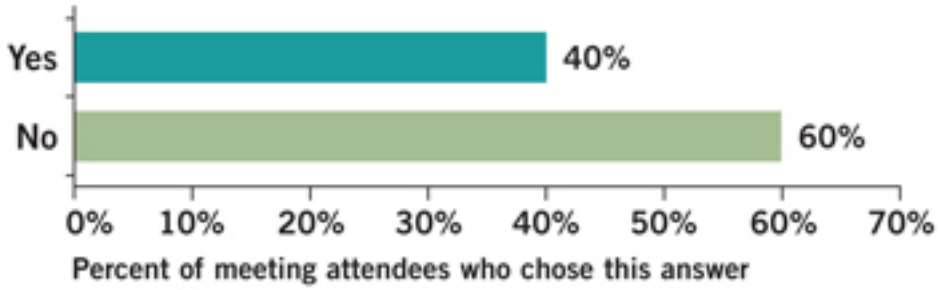
DR LOVE: One of the issues that has come out, Mike, over the past couple of years is the management of the older patient. And, of course, when we think about CLL, we often think of an older patient. So we presented this patient to this group and said: You have an 81-year-old patient, normal-risk cytogenetics, but needs treatment. What's your likely therapy? And this is very different, Mike, than what we saw last year or even the year before. We've seen a real movement now toward obinutuzumab/chlorambucil. Mike, how do you approach patients like this?

DR WILLIAMS: I agree, it is quite a change from last year. This is, in fact, our treatment of choice for older patients. In this case, it's an 81-year-old who's healthy. But many of our older patients have significant comorbid problems. I think an antibody that has higher efficacy, which obinutuzumab appears to have from randomized data, relative to rituximab, combined with a traditional alkylator, is an active regimen and one that I find easy to titrate in terms of dosing and schedule, especially for the chlorambucil. You can get good disease control and symptom control with very modest toxicity with that.

DR LOVE: Brad, one of the things that we've heard from docs in practice is concern about the infusion reactions. We hear docs thinking twice about this drug in older, more frail patients. Yet from the investigators we hear this is usually only a problem in the beginning and usually easy to manage. What's your own experience, Brad?

DR KAHL: There is more infusion toxicity with obinutuzumab relative to rituximab. You just have to be ready for it. It's usually a first-dose issue, so the first day of administration can be a long day. But these infusion reactions occur while the patient's with you in clinic, so it can be managed. Once you get through it, then it's usually smooth sailing after that.

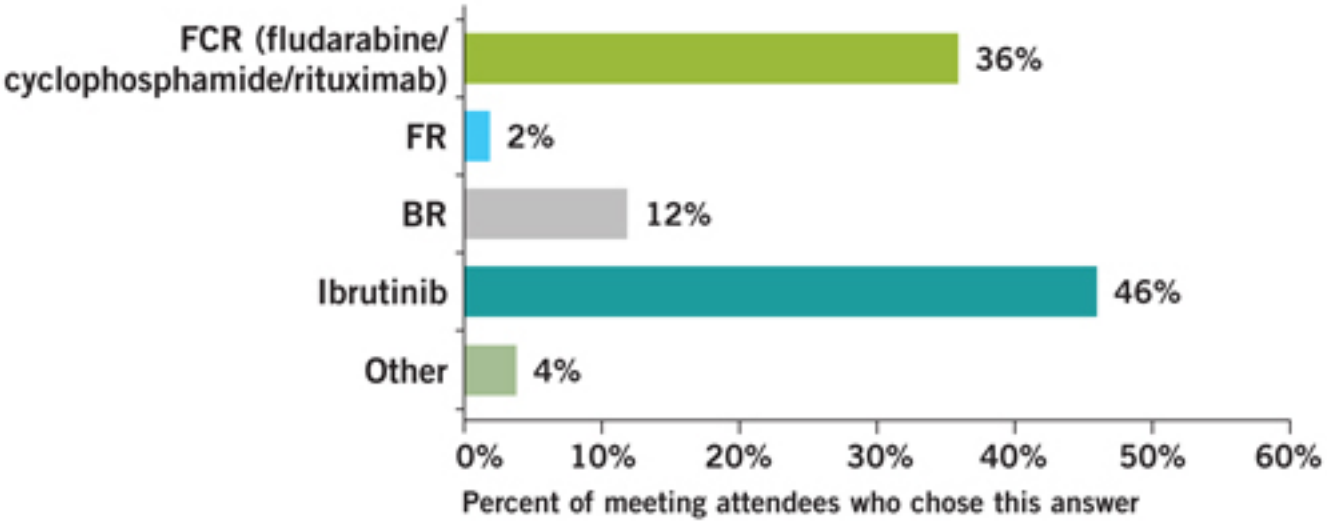
A younger, otherwise healthy patient with asymptomatic CLL meets the criteria for observation without treatment but has del(17p). Would you treat this patient?



DR LOVE: Another question — and, Michelle, I thought this is interesting, because I think that the thought about (del)17p adverse cytogenetic situation with CLL gets a lot of people very nervous — and the question is: If you have a patient who otherwise does not meet the criteria to be treated but has 17p, is that enough to treat? And you can see the audience is very split. How do you think it through?

DR FANALE: I would favor still not treating the patient. If the patient needed treatment, then of course agents like ibrutinib and such could be considered. But if the patient's really asymptomatic, has very low level of disease, I don't think the data at this time point would still favor to go ahead to treat. But I could see it from either side. A young patient who wants, definitely, treatment, those patients often could start asking for some type of treatment with the concern that they know that the risk is very high for bad outcomes if the disease progresses.

What is your usual preferred initial regimen for a younger (60-year-old) patient with CLL and del(17p) who requires treatment?



DR LOVE: Mike, this is a very interesting answer. We've actually seen this in all 3 cities so far with this series. I've asked 25 investigators, and they all say the same thing, which is ibrutinib, and yet you see a significant fraction of docs in practice saying FCR. Any thoughts, Mike?

DR WILLIAMS: I think it's becoming very clear that ibrutinib is *the* drug of choice if you've got a 17p deletion, either in the front line or the relapsed setting. FCR has activity but also offers some other toxicities. I think you really need ibrutinib on board with this patient.

I think the challenge for me with younger patients like this is: I get ibrutinib on board up front. They typically will respond. But we know that their durations of response aren't quite as long as we see with the non-17p type. Then what do you do with allotransplant?

DR LOVE: Craig, the other issue is relating to the younger patient who doesn't have (del)17 but needs to be treated. In general, we've been hearing people using FCR, which continued after the study. But one of our faculty last week in Chicago, John Leonard, said, "I think we should use ibrutinib." In a non-(del)17p situation, Craig, how do you think that through? Do you think there's a logic to use ibrutinib presumably indefinitely for a patient like that?

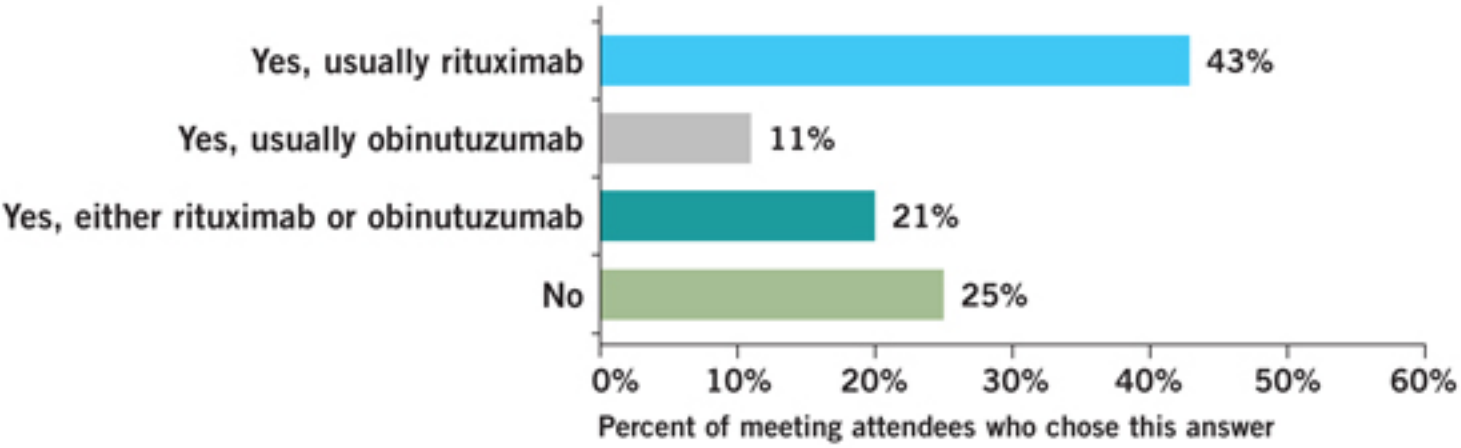
DR MOSKOWITZ: There are people who have never relapsed from FCR in the MD Anderson data set. So I will say that I am on the FCR camp in this setting, although I will say, in my career, which is getting long, ibrutinib is the best drug I've ever seen in CLL/SLL. When patients come back the next day with a complete response on physical examination, that's unheard of in lymphoma management. So I'm waiting for the ibrutinib studies to read out. But for now it's FCR for me.

DR LOVE: Brad, any comments on that? Are there trials out there attempting to stop therapy, which is the thing everybody's looking for?

DR KAHL: If you're having that discussion with a patient about ibrutinib versus FCR, you have to get into the discussion about: If you do FCR, your therapy will be done in approximately 6 months, whereas if you go on ibrutinib, you will be on this for we don't know how long. Some patients might prefer the option of taking a therapy and being done with it in 6 months. I totally get that. I've thought, "What would I do?"

It's really the mutated patients, the CLL patients with the heavy-chain mutations, that appear to get the plateau and the progression-free survival curve with FCR. There's 3 different groups that have shown this now: MD Anderson and the German group, and then I just saw another paper in *Blood* from a group in Europe. So if you're a young patient with the mutated version of CLL, I'm thinking FCR right now, as still your best choice.

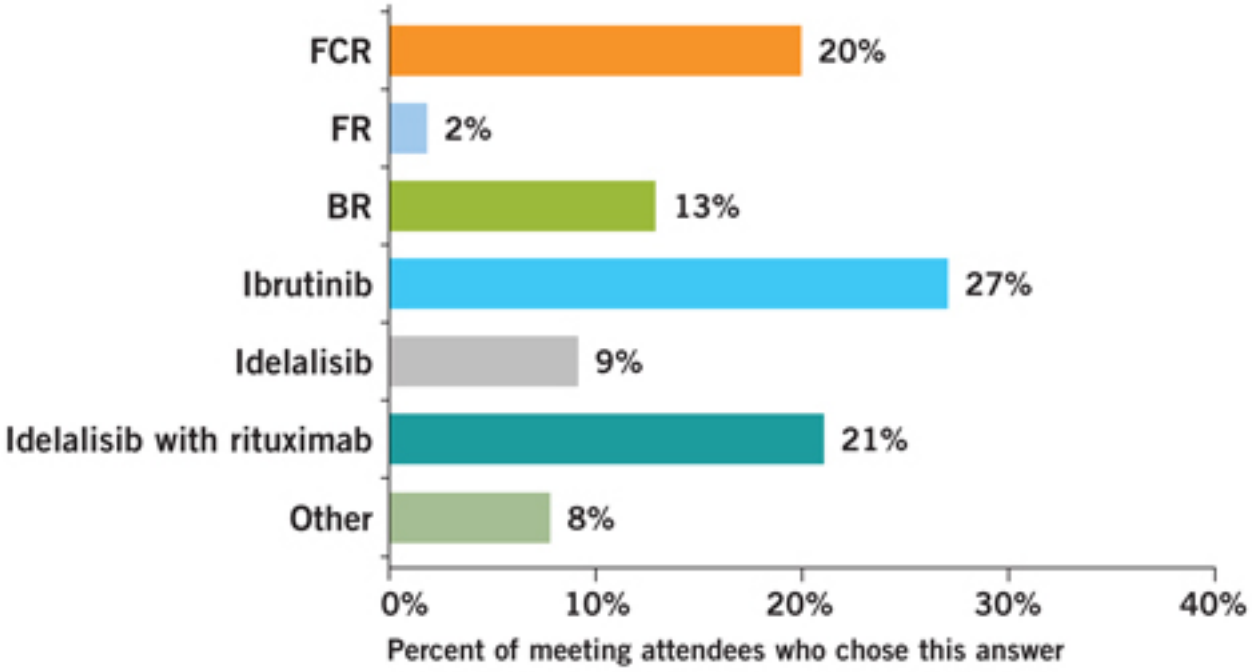
Are there patients with CLL to whom you administer an anti-CD20 antibody alone?



DR LOVE: Mike, it seems like we see a lot of monotherapy with anti-CD20 in CLL in the community. You can see here, the majority of the audience will use an anti-CD20 agent, either or both. What are your thoughts about this strategy, Mike?

DR WILLIAMS: When I saw this question, I immediately thought of a number of patients that I follow. It's usually part of the discussion. These are people who want to avoid any cytotoxic chemotherapy or they have a lot of comorbid disease and you're trying to be very careful about how you treat them. I will use a single-agent monoclonal anti-CD20. I have used, in some situations, obinutuzumab as front line, or rituximab. They do have activity. I think obinutuzumab appears to clear faster, so there is a role for them, but it's usually in a selected setting where you're not thinking you want a remittive therapy but you want to control symptoms and disease.

In general, what treatment would you recommend for a younger patient with CLL and del(17p) who requires treatment but is receiving full-dose anticoagulation for atrial fibrillation?



DR LOVE: Obviously, there's a lot of debate and discussion about the patient who needs anticoagulation that you want to give ibrutinib to. We've already established the fact that (del)17p, you're thinking about ibrutinib right from the front, but what about the patient who's on anticoagulation? We see a spectrum. Some people would use FCR, others would use the ibrutinib in spite of the fact that the patient's anticoagulated, others would use idelalisib with R, which is actually approved in CLL. Brad, how do you think it through?

DR KAHL: Really tough decision-making in this scenario. Ibrutinib certainly increases the bleeding risk, probably through an antiplatelet mechanism. So patients who are on an anticoagulant affecting the clotting, the cascade in the protein system, combined with this possible antiplatelet effect, is a high-risk situation for bleeding. I'm not saying ibrutinib is absolutely contraindicated in that situation but may be relatively. You have to think long and hard about that. Personally, in this situation, I might opt for the idelalisib/rituximab combination to avoid the bleeding risk situation in a case like this.

DR LOVE: Mike, obviously idelalisib-R is approved in CLL. Any way to indirectly compare efficacy? We can talk about tolerability too.

DR WILLIAMS: The efficacy is perhaps modestly less with the idela-rituximab combination. There's the twice-a-day administration. There's concern about the later autoimmune effects of pneumonitis and maybe colitis. But it's certainly got good activity, including in higher-risk subsets like 17p deleted and 11q-deleted. It's a valuable regimen to use. This is one of the settings where I agree completely with Brad's comments about where I think you would have to consider this.

DR LOVE: Craig, have clinical bleeds been seen with ibrutinib?

DR MOSKOWITZ: I've had patients who have died from ibrutinib in this setting. I would be more dogmatic. I wouldn't give ibrutinib in somebody in this situation. There are other options. I think this is the exact indication to give idelalisib. For my money, I think it's not as good as ibrutinib, except in this exact setting, where it's a very good drug. Years ago, we didn't have anything to give these patients. Now we have a laundry list of stuff that we can give. So why take the risk? I'm uncomfortable with it.

DR LOVE: Brad, another thing that's kind of popped up into our consciousness has been atrial fibrillation as a result of ibrutinib. Have you seen that? And what do you do in that situation?

DR KAHL: Yes, I have seen it. I think a patient who has atrial fibrillation, that's not a contraindication, because they already have it. You can't give them atrial fibrillation at that point. But if a patient develops atrial fibrillation — I've that happen in my practice. I've stopped the ibrutinib because you have to put the patient on anticoagulation at that point. Then I usually go to idelalisib-rituximab or some other alternative.

DR LOVE: When you stop it, does the atrial fibrillation usually revert, or what happens?

DR KAHL: That's a good question. I don't know the answer. In the two instances where I've seen it, the atrial fibrillation did not revert. But I'm sure there are anecdotes out there where it has.