Expert Answers to Common Questions for Advancing the Standard of Care for Relapsed/Refractory Follicular Lymphoma

Ajay K. Gopal, MD: Hello, and welcome to this educational activity entitled, *Expert Answers to Common Questions for Advancing the Standard of Care for Relapsed/Refractory Follicular Lymphoma.*

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Here are my conflicts of interest/financial disclosure statement.

These are the learning objectives that we hope to cover today.

As part of this activity, participants were surveyed, and we reviewed the frequently asked questions. As you can see on the left-hand figure, most questions, or 79%, were related to treatment options for patients with relapsed/refractory follicular lymphoma, with other topics being much less frequent.

Within this category of treatment-related questions, they spanned a variety of areas, including phosphoinositide-3 kinase (PI3K) inhibitors, first-line treatment options, chemoimmunotherapy, combination therapy, general treatment questions, questions regarding immune checkpoint inhibitors, specific questions regarding obinutuzumab transplant, as well as general guidelines on treatment selection.

We are going to cover a number of these today to try to address some of the more frequent or interesting questions that were brought up during this activity.

These are the questions that I will be covering. First, is there a way to predict who will have an early relapse after upfront chemoimmunotherapy? Second, in patients who experience autoimmune complications related to PI3K inhibitors, is there any evidence

of immune-mediated augmentation of their response? Third, when would you consider autologous transplant for patients with relapsed or refractory follicular lymphoma, in the third line, in the fourth line? And, finally, are there any data on programmed cell death protein 1/programmed cell death protein ligand 1 (PD-1/PD-L1) inhibitors in follicular lymphoma?

Let's start with the first question. Is there a way to predict who will relapse early after upfront chemoimmunotherapy?

The first take-home point is that the current prognostic models are imprecise. There are a variety of models, which are somewhat useful for predicting outcome but not as useful for predicting which patients will suffer early relapse. There is the FLIPI, the FLIPI-2, the PRIMA-FLIPI, and the M7-FIPI, which includes a molecular profile of the patient's tumor. Unfortunately, these are not accurate and reliable for predicting early relapse.

Specifically, data from clinical trials suggest that those who have a positive end-of-treatment positron emission tomography (PET) scan that is FDG avid are at higher risk for relapse. These are data from the PRIMA trial with chemoimmunotherapy with or without rituximab maintenance. However, I think most of us would recognize that a positive PET scan is not a favorable outcome, but we really want to know prior to that, particularly in our patients who do not have positive PET scans, who might be at higher risk for relapse.

Data from the British Columbia Cancer Agency include a variety of patients treated with bendamustine and rituximab. They were able to show that, importantly, the majority of those that had early relapse had transformed disease. So, 76% of the patients who had early relapse were demonstrated to have disease transformation. They also showed that only baseline elevated lactate dehydrogenase (LDH) was associated with early progression of disease by 24 months.

This may not be a surprise because many of these patients may have had occult transformation at diagnosis and were probably inadequately treated with bendamustine and rituximab. Nevertheless, an elevated LDH may be useful when using a bendamustine/rituximab regimen to predict for early relapse. However, this also may

prompt one to search for transformation and treat them with an anthracycline-based approach if this is found.

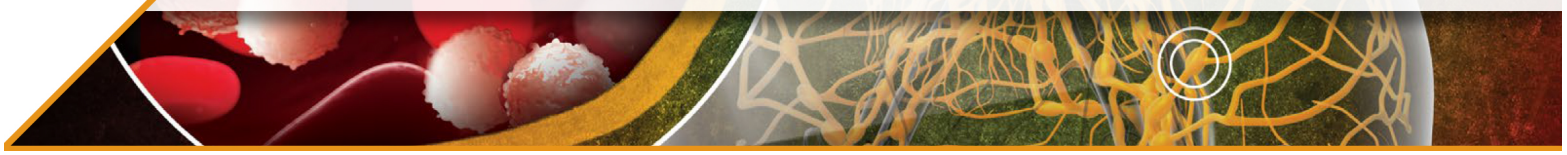
More recently, a group looked at 2 prospective trials to try to sort out a scoring system that could identify patients that were at early risk of relapse. This is the so-called FLEX index, Follicular Lymphoma Evaluation Index. These were in a discovery set from the Gallium trial. This is a trial of chemoimmunotherapy, either comparing obinutuzumab with rituximab plus chemotherapy, and they identified 9 adverse factors, some of which are quite difficult to test on a routine basis, but many are fairly straightforward.

These included male sex, bulky disease over 7 cm, histologic grade 3A, greater than 2 extranodal sites, an ECOG performance status greater than 1, anemia with hemoglobin less than 12, an elevated beta-2 microglobulin, and peripheral blood natural killer cell count less than 100 (this is not a routine test at most centers). For number 9, elevated LDH was dropped as an adverse factor.

They then conglomerated these factors into a risk score and defined low-risk patients as 0 to 2 factors with a 91% 2-year progression-free survival or a 9% risk of early progression, and those with 3 to 9 factors with a 25% risk of early progression. This was validated in the Sabrina trial, which evaluated subcutaneous rituximab.

The differentiation is shown on the left between the low-risk and high-risk patients. Although there is some differentiation between the groups, even in the high-risk group, most patients still do well. It is not likely the most useful predictor to say that patients are more likely to have an early relapse than not, though it does help potentially identify patients who are at higher risk for this occurrence. The challenge, of course, is that one of the factors is nonstandard. The right-hand panel shows various outcomes with different chemotherapy backbone regimens.

Let’s move on to the second question. In patients who experience autoimmune complications related to PI3K inhibitors, is there any evidence of immune-mediated augmentation of their response?



This is really a clever question brought up by a number of participants. We do know that in addition to the direct B-cell receptor signaling pathway inhibition that occurs with PI3K inhibitors, preclinical data also suggest that PI3K inhibition reduces regulatory T-cells and potentially reduces myeloid-derived suppressor cells. We also know clinically some of the toxicity appears to be autoimmune, such as colitis, hepatitis, pneumonitis, hyperglycemia, and hypertension may be through a different mechanism of action. We also know that patients who have had less prior therapy are at higher risk for toxicity such as hepatitis.

We also know from PD-1 inhibition that patients who have immune-related adverse events tend to have higher response rates. So, the participants hypothesize that potentially this toxicity could be associated with a favorable response.

There are very little data in this area. We and others presented this retrospective analysis of prospective trials using idelalisib at the EHA 2020 meeting. Dr. Wagner-Johnston was the lead author on this abstract, and we looked retrospectively at patients with these supposed autoimmune complications of elevated transaminases and colitis.

With many caveats of a retrospective non-preplanned analysis, there did appear to be at least a numerical association of higher response rates in those that had, for example, elevated aspartate aminotransferase/alanine aminotransferase (AST/ALT; 89% versus 51%), duration of response (37 versus 11 months), and 39 versus 9 months in terms of progression-free survival, with the latter 2 being nonsignificantly and statistically significant, respectively. There was also a nonstatistically significant incidence of grade 3 colitis with improved overall response rate and progression-free survival.

These are very provocative but very limited data with many caveats, and there are many ongoing prospective studies looking at taking advantage of this immune-mediated pathway of PI3K inhibitors in combination with other agents.

Let’s now turn to the third question. When would you consider autologous transplant for patients with relapsed/refractory follicular lymphoma? Why would you consider an autologous transplant? These are some of the potential reasons.

One is that it is a relatively short duration of treatment. In 6 to 8 weeks, one can be through the acute period, and this may be in comparison to months and months and months of ongoing oral therapy. Many patients can enjoy long remissions off treatment of 5-plus years. Nowadays, the treatment-related mortality is really quite low on the order of 1% to 2%. Compared to many expensive regimens that are ongoing for many months to years, it is relatively cost effective, around $100,000.

The other important point here is that this also treats occult transformation, which is often an issue in patients, as I showed you earlier, with early relapse. High-dose therapy and autologous transplant can be useful if one is suspecting that there was occult transformation to diffuse large B-cell lymphoma.

Which patients tend to do better with autotransplant? This is a series, some years ago from our center, where we looked at the FLIPI score and found that those who had a lower FLIPI score, 0-1 or 2 did much better than those with a higher FLIPI score. We also showed that the chemosensitive disease did better, and this is really a prerequisite for going to autotransplant to have chemoresponsive disease.

Other groups have looked at predictors for outcome after autotransplant. This is from the Nebraska Group, looking at the number of prior lines of therapy. For those who have had 1 or 2 prior lines, the outcome appeared to be better than for those who had 3 or more prior lines of therapy.

More recently, the CIBMTR tried to tease out this group of early relapse and tried to figure out what was autotransplant beneficial in this population. These were patients that had either less than a partial response after frontline chemoimmunotherapy or had progressive disease within 2 years. They compared those that did not get autotransplant versus those that did, and in aggregate, they showed no difference in 5-year overall survival.

However, if they looked at those who had early relapse and had a transplant within 1 year of that early relapse, they showed a 5-year overall survival of 73% versus 60% as shown on the right. This would suggest, with caveats of retrospective analyses, that transplant early after progression within 2 years may be beneficial versus not.

The German Low Grade Lymphoma Study Group also looked at their data regarding autotransplant for early relapsed follicular lymphoma. They looked at all of their relapse follicular lymphoma, but most of them, or 70%, had this progression of disease at 24 months (POD24) phenotype. They looked at 162 patients. They excluded those who had early failure. In aggregate, shown in the first figure, there was an improvement in progression-free survival for those who had autotransplant.

They excluded patients who had chemoresistant disease. You are comparing, in the blue curve, chemosensitive with no transplant versus, in green, chemosensitive with transplant. There was an improvement in progression-free survival; not a statistically significant improvement in overall survival.

They then went on and looked specifically at those that has early relapse progression of disease within 24 months. I want you to focus on the left, here, on the green and the blue curve. On the left, the POD24 with autotransplant had a statistically significant improvement in progression-free survival as compared to those who did not, despite having chemosensitive disease. These had no sign of reduction failure.

Maybe that's not a surprise, but what they were also able to show is that in the same comparison looking at overall survival, if you had early progression and you had chemosensitive disease, you had an improved overall survival with transplant versus no transplant. This was not a randomized comparison. There may have been other features that were different among these patients in terms of their suitability for transplant. Likewise, transplant may have treated occult transformation that was not obvious by biopsy. Nevertheless, these are provocative data that suggest, for those with chemosensitive early relapse, autotransplant may be beneficial.

When will we consider autologous stem cell transplantation? Typically, in the second or third line, but not beyond. For POD24, patients do need to have chemoresponsive disease, and ideally, the best outcome would be the ones with a low FLIPI score of 0 to 2.

Let's now turn to PD-1/PD-L1 inhibition in follicular lymphoma. Are there any data with this class of drugs?

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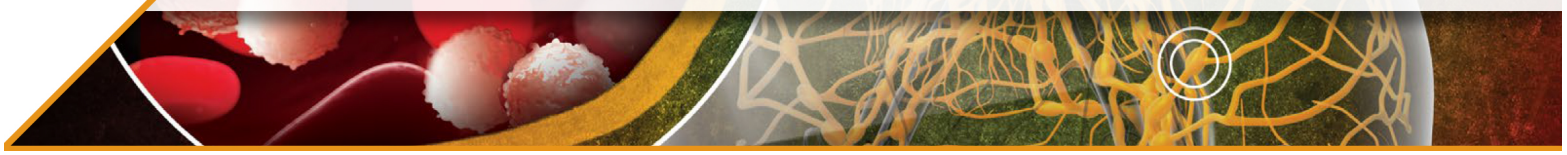


We know that follicular lymphoma is characterized by a complex microenvironment. There are tumor-infiltrating CD8(+) T cells, there are follicular regulatory cells, lymphoma-associated macrophages and mast cells, and a variety of other follicular helper cells, dendritic cells, and reticular cells, which are all likely contribute to the tumorigenic milieu within the lymph node.

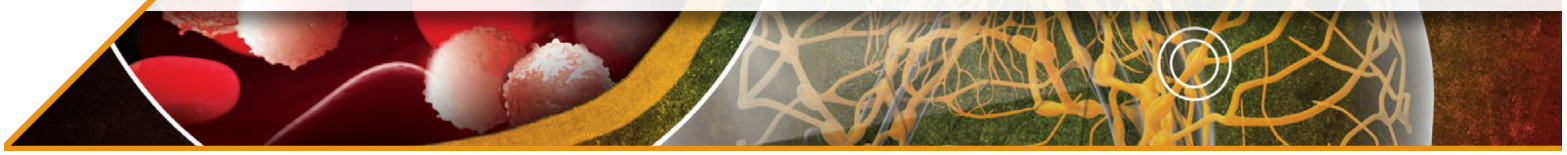
What are the clinical data? There were some early encouraging phase 1 data suggesting, on the left, that an overall response rate up to 40% was observed. However, this was a very small study, and, as we know, many times, the initial early data, particularly from phase 1 trials, don't always translate into larger phase 2 studies where the accrual is not gated and the eligibility may be more representative.

On the right, this is the CheckMate 140 trial. This was a study by Armand and colleagues looking at 92 patients with follicular lymphoma, and disappointingly, they only saw an overall response rate of 4%. The median progression-free survival was only 2.2 months. This was a very disappointing study. I think we still have a lot to learn regarding PD-1 and PD-L1 and follicular lymphoma.

There are other ongoing studies particularly in combination with other agents. However, of course, if the combined agent is effective in and of itself, it is often challenging to separate the activity of the combined agent from the PD-1/PD-L1 inhibition.

We have a study at our center looking at PD-1 inhibition with pembrolizumab as the initial therapy for follicular lymphoma with a hypothesis that these patients are immunologically replete and have not been treated with multiple cycles of chemotherapy. That study is ongoing, and we hope to see what the activity might be in that setting.

Key takeaways include that an elevated LDH at baseline, a positive end-of-treatment PET scan, and a high FLEX score is associated with early progressive disease in follicular lymphoma. Retrospective analyses suggest that responses to idelalisib may be associated with immune-mediated adverse events in follicular lymphoma. However, more prospective data are needed to answer this question fully.



Autotransplant can be considered in chemosensitive second- or third-line patients with follicular lymphoma or in those with POD 24 in the second complete response or partial response. Unfortunately, single-agent PD-1 therapy appears to have limited activity in relapsed/refractory follicular lymphoma, and other studies are ongoing with combinations or using it as part of initial therapy.

Let's wrap up by looking a little bit at some of the guidelines derived from the NCCN regarding second-line and subsequent therapy for follicular lymphoma. These include bendamustine plus obinutuzumab or rituximab. For those who have not had an anthracycline, one may consider CHOP plus obinutuzumab or rituximab, CVP similarly, or lenalidomide and rituximab as second-line therapy.

Other regimens include ibritumomab tiuxetan, lenalidomide, particularly if patients cannot tolerate anti-CD20 or don't express CD10. Lenalidomide and obinutuzumab have been published in a single-arm study. Obinutuzumab is a single agent. Of course, the PI3K inhibitors, which are approved for after 2 prior therapies, including copanlisib, duvelisib, and idelalisib. Rituximab can also be used for relapsed disease. Recently, tazemetostat and also been approved. This is approved for those with *EZH2* mutation–positive release refractory disease after 2 prior lines of therapies or for *EZH2*–wild-type relapse refractory disease in patients who have no satisfactory alternative treatment options.

With that, I thank you for your attention and for participating in this activity.

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