Current and Emerging Therapies for FOLLICULAR LYMPHOMA: Solving Practice Challenges in Community-Based Interprofessional Care Teams

Transcript

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Introduction

As a brief introduction to the program, we will highlight several key background points related to follicular lymphoma. Follicular lymphoma is the most common indolent lymphoma, making up a significant proportion of the nearly 70,000 new cases of non-Hodgkin lymphoma diagnosed every year in the United States. The median age of diagnosis for follicular lymphoma is in the mid-60s, but it can occur in just about any age. Follicular lymphoma is a classic germinal center-derived malignancy, meaning arising from the follicle center. And a hallmark genomic translocation is a 14:18 translocation which encodes the anti-apoptotic protein BCL2 rearrangement of which is a large genomic event in lymphoma genesis of follicular lymphoma. Though follicular lymphoma is common, it is notable that the death rates from follicular lymphoma have steadily been declining once we entered the modern era with the introduction of rituximab in 1997. Currently the five-year overall survival is estimated to be about 90 percent and, currently, we would actually estimate that the vast majority of people diagnosed with follicular lymphoma can expect to have a normal life expectancy compared to their age-matched controls. Dr. Abramson begins the discussion.

Disease State Overview and Unmet Needs

Jeremy S. Abramson, MD: Among the many types of non-Hodgkin lymphoma (NHL), there is close to 80 different subtypes, follicular lymphoma constitutes 22% of all lymphomas which is second only in incidence after diffuse large B-cell lymphomas (DLBCL).

We have historically graded follicular lymphoma, grade 1, 2, 3A and 3B, based on the number of centroblasts or large cells located in the high-power field. More recently, in the last decade, grade 1 and 2 have been combined as grade 1 and 2 and then subsequently grade 1 through 3A have been combined as indolent follicular lymphoma whereas rare cases of follicular lymphoma 3B have been separated out as more akin to diffuse large B-cell lymphoma.

Recognizing this evolving classification, the most recent iteration of the World Health Organization (WHO) classification of tumors does away with grading. Pathologists have decided they no longer need to count centroblasts to as close a degree as they classically have and have taken grade 1 through 3A follicular lymphoma and redefined that as classic follicular lymphoma, our low-grade or indolent follicular lymphoma. Grade 3B follicular lymphoma, which includes sheets of large B-cells, has now been renamed as follicular large B-cell lymphoma, including the large B-cell lymphoma terminology that reminds us to retain it akin to diffuse large B-cell lymphoma, its aggressive B-cell lymphoma counterpart.

There are some distinct entities in follicular lymphoma that are worth understanding. One is in situ follicular lymphoma or in situ follicular neoplasia which is the colonization of a small number of these cells in a lymph node excised for likely other reasons or for reactive changes without any distortion of the nodal architecture and this represents an in situ, not a fully neoplastic, lesion. There is a pediatric type of follicular lymphoma which occurs in children and some young adults, typically this is localized, very aggressive in histologic appearance. It typically lacks BCL2 translocation and expression which is one clue along with its limited stage and young age of presentation. Despite its aggressive appearance under the microscope, can be treated with either surgical excision alone or local radiation therapy.

There is a duodenal type of follicular lymphoma which typically occurs primarily within the intestinal tract, most commonly in the third portion of the duodenum. This is typically identified incidentally on an endoscopy as a little patch of "whitish" or nodular tissue. This is a very indolent variant of follicular lymphoma. It typically does not advance beyond the duodenum. I usually treat this with low-dose radiation therapy or rituximab monotherapy and rarely additional treatment would be required.

We historically, and still to this day, consider risk stratification with the Follicular Lymphoma International Prognostic Index (FLIPI). The five risk factors are advanced age, advanced stage, elevated lactate dehydrogenase (LDH), anemia and involvement of more than four nodal regions, not nodes. With historical data, divided patients into three distinctive risk groups, with the high-risk group, FLIPI 3-5, having a two-year progression-free survival (PFS) of only 42%, but importantly given the indolent nature of this disease, a two-year overall survival of 87%.

We also know that more recently we have evidence that progression of disease within 24 months of diagnosis or initial treatment (POD24) in follicular lymphoma has been associated with an inferior overall survival and patients who have progressive disease within two years of initial chemoimmunotherapy have a significantly inferior outcome compared to those patients without progression of disease within 24 months. About 80% of patients do not have POD24, which means only 20% of patients fall into this high-risk group. Even within this high-risk group of POD24, the five-year overall survival is still 71% in the recent analysis using the National LymphoCare Study data and progression of disease within 24 months really does require a biopsy because many of these patients may not actually be progressing with follicular lymphoma, but rather with transformed disease to diffuse large B-cell lymphoma. I do consider POD24 as an important prognostic factor in follicular lymphoma.

Follicular lymphoma remains an incurable disease, though highly responsive to treatment. Historic data tell us that each additional line of therapy is associated with a shorter progression-free survival, although I would caveat that this does not include modern treatment advances, including bispecific antibodies and chimeric antigen receptor (CAR) T-cells which I think stand that historic trend on its head and has substantially improved the outlook, even for high-risk patients with follicular lymphoma and even those with POD24.

The important take-home is that follicular lymphoma, in general, is an indolent disease with a favorable prognosis. Most patients will present with advanced stage, but most patients will also have a normal life expectancy.

Current Treatment Landscape

This is how I think about follicular lymphoma at the time of diagnosis. I do the classic staging evaluation which would typically include a positron emission tomography/computed tomography (PET-CT) scan. For patients with localized disease, we think of those patients as potentially curable. This is only about 10%of patients who have truly localized disease by PET-CT, but if they do, I consider radiation therapy and would strongly recommend radiation therapy to a total dose of 2400 centigray, unless the location prohibited safe radiation application. For rigorously staged follicular lymphoma, the cure rate is over 80% for localized disease treated with radiation therapy.

Roughly 90% of patients will present with more advanced-stage disease. Among these patients, we consider whether they are low tumor burden or high tumor burden. Low tumor burden patients, based on the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, can be observed and the standard of care has not changed in this regard. We do not treat follicular lymphoma just because it is present. Rather, we treat follicular lymphoma only if we have bulky disease, symptomatic disease, disease resulting in cytopenias or threatening organ function. There are occasional cases of advanced-stage, low tumor burden disease that are symptomatic. For example, cervical nodal disease that might only be a couple of centimeters but would be symptomatic to the patient that they can notice interfering when they are shaving or putting on make-up. For those patients with low tumor, advanced stage disease, I will consider rituximab monotherapy, typically four weekly doses followed by four consolidation doses at two-month intervals.

For advanced stage, high tumor burden disease, these are patients with any single lesion more than 7 cm or three or more sites greater than 3 cm as well as patients with leukemic-phase disease, bulky splenomegaly, or symptomatic disease. For these patients, we are typically considering systemic therapy and we will talk about chemoimmunotherapy for these patients. If a patient has advanced stage disease but has just a single site of symptomatic disease such as an axillary node is 5 cm and it is annoying under their arm, but all the other sites are non-concerning, then very low-dose radiation to the single site can provide effective palliation and may delay the need for systemic therapy and that palliative dose of radiation is just two fractions of 200 centigray, 4 gray over two days, extremely effective palliative therapy for localized follicular lymphoma in need of cytoreduction.

Our initial options for management of advanced stage follicular lymphoma, we usually use bendamustine today combined with either rituximab or obinutuzumab and we will go through the data for obinutuzumab from the GALLIUM trial. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and cyclophosphamide, vincristine, and prednisone (CVP) remain options for these patients and I will highlight when I might use something other than bendamustine. Lenalidomide/rituximab (R^2) is not U.S. Food and Drug Administration (FDA)-approved as initial therapy, but does have a National Comprehensive Cancer Network (NCCN) guideline indication based on the Rituximab Lenalidomide versus Any Chemotherapy (RELEVANCE) trial and is an option for a patient who really needs combination therapy, but who is very strictly opposed to a traditional chemoimmunotherapy approach. I mentioned rituximab for lower tumor burden disease. Maintenance rituximab or obinutuzumab based on the initial antibody chose for up to two years in the absence of

progression or intolerance is always a consideration for maintenance therapy after chemoimmunotherapy and does prolong progression-free survival.

In considering rituximab for low tumor burden patients, there is a randomized trial that evaluated the efficacy of rituximab in asymptomatic patients with low tumor burden disease. This is all grade 1 through 3A, with a favorable performance status, and patients received either no treatment, rituximab for four doses or rituximab with 12 doses of maintenance therapy. We can see that rituximab is highly effective in these low tumor burden patients. Compared to observation, however, there really is no difference in overall survival at three years. We do not prolong life expectancy by treating with rituximab earlier. This is why I only use rituximab in low tumor burden patients if they are symptomatic and require treatment. If they are asymptomatic, my preference is to observe patients with follicular lymphoma who may never need treatment or may not need treatment for many years.

The Study group indolent Lymphomas (StiL) trial compared rituximab/bendamustine (BR) to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). This very important trial did lead to a change in the standard of care based on these results, which showed a progression-free survival which favored bendamustine-based therapy. It was double that of R-CHOP with a 69.5-month progression-free survival for BR compared to only 31.2 months with R-CHOP. There was also a better complete response (CR) rate with BR. There are different toxicities. I generally find bendamustine to be a better-tolerated drug. It does not cause hair loss, it does not cause neuropathy, it does not require high-dose steroids. It does cause cytopenias and it does cause more prolonged cytopenias and more prolonged lymphopenia and patients are at more risk for opportunistic infections and late infections after bendamustine due to prolonged cluster of differentiation 4 (CD4) depletion and I recommend that all patients getting bendamustine receive pneumocystis and antiviral prophylaxis.

What about the choice of monoclonal antibody? The GALLIUM trial evaluated either rituximab or obinutuzumab in a randomized trial combined with the center's choice of chemotherapy in patients with previously untreated advanced stage follicular lymphoma. The site could choose as their chemo backbone CHOP, CVP or bendamustine. Importantly, it was not chosen by the treating investigator and so it was not informed by patient factors, meaning I would worry that older, less fit patients would get bendamustine, the younger patients would get CHOP. That was not the case. It was site-specific, not patient-specific.

What this trial showed was that there was a benefit favoring obinutuzumab over rituximab. Now, the benefit was not dramatic. There was a 7% improvement in progression-free survival at three years which amounted to a 33% reduction in risk of progression favoring obinutuzumab. There was no difference in overall survival and there was no difference in needing new treatment at three years. There was slightly more adverse events in the obinutuzumab arm and those were more infusion reactions and more neutropenia. I should also emphasize absolutely no difference in overall survival between rituximab and obinutuzumab based regimens. The choice of chemotherapy backbone was not the primary endpoint of this study. This was chemoimmunotherapy with rituximab vs. chemoimmunotherapy with obinutuzumab. There was not a significant difference in progression-free survival between the obinutuzumab-CHOP arm and the bendamustine-obinutuzumab arm. Furthermore, patients who received bendamustine as their chemotherapy did have a higher rate of treatment-related mortality and that was primarily due to lymphopenia and increased infectious deaths, not only opportunistic infections, but also sepsis. While obinutuzumab does improve progression-free survival, it does make me reflect on whether bendamustine is the best chemo backbone for all patients because it does increase infectious-related toxicities. In my very young patients, I will consider obinutuzumab-CHOP. For older patients, I still think bendamustine is better-tolerated, but I am very cautious about infections. I give infection prophylaxis to all of those patients and especially patients receiving maintenance therapy. I typically will not stop their prophylaxis until I confirm that their CD4 count is over 200 cell/mm3. For patients receiving bendamustine-based therapy, consider opportunistic infections along with other more typical infections in your fever work-ups.

How about avoiding chemotherapy entirely? The success of rituximab-lenalidomide in the relapse/refractory setting led to a randomized, 1:1 trial of over 1,000 patients comparing rituximab plus chemo (R-Chemo), the physician's choice of CHOP, CVP or bendamustine, with rituximab compared to lenalidomide with rituximab. This study was designed as a superiority study to show improved outcomes favoring lenalidomide/rituximab. It did not show superiority. What it did show is equivalence, however, the study was not defined as a non-inferiority study and thus did not meet its primary endpoint for regulatory approval. But, the complete response rate, progression-free survival and overall survival were identical between the R-Chemo and the lenalidomide/rituximab arms. There was more neutropenia in patients who get chemotherapy. There was more rash in patients who get lenalidomide. I do consider this a highly-

effective strategy for patients who really want to avoid chemotherapy. I think lenalidomide/rituximab is a perfectly appropriate option. I typically still give chemoimmunotherapy up-front for these patients and reserve lenalidomide/rituximab as my second-line treatment of choice. This is a guideline-indicated option for patients wishing to avoid chemotherapy.

How do we approach patients in the relapse/refractory setting? We have many options now for relapse/refractory follicular lymphoma. Historically, we had chemotherapy, then we had more chemotherapy and then we had more chemotherapy after that. Those were the days when follicular lymphoma did not have the best reputation. We have quoted an overall life expectancy of 15 to 20 years and a shorter response with each subsequent line of therapy.

Today, we not only still have chemoimmunotherapy, but we have lenalidomide-based therapy. We have low-dose radiation therapy, which is a highly effective, palliative therapy. We have mosunetuzumab which is a bispecific antibody. We have CAR T-cells. We have the enhancer of zeste homolog 2 (EZH2) inhibitor, tazemetostat. Copanlisib is a phosphoinositide 3(PI3)-kinase inhibitor, a pan PI3 kinase inhibitor, mostly at alpha (α) and delta (δ). This drug was withdrawn from the US market recently so you probably have not been treating much with copanlisib. Neither have I, nor has anyone else; hence it being withdrawn from the market. We rarely do stem cell transplant in the modern era of follicular lymphoma.

When we are thinking about how to select an option for the patient, we think about the types of initial therapy. We do not typically go back to chemotherapy. We think about their quality and duration of initial remission; meaning did they achieve a CR, did they have POD24? We always consider at progression, could they have high-grade transformation? I always biopsy patients at relapse or progression to look for any clonal evolution in those patients. We think about the patient's fitness for different treatments: age, functional status, and comorbidities. Then patient preferences in terms of benefit, toxicity, efficacy/toxicity ratio, time limited vs. medium-length therapy vs. continuous therapy and whether there are biomarkers that might help guide a particularly effective treatment to a given patient.

There are a number of potential, exciting options in development for follicular lymphoma, but novel available options today that are currently in practice for follicular lymphoma include bispecific antibodies. It includes CAR T-cells. It includes EZH2 inhibitors and it includes lenalidomide. Others that are under investigation, but not currently having a defined role include histone deacetylase (HDAC) inhibitors, venetoclax or other BCL2 inhibitors, or immune checkpoint inhibitors.

CAR T-cells are one of the more recent and more exciting advances across lymphoma. We collect out a patient's own T-cells. They are genetically engineered using a lentiviral or retroviral vector. Those cells now express an anti-CD20 receptor linked to a co-stimulation and intracellular signaling domain. That bionic T-cell is then injected back into the patient after a lymphodepleting chemotherapy and the patient's own T-lymphocyte is now genetically engineered and bionic, directly recognize and eradicate their CD20-positive lymphoma cell. The first FDA-approved CAR T-cell for follicular lymphoma was axi-cel or axicabtagene ciloleucel. The pivotal ZUMA-5 study had follicular lymphoma and marginal zone, although the FDA label is limited to the dominant population which is follicular lymphoma.

These patients had a median of three prior lines of therapy, so these were heavily pretreated patients. The majority had chemotherapy-resistant or refractory disease. Despite being heavily pretreated and high-risk, the complete response rate in follicular lymphoma was 79% whereas two-thirds of patients with marginal zone lymphoma achieved a complete response. A median progression-free survival was quite prolonged at 40.2 months and a number of patients remain in ongoing remission at last follow-up. When we think about CAR T-cells, we think about cytokine release syndrome (CRS) and immune effector cell-associated neurologic toxicities (ICANS). Axi-cel is the most toxic of the FDA-approved CAR T-cells and CRS and neurotoxicity occurred in 82% and 59% of patients respectively, though this is entirely manageable and reversible and we now intervene early for these toxicities, turn them around quickly and prevent the vast majority of patients from progressing to high-grade CRS and neurotoxicity, which were seen in only 7% and 19% of patients respectively in the ZUMA-5 trial. Axi-cel is a highly-effective option for patients with multiple relapse-refractory follicular lymphoma.

Tisagenlecleucel (tisa-cel) was studied exclusively in follicular lymphoma in the pivotal ELARA trial. The ELARA trial had a similar design to ZUMA-5 with lympho-depleting fludarabine plus cyclophosphamide (FluCy) or bendamustine. These patients actually had a median of four prior lines of therapy, so the tisa-cel patients were more heavily pretreated than patients in the ELARA trial than the ZUMA-5 trial and also had more patients who had POD24. Of the 94 patients, the complete response rate was outstanding at 68%. At two years, 57% of patients remain progression-free and among responders, two-thirds of patients remain progression-free at two years. Responses could be durable and prolonged and are

ongoing in a significant proportion of patients, including patients with POD24, advanced stage disease and high-risk features.

Tisa-cel is a lower risk CAR T-cell. It uses a tumor necrosis factor superfamily member 9 (TNFSF9/4-1BB) co-stimulation domain. It has lower rates of CRS and neurotoxicity at only 48.5% and 37% respectively, much lower rates than with axi-cel. The rates of severe CRS and neurotoxicity are dramatically lower with remarkably no cases of grade 3 or higher CRS and only 3% of patients on the ELARA trial having neurologic toxicities of grade 3 or above. If I am going to use a CAR T-cell in follicular lymphoma, I am, typically, reaching for tisagenlecleucel. Tisa-cel is not the CAR T-cell I prefer in diffuse large B-cell lymphoma where I do prefer lisocabtagene maraleucel (liso-cel) and axi-cel, but in follicular lymphoma, tisa-cel has a more favorable safety profile which is more amenable to a low-risk, indolent population and the response and quality of response are excellent.

There are considerations in who is being selected for a CAR T-cell. In my experience, the vast majority of patients are eligible for a CAR T-cell treatment. We do not have an upper age limit to treat with CAR T-cells. Patients do have a performance status of 0 to 2 (based on Eastern Cooperative Oncology Group performance status scale). Patients should not have any active, uncontrolled infections. We have to be able to collect out T-lymphocytes. Patients must have adequate caregiver support and stay near the treating center for the first 30 days of treatment. Those logistic issues notwithstanding, the vast majority of patients are appropriate candidates for CAR T-cell therapy if that is the best option for them. Until very recently, for patients who had chemotherapy-refractory disease who are also resistant to lenalidomide-based therapy, my preferred third line option would have been a CAR T-cell.

Today, I do not prefer CAR T-cells in the third-line management for most patients. Instead, I prefer bispecific antibodies. Bispecific antibodies are newly available and FDA-approved in follicular lymphoma and unlike CAR T-cells, they are off-the-shelf treatment options (manufactured and readily available) for follicular lymphoma and thus, a bit easier for an indolent lymphoma population whereas CAR T-cells remain available as a future option in most follicular lymphoma patients.

The one current FDA-approved product for relapse/refractory follicular lymphoma is mosunetuzumab which is an anti-CD20 bispecific monoclonal antibody which was studied in patients with relapse/refractory follicular lymphoma, grades 1 through 3A, with a median of three prior lines of therapy and at least two prior lines of therapy for eligibility. This is a T-cell activating therapy, bispecific antibodies have one binding domain for CD20 and the other binding domain for CD3, so what the bispecific antibody does is it binds to the tumor cell directly and then it binds directly, by throwing a lasso around and pulling in the patient's own (autologous) T-cell for a "cytotoxic kiss", directly inducing cell-mediated cytotoxicity. This means the bispecific agent is activating T-cells and there is a risk of cytokine release syndrome, similar to CAR T-cells, though typically more muted. To mitigate the risk for cytokine release syndrome, bispecific antibodies are given by step-up dosing, so mosunetuzumab is given 1 mg on day one, 2 mg a week later and then a full 60 mg dose on day 15 of cycle one. On cycle two, the patient receives 60 mg and then for subsequent 21-day cycles, the patient receives 30 mg on day one through cycle eight. After cycle eight, patients who are in a complete response stop treatment whereas patients in partial response can continue for additional cycles.

Among 90 patients evaluable in the pivotal phase 2 trial for mosunetuzumab, the overall response rate was 78% and the CR rate was 60%. These responses can be durable with a two-year progression-free survival of roughly 51% and a two-year duration of response of roughly 61%. This is extremely favorable compared to other off-the-shelf products. The CR rate and durability are not as high as CAR T-cells, but they are awfully close and they are much more logistically easy in an indolent patient population. I am typically favoring mosunetuzumab with reserving CAR T-cells for subsequent lines of therapy. It is also very well-tolerated. CRS occurs in a minority, 44%, but isalmost entirely low grade with grade 3-4 CRS occurring at 2%. Neurologic toxicity is very low at 5% and no cases of severe neurologic toxicities.

In my practice today, I typically use chemoimmunotherapy front-line, lenalidomide-based therapy in second line. Now, I will usually use mosunetuzumab as a third-line therapy and reserve CAR T-cells as a fourth-line treatment for most patients.

What about other available options? There are selected options I would consider in certain patients, such as tazemetostat. Tazemetostat is an oral EZH2 inhibitor. It is taken once a day and it is extremely well-tolerated with very minimal toxicities, virtually no grade 3 or higher toxicities. This epigenetic modifier was studied in a pivotal trial of relapse/refractory follicular lymphoma which included patients with an EZH2 mutation or without an EZH2 mutation. EZH2 mutations are seen in about 25% to 30% of follicular lymphoma. Among the EZH2-mutated patients, the overall response rate was 69%. Majority were partial responses, unlike bispecific antibodies and CAR T-cells, but the median progression-free survival was encouraging at 13.8 months.

In wild-type patients, the overall and CR rates are lower. The progression-free survival, interestingly, is similar and that is because these patients can experience prolonged stable disease as well. This is a well-tolerated drug, but it does not have high rates of complete response or particularly lengthy progression-free survival. I am still favoring bispecific antibodies and CAR T-cells ahead of tazemetostat, but if patients have been failed by immunotherapy (CAR T-cell or bispecific antibody), then I would consider EZH2 inhibition earlier. If a patient receives a bispecific antibody, then progresses, and is not interested in CAR T-cell treatment and they have an EZH2 mutation, which is worth evaluating for, then tazemetostat would be a perfectly appropriate third-line or later option in EZH2-mutated patients.

PI3 kinase inhibitors never caught traction in this disease mostly due to toxicity reasons. This led to copanlisib's low uptake and withdrawal from the market .

What about high-risk patients who progressed within 24 months of initial chemoimmunotherapy (POD24)? We see good response rate and progression-free survival with lenalidomide/rituximab and lenalidomide/obinutuzumab. I am usually using lenalidomide-based therapy as my second-line treatment in these patients. The copanlisib, which is now off the market, had a response rate of 58% with an 11-month median progression-free survival. Tazemetostat, in EZH2-mutated patients, has a response rate of 63% and a progression-free survival of 13.8 months. We are seeing better CR rates and better progression-free survival with the newer drugs, particularly mosunetuzumab, axi-cel and tisa-cel. We see complete response rates in the majority of patients, more than 50% with mosunetuzumab and tisagenlecleucel. If we look at durable progression-free survival, it has not been reported in this subset for mosunetuzumab, but you can see the majority of patients remain progression-free at 12 and 18 months after CAR T-cell therapy.

This is how I treat advanced-stage follicular lymphoma today. If patients do not meet indications for therapy, I monitor with surveillance. If patients do meet indications, I am typically using chemoimmunotherapy, usually bendamustine/rituximab for older, frailer patients. For younger patients, I will give obinutuzumab/CHOP and try and avoid the bendamustine, given the excess toxicity signal. For those patients who have progression of disease within 24 months, I will use lenalidomide-based therapy. For the patients experiencing POD24 that have progressed within two years of rituximab-based chemotherapy, I will usually use lenalidomide/obinutuzumab as their second-line treatment. Whereas patients without POD24, I will usually use rituximab/lenalidomide.

For patients who progress after lenalidomide-based therapy and need a third line therapy, in my practice, I am more inclined to give CAR T-cells to a POD24 as a third-line treatment because the patient has shown a more aggressive natural history though mosunetuzumab would also be an appropriate consideration. For those patients who have a lengthy up-front treatment response and did not respond well to rituximab/-lenalidomide, mosunetuzumab is the most convenient third-line therapy for that patient. CAR T-cells are also an option if a patient prefers a one-time treatment of choice and tazemetostat is also an option if the patient has an EZH2 mutation. Fourth and later lines of therapy is effectively determined by what the patient has not already received among the treatment options.

The up-front treatment has evolved, but particularly the relapse/refractory treatment has evolved dramatically with introduction of two classes of highly-active immunotherapies, including CAR T-tells and bispecific antibodies as well as availability of the EZH2 inhibitor and now less so the availability of the PI3K inhibitor, copanlisib.

Emerging Therapies

What about emerging treatment options on the current landscape? There is a third CAR T-cell, lisocabtagene maraleucel, FDA-approved for diffuse large B-cell lymphoma, but as a second- and third-line treatment for large B-cell lymphoma. The lisocabtagene maraleucel (liso-cel) product has now been reported in the pivotal TRANSCEND FL trial which evaluated 101 patients with multiplyrelapsed/refractory follicular lymphoma. These patients had a median of three prior lines of therapy and the primary endpoint was response rate. These data showed a remarkable complete response rate of 94%, the highest CR rate reported of any drug in relapsed follicular lymphoma, including the other CAR T-cells and bispecific antibodies.

We are at limited follow-up, but at one year, 81% of patients remain progression-free. This is a well-tolerated CAR T-cell. It also uses a 4-1BB co-stimulation domain like tisa-cel, so liso-cel has lower rates of CRS and neurotoxicity which were observed in this study in 58% and 15% of patients respectively. Severe CRS and neurotoxicity were seen in only 1% and 2% of patients respectively, so these toxicities were almost entirely low grade. These data will be submitted to the FDA to try and expand the liso-cel label into relapse/refractory follicular lymphoma.

There is also another bispecific antibody called odronextamab which is also an anti-CD20 anti-CD3 bispecific antibody, also administered by step-up dosing and then dosed until progression or intolerance. This intravenously-administered bispecific antibody, studied in the ELM-2 trial, resulted in a CR rate of 75%, an excellent CR rate, with a median progression-free survival at just under two years. The CRS and neurotoxicity rates were 57% and 1% respectively and almost entirely low grade.

We also have some early data on combining bispecific antibodies with rituximab/lenalidomide, chemotherapy-sparing combination strategy. This study used the subcutaneously administered CD20 bispecific epcoritamab in combination with lenalidomide and rituximab, in patients with relapsed/refractory disease. The overall response rate was 95% with a CR rate of 73%. I am not convinced this combination is any better than a bispecific alone or certainly better than a CAR T-cell. The combination did slightly increase CRS and neurotoxicity when combining with lenalidomide, but entirely low grade.

This is not the regimen I would recommend as a standard option. The only bispecific option I recommend today for relapsed/refractory follicular lymphoma is mosunetuzumab. This is different from the two bispecific antibodies approved for diffuse large B-cell lymphoma today which are epcoritamab and glofitimab.

There are several exciting investigational options in the current pipeline and it is important to always consider clinical trial options as a way of advancing novel agents in development and in the betterment for the care of patients.

Management of Adverse Events & Transition of Care Considerations

The last module is going to cover how we think about adverse events and multidisciplinary management. With CAR T-cells and bispecific antibodies, I have been stressing cytokine release syndrome and neurologic toxicities. We do see other toxicities, both CRS and neurotoxicity are short-term toxicities. It is important with CAR T-cells to also remember late toxicities, including prolonged cytopenias, ongoing risk of infection, prolonged B-cell aplasia and associated hypogammaglobulinemia. For patients who have recurrent or severe infections and IgG levels less than 400 mg/dL, it is important to give those patients replacement IVIg because they can have prolonged B-cell and T-cell suppression with multiply pretreated disease and lymphodepleting chemotherapy. I also continue these patients on prophylactic trimethoprim/sulfamethoxazole and acyclovir (or equivalents) and I only stop their pneumocystis and antiviral prophylaxis when their CD4 count has recovered to 200 cell/mm^3 or above.

Cytokine release syndrome is managed algorithmically and that is with generally supportive care for grade 1, although I do intervene earlier for axi-cel because it is a more toxic product than tisa-cel or liso-cel. At grade 2, if not earlier, we give the interleukin-6 (IL-6) receptor antibody antagonist, tocilizumab, which typically improves CRS within minutes to hours. This is often combined with corticosteroids as well along with supportive care. Grade 3 or higher CRS, we are treating with tocilizumab and dexamethasone and any intensive supportive care as needed. For severe life-threatening CRS, we are often including high-dose methylprednisolone, vasopressors, as needed, although this is rarely required in CRS management today because we typically turn it around very nicely with tocilizumab with or without corticosteroids and most of these patients never progress beyond grade 2. There are several investigational agents that we use in severe cases that are not responding to tocilizumab and steroids and that includes anakinra most notably.

Neurologic toxicity, importantly, does not respond to IL-6 receptor antagonists, but it does respond to corticosteroids. This usually occurs after cytokine release syndrome, so usually patients develop CRS, then it starts to abate and then their neurologic toxicities begin. Symptoms of neurotoxicity include word-finding difficulties, changes in mentation, excess sleepiness, somnolence, rarely a comatose state or seizures, which is extremely rare. For grade 1 neurotoxicity, such as word-finding difficulties, we are typically not intervening other than supportive care and prophylactic levetiracetam. For grade 2 or higher, we are starting corticosteroids. If they have concomitant CRS, we will also use tocilizumab, but not for isolated neurotoxicity. There is investigational evidence that anakinra for prolonged neurotoxicity may provide some benefit and be steroid-sparing. For severe neurotoxicity, we treat with high-dose methylprednisolone.

For patients who are on prolonged corticosteroids, that does significantly increase their risk for infections and so we make sure that these patients are not only on pneumocystis and antiviral prophylaxis, but we will start antifungal prophylaxis if patients are on prolonged corticosteroids. If patients develop fevers, they should be evaluated for cytomegalovirus (CMV), among other opportunistic infections as well. For neurotoxicity, we always include our neurologists as a consult. The

neurologists often want an electroencephalogram (EEG) to evaluate for potential complications in terms of seizures.

We do use levetiracetam as seizure prophylaxis. We will usually do levetiracetam up through day 30, although I will often stop it earlier if patients have had no toxicities. Tumor lysis prophylaxis can be offered to high tumor burden patients but is not a common risk with CAR T-cell therapy.

I mentioned prophylactic strategies and thinking about prolonged cytopenias, prolonged lymphopenia, prolonged CD4 lymphopenia and prolonged hypogammaglobulinemia which may prompt IVIg replacement.

Lenalidomide can commonly cause diarrhea which may require dose reductions which usually allows lenalidomide to be tolerable. Rashes are fairly common with lenalidomide as well. Rashes often go away with very low-dose corticosteroids and may not even require a dose reduction, but can if the rash becomes recurrent. Lenalidomide does cause cytopenias, neutropenia, thrombocytopenia particularly, so that is something to be aware of.

The multidisciplinary team reflects the care required in management of lymphoma patients, particularly patients receiving these active immunotherapies, such as CAR T-cells and bispecific antibodies. Oftentimes, REMS programs involve required training for staff caring for these patients. It requires multidisciplinary care, including nursing, nurse practitioners, physicians assistants (PAs), nurses, pharmacists, social workers, administration, neurologists, occasionally critical care and others. It is important to engage the entire care team in management of these patients.

The takeaway for novel therapies is that we have exciting treatment advances across the spectrum in follicular lymphoma. There are unique toxicity profiles, but these are manageable and reversible and optimal care of follicular lymphoma, as other diseases, does require interprofessional collaboration and multidisciplinary care.

I will summarize this presentation by saying that follicular lymphoma is the most common indolent lymphoma. It is highly responsive to treatment. It does remain incurable in the modern era, but the goal of treatment is to prevent the disease from ever impairing quality of life or length of life and to achieve a normal life expectancy in the vast majority of patients using available treatments. Those available treatments include no treatment at all if a patient does not need treatment at a given interval since we do not want our patients on treatment for most of their lifetime. If we achieve our goal of preventing the disease from ever becoming life-threatening or impairing quality of life, then we have effectively achieved the same outcome as cure, but through different means. There are numerous options available beyond front-line chemoimmunotherapy, including novel targeted agents and novel immunotherapies, including CAR T-cells and bispecific antibodies.

Treatment is individualized, given these numerous options available including the patient's own age, fitness and preferences, the disease behavior and kinetics of progression, whether the patient has progressed within 24 months or not of initial chemoimmunotherapy, the patient's desire for time-limited vs. continuous therapy and other weighing of efficacy and benefit ratios.

Supportive care management of toxicities is an essential component to any treatments we administer in oncology. That is as true in follicular lymphoma as anywhere other malignancy and education of patients, of ourselves (healthcare providers and team), of their caregivers and multidisciplinary collaboration is essential to optimizing outcomes.

With that, I will thank you very much for your attention. ▪

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