AGGRESSIVE LYMPHOMAS

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Our first topic this morning is a lecture on the Nuances in the Management of Aggressive Lymphomas. Please join me in welcoming Ms. Michelle Wisniewski and Dr. Paul Hamlin of the Memorial Sloan Kettering Cancer Center.

DR. HAMLIN I have the pleasure of working with Michelle as part of our APP team, and some of our members are here. The goal today is going to be to give you a sense of some of the intricacies of large cell lymphoma management today. We'll touch on some of the themes that are in development in terms of advances, some of the side effect profiles, the prognostic and predictive markers, and where we're headed in terms of a better understanding of molecular disease biology.

Our disclosures. Non-Hodgkin lymphomas end up being one of the most common hematologic cancers, large cell lymphoma being the most common among the lymphomas. The prevalence is high since many people are cured and live with indolent lymphomas for years and decades. There’s about 80,000 cases a year and 20,000 deaths, and we're working hard to diminish the death from lymphoma and making great strides over the last decade.

From 2007 to 2011, the incidence rates increased. They increased slightly more in men, and the lifetime probability of developing lymphoma is about one in 42 or one in 52 for male or female. What accounts for some of the increase in the incidence of lymphoma is demographic shifts as baby boomers are coming of age and we're seeing the interplay between the aging process and
lymphomagenesis, and we’ll talk about that a bit. One of the ways that we keep ourselves in business is we change our classification system every few years so that nobody else can do lymphoma. You don’t have to know this exhaustive list, but it’s important to know that from 2008 to 2016, there’s been an update in the WHO classification and what’s called the Blue Book will be published soon.

The Blue Book has made some updates; for this talk, the germane important parts are that our pathologists are now asked to distinguish between germinal center and activated B-cell biology. Michelle’s going to talk about that as we go through a case, and we’ll talk about the implications for therapy.

And the other important distinction is that we’re now starting to call out whether somebody has double-hit or double-expressor biology, and we'll explain what that means, but it has implications for outcome. Those in red are the areas that are either provisional or new diagnoses that cover both the indolent lymphomas, the B-cell lymphomas, the T-cell lymphomas, and Hodgkin lymphomas. Know that this is coming out and that it is a reflection of a better understanding of the genetic basis of lymphoma. As we have that better understanding, we can tease apart the heterogeneity and start to identify unique diseases.

We mentioned that large cell lymphoma is the most common you see; it’s about a third of all NHLs. When we talk about aggressive lymphomas, we think about things like T-cell lymphoma, mantle cell lymphoma, and primary mediastinal lymphoma, as well as Hodgkin’s.
With that I’m going to hand over the mic to Michelle who’s going to talk about a patient we cared for together in clinic. The two of us would see patients often as a shared visit initially to go through the history and the biology, and then alternate our visits with the patient over the course of their entire treatment. It’s a nice collaborative model.

MICHELLE Good morning, everybody. I just want to say this is a real patient. Every time I sit out in the audience and people give us case studies, I’m always like, “I know they made that up. They tweaked it for their talk.” This is a real patient that we cared for for quite a few years. He’s a 79-year-old male, he presented to an outside ER with complaints of right upper quadrant pain, burping, reflux. And he has a past medical history of hypertension, chronic kidney disease, so his baseline creatinine was elevated.

He underwent ultrasound, which showed a quite large mass in the right lobe of the liver, and abdominal MRI confirmed this. Labs were essentially okay with the exception of his ALK phos, and he had an incidental clonal gammopathy noted.

Outside pathology showed a B-cell population that expressed CD20, CD10, Bcl-2, and MUM1, and did not express all the rest of that stuff, and his Ki-67 was about 50%. This is an outside pathology. When we get an outside pathology, sometimes even before we see the patient we’ll submit it to our pathologists for review so we have confirmation. And going through this, I want to know what the CMIC status is and I want FISH on this patient to see if there’s a
double-hit on FISH. We submit that to our pathologists for those questions and that will come back later in the talk.

This patient has a germinal-derived center DLBCL, and I know this because he is CD10 positive. And this is based on the Hans criteria that is also in the NCCN guidelines. And to figure out whether the patient is a germinal center or an activated B cell, obviously, if they’re CD10 positive they are germinal center CD10, as well as BCL6 are germinal center markers. If the patient’s CD10 positive, it’s automatically germinal center. If the patient’s CD10 negative, you have to evaluate the BCL6 status. If BCL6 is positive, you also have to establish the MUM1 status. If BCL6 is negative, they’re nongerminal center, so they’re activated B cell. And the easy way to remember this, which I’m not doing right now, is that CD10 and BCL6 are both germinal center markers and MUM1 is an activated B-cell marker.

DR. HAMLIN I think as Michelle mentioned, too, we keep this on the wall. This is an immunohistochemical way of identifying germinal center versus nongerminal center. We’ll talk about how we’re trying to do that with more sophisticated techniques going forward because IHC is imperfect, so it’ll take a little bit.

Michelle has presented a germinal center large cell lymphoma case, and we’re going to try to understand lymphoma biology. And what you see here is the normal development of a B cell as it goes from a naive B cell to a mature plasma cell. And across the development of the B cell, it transits through the germinal center, and when the defect that leads to a lymphoma arises from the germinal
center, there’s a pattern that’s shown on the left of gene activation that reflects the germinal center pattern. That terminology, if it’s confusing to you, it comes from the fact that there are normal B cells that have the same gene line expression as the lymphoma and so they recapitulate the normal biology. If the defect that leads to lymphoma comes from a later stage of the differentiation, it has an activated B-cell biology. And you see that all of the different lymphomas arise from different B-cell lineage progenitor cells.

We recognize that large cell lymphomas are heterogeneous, that we can cure a large number of these patients. But within that, patients will either do very well or do poorly and how can we tease that apart? Clinically, we know that there’s going to be different outcomes; we have gene expression profiling that’s harkening back to the normal cell component, so we’re comparing the tumor cells in the dendrogram on the left to the normal resting blood B cell or the activated B cells or germinal center. Fascinatingly, primary mediastinal lymphoma and Hodgkin lymphoma are more closely related.

We’ve identified that germinal center large cell lymphomas in orange have a better survival than activated B-cell lymphomas, and that’s true both in the CHOP era and now they are R-CHOP era. How can we correct that differential with new agents? We’ll talk about that.

And we’ve moved to a place where we’re starting to take those patterns of cellular activity and integrate new drugs because we have the ability to target some of those nodes in terms of things like apoptosis and NF-kappaB, and you’ll hear about that.
Going forward, mutational analysis is integrated into the thought process more and more. At our own center, we are doing gene sequencing on every single patient and identifying those abnormalities that are actionable or predictive.

With all of that together, we’re starting to be able to say that large cell lymphoma isn’t just one disease, it’s made up of multiple different genetic entities. And in the near future, we’re going to have treatments that are differential based on those patterns.

How can we integrate that information in a way that it helps us to take better care of our patients? You heard about cell of origin, and I think as of 2016/2017, it’s imperative that your pathologists are giving you that information. Your pathology report shouldn’t just say large cell lymphoma, it should tell you whether it’s germinal center or activated B cell or primary mediastinal, which is a different entity.

We talked about that. And this is showing you that in an R-CHOP era, the germinal center and activated B cell have differential outcomes in terms of prognosis. We can integrate the Hans model and, as I mentioned, this is imperfect, so this is based on immunohistochemistry. Although it recapitulates the gene expression profile to some degree, looking forward we’ll likely use NanoString technology to distinguish between germinal center or nongerminall center in a rapid way, or actually just gene expression profiling overall because that’s becoming much more facile in terms of getting that data back quickly.
Some lymphomas are at an increased risk for central nervous system involvement, and we have a new model, which I’ll go over in a few minutes, that can predict the risk of CNS disease. Then the next step is how do we prevent that? It’s usually methotrexate prophylaxis, either IT or high-dose methotrexate. We alluded to this concept of double-hit, and what double-hit biology refers to is the fact that there are two proteins, MIC and Bcl-2, that when overexpressed conspire together to create a more aggressive biology. MIC is a cellular proliferative signal; those cells want to grow. And Bcl-2 is an antiapoptotic signal, so those cells have a survival advantage.

There’s a couple of ways that those can be deranged. You can have overexpression; hence, the term double-hit or double protein expressors and that’s in red. In blue you see the classical large cell lymphoma outcomes. If you are a double-expressor, meaning that the proteins Bcl-2 and MIC are overexpressed, you do intermediately less well. But if you have a genetic translocation where MIC and usually the partner is immunoglobulin heavy chain, are deranged and Bcl-2, that’s the 14;18 translocation and the 8;14 translocation, about 10% of large cell lymphomas will have both of those, they tend to be germinal center in derivation and they have a very difficult outcome.

On the right-hand side are the outcomes for patients treated with different regimens and we’re still in a period or prospectively trying to prove that one regimen is superior to another. I think what we can say is that although R-CHOP remains the standard, its outcome for double-hit lymphomas is willfully inadequate. And what we have looked at is up-front transplant and programs like
dose-adjusted EPOCH, and most oncologists will prefer those regimens because of retrospective data and now some early prospective data that suggests outcomes are better for that group of patients.

Finally, moving forward, we hope that we can integrate the genetic information into our treatment paradigm, so this is work from our center, Andy Intlekofer, who is one of our new faculty members. What we did with a platform that was uniform, we looked at large cell lymphomas, both transformed and de novo, and asked what are the recurring mutations across the entire spectrum? And what you see in red are eventually predictive markers, so actionable targets, things like BTK can be inhibited with drugs like ibrutinib, and if you have a mutation on an activated B-cell program, we can impact on that, and others are prognostic, or predictive.

MICHELLE We got our pathology back from our pathologists, who gave us the additional information we requested. The pathology expresses less than 20% of CMIC and they did not have the 8;14 or the 14;18 translocation by FISH. 8;14, 14;18, that’s the Bcl-2 and the CMIC. He is not a double-expressor, nor is he double-hit. We did the foundation 1 and that’s all the stuff after it that basically says he has lymphoma.

DR. HAMLIN So, what do we have next?

MICHELLE He presented to us in clinic with new onset pruritus jaundice, dark colored stools, dark urine; this is all since he had presented to the outside ER; happened pretty quickly over a very short span. On labs, his bilirubin was 18.4. We did a bone marrow on this patient because we wanted to know if
there was some sort of discord in biology or if he was -- because he was germinal center we wanted to know if this was maybe an indolent lymphoma that had transformed into a DLBCL, but his bone marrow was negative.

This is his PET, and you can see the giant liver mass, which had a really high SUV as is typical of DLBCL. He also had kidney lesions and the diffuse segmental FDG uptake in the colon; we were pretty suspicious that this was disease. But since it wouldn't have changed treatment, we didn't confirm that.

Now, the kidney lesions are interesting because, as Dr. Hamlin mentioned earlier, there is a set criteria, kind of a guideline now, for high-risk CNS disease, and kidney lesions are definitely on that.

DR. HAMLIN The NCCN guidelines are a helpful tool to look at in terms of the essential work-up. Some of the things that are worth pointing out are for the large cell lymphomas, and for almost any BC lymphoma, is the importance of serologic testing to exclude hepatitis B, since that can reactivate in the setting of monoclonal antibodies; the consideration for lumbar puncture when you are at high risk for CNS involvement; the fact that PET scans are now integrated. There’s a new classification system for R staging in response, so what's important from the Lugano classification, which updated the Ann Arbor classification, are a few points and I'll pull them out.

First and foremost, we really need an excisional biopsy, and this is even more important in the current era where we are trying to get all this genetic information. Those little core biopsies just don’t give you enough material to do the gene expression profiling; the FISH analysis, the cryogenics, in many
instances. As an initial diagnostic material, request that you get that excisional biopsy; if they come with an FNA, that’s not acceptable. For lymphomas that are FDG-avid, which is the majority of them, PET scanning is now integrated into the initial staging, as well as at the end of therapy, and that’s covered and appropriate for our patients.

We’ve done away with the A and B suffixes, so B symptoms are still noted in Hodgkin lymphoma because when they disappear it signifies that the disease is responding, but it’s not part of the staging system anymore. And when you do a PET scan, if there’s no evidence of bone involvement, in Hodgkin lymphoma and large cell lymphoma, we are less frequently doing bone marrow biopsies because one of our colleagues that Michelle’s working with now, Andy Zelenetz, looked at over 2,000 PET scans and was able to show that that correlated very well with the presence or absence of bone marrow involvement. It is important, as in this case, though, if you think there’s an indolent lymphoma that led to the large cell lymphoma, you will miss that with a PET scan making that decision, so in those instances, we still do bone marrow biopsy.

We interpret PET scans in the interim and at the end of therapy based on a program called the Deauville score -- it came from Deauville, France -- and this is based on using the internal reference of the liver in the mediastinum. If the uptake is less than the liver, it’s a score of three or less, and those are usually associated with excellent outcomes. If it’s over the liver or new lesions, that’s usually predictive of worse outcome, although the positive predictive value is not as good as the negative predictive value.
For our patients, we have a number of ways of thinking about them in terms of their likely outcome. One of the essential parts when you’re thinking about a patient that you’re just meeting for the first time is their clinical risk score. The International Prognostic Index with all of our advances still remains important in terms of thinking about it based on age, performance status, LDH, extra nodal sites, and the stage of the disease. In the current era, this still predicts for significant outcome; it’s been revised in the R-CHOP, the same factors predict for outcomes that can vary, and this is survival at 4 years from an 82% survival to as low as 60%. What you’re seeing in the modern era is that there’s no group who’s under 50% in the R-CHOP era, so we’ve improved the survival for everyone, but we can still distinguish between those outcomes. And the revised IPI -- I collapsed two of those groups into one so that you ended up with just three categories.

I mentioned that there’s a CNS risk profile; this is worth being aware of. It’s recently published, the British Columbia Group, as well as our colleagues from Germany, pooled together almost 5,000 patients and they asked what predicts for the risk of CNS recovery, CNS disease in the future? And you can identify in blue a group of patients that have an over 10% risk of CNS involvement. Those were the five factors of the IPI, plus whether or not you had kidney or adrenal involvement. Those extra nodal sites seem to track very significantly with CNS involvement.

With this model, you can start to distinguish who might need prophylaxis and who won’t. It’s modulated by the presence or absence of double-hit biology,
so as a general rule if someone has double-hit biology, their CNS risk is high enough that they warrant IT therapy. And if you remember that as a footnote, it’s probably the best clinically in terms of addressing that.

How we decrease that risk remains a question. IT methotrexate’s been the mainstay for decades. High-dose methotrexate also has its merits and gives you protection of parenchymal brain lesions, which is often what we worry about. In our own practice, we often are incorporating two cycles of high-dose methotrexate, and that’s about 3.5 gm at the end of therapy or interdigitated in between for patients at high risk. This patient certainly would have warranted that.

When we’re in clinic, how do we put this all together? And Michelle’s met the patient and we’re looking to understand who they are.

MICHELLE We now have all the information, and I now have all the information to be able to go to Dr. Hamlin and say, “This is our patient. What are we going to do?” We have the patient age and info, and the age is prognostic; he’s 79, that is a poor prognostic factor. We have the WHO classification; he’s diffuse large B-cell lymphoma. We did the bone marrow biopsy, so we know that there is no underlying indolent lymphoma. His Ann Arbor stage is stage IV, and it involves the liver, kidney, and bowel. He is at high risk for CNS disease, his IPI is high risk. And he has a germinal center phenotype because he was CD10 positive. The Ki67, there were some spots that went up to 80%, but it was around 67, and he did not have double-hit by FISH and he was not double-expressor. So, we have a 79-year-old male that we need to treat.
One of my areas of interest is caring for older individuals and with -- as we mentioned, the baby boomers coming of age, it’s very common that the patient you’re seeing in clinic is going to be in their 70s and 80s with multiple comorbidities and concurrently with large cell lymphoma. And you’re going to be facing the question of, do we treat this patient, number one? We have a curative potential therapeutic regimen, but it has a lot of toxicity associated with it. How can we approach this patient in a thoughtful way so that we offer them the best chance of long-term outcome, but we don’t expose patients who are at risk for toxic therapy if it’s not going to benefit them?

It’s helpful for us to look at in the United States, who are those patients that we treat? We looked at the CR database, we took over 45,000 patients, and drilled down to those who are Medicare Part A and B, and identified that if you look at the patients who are older -- this is over the age of 65 in the United States -- a quarter of those patients never receive any therapy even though they have a curable disease. And one of the important issues is, is that appropriate? Were they so sick and frail that that was the right choice? Or is there other biases at play, is there age at play, is there a lack of understanding of how we could potentially help these patients?

Three-quarters of those patients receive some therapy; often not curative intent and some are chemotherapy, which is the majority, the R-chemotherapy. On the right-hand side what you see is as age increases in red, the percent of patients who are not treated increases and not a big surprise; the octogenarians
more frequently than not, almost a quarter to a third of them are not offered any therapy despite having a large cell lymphoma.

How do we think about this? One of the useful tools that I’ve referred -- again, the NCCN has aging guidelines in cancer -- there’s life expectancy charts. And if we look at our patient at 79, he didn’t have the lymphoma with his comorbidity, if we said he was average health, he’s got a survival that’s predicted to be over 5 years. His lymphoma is life-limiting, and we have to consider how can we address that in a safe and reasonable way? There’s a nice app -- it’s always nice to know that there’s ways of getting this information -- called ePrognosis, which also will allow you to plug in whether the patient’s coming from home or from a nursing facility and what’s their longevity. I think within that framework you can start to come up with an algorithm for making these decisions.

If we think about our patient, he’s over 70, a geriatric assessment’s integral to this thought process, we recommended and use those in our daily clinic. We assess his comorbidity and predictors of early treatment-related mortality. His life expectancy is greater than 2 years, and we want to think about curative intent for him. For patients where life expectancy is less than 2 years, palliative intent is important. You see a reference here to “lighter as we go.” Jimmie Holland spoke on Thursday; she’s from our center. Jimmie’s focused on the aging process and how we are at times even more resilient in older age and start to change our values in terms of what we are focused on. For older
individuals, it’s often quality of life and not quantity and an aversion for toxicity, so we integrate that into our thought process.

For those where we’ve decided that we do want to offer them curative intent therapy, we’ll talk about prophase as a mechanism to try to improve their outcomes and decrease treatment-related mortality and then the different regimens, whether it’s standard therapy or a reduced dose to minimize toxicity. And for patients where we’re looking at palliative therapy, we showed in that same publication I was referring to before, that even just single-agent monoclonal antibody may have an impact on quality and longevity. For most patients with large cell lymphoma, since it’s such a chemo-sensitive or antibody-sensitive disease, some type of therapy will ameliorate their disease-related symptoms.

As of 2017, R-CHOP-21 -- every 21 days for a total of six cycles -- is still the standard. Most of the original studies were eight cycles in the United States. Most of us are comfortable that six cycles is sufficient and that cycle seven and eight add toxicity more than benefit. We’ve asked whether or not dose-dense therapy every 2 weeks is superior to every 3-week therapy, and the answer prior to the addition of rituximab was yes. In the current era, we have two negative studies to say that R-CHOP-21 is the standard. We’ve asked can we do something after R-CHOP to improve our outcomes? Maintenance rituximab, does that help? While it may be beneficial in indolent lymphomas for PFS in large cell lymphoma, those studies unfortunately did not improve the long-term survival. Recently, there’s data about lenalidomide maintenance that also may not meet that mark.
What about up-front transplant? Is that helpful for patients at high risk? We have five randomized controlled trials that suggest up-front transplant doesn’t offer a survival advantage. In one of those studies, you can argue that the high risk group did a little bit better, but my own personal bias is that over time we’ve had convincing evidence that up-front transplant adds toxicity without benefit for the majority of patients. That whole discussion has been renewed with double-hit biology, so I think in that setting, you are identifying that 10% of patients where you can impact their outcome. That part is still an open question.

When we think of why patients with large cell lymphoma don’t do well, there’s two areas that we’re concerned about; there’s early progression of disease and toxicity. A lot of the difficulty we experience is in those first few months, and then there’s late relapses. And the strategies to mitigate those problems are different. We’ll talk a little bit about our patient and what we thought about.

MICHELLE At presentation, our patient obviously had a poor performance status; his bilirubin was extremely high, and this makes him at risk for early treatment-related mortality. We decided to treat him with pre-phase, which for us is rituximab single agent, standard dosing times one, with prednisone 100 mg for 5 days. A week later, his jaundice was almost gone and he was already improving; however, his bilirubin was still 4.9, so we could not give him R-CHOP at that time. He got a single dose of cyclophosphamide, and we got him down to the point where we could give him a 50 dose of R-CHOP.
And subsequently, his bilirubin normalized and we were allowed to finish with the rest of the six cycles.

DR. HAMLIN  This concept of pre-phase was promulgated by Michael Pfreundschuh as an offshoot from the RICOVER-60 study, which was looking at dose dense R-CHOP. What they noticed in their early cycles was that patients had an increased mortality with cycle one and two; that’s where most of the toxicity occurred. The question was, if you’re starting with physiologic reserves that are decreased and toxicities are already present from disease, can we change that dynamic? They gave a pre-phase, and in this case they used steroids plus a single dose of vincristine, which they could give in an outpatient setting, and the goal was to improve those physiologic reserves for patients so that they were less likely to have toxicity. And they were able to show a 50% reduction in those cycle one and two treatment-related mortality.

Colleagues in France have also integrated this into prospective studies and suggested that it is a very useful clinical maneuver. I pointed out for this group -- because you’re the ones who are trying to make those early decisions as you’re going through staging and figuring out how to manage these patients -- a week of steroids, and we took the stance that vincristine is associated with neuropathy and ileus, we’d rather give a single dose of rituximab. One of our fellows that Michelle and I worked with that’s now a faculty member is part of a geriatric assessment study where we were doing geriatric assessments on every single patient serially across their therapy and looking at inflammatory markers to see if cytokine-mediated factors are at play. A small group of patients, about 30,
were part of a pilot that looked at pre-phase trying to see if we could impact on treatment-related mortality.

We talked about that regimen of a week of steroids and a single dose of rituximab, which this patient got because of the hyperbilirubinemia. When we presented this data, the patients were generally in their 70s -- 75 was the median upwards of 85, the total age -- they had high-risk large cell lymphoma overall, a very representative group, germinal center and ABC about 60/40, and this was the outcome. What we were able to show was that with a pre-phase we diminished treatment-related mortality, there was a single event out of the 33 patients, there was no tumor lysis. I think frustratingly we didn’t see modulation of that cytokine milieu with a single week of pre-phase, so how it’s working biologically, we’re still at odds with trying to figure that out. But as a clinical maneuver, this is a very important thing to integrate for our older patients, and it allows over 80% of our patients to get through their treatment program.

One of the other clinical factors not to dismiss is dose modification in the era of immunotherapy. It used to be that you wanted to maintain a relative dose intensity of at least 80%. In the era of chemoimmunotherapy with rituximab, we have been able to maintain pretty high curative outcomes even when we’ve reduced the intensity of the regimen. What you see here is a listing of those reduced intensity programs which may diminish the treatment-related mortality and toxicity. There’s 70 and 50% dose reductions with the CHOP regimen. The R-miniCHOP program was specifically in patients over the age of 80 from our colleagues in France, and what you see is an overall survival at 2 years that’s still
60%. So you can back off on the chemotherapy and make regimens more tolerable, and we can recapture that curative intent for a group of patients.

Our colleagues in the United Kingdom have published on an R-GCVP program using gemcitabine instead of doxorubicin for patients who had cardiac contraindications to doxorubicin. Those patients had about a 60% 2-year overall survival. We have a number of options that start to give us the ability to still treat those really sick patients. I will say that the data with our bendamustine is less enticing, and I don’t believe that that’s a curative regimen. It’s certainly being used in the community, but we have better data with the other regimens that we talked about.

This is just a look at that cardiac comorbidity study from the United Kingdom, looking at the R-GCVP regimen in a group of patients where the ejection fraction was compromised at the beginning.

We had all of that exciting discussion at the beginning about the heterogeneity of large cell lymphoma and cell of origin and now understanding genetics, but have we moved beyond R-CHOP? If what you just heard is still the standard of care, where are we going forward? We’ll talk in a second about some of those efforts in prospective studies to address this.

Most of those efforts have focused on the activated B-cell biology because that group did less well, and we have agents that we believe are distinctively active in that cellular biology. I’m not going to talk much about it, but it may be that we don’t have to integrate new agents, that alternative chemotherapy backbones overcome that biology. The R-CVP regimen, which is used in France,
but not in the United Kingdom, seemed to overcome the negative outcome for ABC. The dose suggested our e-POP data seems to perform exceedingly well in germinal center. There is a randomized study that’s going to be reported very soon out of the NCI and the Alliance Group that’s asking that question. And our own center had used R-CHOP ICE that appeared for the activated B-cell group to do better, but that’s not been randomized.

When we think about targeted therapy, we know that certain agents may distinctly work better in different biology. So what you see in the activated B-cell column is that drugs like bortezomib, idelalisib, ibrutinib, fostamatinib, which is a Syk inhibitor, lenalidomide, may have differential activity in ABC. Many of our prospective studies are asking whether or not you can add these to an R-CHOP backbone and impact on outcome. In the germinal center biology, we have EZH2 inhibitors in early development and Bcl-2 inhibitors, which I believe Jeff Jones spoke about earlier with venetoclax in CLL, and that’s being looked at. That may be agnostic to cell of origins, so it may work just as well in both biologies.

We’ve been integral in a study that’s doing just that, so it asks the question, if we use R-CHOP or G-CHOP, so obinutuzumab as the chemotherapy backbone for large cell lymphoma, can we integrate venetoclax into the early outcome? This was for germinal center or ABC patients. And what we’ve been able to show in a safety lead-in is that we can safely include venetoclax -- the study is ongoing -- as part of the backbone. The regimen going forward ultimately will probably be an R-CHOP venetoclax program, and then that will be leading,
hopefully, to a randomized phase III study. This is nearing or accrual is completed for the phase II in the next weeks.

For the activated B-cell biology, randomized trials have been looking at those agents we talked about, and we have some early hints that we have to exercise some caution. Some of the early trials -- there are at least three, and two have read out -- asked whether or not bortezomib, which impacts on NF-kappaB, could be incorporated with R-CHOP chemotherapy. We found out that that was safe. We could figure out how to do that with some overlapping toxicity with neuropathy.

But two studies now, either using VR-CAP or R-CHOP bortezomib, have failed to show an improvement in progression-free survival for large cell lymphoma. So our initial hype and hope that we could impact on ABC was modulated. What we’re seeing in the right-hand side -- John Leonard from Cornell presented this data -- is that there was no difference from the bortezomib to R-CHOP group, but the survival for the entire group was better and that questions your statistical concepts from the beginning. What I think is at play is that in order to get the ABC and cell of origin information, we’re delaying the ability to get patients on trial, and some of those bad players that have that early toxicity are not making it to the study and as a consequence, the outcomes for everyone was better and we’re not seeing a differential. As we design our clinical trials, as much as the understanding of biology, as well as the way that we carry out the studies, may impact on our ability to tease this out.
Lenalidomide for large cell lymphoma -- we know that there was activity with lenalidomide and that it appeared to be greater in the nongerminal center with a CR rate of 30% compared to 4% in germinal center; that was a signal that was based on chronic active BCR signaling through the B-cell receptor being impaired. What you see here is a cartoon looking at where lenalidomide may be working. We know that the B-cell receptor leads to a pro-survival NF-kappaB pathway and it also blocks a pro-death pathway. When we give lenalidomide, it’s exploiting what’s called synthetically lethality, which means that it inhibits both the pro-survival signal, as well as augmenting the pro-death signal and leading to improved outcomes.

We have some early hints coming out of the Mayo group that the addition of lenalidomide on the right-hand side negates that difference between cell or origin, so in yellow is the activated B-cell group doing less well with R-CHOP therapy, and on the right-hand side we see those curves come together by the addition of lenalidomide. You’ve heard about some of the toxicities of lenalidomide, like rash and count compromise, but it is modulated in these programs by adjusting dose and toxicity is manageable.

This was specifically in elderly patients looking at the lenalidomide R-CHOP program demonstrating overall response rates of 92% and CR rates that were 86%. There’s an exciting signal here and it’s led to a randomized control trial out of ECOG looking at R-CHOP versus lenalidomide R-CHOP stratified by age IPI, and on the backend, we’ll look at that cell of origin.
Another way that we can impact on the BCR signaling pathways is through the use of ibrutinib, a BTK inhibitor. What you see in this cartoon are the nodes as the B-cell receptor is activated. We go through Syk, which we have the ability to target, BTK, PKC beta, and down to the NF-kappaB pathway. In parallel, tonic signaling through the BCR pathway is a PI3-kinase mTOR pathway. We are looking at different ways of impacting on this signaling pathway, as well as this in parallel.

The initial work looking at ibrutinib and relapse/refractory to ABC identified a signal, so ibrutinib was given at 560 mg/m², and these were patients with relapse and refractory disease. You see in the waterfall plot that there was activity for the majority of patients, and in blue were the activated B-cell patients, so this seemed to have differential activity based on cell of origin. That led to a phase I study led by Anas Younes at our group, integrating ibrutinib with R-CHOP, and we were able to establish the safe dose to move forward with an overall response rate in the 90s when you looked across all of the different dose levels, and a CR rate of 70%. Again, there appeared to be a distinction between the cell of origin ABC versus germinal center.

That’s led to a randomized phase III study, which has completed accrual, and we will get a readout from that likely in the next 18 months asking whether the R-CHOP ibrutinib program will overcome the negative impact of cell of origin based on the Hans model.

How did our patient do?
MICHELLE  Our patient didn’t do great, unfortunately. At the end of six cycles of R-CHOP, he still had a pretty significant liver mass with an SUV of 13.9, but the kidney nodule had resolved. So we wanted to biopsy this to confirm that it was still just a regular old DLBCL and it hadn’t changed and to prove that there was still disease there, and unfortunately, there was. It was still the same as his original pathology. The Ki67 in certain spots was still significantly high with an overall of 60%.

What do we do for relapse/refractory DLBCL? As you saw earlier on one of Dr. Hamlin’s slides, in the rituximab era these patients tend to not do very well.

DR. HAMLIN  Today the use of stem cell transplant remains the mainstay for relapse disease when patients are appropriate for that. At the age of 79, we are pushing the limits of bone marrow transplant, and most patients in that age category have enough comorbidity that the treatment-related mortality is too high to consider transplant. We are trying to address that with ways to modulate the conditioning regimens and make transplant approachable for older individuals, but for the majority of individuals like our patient, that wasn’t an option. The data for transplant remains based on the Parma study, which compared DHAP to a consolidate of high-dose therapy program after three cycles of DHAP and showed an important survival benefit.

The CORAL study was a modern and first randomized study asking whether or not a second-line regimen was superior to an alternative second-line regimen. The rituximab ICE program was developed at Memorial, the R-DHAP program used throughout Europe and other parts of the United States. In
collaboration with our French colleagues, the CORAL study asked, is rituximab ICE superior to R-DHAP in a second-line setting? Then there was a second randomization to rituximab maintenance posttransplant. The outcome from the CORAL study was that there was no distinction between these two regimens, that there was, perhaps, slightly more toxicity with the R-DHAP program as a consequence of the cisplatin, but we got to the same place in terms of survival. As of today, we can’t recommend one second-line regimen over the other, and there are a number of different ways to try to get the patient back into remission.

The second part of this study that looked at predictive values was informative. We know that the age-adjusted IPI is predictive of outcome, and we recapitulated that data in this study. But what you see on the right-hand side is frustratingly that the vast majority of patients with relapsed disease -- 187 out of the total population -- had relapsed within 12 months of their prior regimen and had previously received rituximab. By intent to treat -- before you initiated second-line therapy -- their expected survival was under 20%. What that means in the modern era is that the impact of transplant for our patients has lessened because we’re curing more people up front. In the prior era of CHOP therapy, we cured about half of our patients, and then of those that relapsed, we were able to salvage therapy. If you took a fictitious 100 patients, we cured 50 initially and then we cured another 15 by intent to treat with second-line therapy, and about 65% of patients were cured overall. These are younger patients where transplant’s an option.
In the modern era though, we’re curing a larger group of patients upwards of 70% with R-CHOP, and that means that the players with relapse/refractory disease have really bad biology, and only about 50% of those patients will respond to second-line therapy. At the end of the day, the impact from transplant has been lessened for our patients and the challenge to us as oncologists is either to determine whether modern therapies will negate the need for transplant as we explore immunotherapy, or can we integrate better ways of getting patients into transplant since that is the curative approach?

Those same concepts that were at play in the up-front setting are at play in the relapse setting. Just looking at trials at our own center for transplant-eligible patients; we’ve again integrated ibrutinib with the R-ICE program to try to address that B-cell pathway, so ABC biology tends to relapse more frequently. In the relapse setting, if we can target the B-cell receptor, perhaps we can improve the percent of patients who get to transplant. In the germinal center arena, we’re focusing on using an antibody–drug conjugate that targets CD19 on the surface, so that shouldn’t be impacted by cell of origin, and we’ve integrated that into the ICE program. Those are the clinicaltrial.gov indicators.

This is our patient and this was his course.

MICHELLE This is what all of his treatment post-R-CHOP failure. We did give him R-GemOx and, unfortunately, he progressed after three cycles and he progressed pretty significantly. He was then enrolled on a clinical trial using SGN-19, which Dr. Hamlin just described, and he progressed after three cycles. He initially responded really well and then just relapsed. And he, unfortunately,
developed ocular toxicity, which is a problem with SGN-19. He tried to hide it from us for a little while, until his wife flew him in and called me and told me he almost hit a deer and a wall. So we switched him to CEPP and he had a partial response to that, as well, but he still had a huge disease burden.

By the time we got down to enrolling him in the Portola study, which is a Syk-JAK inhibitor study that Dr. Hamlin is running, his disease was so significant that after one cycle we had to make him hospice, unfortunately.

DR. HAMLIN Unfortunately, for our individual, the outcome was he ultimately succumbed to his disease. We did have multiple ways, though, to try to continue to address the disease after he relapsed, even though we were in a nontransplant setting, and as you saw, some of those were clinical trial options based on his biology that we hoped to overcome.

What you’re seeing here are the main pathways involved in the lymphomagenesis, so B-cell lymphomas, and there are multiple places along this cartoon where we have actionable drugs that can be called to bear and may impact on outcome. We see some of the things we’ve mentioned, like lenalidomide, bortezomib, venetoclax, at the setting of Bcl-2. We’ve got Syk inhibitors, we’ve got PI3-kinase inhibitors; all of these are being studied in the relapse setting as part of clinical trials. And if they’re active, then the charge is to try to integrate them in more novel ways.

What are some of those major themes that are at play right now? We’re looking at novel combinations, so less frequently, is this is a gamish of different chemotherapy options. But at our own center we’re looking at romidepsin,
lenalidomide, and carfilzomib, so combining the proteasome inhibitor and immunomodulatory agent, and an HDAC inhibitor to look at epigenetic ways of addressing the disease. Small molecule inhibitors that impact on those different nodes in the B-cell program are being explored, and they’re being explored as single agents. What we all anticipate the future will include is using a combination of oral regimens together to dampen down either on those pathways that are active in parallel -- so a BCR inhibitor and a PI3-kinase inhibitor -- or to prevent the resistance mechanism. If you use two agents, perhaps you can block that escape mechanism from the single agent. That’s the work that’s being done right now across the United States and globally.

We’ve also been excited about the concept of antibody–drug conjugates, and I’m sure most of the room is familiar with a drug called brentuximab vedotin that targets CD30 and has been integrated into the care of patients with Hodgkin lymphoma. We’re trying to take those same constructs into the care of non-Hodgkin lymphoma patients either targeting CD20 or CD19, but these are cell surface proteins that then can be forced to internalize and carry with it sort of as a Trojan horse a toxin or a chemotherapeutic to directly affect cell kill. There’s been some exciting phase I and II data that is supporting that research.

Finally, you’ve heard about immunotherapy throughout the last 4 days; can we engage the T-cell arm of the immune system? The sort of the Holy Grail is not to need transplant because you can use your own native immune system to attack the disease at hand. Can we modulate T cells by taking them out of the body, engineering them, and giving them back to the patient to target those cells
with CAR T cell efforts? Can we use checkpoint inhibitors to take the brakes off your own immune system and wake up that immune system to engage the lymphomas? And are there other ways that we can use antibodies to bring a B cell and a T cell together, constructs called bispecifics or BiTEs, where you’re bringing into opposition the B cell and the T cell and that physical contact engages the immune system?

All of those themes are alive and well. These are not FDA-approved approaches at moment; they exist in the realm of clinical research. But they’re exciting things that we’re going to hear much more about in just 4 weeks at the American Society of Hematology.

We’re finishing with time for questions. I can’t thank enough the team of people that we work with. At Memorial, there’s now an increasingly large group of faculty members who only care for lymphoma patients. We work with a fantastic group of advanced practice providers, both NPs and PAs, that are integral to our clinical research program, our survivorship program. Sharyn Kurtz spoke the other day and is here. Zuli (phonetic) is here, who works on our transplant floor often. This is a collaborative effort among multiple different disciplines. I have to thank all of our nurses, all of our patients, and the whole disease management team. And with that, let us take any questions. Thank you.

MALE Hi, just a question. If in theory we’re able to get this highly refractory patient into a CR and there was no plan for transplant, knowing that that disease would likely just pop right back up again and he’d receive the
kitchen sink, what were your tools that you were going to use to keep him in remission?

DR. HAMLIN The question is, if you had at any point achieved a complete remission with one of those second-line regimens, are there any strategies that might have maintained that patient in remission? It’s an important question that we struggle with. We have contemplated things like alginate transplant with nonmyeloablative approaches for patients in remission even when their age is higher because we’re starting to make those a little less toxic. Today, some of the concepts are incorporating things like CAR T cells into that setting where there’s minimal residual disease, and maybe the immune response can eradicate that clone so that we can enjoy patients having long-term survival.

We absolutely have a number of patients -- I saw both of them last week -- who got antibody–drug conjugates now over 2 years ago and have been in remission with large cell lymphoma. So there are groups of patients who are served incredibly well by the second-line regimens and have durable long-term disease control even if they’re not cured. I think maintenance strategies have frustratingly not been successful in large cell lymphoma, so unlike in low-grade lymphomas where we may continue a monoclonal antibody and we'll see data with things like lenalidomide, in the large cell lymphoma setting if someone is in a complete remission, we often are at that frustrating stage where we monitor them and allow them to recover from toxicity, but we don’t have anything preventative to offer.
FEMALE I was wondering what regimen are you using first line for double-hit lymphomas?

DR. HAMLIN Good. We talked about this because you are seeing a patient next week with Dr. Zelenetz. The question is, for double-hit lymphomas what regimen are we using? We draw the distinction between double-expressors where there’s increase in protein expression and double-hit where there’s a translocation between the MIC and heavy chain, as well as Bcl-2 and heavy chain. What are you doing for your patient? You’re seeing somebody with Andy next week; we were talking about with double-hit.

MICHELLE He’s the double-expressor, not the double-hit. We originally were referred this patient under the impression that he was double-hit and he had been being treated on the outside. He had had a couple regimens and kept progressing, so they referred him to us. We gave him R-EPOCH, got him into a CR after four cycles, and we were having a hard time getting his pathology to review. We were treating this patient based on what the outside people had been telling us, and when we finally got the pathology to review and we got the FISH, he was not double-hit, he was a double-expressor. So the plan to go to transplant was nixed, and he is now on surveillance.

DR. HAMLIN That sort of treatment paradigm reflects the trend overall. There’s about 17 of us who only care for lymphoma patients. We tend to use dose-adjusted EPOCH for our double-hits and our double-expressors. We’ll recommend transplant in patients who have high-risk disease and the FISH double-hit, but even there it’s not uniform across the service.
FEMALE    Thank you. Then along those same lines, there’s a clinical trial going on looking at diffuse large B-cell lymphoma and comparing R-CHOP and R-EPOCH. Do you know when we’ll hear the results of that trial? Have you heard anything about that?

DR. HAMLIN    The question is whether or not the prospective study looking at dose-adjusted EPOCH compared to R-CHOP has been reported out. We should be hearing about that soon. I don't know if it’s at ASH, but they’re doing the final analysis on the outcome data, so we’re anxiously waiting for that. What we do have, which we’re participating with Kieron Dunleavy on, is a MIC--positive large cell lymphoma dose-adjusted EPOCH prospective study. A significant proportion of those patients are either double-hit or double-expressors, and the data, at least in the phase II setting in a multicenter construct, suggests that the dose-adjusted EPOCH program remains a very effective program for those high proliferative rate tumors. It’s that data, as well as our own experience with EPOCH, that has supported it. When you look retrospectively at programs like Hyper-CVAD, it’s not clear that that’s any better and, I think it’s not clear that transplant’s offering us the benefit we’d like.

FEMALE    My name is Ann McNeil. I’m very curious -- your initial patient who was 79, he wasn’t double-hit, but he had significantly bulky disease. If he were 20 years younger, would your treatment strategy be the same if he was 59 instead of 79? I’m very curious; we would never give him R-CHOP, you know that. But I just want to know what you would have done in that case if he was much younger.
The question is, how would our thought process have changed if our patient was younger and transplant was something that would have been in the thought process? I think you could make a case, although I probably wouldn’t have recommended it for an up-front transplant in this individual because of his high risk across the board; he had high-risk clinical features, high-risk biologic features, high-risk CNS features. And in a younger patient, R-CHOP is still the standard of care as frustrating as that is, and if he was in remission, you wouldn’t be wrong to consider a transplant. We have used a program of R-CHOP followed by ICE chemotherapy, that Craig Moskowitz published at our center for high-risk patients and have PFS that’s added 80% 5 years out, so we might have used a slightly different induction regimen for him or dose-adjusted EPOCH based on the prior data with germinal center biology suggests that EPOCH worked exceedingly well. Again, we’re anxiously awaiting the randomized study because the proof is always in a randomized study, and we will have all the gene expression profiling information from the Alliance study to either support or refute the fact that infusional chemotherapy makes a difference.

I think the other thing we probably would have -- in the second line what he didn’t get, and I do think this is important for the group -- I personally will not use ICE chemotherapy as a salvage regimen for someone who’s not going to transplant. The toxicity of ICE chemotherapy does not coincide with our goals of care when someone is not curative. If you’re in a palliative mode, ICE chemotherapy and certainly not more than three cycles is really rough, and it’s
often inpatient hospitalization. What you didn’t see is that he didn’t get a second-line regimen like DHAP or ICE chemotherapy. In a younger patient, that would have been the second-line of regimen. We would have opted to try to put him on a clinical trial given his biology. Corollary to the CORAL study was that when they looked at cell of origin, the DHAP program might perform better in germinal center and the ICE may perform a little bit better in activated B cell. It was underpowered to answer that question, but we tend to make that distinction just internally.

MICHELLE One thing we should mention is if you noticed, he was high risk for CNS disease, but we did not give him prophylaxis; it was because of his bilirubin in the beginning. We couldn’t give him high-dose methotrexate, and it got to the point where when he’s on a clinical trial, he was just progressing and it seemed like a moot point by then. But we did not give it to him in the beginning because of the bilirubin.

DR. HAMLIN That's a good point. We would have integrated that, certainly, in a different scenario.

[END]