WELCOME AND INTRODUCTION

Lauren Berger, MPH

[Slide 1 – Title Slide] Good afternoon. Thank you for coming. On behalf of The Leukemia & Lymphoma Society (LLS), thank you for joining us today. **[Slide 2 – Welcome and Overview]** I'm Lauren Berger, Senior Director of Professional Education & Engagement at The Leukemia & Lymphoma Society. We are committed to improving patients' quality of life through education and support, including professional education such as the program this afternoon. We offer live and archived patient and professional programs, both on the Web and at places like the program today, and you can earn CE (continuing education) credits. Our Information Resource Center is staffed with nurses, social workers and health educators who talk to patients and caregivers and professionals every day to discuss individual treatment options, including clinical trials, and to provide other disease and treatment information and support. The LLS advocates for funding to accelerate the discovery and development of blood cancer therapies and to ensure that patients have access to coverage through insurance coverage and other support that we offer.

To date, the LLS has invested more than $1 billion in research to advance therapies and to save lives. We know that you, the nurses, are treating, educating and supporting patients and that you are the key players in the day-to-day treatment and the long-term survival of patients and in helping their caregivers also. You help them with aggressive disease and for those living with cancer as a chronic disease. As we hear from many patients that we talk to, their nurses are the people that they ask questions of to help them understand their disease and treatment issues, including questions about clinical trials. They report side effects to you, they discuss the complexities of their care, including access to treatment, and that you—the nurses—are there for them at every point in their care. So, on behalf of The Leukemia & Lymphoma Society, thank you so much for the important role you play, each of you, in the patient's and in the caregiver's journey.

Today, our presenters will discuss the nurse's role in caring for patients with hematologic malignancies and will include opportunities for small group discussion. When you registered for the program, you indicated your interest in which topics you wanted to be presented as full case studies and which ones to discuss as shorter and more brief presentations. So, acute promyelocytic leukemia (APL) and chronic lymphocytic leukemia (CLL) will each be presented as full case studies. Myeloma and follicular lymphoma will be shorter presentations today. But after this symposium, they will be recorded as full case studies and uploaded to the LLS website. We'll email you when that is ready and up on the website, and you can view and listen to those programs and earn additional CE credits.

So, for you to earn CE credit for this program, please complete the evaluation at the end of the program, including your state and license number. A certificate of completion will be sent to you within 30 days. Please stay for the entire symposium in order to get CE credit. Our special thanks to Teva Oncology for their support of this program.

[Slide 3 – Faculty Disclosures] I am now honored to introduce our speakers. Emily Bennett is a Nurse Navigator at Winship Cancer Center of Emory University, and she will cover APL. Lynn Rich is a nurse practitioner at JP Wilmot Cancer Center at the University of Rochester, and she will cover CLL and follicular lymphoma. Beth Finley is a primary nurse at Moffitt Cancer Center, and she will cover myeloma. Emily, I am now so pleased to turn the podium over to you.

ACUTE PROMYELOCYTIC LEUKEMIA (APL)

Emily Bennett, RN, BSN

[Slide 4 – Acute Promyelocytic Leukemia (APL): Case Study] Thank you. So, we'll talk about acute promyelocytic leukemia, or APL. It is a rare malignancy, with approximately 1,000 new cases every year. It is a subtype of AML (acute myeloid leukemia). With the introduction of all-trans retinoic acid, which is known as ATRA, into the therapy of APL, this completely revolutionized the management and outcome of this disease. Cure of patients with this disorder depends not only on the effective use of combination therapy but also on critical supportive measures.

[Slide 5 – Outline] This is an outline of the things that we'll be discussing today. **[Slide 6 – Leukemias and Outcomes]** Targeted therapy has indeed changed outcomes in leukemia. You will see that Gleevec® (imatinib) has certainly made a difference in survival in a fatal disease. **[Slide 7 – APL Therapy History]** In the 1950s, it was noticed there was a certain type of leukemia with hemorrhagic syndrome. Subsequently through time, treatments have evolved with a most recent practice being the use of ATRA and arsenic, both targeted agents with excellent disease control. **[Slide 8 – APL Diagnosis – Pathology]** Here is an outline of the presentation of the disease. It is commonly seen with pancytopenia and bleeding. Normal need not mean less chance of bleeding. Delay may cause CNS (central nervous system) bleeds, which is the most common cause of death in APL.

[Slide 9 – APL – Epidemiology] Again, it's a very rare disorder, and you only see about 1,000 new cases every year. Median age is about 55 years, but it is seen between the ages of 20 and 60 years. **[Slide 10 – APL Treatment and Outcomes in Large Trials]** There are very effective and curable treatments with arsenic and ATRA. Let's look deeper into the treatment outcomes in large trials. **[Slide 11 – APL Survival in Large Cooperative Group Trials]** This slide shows APL survival in a large cooperative group trial. These are just examples of large breakthrough clinical trials that show survival in excess of 90%. **[Slide 12 – Australasian APML4]** This is from an Australia trial that shows that adding arsenic to treatment shows excellent outcomes.

[Slide 13 – ATRA/ATO vs ATRA/Chemotherapy] This is the most recent large trial from Italy that shows ATRA and arsenic have survival of 99% in two years. They compared ATRA and chemotherapy versus ATRA and arsenic. Even ATRA and chemotherapy has shown more than 90% survival, but, again, ATRA and arsenic have a 99% better outcome in a group of approximately 130 patients in this particular arm.

[Slide 14 – What Happens Outside of a Trial] So, let's look at what happens outside of a trial. Are we able to replicate the results that we've seen in large clinical trials? Let's review, think about it, discuss it amongst your tables and we'll come back to you.

[Slide 15 – Case Study – Real-World Patient] This is a patient that we may see in real-world practice that most likely will not be enrolled in a clinical trial. Patients with multiple comorbidities are generally excluded from clinical trials, but we commonly see them in our clinical practice. **[Slide 16 – Population-Wide Survival in the US]** Survival of 90% is not a reflection of the outcomes of the general population. The death rate of 5% to 10% is an understatement. Clinical trials that are

changing the sequence of the regimen, adding new medications, or withholding maintenance have only minimal effects on survival. The best outcomes are seen by decreasing early deaths.

[Slide 17 – SEER Data (1975-2008)] Here in the SEER data, the blue line shows you APL outcomes prior to ATRA use. The green line shows the introduction of ATRA into practice. But as we see, the most recent data does not show that the outcomes are improving as seen in a clinical trial. **[Slide 18 – Survival Data From SEER Registries]** Again, the bold, blue line at the top of the graph is another example of SEER data from 2005 through 2011 that showed survival across 13 registries, which barely approaches 80%, and some as low as the mid-50s in others. This is in contrast to the 90% shown in the clinical trials.

[Slide 19 – Early Deaths in APL (Days 1 to 30)] Only recently has there been an increase in recognition that early deaths play a bigger role in outcomes. The Brazilians—here in this graph you'll see—were the first to show this in 2007, and then multiple other centers from almost every major city and major countries have also published data and outcomes that show early deaths are the main reason for poorer outcomes outside of clinical trials in APL.

[Slide 20 – Why Is There High Mortality Outside of a Trial?] So, why are there high mortality rates outside of a clinical trial? **[Slide 21 – Possible Reasons]** Could it be because of selection bias? Possibly. Or, is it because there are only good patients that are selected for the clinical trial? Some people will possibly argue that point. Is the treatment delayed outside of a clinical trial? This has also been looked into, and this is most likely not the main reason. The third is probably the biggest, which could lead to inconsistencies in care. Even prior to ATRA, the Italians have less than 10% mortality because they followed a set guideline.

[Slide 22 – Can We Do Something Different?] Can we do something different, or do we just accept the poorer outcomes in a curable malignancy? **[Slide 23 – Strategy (at GRU)]** Some of the strategies that we've used in our provider cohorts have been developed into a simple strategy at one of the facilities here in Georgia.

There were 17 patients between 2005 and 2009 in which 7 died, which led us to evaluate the outcome. We wanted to do something different to improve the outcome in practice. **[Slide 24 – Methods Used to Decrease Early Deaths]** Some of the methods implemented into the plan used to decrease the early deaths are reviewing the literature, reviewing some of the patient charts, attending some of the national meetings, reviewing and consulting with external providers to review the deaths, and identifying the three main causes of early deaths within the first 30 days. **[Slide 25 – What Is Involved in Our Co-Management]** Some of the things that were involved in our co-management were we managed with the providers outside of our facilities, in some of the main facilities in and around the Georgia/South Carolina/Florida areas, to communicate with those physicians on a regular basis or as many times as needed. **[Slide 26 – Treatment Outside Our Center]** The idea is to co-manage the patients to prevent these early deaths.

[Slide 27 – APL Workup] So, these are some of the things that are involved in the whole APL workup. APL is a medical emergency and should be treated as such. **[Slide 28 – Supportive Care]** ATRA should be started, even if APL is suspected. It can help improve the bleeding. You can save a life by acting quickly, and since the APL FISH (fluorescence *in situ* hybridization) will only be given to you within 24 hours, in a number of labs, you can stop the ATRA once you've diagnosed a patient,

either with another leukemia or with APL. There's no harm done, even if you've started the ATRA and they're, indeed, given a different diagnosis. Harm is only done when you don't treat the patient. Our emphasis is in the supportive care, especially with antibiotics and some of the blood products that we provide to these patients.

[Slide 29 – Treatment of Coagulopathy] Here are just a few of our recommended guidelines for transfusion support. **[Slide 30 – Differentiation Syndrome]** Differentiation syndrome, or better known as ATRA syndrome, is a peculiar problem in the disease. The key thing for nurses to remember is that you must be meticulous in seeing these patients, weighing the patient and keeping meticulous ins and outs of these patients. This is how we're dosing the patient when they are receiving their induction chemotherapy or other treatments involved such as blood products.

[Slide 31 – Treatment: AIDA Regimen Example] This is an example of a good induction regimen available called AIDA (ATRA + idarubicin), after the Italian experience.

[Slide 32 – Older Patients With APL] So, in older patients with APL, the treatment may need to be individualized, meaning we may need to dose-adjust the arsenic or even the ATRA to prevent any further comorbidities with the actual treatment.

[Slide 33 – Nursing Considerations] Here are some of the things that nurses should consider. During the first ten days of treatment is usually when 70% of deaths can occur, and these are unnecessary deaths in this particular disorder. These deaths can be prevented if we just continue to monitor our patients and act quickly when things start to turn south within 30 days of the patient being hospitalized after diagnosis. Remember that, even if the diagnosis is suspected, ATRA should be started immediately.

[Slide 34 – Consolidation and Maintenance] Consolidation and maintenance depend on the induction protocol. It is suggested that they are the same. Once you choose a treatment, be it the anthracycline or the ATRA-based consolidation, stick with it. Don't change.

[Slide 35 – Algorithm] So, this is an example of a 1.5-page algorithm that our providers came up with to assist other facilities that don't usually see this rare disorder or don't treat these patients on a regular basis—to facilitate in helping them in the management, treatment, consolidation and maintenance after patients have been discharged in order to prevent early deaths within the first 30 days.

[Slide 36 – Experience in Other Diseases] So, our strategy was to improve outcomes by improving 30-day survival, and the goal is to streamline the process the same as you would see in stroke patients that are coming through the facilities—how door to catheterization is an important process. This is what we want to see in APL in preventing unnecessary deaths that are seen within the first 30 days of diagnosis.

[Slide 37 – Strategy to Decrease Early Deaths at Main and Affiliate Sites] Again, these are some strategies that we've come up with for dealing with some of the main sites and affiliate sites outside of our core. **[Slide 38 – Survival Pre- and Post-Algorithm]** We're showing the implementation and the concept since we have treated and co-managed 90 patients with only 6 deaths. The plan is working,

so we want to encourage other facilities to adopt or utilize our services to help you co-manage these patients.

This is our present data showing the outcomes prior to the implementation of this concept. Since we have co-managed 90 patients with 6 deaths, which is more in line with the experience in clinical trials, we've not excluded any patients, except for patients that have refused treatment.

[Slide 39 – Planned Coverage on New NCI-ECOG Trial] The planned coverage is we want to expand our experience to the rest of the country, and we're working towards an ECOG (Eastern Cooperative Oncology Group) trial.

[Slide 40 – Resources] So, here are some of the resources that are available for these patients you have. There are no patient assistance programs available to these patients with ATRA. So, our goal is to utilize facilities or a company such as The Leukemia & Lymphoma Society, encourage participation in clinical trials, and also utilize our social workers to facilitate in assisting us with financial assistance for these patients getting their medication, a life-saving medication.

[Slide 41 – Conclusions] APL is a medical emergency. We cannot stress that enough. Deaths can be prevented if we just follow those simple steps—starting ATRA, quick diagnosis, rapid initiation of treatment, which is the ATRA. You do no harm to the patient, whether you start the treatment or not. It just helps in correlation with keeping the bleeding under control. This is a curable disease. It takes our hard work and effort in managing these patients and working with our cohorts, our physicians, our midlevels and also our fellows in getting them on board and understanding the importance of rapid initiation of ATRA. You can save a life by simply starting treatment.

[Slide 42 – Thank You] Thank you for your time. We'll now turn it over to Lynn Rich.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Lynn Rich, ANP-BC, OCN

[Slide 43 – Chronic Lymphocytic Leukemia: Case Study] Good afternoon, everybody. Thank you for coming. I'm excited to be able to present the topic of CLL (chronic lymphocytic leukemia) to you today. I'm glad you all picked it. It's a great topic. It's exciting, it's changing. We've seen more changes in CLL in the past two or three years than we've seen in decades, so I'm glad you picked it. There's a lot to learn. It's a lot of fun.

[Slide 44 – Outline] Today, as I said, we are going to be talking about CLL. Here is the outline. Essentially, we're going to get a good understanding of what CLL is about. We'll define the disease, talk a little bit about CLL versus SLL (small lymphocytic lymphoma), a little bit acute versus chronic, understand a better natural history of the disease, take a look at the epidemiology, understand Rai staging, and goals of treatment, and throughout this story we'll talk about a case study.

[Slide 45 – What Is CLL?] So, CLL—what is it? Chronic lymphocytic leukemia. It's a cancer of the lymphocytes that normally work as immune cells to protect against infections. **[Side 46 – CLL]** It's caused when a single B lymphocyte becomes abnormal because of damage or a mutation to the DNA. Once this occurs, the body no longer controls this cell. So, it continues to divide and lives longer than it should, and this abnormal cell becomes the CLL.

CLL versus SLL. Oh, research, of course. It'll come in, especially in CLL. It's huge for sure. Sorry. Thank you. Anything else? Thank you. Oh, case management. Very big. Very big. **[Slide 47 – CLL vs. SLL]** Okay, so CLL versus SLL, (small lymphocytic lymphoma). It's a variant of the disease in which there are not a lot of abnormal lymphocytes in the blood. The World Health Organization essentially treats the two as the same disease. It's just a different variant of the same disease.

[Slide 48 – Lymph Node Image] Here it spells it out just a little bit. The CLL is actually a dysfunction in the bone marrow, so it's the cells, it's the counts. The SLL, as you're going to see, lymphadenopathy. The disease is going to present mostly in the lymph nodes. So, you'll often see on the chart CLL/SLL, because it doesn't really matter in the treatment course and prognosis. It's really just a better way to designate how that disease is occurring in that patient.

[Slide 49 – CLL vs. Acute Leukemia] CLL versus acute. Everybody in here knows this, but the CLL is slow. It occurs in the mature cells versus acute leukemias that progress rapidly and are the not fully developed cells. Everybody here knows that the ALLs (acute lymphocytic leukemias) will all occur on a Friday afternoon at a quarter to five and be very memorable, and that absolutely impacts clinic infusion, too, obviously—the inpatient team has to roll big time with the acute leukemias.

[Slide 50 – Hematopoietic Blood Flow Image] The general understanding—just the hematopoietic blood flow—is that the early cells are the acutes, and as they progress to the mature under development, we're going to see more of the CLL dysfunctioning, just to get a sense of how it plays out and what's happening with these cells.

[Slide 51 – How Is CLL Diagnosed?] CLL is diagnosed much more easily. It's not that crazy phone call on a Friday. It's the kind primary care picks up. Something's not right. You've got some cells that

are dysfunctional. You ought to go see a hematologist. So, it's far less acute. It's picked up by the primary. They're noticing the elevation in the white blood cell count, specifically in the lymphocytes.

[Slide 52 – Case Study: Maria S.] This brings me to our case study. Her name is Maria, and she was a 76-year-old woman. Reasonably good health, no comorbidities. She was in a small little community. She drove a bus back when she worked. She was in Upstate New York, and she was initially diagnosed in March of 2011. She went to her primary. She had fatigue. "I don't know, I'm just not right. Something's not right." So they drew some blood, and they noted an elevated white blood cell count. It was 30. Again, normal is four to ten. So, the primary sent her to the local oncologist.

[Slide 53 – Normal CBC] A quick review. You all know this, but just to really pin down the significance of lymphocytic leukemia. In the differential, we have the normal ANC (absolute neutrophil count). We're all well aware of that because that's our bargaining point for chemotherapy. But lymphocytes are really what we're monitoring in CLL, and normal is about one to three. In CLL, your criteria to meet CLL are designated by an ALC (absolute lymphocyte count) of greater than five. So, that will be your distinguishing feature to become a patient diagnosed with CLL.

[Slide 54 – Natural History of CLL] The natural history of CLL is considered very indolent, slow growing. You can watch it for five to ten years. Life expectancy could be ten to 20 years. I was telling my team last night, "My son is 20, and I have a patient with CLL who remembers when I was pregnant." So, it's really exciting that these patients are living longer and longer, and he's still doing well. However, some patients need treatment. So, again, I'm talking about this 20-year lifespan, but there are some CLL patients who are diagnosed and progress to needing treatment incredibly rapidly. That's really tough. In the old days, we didn't know. We diagnosed them. We said, "Okay, let's watch." Now, we have ways of finding who those people are who are going to progress rapidly versus those who we're going to watch in five to ten years.

[Slide 55 – Further Staging: FISH] We test this by running a FISH. Big words. Essentially, they're running a test to see what the cytogenetic abnormalities are within that lymphocyte that's causing the problem. They range from mild to moderate to incredibly severe. Those more severe ones, they're going to move. And 13q, you're going to see this lingo. Okay, that's not so bad—17 years potential survivorship versus trisomy 12. The one to remember, because that's really significant in a CLL patient, is a 17p. If you have a 17p, that is a very poor prognostic indicator. Your disease will progress. You will blast through everything, and it's not quite an acute leukemia, but you're really moving forward far faster. That person is not going to be talking about the 20-year anniversary. Their disease is going to roll, and you're going to have to move rather quickly.

[Slide 56 – Case Study: CBC at Presentation] So, in Maria's case, she had a white count of 30. Her ALC was six, and she came from a community hospital. They didn't really run a FISH. They did final staging, CT (computed tomography) scans. Where's the disease? Is it presenting throughout? They did a bone marrow biopsy. She had an 85% population of CLL in her bone marrow, so that was indicator number one. Something's not right. She's got a high burden of disease.

[Slide 57 – Epidemiology] We're switching a little just to epidemiology. How often is this occurring? It's hard to tell in our world because it seems like everybody has it, so it's a very false understanding. There are only about 15,000 per year diagnosed, and 2014 was the expectation versus let's say a breast cancer, 200,000 in a year. So it's quite a tiny population of patients who were diagnosed.

[Slide 58 – Epidemiology (cont'd)] It's the most common type of leukemia. It's considered the disease of the elderly. The median age when people are diagnosed is 70 years. However, it can be as early as 30 to 40 years. They can easily be diagnosed, but it's nowhere near as common. You're going to typically see a 70-year-old be diagnosed.

[Slide 59 – Modified Rai Clinical Staging for CLL] Dr. Rai created this years ago. Don't quote me, 1989. It was a way to stage CLL. So, compared to solid tumors, that's not our world. Very different. In our world, we use Rai staging to tease out when people are diagnosed what's going to happen with them—a better understanding of where their disease is at. It goes from low, intermediate, to high. Each of them has lymphocytosis, a high white count, but it's not as significant as how it's impacting the rest of the body. Is it causing anemia? Is it causing thrombocytopenia? The more it causes that, the higher stage you get. There are specific details as far as 0 to IV, but, in general, when you see Rai stage III, they've got some lymphocytosis. It's impacting the anemia. It's impacting the thrombocytopenia. Again, those are what we're using to help stage the patient, to help us decide treatment according to where they are and which stage they are at.

[Slide 60 – Case Study: Patient] Again, just to bring it back a little bit to our patient Maria—she presented with intermediate Rai stage. If we went back, we would see some lymphocytosis, some anemia, and some thrombocytopenia. Again, local community oncologists started her on rituximab (Rituxan®), single agent. Easy, well-tolerated. Should work well with early stage CLL. Again, remember, she has not had FISH yet; so, she got treated, she got Rituxan and then she started blasting through. In a very short period, she was starting with chemotherapy. Okay, you're not responding. Let's get you some chemotherapy on board. Let's see how you do.

So, she had upfront treatment for CLL. For elderly patients, bendamustine (Treanda®)—Rituxan is pretty much the standard of care. You guys know that; you use that a lot. However, she was climbing. That white count was not responding. Her anemias were getting worse. Her platelets were dropping. She went from an ALC of 30 to 100 on treatment, so that was an indicator something's not right. She should be responding; she's not. Why? Why isn't she?

So, she came to visit her daughter. Her daughter lives in Rochester, New York, university hospital. She says, "Oh, maybe they have things we can offer. The community doctor isn't helping her. What do we do?" They came to us for clinical trials. We'll talk a bit about what's going on, but at this point we were offering her what we have for a clinical trial for a patient who's blasting through disease.

I live in Rochester, New York, which is cold. It's about six hours north of New York. She came from Watertown, Alicia, who's from way up there. That's three hours north of Rochester, so it was bloody cold. She drove down three hours to come see us and see what we have to offer her because something's not right. She's not responding. She needs more help.

So, her daughter was smart. She said, "Get her to an academic center. What else can be done for her?" At this time, she was in a clinical trial. Those of you who are in the outpatient setting are using BTKs (Bruton's tyrosine kinases) pretty regularly now, but a few years ago it was pretty new. It was still in clinical trials. **[Slide 61 – Bruton's Tyrosine Kinase (Btk)]** We gave what was called ibrutinib (Imbruvica®) or a BTK inhibitor. It's a busy slide, but what I want you to walk away with from this is essentially it's a completely different beast compared to chemotherapy. We know that there are multiple chains of molecules that have to exist for a CLL or a lymphoma to grow, so this molecular

chain goes into place. The BTK, the Bruton's tyrosine kinase, is the switch on/off that tells the lymphoma cell to grow or not. So, it's on. It's in overdrive, and the CLL cells grow and grow and grow. So, basically what a BTK is, it turns it off. It's an inhibitor. It's inhibiting the molecular chain to continue. That's telling the CLL cells "don't grow." So, it's a BTK inhibitor. You're going to hear that. You're going to see it, and you can see that on that window there are multiple different sites of where we can turn off this chain reaction that's occurring.

So, the BTK was recently developed, and it's what we tried with her. Again, the name ibrutinib, the dosing is different for different diseases. **[Slide 62 – Ibrutinib: BTK]** But in the CLL world, you're essentially starting at 480 milligrams daily. This was FDA (US Food and Drug Administration)-approved last year. So before this, we had patients like Maria who blasted through BR (bendamustine and rituximab). We went to the next chemotherapy and we went to the next chemo and to the next chemo.

So, it's an exciting, fabulous opportunity to be able to offer these people something other than chemotherapy. It's a different beast. Again, as you understand how it works, it has phenomenal responses and people tolerate it well.

[Slide 63 – Case Study: Treatment Course] This is a little bit busy, but I want to pin down to back where it's pointed to ibrutinib, which is low. Her ALC had started to spike up. She was on another therapy. It wasn't working. She slowly started to climb up to 50. We're like, "okay, her disease is starting to take off again." She went through Rituxan, BR and we put her on lenalidomide (Revlimid®) because we didn't have a trial open at that point. So, we tried our best. It worked for a little while. Eventually, though, that white count, that ALC started to climb up again; so, we needed to offer her something else.

We actually had a trial. We started her on the ibrutinib. What I want you to see by this graph is where it started—ALC of about 50; once you start ibrutinib, it will spike. That white blood cell count doubles to triples, way out of line. So, initially when they were starting this, they were freaking out. Something's not right. It is right. What's happening is, as you take these pills, the cells that have developed in the lymph nodes are getting released and it's getting put into the blood. So when you draw the blood, you're going to see that white count spike up to 100, 200. If you start at 100, you're going to see it going up to 200 to 300,000. It's safe. It's the way it's supposed to work. It goes that way for two months, and eventually it'll start to come down.

You'll even see as this spikes that anemia and thrombocytopenia start to clear as well. So, you're really not watching just the lymphocytosis. It will happen. It has to happen. It's the normal function of ibrutinib. So, it's a big teaching point to your patients for your own self-awareness. This is how the drug works. It's pretty neat; it's not a bad thing. It's just your body doing its best to clear it.

[Slide 64 – Other Nursing Considerations] Other nursing considerations—it's pretty well-tolerated. It's really not very nauseating. It's easy. A second feature, other than the lymphocytosis I just talked about, is the bruising. It will cause bruising and bleeding. If they needed to have an invasive procedure, you have to think of it as Coumadin® (warfarin). It has to be stopped about seven days before and restarted seven days after, so you will be sensitive to that. If somebody's on warfarin therapy, it's a tough drug to give. We at our institution are not giving both ibrutinib and warfarin at the

same time. If somebody's on warfarin, we try to figure out a different way. Do they need it? Can they get through with aspirin? And if it's absolutely necessary, it's not an agent we're ready to use.

I think throughout the country, little by little, they're starting to test it in clinical trials. It's already in the next phase of clinical trials. Can ibrutinib be given to somebody on warfarin? But today it is not a standard of care. It's known to cause diarrhea. It's subtle, three, four days, two-three times a day. It's not been a limiting feature in my practice to have to stop ibrutinib because of diarrhea. It's usually pretty well-controlled.

[Slide 65 – Duration of Response] People obtain a response. Usually get complete remission. We don't know how long it'll last. Even in the 17p population, these people are responding—a year, two years. At this point, there are people on three years tolerating it well. Again, it depends on their cytogenetic profile baseline as far as how long they'll go. In the 17p population, you're lucky if you get two years. But in the non-17p population, people will go much, much longer.

[Slide 66 – Survivorship Issues] Finally, survivorship issues. Social workers are a big help to our group. Obviously, without them, it's a tough practice. These patients have struggles with coping with their disease. They're in remission, it relapses, they're in remission, it relapses. Another point I didn't really say is CLL is treatable. It's not curable unless you're going for a bone marrow transplant. So, people are living with it for life, and it's part of ways to treat/remission, treat/remission.

Secondly, ibrutinib is a very expensive drug. I don't know the finances. It's better that I don't know, because it's too overwhelming. We're fortunate that we have the support of the LLS helping our patients. We get our social workers to ping in. It's important.

One thing I wanted to say—ibrutinib is FDA approved in the relapsed setting for CLL and in somebody else who has already received treatment. They can get ibrutinib, unless they have 17p. So, if you're newly diagnosed with 17p, you can get ibrutinib, insurance covered, FDA approved. Otherwise, unless you have that abnormality, you have to have upfront therapy, and you can only receive it in the relapsed setting.

[Slide 67 – Audience Discussion Question] Then, I have just a question. Many oncologists consider any patient diagnosed as a cancer survivor. What makes a CLL survivor different? What special considerations are required in this population? So just take a minute, think about that.

I guess we want to throw it out to the audience. Does anybody have any questions? So she's asking me if she has somebody in first-line treatment who has a 17p, would I go to ibrutinib or would I go to Rituxan? Bendamustine, absolutely. Bendamustine/Rituxan if they're first line, elderly. If they're still young, the standard of care would be frontline. Non-17p is going to be FCR (fludarabine, cyclophosphamide, and rituximab). That's still the number one treatment of choice for your nonelderly, newly diagnosed CLL patient. So, unless your 17p, you're still going to do your standard of care FCR, Rituxan, then to Rituxan, upfront therapy. But if you're 17p, regardless of your age, I think people are using ibrutinib first because we know—look at our friend Maria. She had BR. So, typical would be monthly for six cycles. She didn't even make it through three. She didn't respond. She responded a little, but the disease would regress; but by the third cycle, blasting off, growing, it's not working.

So, our arsenal of chemotherapies for a 17p patient isn't working, and that's why I think CLL is exciting. We have these options to be able to offer them. You know, and there are other ones. I'm trying to hone in. I'm not an ibrutinib seller. I don't get any money for that. So, idelalisib (Zydelig®) is also on Page 4, CLL. If people grow through ibrutinib, as I said, eventually they'll relapse. We can use idelalisib, which is, go back to that screen with the BTK, essentially it's a PI3K (phosphoinositide 3-kinase), so that molecular chain, instead of it being specifically BTK, it's going to be a PI3K. So, it's a different drug targeting the disease at different spots.

I think not Rituxan at this point. It's helpful, but it's not been standard of care. We have trials right now, actually. We're conducting trials, upfront, newly diagnosed, ibrutinib. So non-17p, that's already established. That's FDA approved. For a non-17p patient, we're conducting trials where you can get R–ibrutinib versus BR. So, they're trying to bring it to upfront therapy. So, it's working its way and I bet you in three to five years we'll get an answer to say "Yes, in the non-17p world, it is a treatment of choice, and it is working better than our standard chemotherapies.

So, in the infusion center world, we're going to be seeing a lot less of CLL patients in the infusion center world. It's going to be the clinic nurses talking these through, giving these oral agents. They won't even make their way to an infusion center. They may when they relapse, and when we have to turn to chemo, we will. But it's evolving where this is not going to be upfront therapy.

Lauren Berger, MPH

Ms. Rich, we have one additional question over here if you don't mind.

Lynn Rich, ANP-BC, OCN

Okay.

Question

I don't really have a question, but I recently went to an educational offering for ibrutinib, and it was recommended, I guess the most thing stressed there was to have your patients take it at night on a resting gut and that significantly decreased the side effects that they were having once they took it at night instead of in the morning.

Lynn Rich, ANP-BC, OCN

Absolutely, I've heard that, and I've actually tried it with patients, and it's worked. So there's this subtle description. Honestly, in the not real elderly, I'm thinking the 80+, they get a little dizziness. I used to think, "Oh, it's in their head." It's not. They feel a little dizzy, so we have them taking it at night. They go to bed and they wake up, and it's fine. So, I don't know if that's an automatic must recommend across the board. I've had so many people tolerate it without any side effects, but I have noticed in the really elderly, octogenarians, are really a little more sensitive, and taking it at night has decreased some of that quasi-dizziness that they've been feeling.

Lauren Berger, MPH

Thank you, Ms. Rich. We have one additional question.

Lynn Rich, ANP-BC, OCN

Okay.

Question

How often do you see the need for dose reductions and how are you managing those patients? We've had some patients who are anemic, so I just want to know how you're managing those patients in your practice.

Lynn Rich, ANP-BC, OCN

In the CLL world, I haven't had to dose reduce as much. It's 480 milligrams. There's a whole other gamut of different diseases. In mantle cell we're using it, and that's at a higher dose—baseline 560 milligrams. We're seeing the diarrhea and we're seeing the anemia more.

It happens, but it's not standard of care that, "Oh, my god, you really need to be prepared for this." This is very subtle, in a few patients, special scenarios where we have had to dose reduce.

I haven't actually had patients in the CLL world where we've had to dose reduce. I keep wondering why we don't just use the CLL dose for everybody because, in the other world, it's working just as well, but whatever. That's what the studies have declared. So, I haven't actually needed to dose reduce in the CLL world for tolerability. It's been pretty well-tolerated at that dose. I'll turn the podium to Beth.

MULTIPLE MYELOMA (MM)

Beth Finley, RN, BSNc, OCN

[Slide 68 – Multiple Myeloma: Case Study] Hi, everyone. My name is Beth Finley. I'm a hematology nurse at Moffitt Cancer Center, and today what I'm going to focus on is multiple myeloma, and I'm even going to put in a little bit of a case study. **[Slide 69 – Outline]** So, here is our outline. I'm going to try and explain the disease, how we think of treatment for that newly diagnosed patient, and nursing considerations for the myeloma patient and also bringing in our multidisciplinary team to help support these patients.

[Slide 70 – What is Myeloma?] So, what is myeloma? Myeloma is a bone marrow condition. It's a malignancy of the plasma cells. **[Slide 71 – "M-Spike" – Monoclonal Paraproteins]** So, if you think of your plasma cells, their whole job in our immune system is to produce antibodies or proteins to help fight infection. Well what happens in myeloma is this plasma cell's kind of like defective and it produces this monoclonal protein, or M spike, M protein. You'll hear the terms used loosely, but it means all the same thing. This is basically their tumor marker.

So, if you take this plasma cell, as you can see from this picture, it produces that antibody. The way I explain it to patients is it's almost like a broken antibody. The most common myeloma patient is IgG (immunoglobulin G) kappa, so that becomes their tumor marker. There's also light chain myeloma patients where their protein is monitored just by the kappa or lambda, and very rarely are there non-secretors, meaning they don't even produce this M protein. We follow those patients more using bone marrow biopsy.

[Slide 72 – Diagnosing Myeloma] So, when the physician is trying to diagnose myeloma, it's like a puzzle. All the pieces have to fit. What we do is a bone marrow biopsy, and the most important part of the marrow is doing what we call FISH (fluorescence *in situ* hybridization), and that's the brains of the myeloma cell. That helps predict if it's going to behave standard risk or it's going to behave aggressively. Blood and urine tests, and when I say urine tests, I mean a 24-hour urine test. Yes, the patients will balk at that. That is not their favorite test, but it is very important, and it is needed. And imaging. We use skeletal surveys, X-rays, to determine lytic lesion. Our field is moving more and more toward PET (positron emission tomography) scans, so a PET scan is warranted as well, but typically we like the surveys, the X-rays.

So, when do you treat it? We're one of those few cancers that just because you have this M protein, it doesn't necessarily mean you treat it. So, yes, try telling the patient that we found it early, but we're not going to treat it early. **[Slide 73 – Diagnosis: "CRAB" Criteria]** When we treat is when they have some type of a CRAB (calcium, renal insufficiency, anemia and bone disease) criteria. They don't need all these. They basically just need one.

So, if you think of hypercalcemia, the myeloma cell is sending out all these cytokines to kind of break down the bone—to break up that marriage of osteoclasts and osteoblasts. So, our calcium is in our bone, you're breaking it down, the calcium leaks out, it goes in the blood and they're hypercalcemic.

Renal failure. The proteins, when they go through your kidneys—think of your kidneys like a sea that clogs it up—and it almost turns like egg white. So, their creatinine goes up. Anemia. There are plasma

cells in the bone marrow. They're overcrowding the bone marrow so you can't produce your normal red cells. And fractures. Pathological fractures can happen. Ninety percent of the patients will present with bone pains, and I put infections on there. We don't necessarily treat, or at least in my experience, I haven't treated a patient on infections alone. They had to have another of the CRAB criteria. But, again, plasma cells are part of the immune system, so patients do get infections.

[Slide 74 – Lytic Lesions] So, here's a slide just showing some lytic lesions. I've seen it to where people describe it on the skulls, salt and pepper look, moth-eaten, but those are the lesions. When patients see them on the skull, they get pretty nervous thinking this is going to affect their brain. But the majority of those are very benign. What we worry about is the weight-bearing bones. So, you can see on the other side where it shows a picture of a humerus, and what you want to look for is a lytic lesion that is 50% or more in the cortex of the bone. They're at a high risk for a pathological fracture. We want to get the orthopedists involved very quickly on those patients.

[Slide 75 – Durie-Salmon Staging System] So if you think of our staging system, in the old days they used Durie and Salmon Staging System. It was pretty complex. As you can see, you're looking at if they're anemic, their calcium, how many lesions they have. What we found out is the majority of the patients fell in Stage III, either A or B, depending on their renal function.

[Slide 76 – International Staging System (ISS)] So, more commonly what is used now is something called the ISS (International Staging System) staging system. This helps with prognosis. It's very easy to use. You go by their serum beta-2 and their serum albumin. It makes it very simple, because you'll hear a lot of times if the patients present and they go to the ER (emergency room) and they're hypercalcemic, they think the ER physician tells them they have metastatic disease. So, our staging system isn't like the other cancers to where at Stage III it's in the lymph nodes, Stage IV is metastatic. Ours is just using this serum, and it's more prognostic features. Obviously, the best—the longest—is Stage I.

[Slide 77 – MM Risk Stratification] So, these are some of the risk factors that we look for in the bone marrow biopsy. If you remember me talking about how the FISH is the brains of the myeloma cell. This is what we're looking for. Seventy-five percent of the patients will be standard risk. They'll behave very indolent, have a good disease course. The high risk, even with all of our new therapies that are out, they still have a very aggressive course, and their prognosis is usually two to three years.

[Slide 78 – Factors Influencing Treatment Choice] So, that newly diagnosed patient comes into the clinic. What do we look for when we're thinking about treating the myeloma patient? Yes, we want to look at their staging system. What are their FISH results? Not necessarily their age so much, but what's their overall health status? How many comorbidities do they have? Also, what's their preference? Our disease is more of a chronic disease. So, for patients in the beginning, especially newly diagnosed, we use a lot of combination therapies. We do give them options. Clinical trials are our first option always. We always want to push the medical field, so research is very important for our patients.

[Slide 79 – Response Criteria] So, you're thinking about response criteria, let's say after they have induction, and I'll kind of talk about that with the case study. But when I first started working in myeloma and I saw this response, I was like, "Holy cow, there's a lot of them in there." But it's pretty

simple. There's stringent complete remission. That just means there's no M protein in the blood or the urine, the free light chains are normal and their bone marrow has no abnormal plasma cells. Complete response means pretty much the same thing, except the plasma cells in the bone marrow are less than 5%.

A very good partial remission is a 90% reduction in the M protein in the blood. A partial remission is 50%. Of course, we have the MRs (minimal response) and the stable disease, which eventually as the disease course progresses, at the end of the disease, stable disease or minimal response is actually okay.

[Slide 80 – Case Study] So, let's start with our case study. Here we have a 61-year-old male. Now, I didn't mention this before, but we do see a lot of younger patients. When we are deciding on therapy with them, we have to figure out—are they working, do they have family, what's their social status? Because it's very important when we go and we talk about therapy.

So, this guy is 61 years old. He is working. He presented with anemia. He went to an outside community doctor and then got a referral to us for a second opinion. He presented with an M spike of 3.6. His IgG was around 6 grams. He had a little bit of a lambda light chain. Beta-2 was 2.3. Albumin is 3.2, therefore, making him an ISS Stage II.

His creatinine and calcium were normal. He did have a little bit of an M spike in the urine, which is about 150 milligrams per 24 hours. His bone marrow biopsy showed 70% to 80% plasma cells. He had lytic lesions on the survey. His FISH report was standard risk myeloma. So you'll see on there the 13q and the translocation 11;14.

[Slide 81 – Treatment Options for Transplant-Eligible Patient] So, when we're thinking about what treatment to offer this guy—obviously, I'm a research nurse, so we always want to think of a clinical trial. Clinical trials help push our medical field. This is how we get all these new therapies to treat myeloma. Like I've said, I'm not sure if I said it recently or not, but in the last two years, we had two new drugs approved to help treat this disease. So, we're making it a chronic disease; patients are living longer.

Unfortunately for this patient, we did not have a clinical trial available to him, so we went with our two standard of care for upfront induction therapy. The one thing I wanted to mention—this is a transplant-eligible patient, so you want to avoid melphalan with the induction. So, we started with either RVD or you'll hear it as VRD. The drugs are lenalidomide (Revlimid®), bortezomib (Velcade®) and dexamethasone. The way we give lenalidomide is every day for 14 days. Bortezomib—my physician always says day 1, 4, 8 and 11, but I really think patients don't understand that. So, the way I describe it is Monday, Thursday, Monday, Thursday and then they get a week off. Dexamethasone is 20 milligrams. They take it the day of bortezomib and the day after. The other option is what we call VDC. So, it's bortezomib—the other name of that is Velcade, by the way—Cytoxan®, or cyclophosphamide, and dexamethasone.

For this patient, he chose RVD because, again, it is a choice. We let the patients kind of help decide on what their treatment plan should be, and a bisphosphonate monthly is very important for bone health. But I'll explain that later on in the presentation.

[Slide 82 – Response: VGPR] So, this was his response. He had a VGPR (very good partial response). Whenever we see a patient, we have them go through about two cycles of therapy, and then we consult the transplant group. It takes time to transplant. You have to get insurance approval. Whenever I talk about transplant, I'm always thinking of an autologous. Very rarely do we do an allogeneic—that means a donor cell transplant. We do, do that, but it's more in clinical trials, high-risk and younger patients.

So, this man went through an autotransplant. He saw the transplant group after a couple of cycles. He had a partial response, so a 50% reduction. They said "Give him two more cycles and then come back, and we'll be ready for transplant."

[Slide 83 – Disease Course] So, here's kind of his disease course. You can see where he started, where he responded. He got into a remission, and then he had a transplant, an autotransplant, which was very good for about a year and a half. Then, he had progressive disease. If you think about induction therapy, then they go to transplant, the average time for them to relapse is about two years. So, he had less than two years. If you think about a standard-risk patient, you would imagine that they would get maybe even a little bit better than two years. But, unfortunately, he relapsed after about a year and a half.

We offered maintenance at the time, because maintenance is still controversial in the myeloma field. We tend to do it toward the patient. We give them the option. We explain the data, and this man chose not to do maintenance with Revlimid and just monitor his bloodwork every three months until he, obviously, progressed about a year and a half.

So, as of now, just kind of an update on him: He is on Revlimid now. It's not really maintenance. Now it's treatment doses, and he's doing very well. He's actually responding.

[Slide 84 – Nursing Considerations] So, what are the nursing considerations that we think of when we think of monitoring myeloma patients? **[Slide 85 – Managing Side Effects]** First, I always think it's important to manage the side effects. This is a noncurable disease. This is a chronic disease, so we have to be good at managing their side effects because, again, if they're having a lot of side effects, they're not going to take their medication.

[Slide 86 – Immunomodulatory Drugs (IMiDs)] So, our first drug class is immunomodulatory drugs, so we call these IMiDs (immunomodulatory drugs). This is your thalidomide (Thalomid®), your lenalidomide, pomalidomide (Pomalyst®). So, I have a little box here of their main side effects. If you think of myelosuppression, lenalidomide and pomalidomide have the most with myelosuppression. So, pomalidomide can definitely make patients neutropenic. The way it's approved is for relapsed/refractory patients. The majority of these patients have already been through transplant, so their bone marrow is not as brisk as it once was before. So, depending on where they're at with their counts when you start pomalidomide, they can drop and become neutropenic. So, you just might want to keep an eye on that. I tend to monitor those types of patients weekly for bloodwork versus lenalidomide to where I do every two weeks for the first 12 weeks once they start that medication.

All these medications can cause blood clots and PEs (pulmonary embolisms), so it's very important for them to be on some type of anticoagulation. They can cause GI (gastrointestinal) side effects.

Thalidomide is huge for constipation, so you always want to make sure you do stool softeners with these patients.

With lenalidomide and pomalidomide, it's more loose stools. I put on there diarrhea, but it's more loose stools, to where they tell me they eat and it just kind of goes right through them.

A rash can happen. It usually starts on their scalp. It's itchy. It can happen on their chest. We usually tell them to take an antihistamine. Anything on the face you always want to look at because there is a rare complication. It's almost like Stevens-Johnson syndrome that can happen with these IMiDs. So, you just want to keep an eye on it and make sure we look at it as nurses and assess it before we give interventions.

Sedation is huge with thalidomide, so they should absolutely take this at bedtime. We usually start them off on a low dose with thalidomide of 50 milligrams, and we work our way up, as long as they can tolerate it.

Neuropathy doesn't really happen with lenalidomide and pomalidomide. Sometimes the patients will tell me they have a little bit of numbing and tingling, but it doesn't progress. It doesn't get worse.

With thalidomide, this absolutely can happen. It happens over time, and it's almost like a sock-glove type of feel, and it is permanent. So, you definitely want to keep an eye on that, and sometimes we have to dose reduce or even take them off therapy.

All these drugs are teratogens, so whenever a patient is started on an IMiD, you have to do the black box warning. They have to promise they're not going to get anybody pregnant, which, again, this is a geriatric disease, so it kind of opens the door for lots of questions. But, in general, they just sign up for the program and they're fine.

[Slide 87 – Proteasome Inhibitors] So, moving on to our other class of medications—proteasome inhibitors. This is your bortezomib and the new kid on the block, which is carfilzomib (Kyprolis®). The way it's given, as you can see with bortezomib—I kind of talked about that previously—it's twice a week, two weeks on/one week off. The way carfilzomib is given, it's back to back. So it's more like a Monday/Tuesday, Monday/Tuesday, Monday/Tuesday and then they get a week off. Bortezomib—more and more we're using it as sub-Q (subcutaneous) because of the neuropathy. Seventy-five percent of these patients that are on bortezomib will get some grade of neuropathy, and there was a trial recently done to where if we give it sub-Q, the rate is 35%. So, we're definitely moving more towards sub-Q bortezomib. And, of course, carfilzomib is intravenous (IV).

They both can cause myelosuppression, but it's mainly thrombocytopenia. Day 8 for carfilzomib is the nadir and day 11 for bortezomib. So, it's just something you want to keep an eye on. Neuropathy—with bortezomib, it's huge. You definitely, if you're giving this medication, you want to constantly ask them about numbing and tingling, shooting, burning, aching pain. You want to keep an eye on this because sometimes we have to dose reduce.

Carfilzomib doesn't really cause neuropathy. Now, most of these patients—because of the way carfilzomib has been approved—had to have bortezomib before they can even get this medication.

So, the majority of them already came with some form of neuropathy, but I have not seen that carfilzomib actually causes it in my experience.

Zoster—any patient on a proteasome inhibitor should have some type of antiviral along with it. It can reactivate that virus.

Dyspnea—definitely with carfilzomib. You've got to watch. The way it was approved as cycle one, we do it with hydration. So, you've got to be careful of giving that elderly patient too much fluid to where it kind of pushes them over the edge. So, we drop the fluids after the first cycle, and that seems to help with the dyspnea.

Fatigue is a given. These patients have been through transplant, their disease is active, and the treatment can cause fatigue. So, fatigue can happen with pretty much all of our therapies.

GI—there's not a lot of nausea and vomiting with these. I know after bortezomib, and even carfilzomib, sometimes they'll tell me they might have diarrhea the next day, but it's very well-tolerated. Again, it's quality of life. We want these patients to be able to go on their trip. So, we want to do the least amount of side effects for these patients. Very rarely there are some cardiac and pulmonary side effects with carfilzomib. But, again, it's very rare.

[Slide 88 – Steroids (Dexamethasone/Prednisone)] So here is our corporate for all the side effects. These are steroids, dexamethasone. If any of you have ever taken care of a myeloma patient, you'll notice that we sprinkle dexamethasone on everything. They cause the side effects. That newly diagnosed patient sitting in front of me gets petrified of the word chemotherapy, and I'm like, "No, no, no, no, it's steroids that cause the side effects." I listed a few. As you can see, there's mood swings, irritability, insomnia, hyperactivity, edema—the list goes on. We're very quick to dose reduce on steroids, so don't be afraid if your patient is having a lot of issues. Ask the physician. Talk to the physician about a dose reduction. It's something that we commonly do.

[Slide 89 – Nurse's Role] What is my role as a nurse? I feel like I need to educate them, support them and I did touch a little bit on my case study about how complex a regimen can be. The average age of diagnosis is 65 to 70 years. So, you have this elderly patient that came in with a whole list of comorbidities and three pages of medications, and now we're adding more medications on there. So, it's important to give these guys calendars. Write it down. Once they get past that newly diagnosed phase, they get better at understanding how we give these regimens.

We want to improve their quality of life by helping to manage side effects, whether it's from the disease or the therapy. We want to manage them to where it keeps them on therapy, and they live a good quality of life. Not quality of life of what I think. It's always what the patient thinks.

The old saying, "It takes a village to raise a child." Well, guess what, same thing with myeloma. We want to help these patients, their caregivers and their support system throughout this entire disease process.

[Slide 90 – Bone Health] Bone health is very important with our patients. They should all have bisphosphonates on board, monthly for the first two years. As a nurse, what I want to look for is invasive dental procedures. They should not have any teeth extraction or anything invasive while on a

bisphosphonate. You want to hold it, let them go through the procedure. After they heal, you want to restart it. The whole idea of those X-rays in the beginning is to prevent a pathological fracture. So, if there's a lesion that's 50% or more in the cortex of the bone, you want to get the orthopedists involved. They might need to place a rod there. Same thing with our neurosurgeon. Compression fractures are pretty common in myeloma. They have a fantastic, phenomenal procedure that helps with pain called a kyphoplasty.

All in all, pain control is very important. If you remember me saying at the beginning, 90% of newly diagnosed patients present with bone pain. So, narcotics are huge. You want to avoid NSAIDs (non-steroidal anti-inflammatory drugs). Do not take over-the-counter pain medicine. Why? NSAIDs, if you think about it, decrease the blood flow to the kidneys. Myeloma's hard on the kidneys, so we definitely want to do narcotics. Having an elderly patient take a narcotic, I understand it's difficult. Lots of education and letting them realize that the over-the-counter medication is more harmful than the narcotic.

[Slide 91 – Renal Health] Renal health. These patients can get renal failure very quickly. Hypercalcemia, dehydration, CT (computerized tomography) scan dye, IV CT scan dye—you want to avoid that—NSAIDs, some of our antibiotics, gentamicin, tobramycin and even bisphosphonates. We think it's more how fast you infuse the bisphosphonates that can harm the kidneys. But you want to make sure they're drinking and they're staying hydrated.

[Slide 92 – Anemia] Anemia can be caused by the disease and the treatment, so we want to support them. Again, it's quality of life. If they're short of breath, they're not moving around, they're tired, give them a blood transfusion or maybe they even need erythropoietin-stimulating agents. Fatigue is a vicious cycle. It can happen because of anemia, treatment, lack of exercise, **[Slide 93 – Safety and Mobility]** so it's something definitely we want to get our physical therapy, our occupational therapist involved.

Nutrition and hydration—very important. If you ask a geriatric patient how much they're drinking, it's usually a cup of coffee in the morning and a little bit of sweet tea for dinner. So, you want to make sure they are hydrated and explain it to them. How much hydration do they need?

Their psychosocial well-being. How's their support system? Sleep disturbances—is this because they have anxiety/stress? Is it financial stress? Is it the dexamethasone? **[Slide 94 – Multidisciplinary Team Approach]** So, this is something you want to keep in the back of your mind to always talk about with the patients. You want to get the multidisciplinary team approach. You want to get all of our social workers involved. I already mentioned the physical therapist, the dietitian, the pharmacist. It's a village to support these patients.

There are lots of financial assistance programs out there. We're very blessed to have The Leukemia & Lymphoma Society help our patients. There's Chronic Disease Fund, Patient Network Access. Even the pharmaceutical companies help these patients find programs to help pay their copays for therapy.

[Slide 95 – Summary] So, in short, multiple myeloma is a chronic but a very treatable disease. We have lots of new drugs. We've had two approved in the last two years. We have a few more that we're hoping to be approved this year. So, we're making patients live longer. Treatment decisions are

individualized. We always take into consideration the patient, their support system. Are they working? Are they not working? We want to manage their side effects. We want to help them maintain their quality of life. As always, let's get our other team involved. Let's get the social workers, the physical therapists, the dietitian. Let's get everybody involved and help support these patients and their caregivers.

[Slide 96 – Thank You] So, at this time I wanted to thank The Leukemia & Lymphoma Society for all their support for our patients, our nurses, our healthcare providers by providing financial assistance, education materials that are on the Web, in booklets, through chapters across the country.

As a nurse, I am very appreciative of the professional education programs bringing the newest information and understanding of the hematological diseases. So, thank you again to The Leukemia & Lymphoma Society.

FOLLICULAR LYMPHOMA (FL)

Lynn Rich, ANP-BC, OCN

[Slide 97 – Follicular Lymphoma: Case Study] Good afternoon. My name is Lynn Rich. I'm a nurse practitioner from Upstate New York in Rochester. Today, I'm going to talk to you about follicular lymphoma, and, most specifically, we'll try to embrace a case study to help better understand the disease.

[Slide 98 – Outline] Here's an outline, and we will essentially define the disease; talk a little bit about epidemiology, how often is this occurring; take a look at the natural history of the disease, the fact that it's indolent versus curable; approved treatment options, including rituximab (Rituxan®) maintenance versus observation; use of idelalisib (Zydelig®); and different communication strategies using support of social workers. At the very end, we'll explore some resources in survivorship challenges.

[Slide 99 – Lymphoma] So, just to start off, let's take a look at what lymphoma is. It's the general name given to a group of cancers that affect the lymphatic system. It includes the lymph nodes, plasma cells, spleen, lymphatic vessels and bone marrow, including immunoglobulins. Remember, it's the immune system that helps protect against disease and infection. So, a dysfunction in the immune system is kind of what brings lymphoma.

[Slide 100 – Lymphoma] Lymphoma is broken up into non-Hodgkin's and Hodgkin's lymphoma. There are at least 50 different subtypes of non-Hodgkin's lymphoma. Hodgkin's lymphoma has only approximately five different subtypes.

[Slide 101 – Follicular Lymphoma (FL)] Follicular lymphoma is thought of as a B-cell, non-Hodgkin's lymphoma versus T cells. It is damage to DNA of one of the parent B cells that causes a malignant transformation, resulting in uncontrolled and exaggerated growth of the lymphocyte. As you can see here, these are the hematopoietic stem cells that initially produce. As they progress down the line and develop, we can see that the more mature cells are the dysfunctional ones in the hematopoietic system.

[Slide 102 – Follicular Lymphoma (FL)] Follicular lymphoma is the second most common subtype of non-Hodgkin's lymphoma. The average age at diagnosis is 60 years old. It's thought of as an indolent or very slow-growing disease. It's treatable, but not curable. What we mean by that is, when treatment is necessary, we use a list of arsenals which help guide us as far as our future treatments.

[Slide 103 – NHL: Epidemiology] Epidemiologically, how many times does this occur for non-Hodgkin's lymphoma? Seventy thousand new cases occurred in 2014. As you can see, the bright orange is the diffuse large B cell. It's the number one most common lymphoma. The second is the blue piece of pie, and it's showing that follicular lymphoma being the second most common. T cell is less common, and the pink is all the different lymphomas. As I said, there was 50+. So, take out the top two, and there's all the rest of the different lymphomas—mantle cell, marginal zone, all the multiple different kinds of lymphomas that are occurring.

[Slide 104 – Case Study: MB] So, what we thought we would do is bring in a case study, because that always helps us better understand a specific disease. What I am presenting to you is a patient of mine. Her name is Martha, and she is a 57-year-old married female. She's a third-grade elementary teacher. She essentially presented with abdominal fullness; sweats, which we described those as sweats occurring cyclically, mostly every night around the same time, causing one to change her pajamas and sheets because the sweats are so significant. So, it's different than a menopausal, "Oh, I felt hot. I felt sweaty." This is cyclical. They can describe to you sweating of sheets, changing pajamas and them occurring cyclically at the same time.

Next is fatigue. It's very, very common. We see that in a lot of our world. But this fatigue is quality of life limiting. It's changing their daily behavior. It's impacting everything they're doing.

[Slide 105 – Ann Arbor Staging System] Finally, lymphadenopathy—multiple sites of lymph nodes throughout the body. By that, we have to better understand and stage a patient with follicular lymphoma. When we stage in follicular lymphoma, we have a very specific staging system. It's called the Ann Arbor Staging System. Stage I is described as one isolated site of disease. Stage II occurs when there are two sites of disease that are occurring both above the diaphragm or both below the diaphragm, so either or, versus Stage III which is above and below the diaphragm. A Stage IV is above and below the diaphragm, including organs or bone marrow involvement. So, a Stage IV will be declared by either non-nodals, organ, or bone marrow involvement.

[Slide 106 – Case Study: MB] So, when we first meet someone, we do CT scans and that better allows us to identify what stage they're in. Our patient, Martha, was noted to be a Stage III, and by that we noticed she had bilateral axillary. So, she had lymph nodes under both arms. They were small, but they were there. Secondly, she had a very large abdominal mass. It was ten centimeters, and she is quite thin and petite; we were actually able to feel that, so that was really how she presented with that full abdominal fullness. Secondly, she had a small inguinal or a groin node. She did not have bone marrow involvement, so that kept her at a Stage III. You note above and below the diaphragm there were no organs involved, and the bone marrow was negative. So, again, she was a Stage III.

[Slide 107 – Treatment] So, when we first meet someone, we have to explain to them that we're on a marathon. We're going to treat you when we have to. For as long as we can, we're going to try to not treat someone. If they don't need treatment, that's great. Then, we continue to follow them. Oftentimes we meet them at an earlier stage, and we can watch their disease. Treating them early does not help their prognosis. Remember, it's a marathon. We're going to treat, put them in remission. Treat, put them in remission. The longer they go in between each chemotherapy regimen, the longer their survival lifespan is. So, we do what we call watch and wait; now, actually, we're trying to describe it as a time of observation. So, it's not necessarily watching and waiting. We are observing them and we're actively observing. It's a kind of attempt to try to get patients to not be so intimidated by that idea. It's very scary to say, "What do you mean I have cancer? What do you mean you're not going to do anything? What do you mean we're going to watch it?" So, we describe it as actively observing until the time comes when we actually need to treat.

Just to better understand, we stage to I to IV, but follicular lymphoma is also described as either a Grade 1, which is very slow growing; a Grade 2, moderately growing; or Grade 3, which is aggressively growing cells under the microscope. So, not only do we stage somebody, we stage them

with what grade their actual lymphoma is, and that's found by the pathologist under a microscope guiding us about what grade they're at.

[Slide 108 – Ready to Treat] When we actually decide about whether or not somebody is ready to treat, because, remember, our goal is to not treat. We want to have them live as long as we can without actively coming in with treatment.

So, in follicular lymphoma, the criteria guide us about when or whether or not we need to treat, such as if there are more than three sites of disease, three centimeters or more. Number two, if one node measures seven centimeters or more. Cytopenias, refractory thrombocytopenia disease. So, they have low counts, and they're not recovering. They're lingering, they're low—that's potentially causing them trouble. Whether or not they have effusions and whether or not they have symptoms of disease or B symptoms. That's what I described earlier—night sweats, fevers, weight loss. If they're having any of those, that will actually impact whether or not we're ready to treat. Finally, if they have threatened organ involvement or an elevated LDH (lactate dehydrogenase).

So, in our patient's case, she was ready to treat. We can see that just by the number two—one node measuring seven centimeters. She had that. She had a ten-centimeter node. She actually had B symptoms, and she had more than three sites of disease. So, she clearly fits criteria and is ready to proceed with treatment.

[Slide 109 – Case Study: MB] So, in her case, we treated her with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone)—that's the old standby. It's what we've been using for years and years in lymphoma. She underwent this in 2007. She attained a complete remission, which is most expected with follicular lymphoma. Patients typically will respond to disease. It's just a matter of how long their remission will last.

Secondly, we'll consider maintenance with rituximab versus observation. Now back in '07, that wasn't an option. We were not doing maintenance therapy. That has become a little bit more in fashion, and there are different criteria. Whether we do maintenance Rituxan® (rituximab) is a decision if it's upfront versus consolidation, meaning, in her case, it would be to consolidate, to complete therapy, and to try to contain the remission. We considered the expected response, the impact on overall survival, quality of life and financial impact. So, maintenance Rituxan is often thought of as a lot of considerations that providers will discuss with them about whether or not they want to proceed with that.

[Slide 110 – Case Study: MB] In Martha's case, we did not do maintenance rituximab. That was not standard of care back then. It wasn't something that was considered. It's much more upfront therapy, considered consolidative therapy with upfront in this year, 2015.

So, she actually relapsed in May of 2008, so she only got a year. So, that's not very long. The typical time until relapse with upfront R-CHOP therapy for follicular lymphoma is three to five years. She relapsed in only one year, so that was pretty concerning. That's an indicator that her disease was behaving more aggressively, and it was more the Grade 3. She responded but the disease came back rather quickly.

So, in 2008, the treatment of choice was to proceed with an autologous stem cell transplant, which she did. She was still young—less than 65 years old. We felt she could tolerate this quite well. She underwent salvage therapy, which is a chemotherapy regimen to get her ready for the autologous transplant. She underwent two cycles. She did very well. She did the autologous transplant and obtained a complete remission in September of 2008. So, she did well with that, and happily it put her in remission.

[Slide 111 – Case Study: MB] Unfortunately, she relapsed in 2014, but that's pretty good. She went six years off the autologous transplant. She did well. Now, we're basically in December of last year. She was essentially asymptomatic, but she did experience some mild abdominal fullness. We rescanned her, which is pretty typical to take a peek since she did experience this fullness. There was concern there could have shown some disease progression. She had the CT of the abdomen, and it showed an increase in disease. So, now at this point, is she ready for treatment? Now, we're wondering "What are her treatment options?"

Multiple chemotherapies—we can certainly consider that.**[Slide 112 – Idelalisib – What Is It?]** But now we have an exciting new option called a PI3K (phosphoinositide 3-kinase) inhibitor, otherwise known as idelalisib. Now, a PI3K inhibitor is a really relatively new mode of treating lymphoma. If we think about what that is, we understand that, in order for a lymphoma to grow, there is a multiple molecular chain that must progress from one's chain reaction from one molecule to the next. A PI3K is what they identify as one of those specific molecules that they know is necessary for lymphoma to grow. So, this inhibitor, just as it describes, inhibits the PI3K to actually move from one chain to the next, so it stops the flow of this molecular chain reaction and the lymphoma can no longer grow.

[Slide 113 – Idelalisib] So, the drug we describe is idelalisib, and it's an oral agent which is exciting. Most of these patients have seen multiple different chemotherapy infusional treatments. It's a pill, so it's pretty well tolerated. It's FDA (US Food and Drug Administration) approved in 2014, so just last year. It has become available to any patient who has relapsed follicular lymphoma.

So, not in the upfront, meaning if you're newly diagnosed and you have disease, idelalisib is not available for you at that point. It becomes a choice if one has relapsed disease. It's also used in CLL/SLL (chronic lymphocytic leukemia/small lymphocytic lymphoma). So, it's an exciting new option, and patients are pretty excited about it because it's essentially very well-tolerated. **[Slide 114 – Side Effect Profile]** There are a few side effects that are important to understand with patients using this drug. There's a concern for pneumonitis. So, what we mean by that is they have cough, shortness of breath and it's a new change in their quality of life and in their breathing. So, when one comes in with new shortness of breath—it's actually quite subtle when it first presents—but it's important to stay attuned to that because if a pneumonitis develops, it can actually make you quite ill, quite quickly, oxygen-dependent and requiring steroids. It's very important to stop the drug and resolve the pneumonitis in order to move forward.

Secondly, there's colitis. So, in general, patients do quite well for a few weeks to a month. But after some time, four to six weeks, they slowly may develop episodes of diarrhea in one or two, three a day tolerable, every other day, something we're not particularly concerned about. But if it progresses and they're occurring three to five times per day for multiple days on end, clearly that's a sign of intolerability and the drug must be stopped. It can develop and become a true oncologic emergency if it progresses without stopping disease. Finally, there's concern for an evolution of liver function

abnormalities in general. What I mean is the LFTs (liver function tests) will spike, and it usually doesn't occur until at least four to six weeks once on the drug. You typically see normal functions, normal function and it can spike right up.

So, actually, with our patient Martha, we actually saw that. She tolerated the drug quite well. Four to six weeks into it, she was doing well. At the six-week point, her LFTs, out of the blue, were spiked to four to five times normal liver function. So, we actually had to stop the drug. If you don't stop, they can become quite ill, and yet again it's an oncologic emergency. So, we stopped the drug. Over time you'll see it slowly work its way down, and she actually did slowly work itself down. It's taking at least eight weeks, which is pretty common from what I understand. Six to 12 weeks is very reasonable for LFTs to recover.

Once they do recover, we want to restart the medication but at a lower dose. So, there's a 75% chance that patients will attain normal LFTs. Once that happens, you can restart the medication. However, it's at the lower dose. So, a standard dose is 150 milligrams BID (twice a day), and the new dose, if one needs to get restarted on medication, is 100 milligrams BID. So, typically once they go to the lower dose, it's better tolerated, and we no longer see those elevated LFTs.

[Slide 115 – Things to Consider] So, when we think about patients with relapsed follicular lymphoma and we're excited about trying one of these new agents, it's important to decide whether or not this patient is a good candidate. We get all excited. Oh, it's just a pill, twice a day. It could be somewhat challenging in your gerontological population. Fortunately, she was 57 years old—she's still pretty spunky. She was a school teacher. She's incredibly anal and attentive to details. She writes out calendars. She knows exactly what she's doing with her doses, so it's very easy. She is an excellent candidate actually to undergo oral agents at home.

However, if one is not the case, I think it's important to bring in the social worker. They'll help you assess the medical literacy and the implications. If they're old, they don't understand the language, it could potentially be quite difficult for patients to manage. So, it's important to make sure they are in a receiving end to be able to tolerate the instructions and follow through on what they're supposed to.

Secondly, there's financial assistance. This is an incredibly expensive drug. Fortunately with the FDA approval, it's covered by insurance if it's in the relapsed setting. But even in those cases, it's still somewhat concerning, so we think about what are the potential sources of assistance. Happily, The Leukemia & Lymphoma Society is very supportive and helpful, and we very much appreciate their impact in allowing our patients to get the medications they need.

I talked a little bit a minute ago about whether or not they're good candidates. I think just to really specify—are the patients able to follow instructions? We often suggest, as nurses, our role is to help them make sure they better understand what they're supposed to do. **[Slide 116 – Communication Strategies]** We often suggest creating a calendar, when to take the pills, when to get their blood drawn and how to follow up if there are issues.

So, we talk to patients. We talk to them regularly on the phone, consider MyChart®, which is our lingo for being able to email patients and respond to them over the computer. It's been quite helpful.

Eventually, patients will evolve to monthly visits if it's well-tolerated. **[Slide 117 – What Happened to MB?]** What happened to Martha? She began idelalisib at 150 milligrams BID. She did quite well. She had no issues. She felt well. She didn't experience nausea. It's a very well-tolerated drug. It typically does not cause nausea.

She tolerated 150 milligrams twice a day up to six weeks; around eight weeks, again, she actually had escalated LFTs, so we had to stop the drug. To date, actually, she's still off the drug. But it's only been, at this point, eight to ten weeks. We have seen them come back to almost normal. Now, at this point though, only two times normal as opposed to four to five times normal. So, she's working her way back to normal LFTs, and we expect her to be able to get back on the drug.

[Slide 118 – Resources – Survivorship Issues] Finally, as I mentioned earlier, there's a little bit of importance to make sure we recognize the different resources. These are survivors. Patients with follicular lymphoma will live many, many years. It's important to make sure we offer them all the resources we have. The Leukemia & Lymphoma Society is a fabulous resource. We have local chapters. They support our patients regularly. We also can suggest the YMCA. There's an exercise program which is really important for patients to maintain normal health, and fitness really ultimately helps with their ability to cope with their survivorship. We also make it an important goal to make sure all of these patients have survivorship care plans.

[Slide 119 – Thank You] Thank you to The Leukemia & Lymphoma Society for supporting patients by providing financial assistance, educational materials on the Web, in booklets and through LLS chapters across the country.

As a nurse, I also appreciate the professional educational programs bringing the newest information and understanding hematologic diseases.