TRANSCRIPT
Administration and Management of Current Therapies
for Hematologic Malignancies
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Slide 1: Administration & Management of Current Therapies for Hematologic Malignancies

Lauren Berger:

Good afternoon. I'm Lauren Berger, Senior Director, Patient Services Programs at The Leukemia & Lymphoma Society. I'm pleased to welcome you to *Administration and Management of Current Therapies for Hematologic Malignancies.*

I would like to thank Millennium: The Takeda Oncology Company, and Spectrum Pharmaceuticals, for their grants to support our program today.

It is now my pleasure to introduce Pamela Haylock, The Leukemia & Lymphoma Society's National Patient Services Committee Chairperson.

Pamela Haylock:

Well, as an oncology nurse and a former ONS national president, I think it's really exciting to see all of you here. And I have been serving on the LLS board now for the last couple of years. And I would just like to suggest to all of you that you really look at who and what LLS does. So again, I'd like to welcome you here and I'm just going to take a couple of minutes of your time to tell you a little bit about LLS. So when you have a patient who has some kind of a blood cancer, blood dyscrasia, whatever it is, that LLS is one of the very first resources that comes to your mind.

LLS or The Leukemia & Lymphoma Society is the world's largest voluntary health organization that's dedicated to finding cures for leukemia, lymphoma, myeloma and other blood cancers. LLS sees itself and truly is the voice for blood cancer patients and we advocate for policies that accelerate approval of new treatments and ensure access to quality coordinated care for these patients and families.

I bet you didn't know that since 1954 LLS has invested almost $900 million in research to advance therapies and also save lives. The research grants fund many promising breakthroughs. And in fact, between 2000 and 2012, almost half of all of the cancer drugs that have been newly approved by the FDA were developed first for blood cancer patients. So even though something is specifically for a blood cancer patient now or in that research track, the benefits extend way beyond to patients who have solid tumors or other kinds of neoplastic processes.

We do continue to invest in research, patient support programs and services, to improve the quality of life for patients and their families.

Another important part of that mission is to bring you and your colleagues the latest information about advances in treatment for blood cancers. And I have to say also things that aren't quite in that category of blood cancers, things like MDS, LLS has tremendous resources for those patients, informational resources for you, to help you better understand what these patients' needs are. So we can help you manage these patients for the best outcomes that are absolutely possible.

So I'm happy to learn with you today. I'm very excited about the presentations you'll hear and work together with you to discuss key issues in caring for patients with hematologic malignancies and other blood dyscrasia problems.

So thank you very much and have a great afternoon and a very productive session here. Thank you.

Slide 2: ONS Disclaimer

Lauren Berger:

Thank you, Pamela.

Continuing education is essential for each of us. So today through discussion of case studies, our presenters, Amy Goodrich, Kevin Brigle and Sylvia Wood will discuss methods of administration of new drugs to treat patients with blood cancers, monitoring and managing side effects, treatment adherence and communication touch points for you and for your patients, areas that each of you are responsible for on an ongoing basis.

Now I am honored to introduce our panelists. Our first speaker is Amy Goodrich, nurse practitioner at Johns Hopkins Kimmel Cancer Center in Baltimore, Maryland. Ms. Goodrich will discuss monoclonal antibodies in hematologic malignancies. Following Amy's presentation, Kevin Brigle will talk about new treatments for CML, the nurse's role in side effects management and therapy adherences. Dr. Brigle is an oncology nurse practitioner at the Massey Cancer Center, Virginia Commonwealth University Health System. And following Kevin, Sylvia Wood will discuss new treatments for myeloma, the nurse's role in administration, side effects management and patient education. Dr. Wood is an adult nurse practitioner and associate director of the bone marrow transplant clinical research program, hematologic malignancy transplant program, at Stony Brook University Medical Center in Stony Brook, New York.

Amy, I am now pleased to turn the podium over to you.

Slide 3: Monoclonal Antibodies in Hematologic Malignancies

Amy Goodrich:

Thank you. So I'm going to start today with talking about monoclonal antibodies in hematologic malignancies. And there's a question and answer period after each of these sections, so write your questions down and we'll get them answered afterwards.

Slide 4: Case Study #1

So this is our first ARS, and is in reference to our case study. A 74 year old female with CLL and you can see her counts on the screen. Her white count's high, her other numbers are low. She is receiving single agent rituximab on a clinical trial. She gets her standard premeds, she gets a standard first infusion titration. She spikes a fever, she rigors, she gets hypotensive, she has wheezing and bronchospasms. She needs lots of supportive care, nebulizer, oxygen, she needs steroids.

Slide 5: Case Study #1

So she's stabilized, we stop her rituximab and give her running meds overnight. She does fine. She comes back and gets the rest of her dose the next day and she gets all the rest of her infusions without issue.

Slide 6: Question #1

So this is your question. Did this patient have an infusion-related reaction or an allergic reaction to her rituximab?

Okay, 95% of you say infusion-related reaction, 5% say that she had an allergic reaction..

Slide 7: Case Study #2

This is our second case study. A 65-year-old gentleman with relapsed follicular lymphoma. He's getting CHOP with rituximab as third-line therapy. All his prior therapies had included rituximab.

Slide 8: Case Study #2

So this is a very busy slide. But what it really shows you is that he starts out cycle 1 with typical premeds and has a pretty typical reaction. Cycle 2, he has more reactions and so we say well, we've got to just pile some more premeds on him. So for cycle 3 he gets steroids and he gets Zantac® or ranitidine and he gets his acetaminophen and his diphenhydramine and all the things that we can think of, including Claritin®.

And so what happens is when the infusion increases to over 50 or 75 mg/hr, he starts to react. So we give him half of the dose very slowly and he comes back the next day and he gets the other half without problems.

Fourth cycle, he comes in, we give him maximum premeds. We're planning on giving him a two day infusion for his fourth cycle. What happens to him, is that he starts to have chest pain and shortness of breath. .

Slide 9: Question #2

So for him, did he have an infusion-related reaction or is he having an allergic reaction to his rituximab?

Okay, so 90% say he's having allergic reaction, 10% say he's having an infusion-related reaction.

Slide 10: History of FDA-Approved Monoclonal Antibodies for Hematologic Malignancies

So let's step back and talk about monoclonal antibodies and hematologic malignancies in general. So rituximab was our first monoclonal in cancer therapy, approved in 1997. And then in 2000 Mylotarg® was approved and hopefully you're all aware that's off the market now, but it was on the market for several years. In 2001 alemtuzumab or Campath® was approved, 2002 Zevalin®, and 2003 Bexxar®. So then we had a dry spell. We went from 2003 to 2009 without any new drugs and then Arzerra® or of atumumab was approved. Our most recent antibody approval is brentuximab vedotin or Adcetris®. So we've got quite a few monoclonals for use in our hematologic malignancies patients.

Slide 11: Types of Monoclonal Antibodies

So I just want to step back and take a minute and talk to you about monoclonals because I really want everyone to leave here feeling more comfortable using monoclonals, both in hematologic malignancies and your non-hematologic malignancies patients.

So what this slide is showing you is the all gray antibody, is a mouse antibody. And we do have murine or mouse antibodies that are used today as part of the Bexxar regimen. But decades ago, when these monoclonal antibodies first started being engineered, that's all we had. And so we would give murine antibodies to patients and their immune system would recognize them as being foreign and actually kill them before they had any chance to have anti-cancer activity. Patients also had anaphylactic reactions more frequently than we see today. So then we got smarter and we were able to peel out more and more of the mouse portion of monoclonal antibodies. And you can see that going across this screen. They are chimeric and humanized and the last one is a fully human antibody. So that's an important point, because the arms of the antibodies are what grabs the target. And the tail is what calls the immune system. And I'll be talking about this in a little bit.

Slide 12: How antibodies work

So how do monoclonal antibodies work? And these are big words here. Apoptosis, neutralization, antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. I want you to look at this screen and say does the mechanism of action have one word or more than one word? That's all I want you to remember. And everybody can remember that. One word or more than one word, that's what I want you to remember. So when you're giving a new monoclonal antibody and you're reading or learning about mechanisms of action, you're going to come away knowing what to expect based on whether the mechanism of action has one word or more than one word in it.

Slide 13: Apoptosis

Apoptosis is programmed cell death. For antibodies that work by apoptosis, the antibody hooks on to the target and causes some essential function in that cell to stop, that allows the cell to die. So that's an easy concept, the light switch goes off, and the cell dies. That's very straightforward. And it's one word, right, apoptosis.

Slide 14: Neutralization

Neutralization. Really the best example of neutralization is Herceptin® or trastuzumab, where the trastuzumab hooks onto HER2 and it changes signaling within the cell, which leads to cell death.. So it hooks on, there's intracellular change, turn something off, again a light switch goes off and that cell dies. And that's one word, neutralization.

Slide 15: Antibody-Dependent Cellular Cytotoxicity and Complement-Dependent Cytotoxicity

So this slide is busy. And it's okay that it's busy because what you're meant to see here is that these are the more than one word mechanisms. This is antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. They just have more than one word. And all

it means is when those antibodies hook onto the target, they cause a flooding of the immune system. They cause lots of chemical reactions to take place in the body. They have more than one word and they cause lots of chaos in your patient's bloodstream. And when you get home you can look at that and see what they do in more detail. They call in different parts of the immune system to come and attack the cell. And it's very dramatic. But they have more than one word. More than one word is drama and one word is just the light switch goes off.

Slide 16: Conjugated vs. Unconjugated

The other thing is any of these antibodies can be either conjugated or unconjugated. An unconjugated monoclonal antibody is just the Y, the two arms and the tail. A conjugated monoclonal antibody is something that has a substance attached to the tail. So it might be a piece of radiation, which is our Zevalin and our Bexxar. It might be a toxin, which is Mylotarg and also brentuximab. So in addition to working by those other four mechanisms, these conjugated antibodies also take an additional therapy directly to the targeted cell.

Slide 17: Infusion Reactions During Monoclonal Antibody Therapy

So let's go back to our reactions. The vast majority of monoclonal antibody reactions are due to cytokine release syndrome. They're infusion reactions. Cytokines are chemical messengers. They serve normal functions. They're interleukins, they're interferons, they're TNF, they're colony-stimulating factors. You know all these words, you know what these things are, you talk about these things and hear about these things. In a normal immune system they have very normal functions. They promote or inhibit cell growth, they call other parts of the immune system, they do all sorts of normal messaging. But when you're giving a monoclonal, this is happening on a grand scale, and when the targeted cell is destroyed, all of the intracellular contents dump out into the bloodstream of this patient, so it wreaks chaos in that patient's body.

Slide 18: Cytokine Release Syndrome/Infusion Reaction

Cytokine release syndrome, and thus infusion reactions, are most common with the first infusion because the highest number of cells are being targeted, so that chaos is the most widespread with the first infusion. Reactions generally occur within a couple of hours of the infusion starting, and thankfully most of these infusion events are mild or moderate. They're rarely severe, but they can be. And then they lessen as you give more of the drug because you have less target cells.

Slide 19: Cytokine Release Syndrome/Infusion Reaction

In looking at this slide, the difference between a severe infusion reaction, where patients have excessive reactions shortly after the infusion is initiated and a true allergic reaction, is that the symptoms get worse every time with rituximab allergy. That's the biggest hallmark of the difference. True allergic reactions account for a very small number of your infusion reactions. Both can be fatal.

Slide 20: Signs and Symptoms of Anaphylaxis

So signs and symptoms of anaphylaxis are on this slide. Anaphylaxis is different from infusion reaction. Patients rapidly go into respiratory distress/failure and cardiovascular collapse.

Slide 21: Grading of Infusion-Related Reaction

I wanted to be sure everyone understands how infusion reactions are graded. That when clinical trials are done, this is the grading scale for infusion-related reactions. Grade 1 reactions are mild, transient, and require no action. A grade 2 reaction requires infusion interruption, symptom-directed management for less than 24 hours and rapid control of symptoms. Grade 3 reactions are prolonged, don't respond rapidly, and often include hospitalization. So you know that most of the infusion reactions you're seeing are grade 1 and 2. It doesn't mean they're not scary, it doesn't mean that it doesn't take a lot of time for you to get that patient under control. It doesn't mean the patients are not scared to death. But this is the life-threatening based scale. And I think it's important for you to understand that because when our trials are being done, if patients have grades 1 and 2 reactions, those are considered very safe, from a scientific perspective. And then, of course, grade 4 infusion reactions are life-threatening and grade 5 is fatal infusion-related reaction.

Slide 22: Grading of Anaphylaxis

And then anaphylaxis grading, as you can see, is different. It starts at a Grade 3. There is no grade 1 or 2 anaphylaxis. Symptoms are severe at the onset and rapidly worsen without aggressive intervention.

Slide 23: Rituximab

I just want to spend a couple of slides on each of our antibodies. So rituximab is an anti-CD20 chimeric monoclonal antibody. This was our first monoclonal antibody. Rituximab taught us about infusion-related reactions and management, as well as the importance of patient education. Rituximab depletes B-cells from the peripheral blood and the bone marrow and the lymph nodes. It has a broad indication, 375mg/m2 is the most common dose, but 250mg/m2 is given with Zevalin and 500 mg/m2 is recommended in some combination regimens.

Slide 24: Administration Schedule for Rapid Rituximab Infusion

And so by a show of hands, who is not doing rapid infusion rituximab? Okay. Your job is to go home and ask why you're not doing rapid infusion rituximab. Once a patient tolerates rituximab, usually after a first or second infusion, you can dose them, giving 20% of the total dose over 30 minutes and then giving the remaining 80% over an hour. This significantly reduces the time that patients are in your chairs. It's very safe, there are many references in the literature, including on this slide and also on the package insert.

Slide 25: Alemtuzumab

Alemtuzumab is Campath, a humanized monoclonal antibody, which targets CD52. Its primary mechanism of action is ADCC. And if you think about where CD52 is, it is found on B-cells, T-cells, monocytes, macrophages, dendritic cells, NK cells, granulocytes, bone marrow

stem cells and also other normal tissue. This is why your patients receiving Campath have such different issues than with rituximab; because CD52, the target, is on many cell types. Patients have lots of reactions because the main mechanism of action has more than one word in it, ADCC. Patients are at great risk of infection because CD52 is present on multiple cell types involved in immunity.

Slide 26: Radioimmunotherapy

Radioimmunotherapy (RIT). This includes Zevalin and Bexxar. These are indicated in relapsed low grade lymphomas, although they can be given as consolidation after initial therapy, as well. Most patients receive RIT for relapsed or refractory disease. Both Zevalin and Bexxar are anti-CD20 conjugated monoclonal antibodies. The "tail" of the Y contains a piece of radiation (Y^{90} with Zevalin and I^{131} with Bexxar) so that when the "arms" attach to the target cell, not only does the monoclonal antibody work by the four mechanisms we discussed earlier, but the attached substance, in this case, radiation, also targets the cell. RIT offers a way to deliver radiation therapy directly to the disease. This is important in lymphoma, where patients often have multiple areas involved, making traditional external beam radiation therapy impractical.

Slide 27: Radioimmunotherapy Side Effects

I'm not going to go through this in great detail, but the side effect profile is different for these drugs. Cytopenia nadir starts about four weeks after dosing and the nadir can last four to eight weeks, so there really are some different little flavors to managing these patients.

Slide 28: Ofatumumab

Ofatumumab, which is one of our relatively new drugs, anti-CD20 monoclonal, it's indicated for CLL, and again CD20 is on B-cells, normal and abnormal B-cells. Not on bone marrow. And the mechanisms of action have more than one word, so you know you see reactions with ofatumumab.

Slide 29: Brentuximab-Vedotin

Brentuximab is an anti-CD30 monoclonal antibody. And it's conjugated with MMAE, which is a very toxic drug given by itself, but when you hook it onto a CD30 antibody, the MMAE gets into the cell and causes the cell to turn off. So because the main mechanism of action is apoptosis, for those of you who have given brentuximab, you know that patients tolerate it well. So its main mechanism of action has one word and they tolerate it well.

Slide 30: Minimizing Infusion Reactions

When you are giving a monoclonal antibody, what do you need to know? Patients who have a strong allergic history have higher incidences of infusion events. You need to know the target, the tumor burden, the patient risk factors, you need to know the mechanisms of action, you need to know what to premedicate with and how the drug is given, you need to monitor per package insert, you need to know what you're going to do if the patient does react, whether it's pharmacologic or non-pharmacologic interventions.

Slide 31: Premedications and Black Box Warnings

This is a quick slide of black box warnings. And brentuximab is the only one without a fatal infusion black box warning.

Slide 32: Patient Education

Patient education. So you need to do your antibody education, stressing the difference between immunotherapy and chemotherapy, you need to talk to patients and caregivers about expected side effects, premedications, how you're going to manage side effects if they happen, what the patient should expect, both in the clinic and once they get home. At discharge from clinic, be clear if you want patients to take running meds at home based on infusion reactions in clinic but also, whom they should call and what they can take at home if new fever, itching, etc, occur.

Slide 33: Case Study #1

So let's loop back to our case studies. This is our elderly female who has severe reactions to her rituximab, goes on to get all the rest of her doses without problems.

Slide 34: Question #1

This is an infusion-related reaction.

Slide 35: Case Study #2

Our 65 year old third-line therapy whose infusion events get worse every time.

Slide 36: Question #2

He's having an allergic reaction to his rituximab.

That is my last slide. I'll take questions now.

Audience: Hi, I'm not familiar with brentuximab, we haven't used that where I work, but we do use rituximab a lot and I almost feel like we should give a hypersensitivity kit with every rituximab because we have a lot of reactions. And right now we have one gentleman that he's reacted like the last three times I think, and now he's on maintenance rituximab, which we're still thinking of doing. The brentuximab, are they ever thinking of using that as kind of like Abraxane® is for those who have reacted badly to rituximab?

Amy Goodrich:

No, because the target for rituximab is CD20, which is on B-cells and B-cell lymphomas. The target for brentuximab is CD30, which is on Hodgkin lymphomas and on some T-cell lymphomas. So all those patients that you're having issues with, they don't have CD30.

Audience: Okay, thank you.

Amy Goodrich: Good question, though. Anybody else?

Audience: I would be curious, event reporting. In our institution we report events, safety events, clinical events, with any kind of infusion reaction. At what point do you think it's a reportable event?

Amy Goodrich: Well, that's a good question and I think that if they're grade 1 and 2, they're expected. I would recommend if they're grade 3 or above, it is reasonable to report those because these are the patients who are being hospitalized, have life-threatening events or die from the infusion reaction.

Audience: That's what we thought. Any time they need another level of care.

Amy Goodrich: Right.

Audience: Probably report.

Amy Goodrich: That's a good trigger.

Audience: But anybody who just gets regular premeds or is able to finish their medication with intervention, probably not report.

Amy Goodrich: Exactly. Because those are expected side effects for most of these drugs.

Audience: Vicki from Montana. We give rapid infusion Rituxan® and our patients love it because you know they've got to get back to the farm and get things done. We also give it for like Waldenstrom's macroglobulinemia, all of that. We're rapid infusing them all. That's okay?

Amy Goodrich: It's okay. If they meet the criteria, it's okay. Absolutely.

Audience: I have a question on that also. For people receiving maintenance rituximab, so they're coming in every three months or so, would they be able to get the rapid infusion?

Amy Goodrich: Yes, the criteria is that they have received rituximab within the previous four months. So if you're giving your maintenance every two or three months, yes, they can come right in, get their 90 minute infusion and go.

Audience: And my other question is, you said daily prednisone? So not all of our patients receiving rituximab...

Amy Goodrich: Right. So that was the gentleman who was having worsening infusion events. In my practice we do not routinely give steroid premeds. He was an exception to the rule.

Audience: Thank you.

Audience: How long has the rapid infusion Rituxan been used? Because I know our boss is probably going to be resistant to that.

Amy Goodrich: The first time I became aware of it was in a clinical trial that we did in 1999. Over the years, many trials used rapid infusion. Are there any other questions?

Okay, then I'm going to hand you over to Kevin, who's going to talk to you about CML.

Slide 37: New Treatments for CML

Kevin Brigle:

Thanks, Amy. So I'm going to talk today about new treatments for CML and roles in side effect management. We have some novel drugs out here now, and there are a few interesting things to know about them.

Slide 38: Chronic Myelogenous Leukemia

CML in general, as noted up on the first slide, is an accumulation of incompetent mature granulocytes. So lots of white cells, lots of granulocytes, but they're nonfunctional. So patients may have a lot of those granulocytes, but they still run into problems.

This was the first human malignancy identified to have a known consistent chromosomal marker and that chromosomal marker, or the hallmark for the presence of this disease, is this reciprocal translocation between chromosomes 9 and 22 that results in the presence of this Philadelphia chromosome, so named because in 1960 it was identified at Fox Chase, which was in Philadelphia, so they gave it that particular name.

That 9;22 translocation actually fuses parts of two genes, the BCR gene and the ABL gene together, which results in the creation of a new protein, which is a tyrosine kinase. And that very tyrosine kinase then is what's responsible, and is the critical factor for the genesis and the continued accumulation of those cells.

So what we need to do to treat CML is to target those cells which contain that Philadelphia chromosome, and to target that protein tyrosine kinase specifically. And to do so we've developed tyrosine kinase inhibitors. And these are the mainstay we have for treating this disease. The first one was developed in 2001. We have a variety of them since.

This is not a curable disease, even with these tyrosine kinase inhibitors. We can control the disease with these inhibitors, but none of them are curative. The only actual curative modality is transplant, which we know does have a few of its own problems.

Slide 39: The Philadelphia Chromosome

So if we look up here on the left, we'll see the cartoon showing the genesis of the Philadelphia chromosome. We see chromosome 9 and chromosome 22. We see BCR-ABL at the distal ends of those chromosomes. And we'll see that there's a crossover reaction and basically part of BCR and part of ABL switch between those two chromosomes. And so we have the 9, which gets a little bit longer, and the 22, which gives rise to that BCR-ABL fusion or that is the 9;22, that's the Philadelphia chromosome that we see here .

And if you look over on the right of this slide, you can see a typical karyotype. And on the karyotype, if you look at chromosome 9, you can see the one chromosome 9 is just a little bit

longer. That's because it's accumulated some additional material. And look down at chromosome 22 and you see that's a little bit shorter. That shorter chromosome 22 is the Philadelphia chromosome.

So when we look at patients' response to treatment, this is what we look at. We look at a karyotype. As we monitor their response along the way, we look for the disappearance of that Philadelphia chromosome in these chromosome spreads.

Slide 40: Gleevec®: The Proof of Principle

So how do we target this particular tyrosine kinase? Well, we have the tyrosine kinase inhibitors, and up on the top of this slide you can see what this BCR-ABL protein does. There's actually an effector molecule, that's the green one. It's a substrate, which when binds to that tyrosine kinase, it gets phosphorylated and that is represented by the little red dot shown there. When that substrate is phosphorylated, it becomes active. And it's that active effector molecule then that goes forward to basically turn on all the genes that are necessary for proliferation and cell division.

And so how do we stop that phosphorylation from occurring. And so a drug was developed, which basically competes with that substrate. So you can see it fits into the binding spot, the orange one shown there. It goes right into that binding spot and prevents that substrate from binding. And if we can't get phosphorylation, then we do not get that accumulation, that downstream activation. If we don't get that downstream activation, not only do the cells not grow, but they actually undergo apoptosis and they begin to die.

And so this really was a proof of principle drug as far as oncology goes. It was actually the first drug where we said to ourselves, we can have a drug that targets only the cancer cells and leaves all the normal cells alone. And it works because again, this new tyrosine kinase is only in cancer cells. It doesn't exist in any other cells.

So prior to the development of Gleevec®, for those of you who've been around a while, you know that median survival with CML was about three years if you didn't undergo a transplant. So it was a fairly deadly disease. And now we think of this disease as basically being a chronic disease and patients should, if they take their drugs correctly, live fairly normal lives.

Gleevec is good. I've always described it as a triple rounding home, but it's not a home run. Resistance can develop to the drug. It does have a number of side effects, as probably most of you know. And scientists set out then to engineer a new Gleevec or a better Gleevec and currently we now have five available to us. There were two that were just approved this past year. And in addition to targeting this tyrosine kinase, you'll see that we also have another type of treatment for this disease as well. It's not a tyrosine inhibitor, but we'll get to that a little bit later.

Slide 41: Definitions of Response in Chronic Phase CML

So when we're looking at monitoring patients and how they respond, we can look at the hematologic response, a cytogenetic response and a molecular response. And this table shows you what those responses mean and also how frequently we're going to be monitoring these patients.

So from a very kind of a macro level, we look at hematologic response and we should see their peripheral counts normalize. White count, platelets, all those go back to normal.

And we can look at a cytogenetic response. And again, we're looking for the presence of that Philadelphia chromosome. And we can usually look at about 20 spreads and go to a higher level of sophistication. Or we can do FISH analysis or fluorescence in situ hybridization. That's a slightly different cytogenetic analysis, which is more automated, and lets us look to at around one in 500 cells.

And then lastly we have the molecular response looking at PCR or polymerase chain reaction. This is much more sensitive and allows us to look at cells, at a level of one in 100,000.

Slide 42: Monitoring Response: Assay Sensitivity

So when we think about monitoring response, and I know this picture is not in your workbook, but there are bullet points. When patients are first diagnosed, of course, we look at the hematologic response. And even if their white count normalizes, we know that there are plenty of those cancer cells remaining, plenty of those Philadelphia chromosome positive ones still present.

So we get a little bit more detailed and then we start looking at the cytogenetics and the FISH. And we can go down again to the level of about a 2-log reduction before we're going to say well, there's probably still cells there that are Philadelphia chromosome positive, but we can't detect them with that technology.

And so that's why we developed RT-PCR, the reverse transcriptase polymerase chain reaction. Again, it takes us down to about one in 100,000 cells. And as our treatment progresses, years down the line, that's really the only way we can possibly detect this Philadelphia chromosome. And so that's what we use this PCR as the mainstay of detection, once patients are into a cytogenetic remission.

Slide 43: Expected Response versus Time

With those definitions in mind and the monitoring frequency that we have shown what's the expected response and how do we know if our tyrosine kinase inhibitors are working?

And so, in this slide time is shown on the left and that's actually time from starting the tyrosine kinase inhibitor, three months down to 18 months or any time down the line. And also shown is the time to get an optimal response, and which is what we'd hope to see, and then there is the suboptimal and the failures shown in the middle and the far right columns.

And so if we do not see an optimal response, or we start to see a suboptimal response or a failure, that means that we're doing something wrong or there's something with that particular CML that's not responding to the tyrosine kinase inhibitor that we're using, and we need to switch tyrosine kinase inhibitors.

So these are time markers that we hit, or we try to hit on every single patient, and if we don't hit those markers, then it's time to switch tyrosine kinase inhibitors. And this day and age, we have a lot more choices that we didn't have a couple of years ago. And so it makes management a little bit easier.

Slide 44: Question #1

Okay, question number one. What symptom is common to all of the oral tyrosine kinase inhibitors? Constipation. Headache. Fluid retention. Prolongation of QTc interval.

Alright, fluid retention, 60%. And that's good. For those of you who did not know that, hopefully we'll get more understanding of that as we go through the talk.

Slide 45: Case Study

. So let me introduce you to JR. JR is a 33-year-old gentleman who was diagnosed with chronic phase CML. He was started on imatinib or Gleevec at the 400 milligram daily dose. And unfortunately, developed grade 3-grade 4 diarrhea and, unfortunately, this wasn't able to be controlled with our normal treatments. So we were thinking we'd probably have to switch this guy to another kinase inhibitor.

So why did we start him on Gleevec? So if you look at the table, at the time he was diagnosed, let's say early last year, there were three tyrosine kinase inhibitors available to us. We had imatinib, dasatinib and nilotinib. Again, the imatinib is Gleevec, and it has been around a long time and was certainly an appropriate choice. All these are NCCN recommended first line choices for treating CML patients. You can see they have different dosing requirements. So if we look at Gleevec, which is typically taken with food, although it's not required to take it with food, but sometimes helps with nausea. Sprycel® or dasatinib can be taken any time with or without food. And nilotinib needs to be taken twice daily without food. If you take it with food, unfortunately, it changes the absorption characteristics, so that has to be taken on an empty stomach.

And in the left column, look at the side effects. All of them have neutropenia and thrombocytopenia in common. And of course, fluid retention as well. And these also have their own unique side effect characteristics, as opposed to having just some common ones. With dasatinib, the pleural and pericardial effusions are a little bit more common. And of course, there's a black box warning on nilotinib for the prolongation of the QTc interval, and so that's an important factor when we're thinking about treating patients with this drug.

So for a lot of patients when we're thinking of starting a tyrosine kinase inhibitor or switching a tyrosine kinase inhibitor, we look at the side effect profile. And we ask, is the patient able to tolerate this one, is there something specific to that patient's past medical history that won't allow that.

In our gentleman's case, though, he's 33 years old, healthy, has absolutely no problems, And for him it really wasn't those side effects, besides his diarrhea that we couldn't control, so for him we were looking at dosing schedule . And certainly an active 33 year old wasn't going to be looking forward to a medication he took twice daily on an empty stomach. And so dasatinib was going to be the choice drug for him.

Slide 46: Intolerance to Therapy

So we talk about people being intolerant to therapy. In terms of tyrosine kinase inhibitors, what does that actually mean? Those bullet points are listed here. Obviously life-threatening grade 4 toxicity would qualify. More what he had however, was a grade 3, grade 4, non-hematologic toxicity that we basically just couldn't control. Now we normally don't think of grade 2 toxicity as being too significant, but it is if it affects your quality of life. So recurrent grade 2 non-hematologic toxicity is another reason to think about switching tyrosine kinase inhibitors. We'll talk later about how controlling those side effects and quality of life are huge in

terms of adherence to these medications. And lastly grade 3 or 4, hematologic toxicity, is another reason to think about switching tyrosine kinase inhibitors.

Slide 47: Symptom Management

Listed here are a whole variety of adverse events that you can see in patients who are taking these various tyrosine inhibitors and they go from the more mundane, when we think about nausea, constipation, diarrhea, things like that, down to elevated liver enzymes, pancreatic enzymes. There are some very nice evidence-based interventions that we can use for a variety of these side effects. Some of these just require monitoring, like the liver enzymes and QT interval, that needs to be monitored as well in patients. We need to make sure that they're not taking drugs that can also be synergistic and increase that QT interval. So we have to think about the symptoms and how we can manage those.

Down at the bottom of this slide, note that it says for all of these symptoms, consider dose reduction for some of these tyrosine kinase inhibitors. We can actually reduce the dose and prevent or lessen those side effects. We can do a short treatment interruption and that was more common in the past when we did not have five tyrosine kinase inhibitors to choose from. We do not like to do that now. More often what we're going to do is switch to a different TKI. Again, taking care of these side effects is really critical in keeping these patients adherent to their medications.

Slide 48: Case Study

So let's go back to our case study. And so after starting dasatinib, he achieved a very rapid reduction in his BCR-ABL levels and we're looking at this by the PCR and this occurred by three months. And he had a complete response by nine months. And then unfortunately if you look at the graph, you'll see that he kind of waxed and waned, so he saw a rise and fall of those BCR-ABL levels. And so the question to us was, is this guy developing a resistance to the particular drug that he's on. And typically when you see a pattern like this, that's not the case. When you see an up and down pattern, it more suggests that the person is not exactly adherent to their medication. So when they're on their medication BCR-ABL levels are down. When they're off their medication it's up. And that's bad because that does lead to resistance and the development of resistant clones. So while this pattern suggested adherence and not resistance, it can certainly lead to the development of bad mutations and resistance.

Slide 49: Adherence to Therapy

So these next four slides are going to talk about adherence to therapy and oral agents and I know there was a great talk yesterday, a good hour and a half session on adherence to medication, oral medications specifically. And I hope some of you had the opportunity to attend that. But I have four slides that might hit the highlights of that talk and they are not really going to do justice to it all, but again we'll just hit the highlights here.

So if you look at the definition at the top, adherence is the extent of conformity to the recommended treatment plan by the provider, with respect to dose, timing and frequency.

So it's not just taking the medication, but taking that medication correctly.

In 2009 there was a study published in *Blood* that looked at the patients who had been on Gleevec up to that point in time. And it noted that about a third of those patients were non-adherent to their Gleevec. So we have a great drug, but they weren't taking it correctly. Only 14% of patients were actually taking it exactly as it was prescribed.

So adherence can be a difficult problem with even these tyrosine kinase inhibitors, which really have great efficacy.

And I know you heard yesterday, the *Journal of Oncology Practice* which just came out this past week, described how ASCO-ONS is updating their chemotherapy guidelines. And their guidelines are going to be such that the majority of those nine new recommendations are talking about oral medications. And certainly I know it's true in most practices that we treat oral medications differently from IV medications. And all the new guidelines are going to suggest or recommend that we treat them exactly the same in terms of monitoring, education and the like. And so look forward to those guidelines coming to your infusion center.

So the World Health Organization attributes non-adherence to five interrelated factors shown here as the health system, socioeconomic concerns, condition-related, therapy-related and patient-related factors. And we'll talk about those after we go through this next ARS question. So get ready here.

Slide 50: Question #2

Costs for patient education concerning oral medications are increasingly covered by insurance companies.

So when you educate patients about their oral medications, are you getting reimbursed for that?

Let's look. Right, false. And so we'll get into that as well, but yes, it's not readily reimbursed for the most part.

Slide 51: Factors Affecting Adherence

So what are some of the factors affecting adherence? And again we see these factors from the World Health Organization. First are the social/economic factors including language proficiency. So think about literacy and when you're talking to patients and even the literature that you give them, is that effective? Next are the healthcare system factors and condition-related factors. Patients, when they're doing well don't have symptoms. So it's that lack of symptoms that can affect adherence. And the chronicity of the problem we are treating. We know that as problems become more chronic and patients take their medications, and we know this from primary care colleagues, that they're less likely to take their medications on time. There are therapy-related concerns. The complexity of the regimen and how long you have to take that particular agent. And lastly are the patient-related factors as well. So that's anything from cognitive impairment, their support, mobility and things like that. And when we talk about these factors being interrelated you can see that you could actually cross these back and forth into different rows. And so there's a whole variety of factors you have to think about when you have patients on oral medications.

Slide 52: Oral Medications

This slide just kind of highlights what was illustrated yesterday in that nice hour and a half long session on adherence. But right now, 25% of your oncology drugs are going to be oral formulations and that's going to do nothing but increase in the future. You're going to see more and more oral medications. You know, when you're in the infusion room, we can take care of education and adherence, but when these patients are at home, the problem of taking those medications correctly really falls on the patient and their family as well.

So if we look at adherence, and from an oncology standpoint, we generally ignored that with patients in the past. Because we're giving you a drug, it's for cancer, my gosh, you're going to take it. So you know what's good for you and you know what happens if you don't take it. But that doesn't tend to be the case. Patients are equally adherent to their cancer medications as they are with some of their other medications. So we can't rely on them just being cancer patients as being "good patients" who are going to take all their medications.

And as cancer becomes more of a chronic disease and these drugs become long-term, again we can look at the experience our fellow practitioners in primary care. If you look at hypertension meds, diabetes meds, the actual adherence rate is about 50%. And probably for long-term patients on Gleevec, it might run around 50% as well and this is what some of our more recent studies would show.

And so sometimes it's just difficult to tell patients you need to take every dose of medication. If patients miss a dose of Gleevec, they certainly don't feel bad in any way, shape or form. And sometimes it's also just a matter of the number pills they have to take. So they're taking all these other medications and then I have to sequence these new drugs in, some with food, some without food. So it's the sheer number of pills that you have to take and sequencing as well.

And some of the other things you'll see, too, is that primary care providers may start patients on medications, especially proton pump inhibitors, which should not be used with these medications. And so patients can get side effects just because other providers aren't familiar with the medications that we're prescribing. And more and more patients are going to be out in the primary care world while on these oral oncology agents.

So nonadherence can sometimes just be unintentional as well. Patients just forget and that actually does happen for some patients. And other times they will say well, I think I'm doing it right, but in truth they're not taking their medications quite right. They skip, they miss a dose, they say well, I'm going to double up on the dose and that's not quite right either. And sometimes they can get toxicity from doing this. Sometimes patients just under-report side effects as well. For example, diarrhea, which you might be able to help them with. If they can't control that diarrhea, the drug's not going to be absorbed as well, so they're not actually getting the full dose. And sometimes it's just timing. So if you take this gentleman, who's 33 years old and you put him on nilotinib. He likely goes out a lot at night and, I can guarantee he's not going to take that second daily dose without food. And so you have to think about, is the drug we are using fitting into a patient's lifestyle.

Slide 53: Improving Adherence

So how do we improve adherence? There's a number of interventions that we can talk about here. There's the oral chemotherapy nurse. I don't know how many of you have such a nurse in your clinic. We don't have one. They're not terribly common because it's not reimbursed. With this nurse, we see one-on-one basic interaction with the patient prior to starting the medication. We identify problems and ask "how can we solve these problems even before they start?" Unfortunately, again, that's not reimbursed or it is rarely reimbursed. I don't think there's a single insurance company that does so and that really gives us the opportunity to lobby the insurance companies to begin doing so. And again, managing side effects is so very important. Some of the insurance companies do have what we call "adherence programs", where they have case workers who will call the patients. Again that's far and few between, but there are a couple that do so. We have one that serves Virginia which actually does that for patients. The dispensing pharmacy can also play an important role. There are some specialty pharmacies such as Diplomat and Biologics, which do a very good job helping patients. Again these are mail order specialty pharmacies. We use them when we can because they really help keep patients on track as well. They give them counseling in between prescription refills. You'll find that some of the major medical centers also hire "clinical pharmacists", who will actually be in the clinic to talk to patients about their oral medications. We can certainly just do reminders from the clinic, emails, texts, things like that. Online calendars are available as well. If you put it on your Google calendar, the account can email you to inform you to take your medication. There are some great apps out there as well, some good smart phone apps. There's a couple I've listed here that really get good high marks. Pillboxie and Rxmindme, these are for iPhone and iPhone-like devices. MedCoach is actually for Android and IOS devices as well. So there are some really nice ones for meds in general, but we can certainly add tyrosine kinase inhibitors in the med list as well. The Leukemia & Lymphoma Society has a tracker which patients can do online as well. But again, be aware of that kind of alert fatigue where patients are getting texts all day long, alerts and things like that. So they're going to respond to this alert and then at some point in time, it may just become like another text coming in. So due to this alert fatigue, electronic reminders may not work after a period of time. We have low tech, written calendars as well. Sometimes that allows people to better track side effects. And also this Hawthorne effect, when you ask patients how are they doing or have them actually write down how they are doing and bring this in to you. Patients often over-report compliance when they know you're watching and they want to please you. So very often when patients do that self-reporting, it's a little bit less honest than it suggests.

Slide 54: Case Study

So back to the study. So JR, was put on dasatinib and obtained a partial cytogenetic response by nine months. He never achieved a major reduction in his BCR-ABL levels. Then he experienced a rapid increase in those BCR levels over the next 12 months and you can see this on the graph below. Mutation analysis showed the presence of this T315I mutation. Oftentimes, when we see this rapid increase, it means we have now developed a mutation and that the tyrosine kinase inhibitor is not working. So if you recall the first graph earlier in the talk, we kind of had an up and down of the BCR-ABL levels. This is a straight up trend, even if the patient is taking their medication.

Slide 55: Question #3

So question 3. This is the last one. Which oral drug is effective against the T315I mutation?

Alright, answer says ponatinib, very good. A fairly well educated group here.

Slide 56: Treatment Options Based on *bcr-abl* Kinase Domain Mutation Status

Let's move on here. When patients do develop resistance, we'll often do mutation analysis and there are about 100 known mutations that can develop in these patients. When do we perform mutation analysis? Well, there's really no absolutes on this. There's a couple of guidelines shown there and include inadequate initial response, loss of response, or if they progress to acute leukemia. And so those are the times you might think about it. Most of the mutations are actually responsive to other tyrosine kinase inhibitors. There's a couple that can be problematic. Those are shown here on this table, going down the line in the first column. And in the second column then, the NCCN treatment guidelines detailing what would you use to treat patients who have those specific mutations. And a couple of those medications we haven't talked about yet, but we will. Really particularly troublesome mutation is the T315I mutation and we really had nothing up until the last four months or so to treat patients who had that particular mutation. Those patients basically had to go through transplant or they would progress. But now we actually have something and we'll talk about that.

Slide 57: Protein Translation Inhibitor

JR was taken off of tyrosine kinase inhibitor and he was switched to this drug called omacetaxine mepesuccinate. Long word, and much easier said, as Synribo®. This is the only approved agent that's not a protein tyrosine kinase inhibitor and it's effective against that T315I mutation as well. And as we look down in the table there, we can see that this drug was approved in October of 2012. And we can see the dosing shown here. And change the dosing – your handout actually shows this a little bit different. That's 125 milligrams subcu, q.12 hours. So that's given twice daily, not just once daily that is in your handout. It is given every 28 days. And then once you have a hematologic response, it's given for seven straight days, again every 12 hours, which is repeated every 28 days.

So this has to be done twice a day. That can be somewhat problematic because a lot of clinics aren't open 12 hours. And so sometimes that requires being a little creative and finding a place, to have patients get their early morning or late evening injection. The FDA has not approved patients to reconstitute and self-inject this medication. So that twice daily thing can be a little bit of a complication.

Side effects are shown on the right. Neutropenia, thrombocytopenia are common and are usually managed very nicely with a little dose reduction.

Slide 58: Case Study

Let's look at JR again. He actually was started on this medication, and got that great hematologic response as we were hoping for. But he didn't like being tied to those every 12 hour injections. At least once a month, once he responded, he began missing doses again. And so he

was going to get in trouble here again. And so he said now his side effect was just plain inconvenience and that can be a huge side effect especially if we have a way of taking care of it.

In this case we did. So we now have two other protein kinase inhibitors that are available. One is bosutinib. The other is ponatinib, as you see in this slide. One of these is effective against that T315I mutation and that's the ponatinib. Why wasn't he started on that originally? Because that actually wasn't available at the time. The Synribo was.

So we can see with these two medications, both were approved late last year. Bosutinib, given 500 milligrams daily, and needs to be taken with food. Whereas the ponatinib can be taken, 45 milligrams, with or without food, makes no difference. Side effects, you can see over on the right. Again, neutropenia, thrombocytopenia are common.

If we look down at the ponatinib, it has two black box warnings. Arterial thrombosis and hepatotoxicity. So two things we need to pay close attention to and monitor patients for.

How bad is the arterial thrombosis? A little bit difficult to say because this is a relatively new drug. So in the studies it was relevant, but we don't know in real life if it's going to be as significant as it was in the studies.

So due to his young age also, while he was started on ponatinib, he was also sent for work-up for an allogeneic transplant. Because if this ponatinib doesn't work, that's his only chance at long-term survival.

Slide 59: Case Study

Okay, so here's the end. Prior to starting ponatinib, he participated in a nurse-led, one-one-one education session. A pill reminder app was loaded onto his smart phone. He was shown how to use it, but he probably knew how to use it and how to transmit that information directly to the clinic nurse. He and the clinic nurse actually made periodic phone calls, to make sure that he was on target, and then later they just simply agreed to text each other. He achieved a complete molecular remission within nine months and to date avoided the need for an allogeneic bone marrow transplant. And he continues to text his clinic nurse. I assume that's all about medications.

Slide 60: Question #1

So again, what symptoms are common to all the oral tyrosine kinase inhibitors? You did a good job on that. Fluid retention.

Slide 61: Question #2

Costs for patient education concerning oral medications are increasingly being covered insurance companies. You are right, that is false. They like to cover as little as they can, but hopefully we'll get that changed.

Slide 62: Question #3

And which oral drug is effective against the T315I mutation? And that is the new one, ponatinib. Again omacetaxine mepesuccinate is as well, but that is not an oral medication, that's the subcu medication.

And with that, any questions?

Audience: Not a question, but just an FYI. I've learned that Gleevec goes generic next year. So that has a lot of implications for what drug you might choose for the economic issues. Were you aware of that?

Kevin Brigle: Yeah, it goes generic in 2015 actually. Gleevec's had a tough life. First came out in 2001, it was $30,000 a year. In 2012 it's now up to $90,000 a year, so a big jump. So I'm not sure what the cost of the generic is going to be. But yeah, it will, I think, impact choice. When you think about patients having a 20% co-pay, you know, $100,000 a year, that's a chunk of change for a co-pay.

Lauren Berger:

Thank you, Kevin. We'll now turn the podium over to Sylvia.

Slide 63: New Treatments for Myeloma

Sylvia Wood:

Thank you. So it is my honor to be able to talk with you about multiple myeloma and the nurse's role in treating multiple myeloma.

Back in 1847 Dr. Henry Bench Jones identified the classic proteinuria of multiple myeloma, but it wasn't until the development of melphalan and that was in the late 1950s, that there was any therapy to treat the disease. Melphalan and prednisone have been the backbone of therapy for over 40 years and it wasn't until the 1990s with the development of high dose chemotherapy and stem cell transplant that we had anything effective to treat multiple myeloma.

There's been a paradigm shift of treatment approaches with advances in molecular biology and genomics. This has led to the understanding and therapeutic value of thalidomide and the development of newer immune-modulatory drugs such as lenalidomide, and the breakthrough in identifying another target, proteasome inhibitor, with bortezomib, that has dramatically changed how we treat our patients, in combination with these therapies that are highly active targeted agents, we've improved our patients' survival.

In simple terms, success of treatment requires two things. The right treatment, but the right management of the patient on that treatment. And my talk today will be about the critical role nurses play in the management of patients on these newer targeted therapies, specifically two drugs approved by the FDA. One, carfilzomib in 2012. And the second, pomalidomide. Both for relapsed-refractory multiple myeloma.

Slide 64: Development of a Myeloma Cell

On this slide, it is a malignant transformation of a B-cell in its evolution to become a plasma cell. And what you see here are early chromosomal abnormalities that alter this normal cell in a condition called monoclonal gammopathy, which is an asymptomatic, pre-malignant state of a plasma cell disorder. And over time there is increased risk for this cell to evolve into a myeloma cell. Not every patient with what we call monoclonal gammopathy of unspecified significance develops multiple myeloma. There is a risk of approximately .5 to 3% per year, based on level of monoclonal protein and other risk factors.

With the abnormal evolution into a multiple myeloma cell, it's the interaction of these malignant plasma cells and the bone marrow that disregulate the function of normal bone marrow and the microenvironment, establishing abnormal angiogenesis, the myeloma cells actually make a home for themselves and these are the hallmarks of disease progression.

So here you see a stem cell and the development to a lymphoid cell, then becomes committed to become a B-cell, and then a plasma cell. The plasma cell is responsible for making immunoglobulins, which are significant in establishing humoral immunity and antibody production.

What happens in the myeloma cell is this cell now is genetically altered and making an abnormal clone of one particular immunoglobulin that is not efficient and causes a reciprocal suppression of the other immunoglobulins.

The genetic abnormalities of the myeloma cell alter the expression of certain adhesion molecules on the outside of that myeloma cell, as well as responses to growth stimuli in the microenvironment. And it's these interactions between the myeloma cells and bone marrow cells that cause cell adhesion, increasing tumor growth, survival of the myeloma cell, migration and drug resistance.

In addition, growth factors such as interleukin-6 and vascular endothelial growth factors stimulate the plasma cell to create a paracrine loop that helps to sustain itself in the bone marrow.

There also is another important pathway called the pro-oncogenic NF-kappa-B pathway, activated in multiple myeloma. NF kappa-B is a transcription factor. It binds to promoters and enhancers of numerous genes, turning them on to encode for cell proliferation, cell adhesion and angiogenesis. Osteoclast activity is increased and osteoblast activity is suppressed, causing bone destruction. Bone destruction and angiogenesis are the hallmarks of multiple myeloma.

Slide 65: Clinical Manifestations of Multiple Myeloma

So in this slide you see the clinical manifestations that happen, that I was just speaking about. The M-protein is the monoclonal protein and immune globulin and you see the actual molecular formation of that Y shape immune globulin. And in it are the light chains that can deposit in the renal tubules, causing light chain nephropathy and the renal failure that we see with multiple myeloma. In addition, the immune globulin can also be deposited on nerve fibers, causing the neuropathy that we see.

We know that the immune globulin is insufficient in protecting us from infection and its one restricted clone, therefore, our patients are exquisitely sensitive to infection.

In addition, both marrow infiltration from the plasma cell, crowding out our normal stem cells, to allow for normal hematopoiesis, our patients with multiple myeloma now are crowded with plasma cells, causing pancytopenia and anemia. In addition, the destruction caused by the plasma cell to the bone itself causes hypercalcemia, bone pain and the numerous lytic lesions and pathologic fractures that our patients have.

Slide 66: Question #1

So moving on to discuss some of the targeted therapies. Here's our first question. Which statements are true regarding Carfilzomib? Carfilzomib is an irreversible proteasome inhibitor. Carfilzomib exacerbates peripheral neuropathy. Carfilzomib is not indicated for patients who have

previously received either bortezomib or lenalidomide. Or carfilzomib primarily inhibits trypsin and caspase-like proteases.

Okay, so we'll go back to that answer after I present you a little more information. But I think you all did very well to start.

Slide 67: Case Study MG

So here's our case study. This is a story about MG. He's a 61-year-old male who presented to our clinic with IgG kappa and heavy and light chain multiple myeloma. He had a CRAB classification and let me explain that to you. The International Myeloma Foundation group of scientists tried to establish a way to determine how to differentiate patients with active multiple myeloma from those who have MGUS, which is the precursor. And they did that by establishing a criteria for evaluating end-organ damage of multiple myeloma. This is hypercalcemia, renal insufficiency, anemia and bone lesions. So our patient had a normal calcium, his renal function was good, he was somewhat anemic and he had a solitary lytic lesion in the left ischium. So a patient has to have one of those four criteria and plasma cells in the bone marrow of 10% to be classified as having active multiple myeloma.

We also classify this disease based on what's called the International Staging System risk, which is based on their beta-2 microglobulin level and their level of serum albumin. He was a stage 1. However, he had a translocation 4;14, which bears high risk. The high risk translocations in multiple myeloma are 4;14, 14;16, deletion 17p or chromosome 1 abnormalities. Those patients with that chromosomal signature, if you will, have median survival of only 2-3 yrs and are resistant to therapy.

His past medical history was significant for type-2 diabetes, hypertension, peripheral vascular disease, coronary artery disease and he was on these medications, Norvasc, Toprol and aspirin.

So just looking at his history, in terms of his comorbidities, we know that he is going to be at risk for renal insufficiency, related to the fact that he's making light chains. In addition, neuropathy related to his peripheral vascular disease, and the potential therapies that we give.

Also diabetes could be exacerbated because most of the regimens that we give with myeloma have dexamethasone.

Slide 68: Treatment History

He went on to receive four cycles of bortezomib. He had a partial response, based on the International Myeloma Working Group, which helps us to delineate the level of response, based on bone marrow involvement and the level of paraproteins.

He went on to receive thalidomide maintenance. However, he could not tolerate that more than eight months and had to stop that, secondary to peripheral neuropathy.

Eight months after being off thalidomide, his disease progressed and he developed renal insufficiency secondary to light chain nephropathy. He came to us in the clinic with increasing fatigue, chronic peripheral neuropathy that had not gotten better off the thalidomide, and had new bony aches.

He was treated with radiation therapy after he was found to have a lytic lesion in the thoracic spine. And then we started him on PAD chemotherapy, bortezomib, adriamycin and

dexamethasone. He did achieve a significant response. The bortezomib was given IV. And he did have increased peripheral neuropathy after four cycles of treatment.

Slide 69: Case Study MG Treatment History

He went on to his second autotransplant and after this transplant he only had minimal residual disease. One hundred days post-transplant he started lenalidomide maintenance and then after five months we saw his paraproteins starting to rise and knew that we were losing control of his disease. He at that time presented with symptoms of fatigue, worsening anemia, elevated creatinine and our concern was that light chains were being deposited in the kidney, and his bone marrow involvement was 60%.

He presented with a little more pancytopenia and at that time we started him on carfilzomib.

And what you see here is the dosing schedule of carfilzomib.

Slide 70: Carfilzomib

There is a Phase II trial that led to the approval in July and it was of 266 patients, they were all refractory to bortezomib and an IMiD. And most of them were fairly pancytopenic.

As a single agent, carfilzomib was shown to have a response rate of 23% and this is what led to its approval as a single agent for multiple myeloma. The median overall survival was 15 months. So patients, in order to be approved to receive this drug on FDA indication, have to have two prior therapies, bortezomib and an immunomodulatory drug and have to show disease progression within 60 days of completing their therapy.

So what you see here in this slide is actually how proteasome inhibitions work. They degrade proteins and influence a multitude of cellular processes, including cell proliferation and DNA repair. What happens is proteasome inhibition leads to an unfolded protein stress response by accumulation of what are called misfolded proteins in the proteasome. And that causes endoplasmic reticulum stress and the cell dies.

But another important pathway that proteasome inhibition works is by shutting down the NF kappa-B pathway. As you remember from an earlier slide, NF kappa-B promotes cell growth and turns genes on and causes proliferation of the myeloma cell. But in the cell NF kappa-B is held at bay in an inactive state by something called inactive kappa-B.

Now inactive kappa-B is degraded in the proteasome. If we stop degrading the inhibitory factor of NF kappa-B, we've shut down the NF kappa-B, stopping the cell cycling, the cell proliferation and the angiogenesis.

So specifically, carfilzomib, this demonstrates potent and sustained irreversible inhibition of what's called chymotrypsin-like protease. Now what does that mean? In the proteasome, there are subunits. They are almost like little choppers, if you think of the proteasome as a trash recycling bin. Those three proteases are called chymotrypsin-like, trypsin-like and caspase-like. Bortezomib is a reversible proteasome inhibitor with affinity for the caspase and the chymotrypsin-like. Carfilzomib is an irreversible proteasome inhibitor with affinity for the chymotrypsin-like.

So what's happening in this slide? Misfolded proteins that are targeted for, destined for degradation and recycling, if you will, are chaperoned to the little cap and they are bound by a

molecule called ubiquitin, which helps the proteasome recognize that this protein needs to be degraded. The cap opens up, the proteins are now in the proteasome, so that these caspases, like chymotrypsin-like, trypsin-like and caspase-like, can degrade the protein. But in proteasome inhibition with carfilzomib, there's an irreversible inhibition of the chymotrypsin-like ring, preventing degradation, that causes an accumulation of these misfolded proteins, that causes endoplasmic reticulum cell stress and cell cycle arrest.

Slide 71: Carfilzomib

So this slide is helping us to learn the indication for carfilzomib. In the Phase II study that was done, what you see on the left, are the common adverse events. Fatigue was high at 49%, anemia, nausea, and thrombocytopenia occurring most often, that you see in your practice, at day nine. And there was a low incidence of peripheral neuropathy of grade 1 and 2.

On the right side you see the side effects specifically related to the carfilzomib. And the dosing that was recommended based on the Phase II study was 20 milligram per meter squared, to monitor patients for potential infusion reactions, and then escalate the dosing to 27 on cycle 2. Dexamethasone is required on the first cycle at 4 milligrams. However, oftentimes dexamethasone can be used as a treatment dose at higher levels. We have to watch out for our patients in terms that have high tumor burden, as they can develop tumor lysis syndrome and in these patients allopurinol would be indicated but tumor lysis in clinical trials was uncommon. They also require IV hydration pre usually 250 cc NS and 250 cc post prn, at least in the first cycle.

Slide 72: Carfilzomib Case Study MG

So based on our case study, with reference to the complications that he experienced on carfilzomib, in truth he tolerated it very well. However, we had to help him get to the clinic twice a week, three times every month, which was a little burdensome for him because he came from far away.

In addition, we had to support his hyperglycemia related to the dexamethasone dosing, and he did require some insulin.

Renal function actually improved on carfilzomib and when you read a little bit more about this drug, there are current studies going on now to prove that this drug can be safely given to patients with renal insufficiency. And actually when you think about it, the drug itself is reducing the burden of those paraproteins that are getting stuck in the kidney.

Infection. He had a paronychial infection that he did not tell us about and felt that this was not something that he had to worry. It was a tiny little spot on his finger. And unfortunately, he came to us when it became an abscess and then he was on antibiotics and despite the fact that he was on antibiotics, developed a septic arthritis and required three weeks of IV antibiotics, which delayed his treatment.

So the reason I'm sharing this with you is that patients require symptom recognition instruction and intervention.

What you see here are key points for nurse management.

Slide 73: Question #1

And so here's our post-quiz. Which statements are true? I think you all got that right to the start.

Slide 74: Case Study MG Treatment History

He relapsed after seven months of carfilzomib and his renal function improved, however, he did relapse with elevated paraproteins and then we started him on pomalidomide, 4 milligrams daily, day 1 through 21, with dexamethasone 40 milligrams weekly. He developed swelling in his leg and we found out that he had a DVT. However, on this drug he was on aspirin prophylaxis. And even though his platelets were on the low side, we felt it was related to his myeloma tumor burden and immobility from the sciatica.

Slide 75: Question #2

So which statements are true regarding pomalidomide? Pomalidomide is indicated for newly diagnosed patients with multiple myeloma. Pomalidomide's mechanism of action is both immunomodulatory and non-immunomodulatory. And pomalidomide, unlike thalidomide, is not a known teratogen. Risk for DVT with pomalidomide is much higher than with either thalidomide or lenalidomide. Risk for DVT is much less with pomalidomide. That is true in part, but we'll find a little bit more out about that in a minute.

Slide 76: IMiDs

So what you see here is a slide comparing the three IMiDs. And this gives you just a brief overview with reference to side effect profile, but also what you see is potency. Under pomalidomide what you don't see is DVT. DVT is a risk with any IMiD. However, on the pomalidomide studies, patients were already prophylaxed, 100% of them had some form, and that's why the DVT risk was very low.

Slide 77: Pomalidomide

So pomalidomide was released in February, based on this clinical study. And the updated results from ASH of 113 patients that remained on the study had an overall response rate of 34%.

Same indication, both bortezomib and lenalidomide, required prior to and have to have demonstrated disease progression within 60 days. The dosing is 4 milligrams day 1 through 21 q 28 days.

Slide 78: IMiDs

So how does pomalidomide work? It is immunomodulatory and it is improving humoral immunity by improving costimulation of T-cells. It inhibits the regulatory T-cells with suppressor effects on the host immune system and enhances NK and NK T-cell function. And enhancement of NK and NK T-cell proliferation.

So in this slide that is not in your book, it simply shows you a cartoon of T-cell stimulation and suppressor of T regulatory cells, which can inhibit humoral immunity, and augmenting the effect of NK and NK T-cell proliferation.

Slide 79: IMiDs

In addition, there's non-immunomodulatory effects of anti-angiogenic activity, inhibiting cell growth, enhancement of multiple myeloma cell apoptosis, inhibiting osteoclast activity and reduction of myeloma stromal cells.

Inhibiting adhesion, inhibiting cell cycle, enhancing apoptosis, inhibiting cell cycle production through prevention of angiogenesis and cytokines, in addition, inhibiting osteoclasts.

Slide 80: Pomalidomide MG Case Study

So some treatment-related issues with our patient. Initially he had trouble with drug access. He was fatigued. He did have an infection, developing pneumonia at day 21 on cycle 2, and had the DVT that we thought was related to his myeloma. Again, the thromboembolic events on pomalidomide were low, however, patients do require anti-thrombotic prophylaxis.

Slide 81: Question #2

So in our post-quiz, which statements are true? We know that the mechanism of action is both immunomodulatory and non-immunomodulatory.

Slide 82: Key Nursing Considerations

So in summary, as nurses, we need to understand the current state of the patient's general health, what are their disease related symptoms and how to pick this apart from their treatment related symptoms, what's the patient's understanding of their disease and their treatment, and their quality of life.

Slide 83: Nursing Guidelines for Enhances Patient Care

The nursing guidelines for enhanced patient care by the IMF Nurse Leadership Board have identified five side effects from novel therapies related to myeloma with these toxicities: steroid-induced peripheral neuropathy, gastrointestinal side effects, and thromboembolic events and myelosuppression.

Slide 84: Nurses Key Role

So nurses' key role is to understand the pathophysiology of multiple myeloma, to really understand the etiology of the disease, related symptoms, complications. Understand novel therapies, their indications, and what preemptive therapies we can put in place to help our patients tolerate these medications, and recognize individual risk factors.

Slide 85: New Treatments for Myeloma

And in closing, what I would like to say, is that as we walk our patients through this treatment, we need to think about our goal, which is to minimize disease and treatment-related side effects, to achieve the highest level of overall survival and health, to maximize their quality of life.

Thank you.

Lauren Berger:

Thank you so much to Amy, Kevin and Sylvia. And thank you to all of you for spending your time with us today. I hope you'll stay in touch with us at The Leukemia & Lymphoma Society. We want to help you in your important roles and to help support your patients. Thank you for all you do for patients and we wish you a great day.