Empowering Myeloma Patients: Strategies for Managing Side Effects

Operator
Greetings, and welcome to Empowering Myeloma Patients: Strategies for Managing Side Effects, a live telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

Welcoming Remarks

Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you, and special thanks to Dr. Noffar Bar for volunteering her time and sharing her expertise with us today. For this program, we would like to acknowledge and thank our supporter, Genentech, a member of the Roche Group.

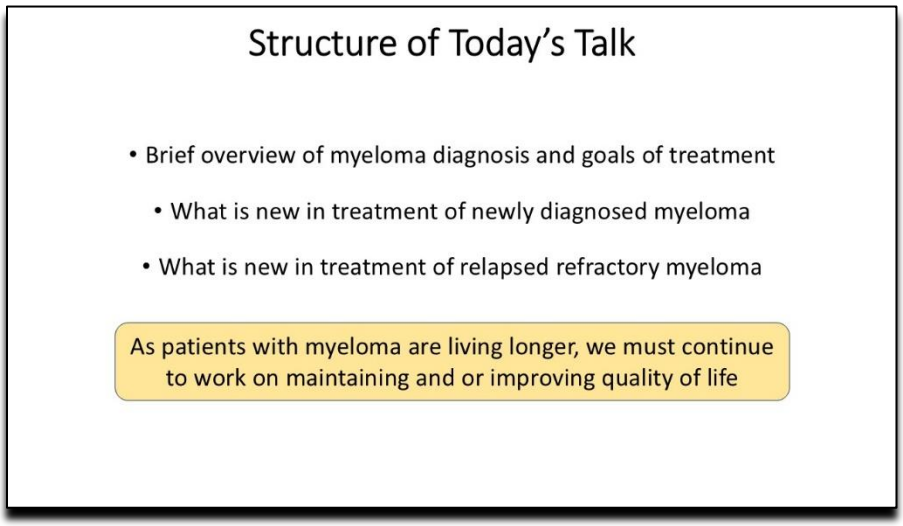
This progress in managing myeloma is expected to continue because of the concerted scientific research effort underway and because of patients' participation in clinical trials with the goal of finding a cure, and, as we will be discussing today, in managing side effects to improve patients' quality of life.

New treatment approaches for myeloma are being studied in clinical trials for patients of all ages and at all stages of the disease. As the leading source of free blood cancer information, education and support for

patients, survivors, families, and healthcare professionals, LLS helps patients navigate cancer treatment and ensures access to quality, affordable, and coordinated care. While research will help us achieve an end to cancer, today LLS assists patients before, during, and after their diagnosis and treatment. Thank you for participating in our program today and allowing us to be here for you.

Disclosures

I am now pleased to introduce our speaker, Dr. Noffar Bar, Assistant Professor of Medicine and Hematology at Yale School of Medicine in New Haven, Connecticut. Dr. Bar, I am now privileged to turn the program over to you.



Structure of Today's Talk

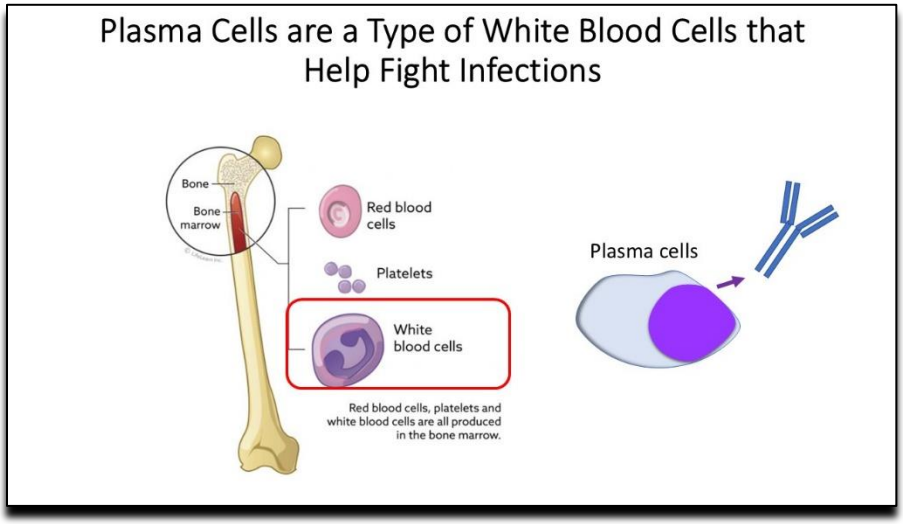
Dr. Noffar Bar
Hi, everyone, and thanks for joining. As Lizette mentioned, I am Noffar Bar. I'm one of the myeloma doctors at Yale. And I treat patients throughout their journey, throughout their myeloma journey at newly diagnosis [diagnosed], when patients progress, when we have discussions about treatment options, when we talk about transplant versus no transplant, and CAR T-cell therapy.

I am particularly interested in this concept called shared decision-making, which is when the provider or the doctor talks to the patients about options, educates the patient about benefits, side effects, and we make a decision together, so it's not one person telling the other what to do but really talking about the decision together. And this is particularly more complex and more involved when we have many different options. And the purpose of this talk is really to empower you to know more about the different options, some of the newer agents we have for relapse disease, to help make these decisions when that time comes.

So, I will talk a lot about common treatments that we use. I will now talk about all myeloma therapies. We might have some time after the talk to talk about some other drugs that I did not specifically mention in this slide deck.

So first we're going to talk about a brief overview of myeloma, the diagnosis, what are the goals of therapy. Next, we'll focus on newly diagnosed myeloma, some of the newer therapies that we use now.

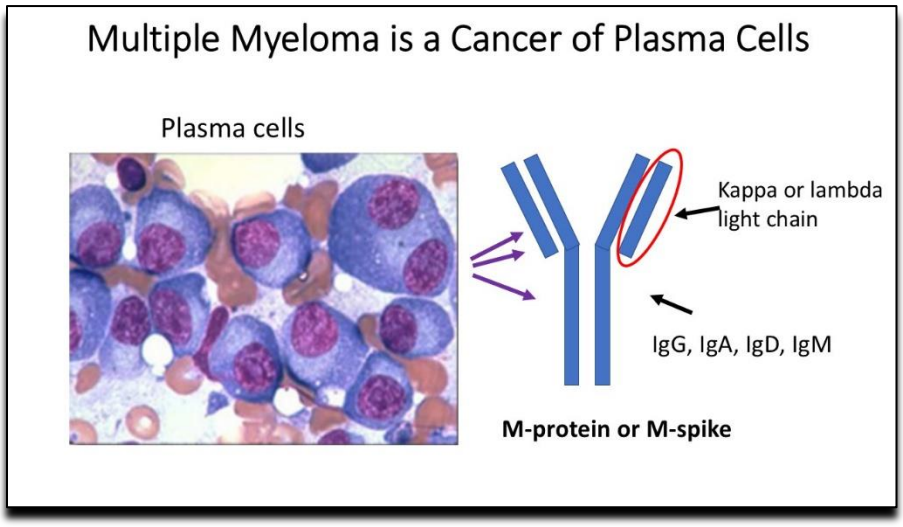
Then we'll talk about the relapsed/refractory myeloma setting, some of the, again, newer agents we use there. And the common theme I hope to show you is that our treatments are getting better, patients are living longer, and in this situation, we really need to continue to work to mitigate side effects, maintaining quality of life. And this is why this talk is so important.



Plasma Cells are a Type of White Blood Cells that Help Fight Infections

So, what is myeloma? Myeloma is a cancer of plasma cells. So, let's talk about what plasma cells are. They are part of our immune system. They are a part of our white blood cells. And they live within the bone marrow.

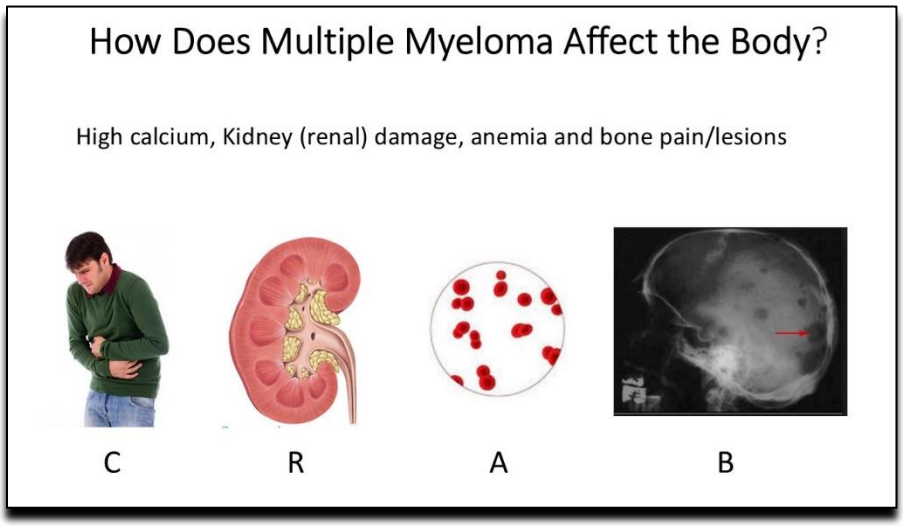
And these are what plasma cells kind of look like at as a cartoon. Now plasma cells, what they are in charge of is making antibodies. They make antibodies to help us fight infections. But when this happens, under normal circumstances the plasma cells are different from one another, and they make different antibodies. So, I kind of think about it, they make cousins. They are similar but different.



Multiple Myeloma is a Cancer of Plasma Cells

But when the myeloma develops, when plasma cells gain ability to multiply and become clonal, when they develop into myeloma, basically the same antibody, and this is a picture of the antibody. We call this the monoclonal protein, the M-spike, M protein, different names for the same thing. This is the protein that the myeloma is producing. And most commonly, this is an IgG then an IgA, very rarely IgD and IgM.

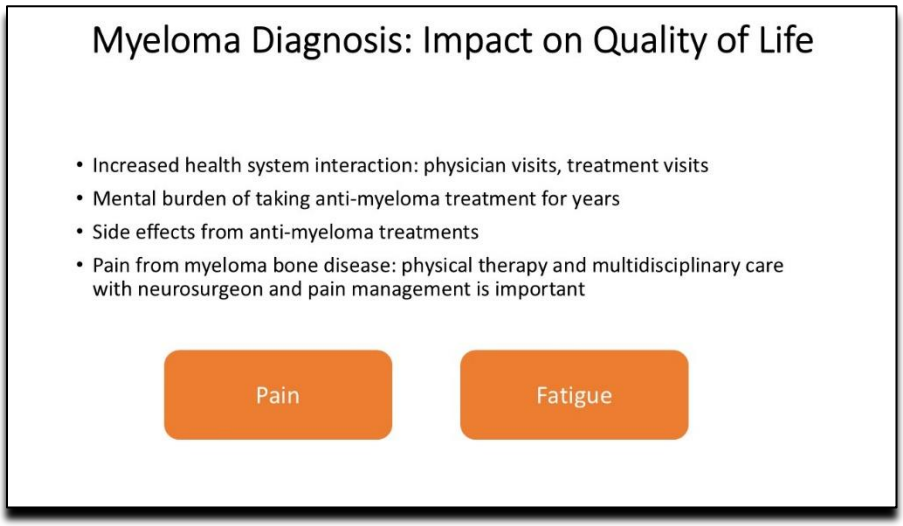
And when we specify the monoclonal protein, we're talking about the full protein which I show you here and a part of the protein, which is the light chains, just a part of the full protein. And you either have a kappa or a lambda. So, this is how we kind of identify that particular clone for that myeloma.



How Does Multiple Myeloma Affect the Body?

Now just having abnormal plasma cells in the bone marrow does not necessarily mean you have myeloma. There are certain criteria. And some of that is the damage it does to the body. So how can myeloma affect the body? Now it's not always the same in every patient, but what can happen is it can cause a high calcium level and what we call C. We're going to spell out CRAB here. The other one is renal or kidney damage. It can injure the kidneys. The third is anemia, for A. And last, it can cause bony lesions or pain, like holes in the

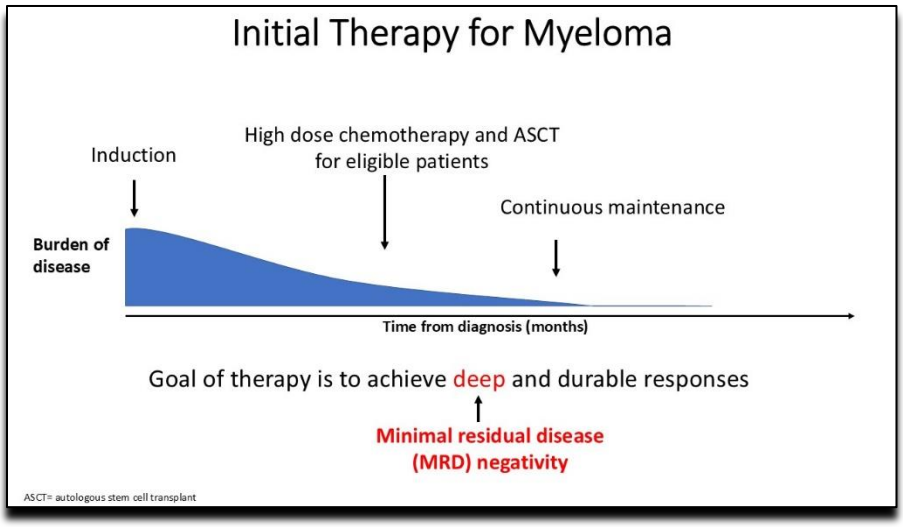
bones. It can also cause kind of a solid tumor version of the myeloma within the bones and outside the bones. So, this is the classic, what we call CRAB criteria.



Myeloma Diagnosis: Impact on Quality of Life

So, when someone gets myeloma, and you guys know this more than I do, how does it affect your quality of life? So just having a diagnosis of cancer and having a lot of increased kind of interaction with the health system is a big life change. You're seeing the doctors, the physicians' assistants, the clinical team frequently. You're getting treatments. Kind of the burden of taking anti-myeloma therapy for years because in myeloma therapy, we don't really stop therapy, for the most part.

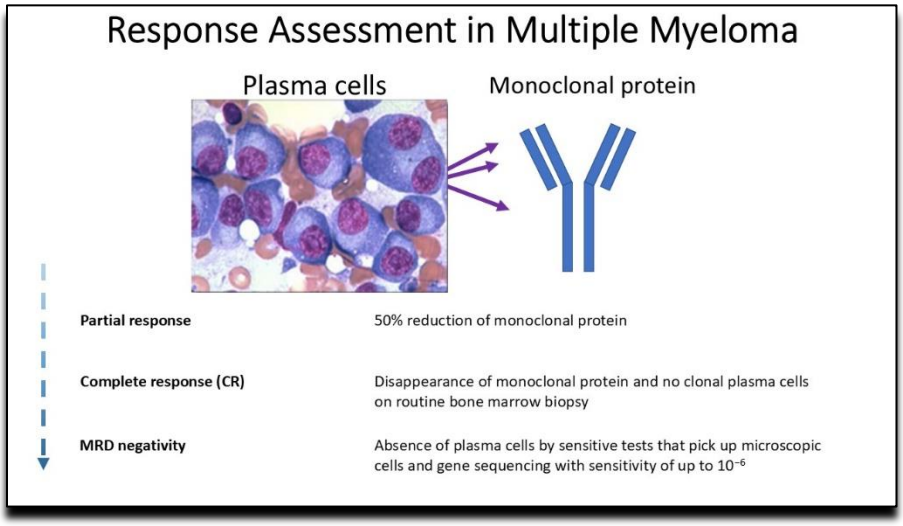
And, of course, the side effects from the anti-myeloma therapy, which is what we're going to focus on today, and then the symptoms from the myeloma itself, like pain, like fatigue, things like that. And this is very individualized depending on kind of where the pain is, what's causing it, what's going on with the bones. But it's very important to have a multidisciplinary approach with pain management and perhaps even, in some situations, neurosurgery.



Initial Therapy for Myeloma

So, what is the goal of therapy for myeloma? Myeloma is not curable, but it's very treatable. I'm sure many people have mentioned that. So, this is what I call the initial therapy for myeloma. And it's kind of a strategy because there's different aspects of this. So here I show you kind of a graph of the disease burden, how much myeloma someone has. A diagnosis, clearly there's a lot of disease burden. And then we use what we call induction to bring down the disease burden, meaning kill more myeloma cells.

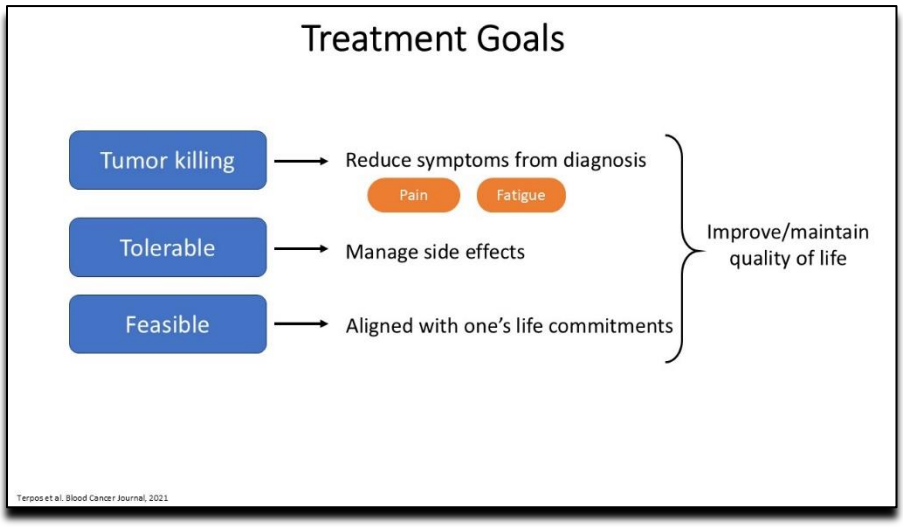
And at some point, there is a discussion about whether transplant is appropriate or not appropriate for that person. And then patients go on to continuous maintenance, regardless if you had a transplant or not. So, these three aspects make up kind of the first line of therapy, although it's a lot of different steps here. And our goal is to achieve deep responses. Deep responses correlate with longer duration of response. And when I mean deep, I mean really deep, that we don't see the myeloma cells anymore. And we call this minimal residual disease negativity. And we'll talk a little bit more about that.



Response Assessment in Multiple Myeloma

So, when we assess response from myeloma, there's different ways we're measuring the myeloma. I showed you the monoclonal protein in the blood. So that's the first step, is we want to make sure that goes down. And if we see a 50% reduction that's called a partial response. If we see disappearance of this protein in the blood and the urine, and then we look at the bone marrow with our eyes, and we don't see the myeloma cells, that is a complete response.

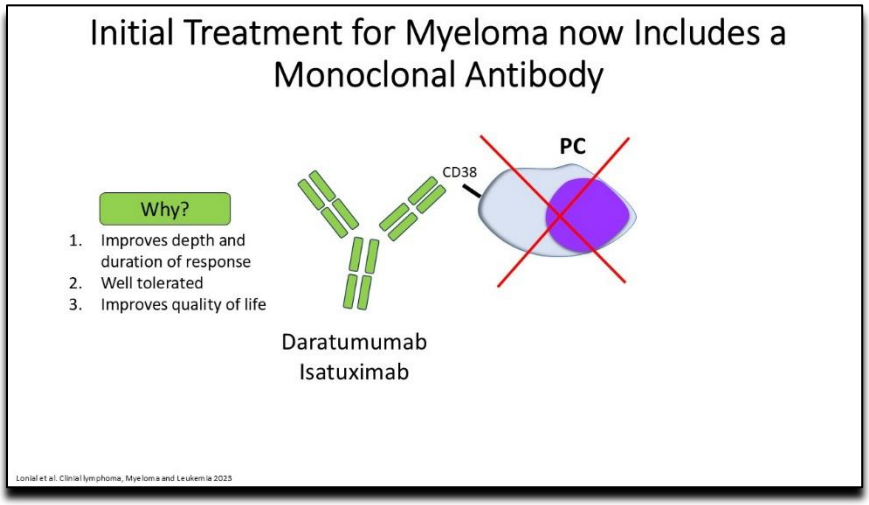
But then, even deeper, when I meant these deep responses, what I'm talking about is when you look at the DNA of the myeloma, and you actually have to identify when someone has more myeloma, so at diagnosis, and then you check the next bone marrow, and you look for that DNA sequence, and you don't see it in a million cells, that's really the deepest response that we strive to achieve, so this minimal residual disease negativity using really sensitive tests.



Treatment Goals

So, some other goals of treatments, of course, we just spoke about tumor killing. And actually, the better we do in terms of killing the tumor, killing the myeloma cells, we actually can improve the symptoms that you come with, so like the pain, some of the fatigue. So that's important. But we also need those treatments to be tolerable, so we need to manage side effects, and feasible. There are different types of treatments and different time points, like when I mentioned the trans [transplant] members, there's no transplant [members].

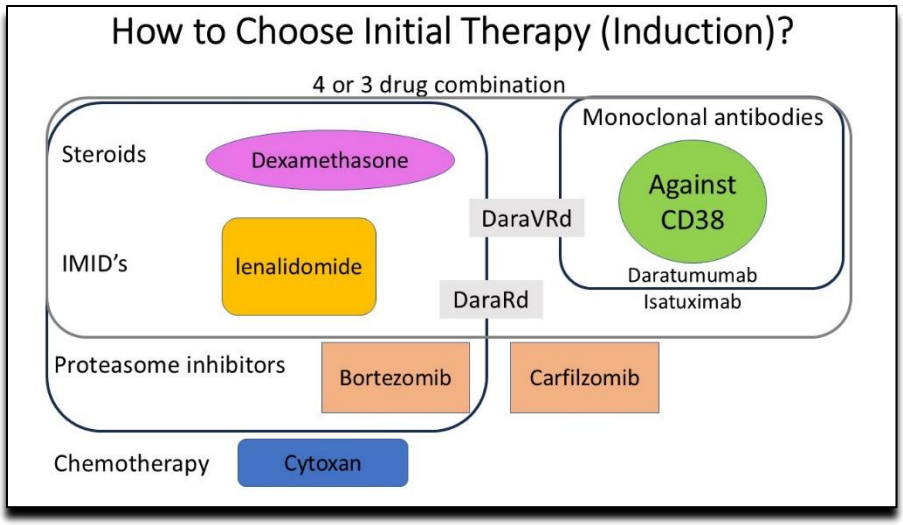
Are the treatment strategies aligned with one's life commitments? What is going on in your life at this time? Are you a caregiver for someone else? Can you not take time off for a transplant? There are all these different considerations to think about. So, all these things go together. And overall, what are we trying to do? Improve and maintain your quality of life while allowing you to live longer and longer,



Initial Treatment for Myeloma Now Includes a Monoclonal Antibody

So, let's talk about kind of what is a little bit newer, and it's not new this year. It's kind of been new in the last few years, is that now we are using a monoclonal antibody that targets this protein called CD38 on the myeloma cell's surface, as I show you here. You might think, oh, that looks like a monoclonal protein, that the myeloma secretes. Because it is. So, it is a monoclonal protein, but it's developed to actually be a drug and kill the myeloma cell.

And here we go, kills the myeloma. There are two drugs out there. One is daratumumab (Darzalex®), and the other one is isatuximab (Sarclisa®). They are slightly different in how they get administered. And most of the time, we are using daratumumab. These days I'm going to focus more on that. So why are we incorporating this monoclonal antibody in our front-line therapy? Because it aligns with our goals. So, it improves depth and duration of response when added to our older therapies. It is well-tolerated, and it improves quality of life, actually, in the studies. They looked at that aspect.



How to Choose Initial Therapy (Induction)?

So how do you choose induction? So, we use several drugs in combination. And I show you here the types, or what we call the classes, of drugs that are effective for myeloma that we can use in induction. And I do want to highlight, I talk very broadly in general, but every patient and every myeloma is very unique. And all these things can be used, but you might not have gotten one for a particular reason. So, this is just more for generalized discussions.

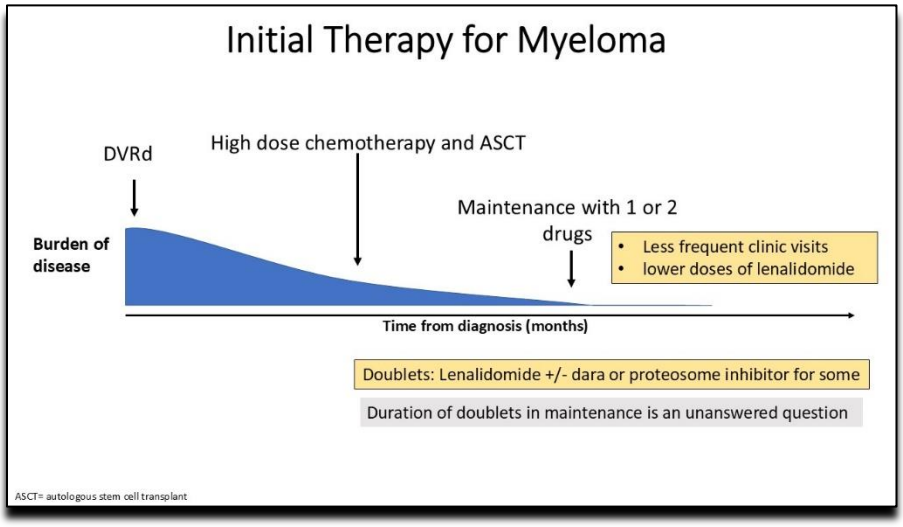
So, steroids. Steroids are used in a lot of our myeloma therapies, commonly dexamethasone (Decadron®). The next class is immunomodulatory drugs, also known as IMiDs, and we use lenalidomide or Revlimid® upfront. And proteosome inhibitors. We have bortezomib (Velcade®) or carfilzomib (Kyprolis®) and traditional chemotherapy, specifically Cytoxan® (cyclophosphamide) that we can use upfront. And then we already spoke about the monoclonal antibodies here, which, again, a few years ago was not part of upfront therapy. And we typically like to use four or three. And that might change. A few years ago, I would say three or two. Maybe in the future, I will just say everyone should get four. But right now, it's four or three. And that really depends on who the patent is, what are the other medical problems they have, or issues, or kind of functional status. How are they doing on the day-to-day?

So, this is the commonly used combinations right now for what we call transplant-eligible patients. That's a term that we kind of want to move away from because that's a whole other topic. So, we're building up on our backbone, which used to be VRd for many, many years, we used bortezomib, lenalidomide (Revlimid®), and dexamethasone, three drugs and induction for most patients.

And now we're adding the daratumumab to it to make dara-VRd. So, this is very common. Very recently, this year, there were two published papers, studies actually looking at this for what I'm going to "transplant-ineligible patients," those patients we don't think might tolerate a transplant. And they tolerated these four drugs well. So, I think a lot of patients can tolerate these four drug combinations. But maybe for certain situations, you do want to take away one of those drugs in what we call the dara RD, or DRD. So really you

are eliminating the proteosome inhibitor here. And this three-drug combination is excellent in this "transplant ineligible" patients and very well.

So just a few comments about the other drugs I put here. Cytoxan® we don't use commonly. However, sometimes when patients have kidney disease at presentation, we cannot use the lenalidomide, so we can substitute the Cytoxan®. And in some situations with very high-risk myeloma, some of us prefer the carfilzomib as opposed to bortezomib.

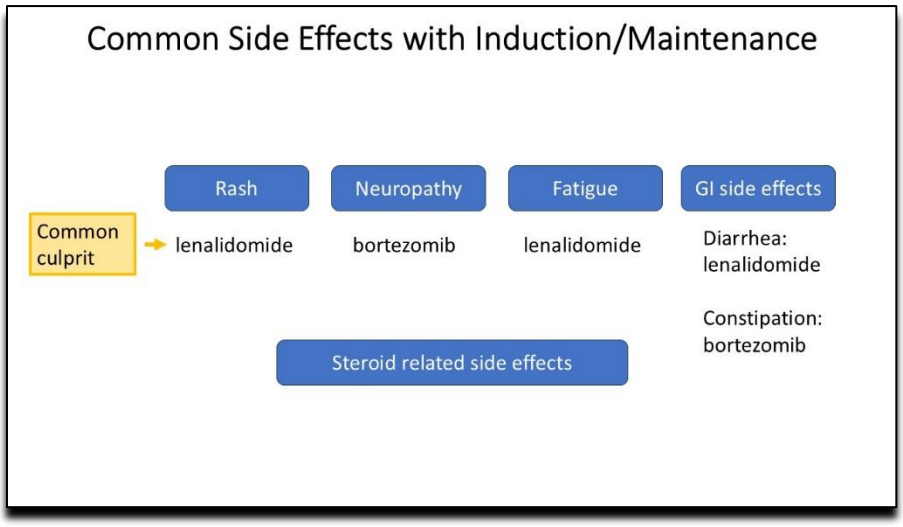


Initial Therapy for Myeloma

So, let's get back to that schema of the initial therapy for myeloma. So, let's say, I'm kind of talking a little bit more in detail here, someone gets diagnosed, they get the four drugs, dara VRd, they get a nice reduction in their myeloma parameters. We're killing a lot of myeloma cells. Yes, no transplant. And then we moved to maintenance. So, a lot that goes on in those first few months of treatments.

You're here in the clinic once a week usually, getting several drugs. If you got the transplant, that's a toxic therapy, you're recovering. A lot is going on. And then you get to maintenance. And maintenance, you take a breather. You catch a breath. And this is supposed to be maintaining, as it's saying, maintaining the response. The visits are less frequent. You're kind of coming back to your normal life, as normal as can be. You're usually in the clinic once a month. And that might vary. The doses of lenalidomide, which is what we use for maintenance, are lower. So hopefully, the tolerance is better.

Nowadays we are sometimes using doublets, meaning two drugs. So, maintenance is one or two drugs. With daratumumab or proteosome inhibitors, for some, and this is very individualized, and the duration of using two drugs versus one is still an unanswered question. So myeloma has evolved and is continuing to evolve. So, there are some unanswered questions. And this leaves a lot of interesting decision-making to be had by doctors and patients. And this is what I like. So, this is where we are.

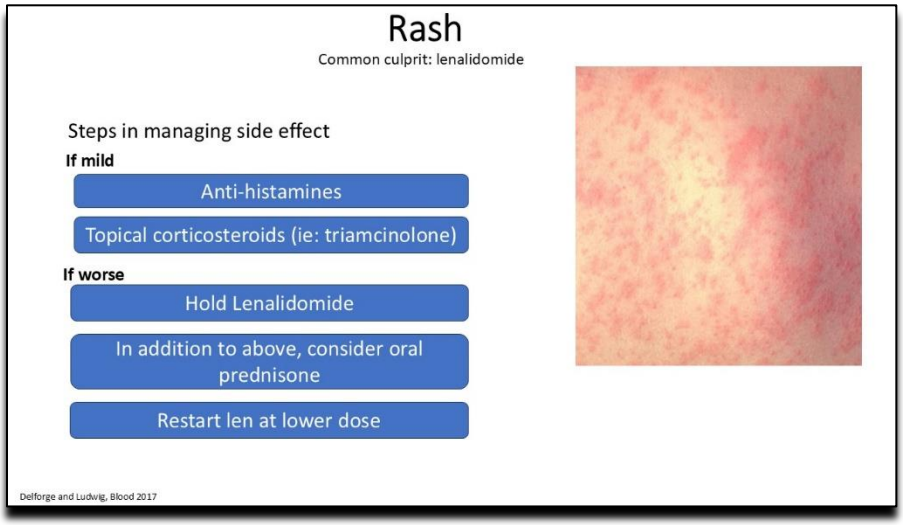


Common Side Effects with Induction/Maintenance

So now let's get to the heart of the talk, which is really focusing on the side effects. So, some of the major side effects patients experience, especially in that first induction part and even in the maintenance, is a rash. But before we get to that, I want to categorize side effects into kind of different thoughts. So there are side effects that, when they occur, we can easily hold the drug or decrease the dose, and the side effect goes away.

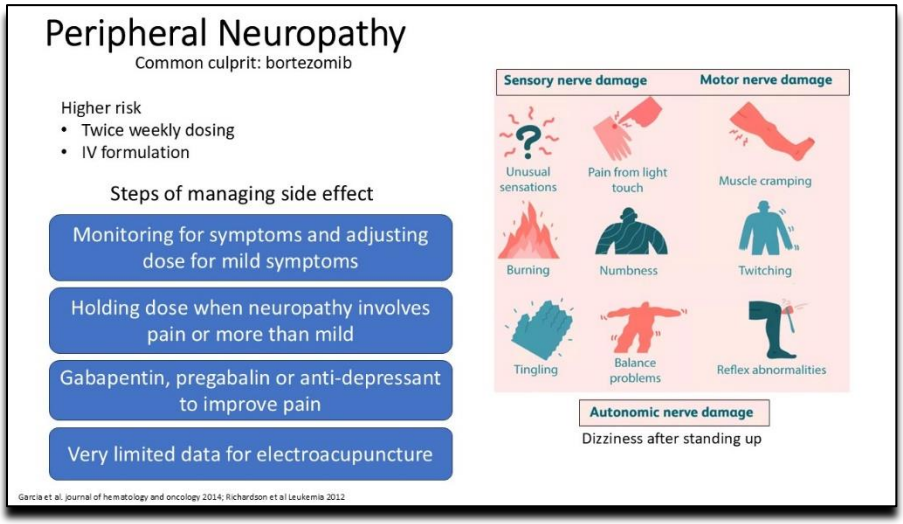
There are some side effects what we call cumulative. It gets worse and worse as you are continuing on the therapy. And when you stop the therapy, it might not completely reverse. So, there are kind of different ways of thinking about management of these type of side effects. And I'll specify that more as I go along each individual drug here.

So, rash. The rash is typically from the lenalidomide or Revlimid®. It typically happens early on when you start the drug? Next is neuropathy. And that's usually from bortezomib. Fatigue is very common, usually from lenalidomide. GI side effects are also common. You can have diarrhea more from lenalidomide and constipation more from bortezomib. But they can vary. And the steroid-related side effects. And I'm going into details of all of these in the next few slides.



Rash

So, with the rash. Management really depends on the degree of the side effect. So, if someone has a mild rash mainly on the forearms, it a little bit bothersome, you could probably continue the drug and treat with steroids topically, that means a steroid cream triamcinolone (various brands) or some antihistamines and get away with it and continue the drug. But if it gets worse, you might need to hold the drug, we do usually do that. So, if it's affecting more of the body, it's really becoming very bothersome, itching or burning. We definitely hold the lenalidomide, and we continue with the topical steroids and antihistamine. But sometimes, we even need to give oral steroids like prednisone (various brands) by mouth. And as, when the rash gets better, and it can take several days, then we can restart the lenalidomide at a lower dose. So, you can re-challenge after a rash. It doesn't mean you can never have the drug, but we do have to dose reduce.



Peripheral Neuropathy

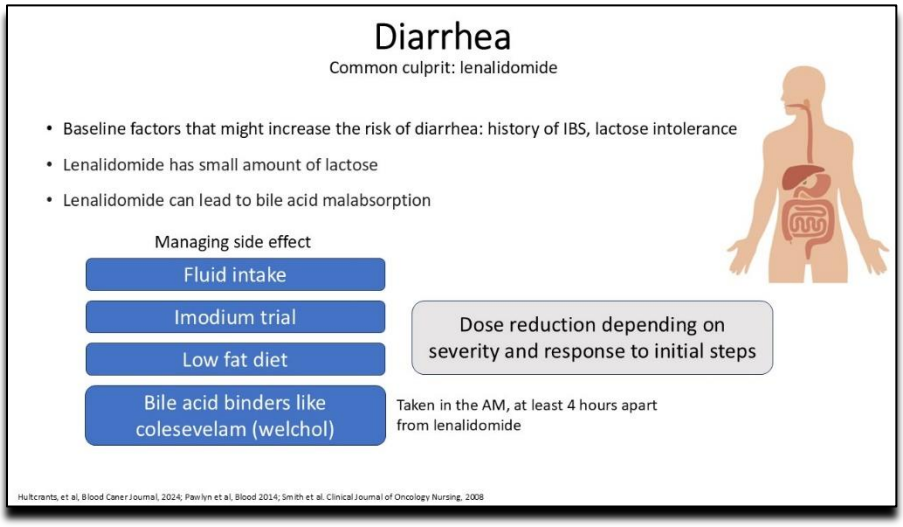
The next topic is the peripheral neuropathy, which might or might not happen. And there are different types of neuropathy, peripheral neuropathy. There's sensory, which is usually involving your sensation, where people can have an unusual feeling, burning, numbness, tingling. It can affect your balance as a result. Or you can have a motor nerve damage. Sometimes people get muscle cramping as a result.

And then something we don't see very often but can, is autonomic nerve damage, which is, typically one of the symptoms is that your body is unable to regulate your blood pressure and heart rate when it moves from laying down, their sitting position to standing up, where you have to kind of regulate this as the blood shifts. So, people get dizzy on standing up, and even sometimes falling. You can have some twitching.

So, there are some risks to develop this. So, some of the situations where there are a higher risk of developing this, one is getting Velcade® (bortezomib) twice, or bortezomib twice a week. So, this is, actually in many clinical trials, they do do twice a week because of regulatory reasons because how it was originally studied. However, we try not to do that if we can. The only situation that you use twice weekly is if someone has a lot of disease burden that's affecting the kidneys, and we want to get those light chains down as fast as possible. We might do that for the first cycle. But after that, always once a week. So that's very important.

And also, the IV formulation, which we don't use anymore, but we used to use in the past, led to more neuropathy. And this is one of the side effects that is cumulative, meaning the more you give, the worse it gets. So, the most important thing is prevention in this situation because if the damage gets more severe, then the chance of it reversing completely are lower. So, you really want to try to catch it early and adjust the dosing, decrease the dosing. If it's very mild, if it's more severe, hold the treatment, wait for some improvement, and then restart at a lower dose. So, this is very important.

Once neuropathy occurs, it takes time to get better. And again, you don't want to add more insult to injury. So again, nerves take a while to regenerate, and you might have pain. And that's when we focus on pain management like gabapentin (Neurontin®), pain management that really targets neuropathic pain like pregabalin (Lyrica®) and gabapentin, sometimes certain antidepressants can help. There is not a lot of data and not really in myeloma but in other cancers of using electroacupuncture to kind of restimulate nerves, definitely is not going to hurt. So, if that's something that's available, it's something to try. But sometimes it's just time and controlling the pain.

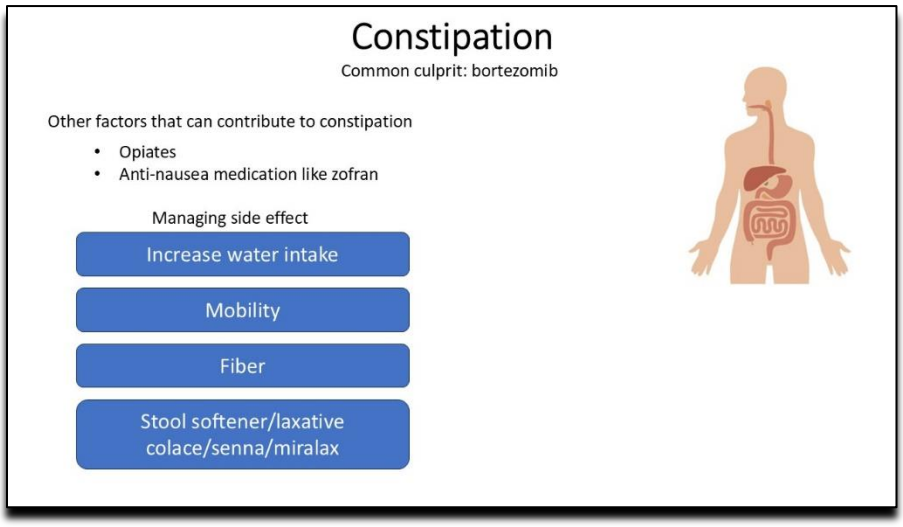


Diarrhea

Next is diarrhea, which is commonly caused by lenalidomide. There are some baseline factors that might increase the risk of diarrhea but not always. So, if you had a history of IBS, or irritable bowel syndrome, lactose intolerance because there is a small amount of lactose in lenalidomide. And over time, lenalidomide can actually lead to bile acid malabsorption. And there isn't a very good test to test for that but something to know and could be treated.

So, again, management depends on the degree of side effects. So, if it's very mild, you have one bowel movement that's a liquid a day. That's, one to two is mild, can be managed by increasing fluid intake, trying Imodium® (loperamide), can take one Imodium and see if it resolves. And if you need Imodium, once every week or two weeks, and that's manageable for you, then that's okay to continue. However, again, if it's more severe, really bothersome, we have to hold the drug and reduce to a lower dose.

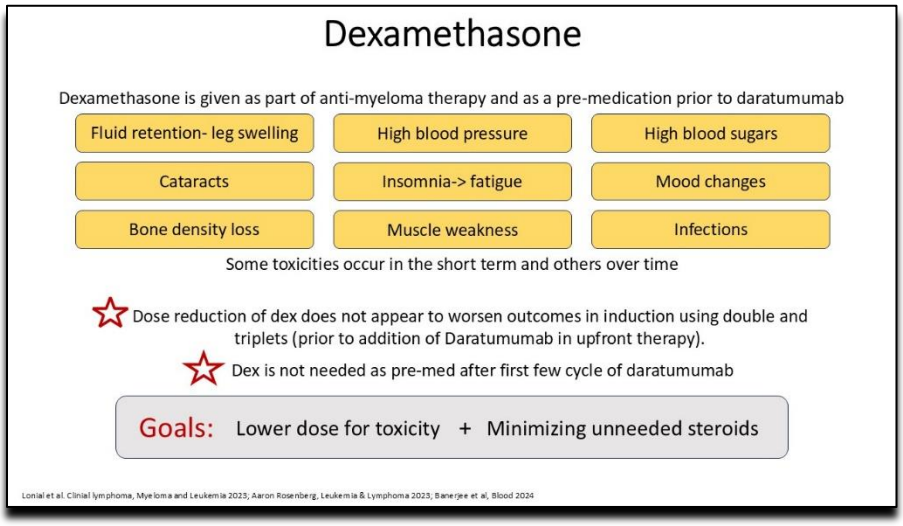
If you tried Imodium, and you tried maybe a low-fat diet, it's not working, one thing to consider is using bile acid binders, like Welchol® (colesevelam). And sometimes it works really wonderfully. So, it's something to try if everything else doesn't work, and you've tried lowering the dose, and you can try this. And typically, you take it in the morning, and you want to take it about four hours, at least four hours apart from lenalidomide, so you can take the lenalidomide in the evening.



Constipation

Next is constipation. And that's usually from bortezomib. Now there are other reasons why someone can have constipation, so it might not be fully the drug, or it might be a combination of things. And sometimes it's not always easy to tease it out. But some other drugs that can cause constipation are opiates, narcotics, like oxycodone (Oxycontin®) and so forth. And when you have bony pain, you might be on this medication and might develop constipation. And bortezomib is perhaps not going to help that.

Also, anti-nausea medications. Not everyone knows Zofran® (ondansetron) can cause constipation as well, so these are things to consider. We don't always want to blame the bortezomib, but it can certainly cause constipation. The first thing you do, is you always want to increase hydration, because that actually helps constipation. Mobility helps constipation, increasing fiber helps. Stool softener, laxative, or MiraLAX® (polyethylene glycol 3350) can then be added on, as needed. We usually don't stop bortezomib or reduce the dose for constipation. But this is one of the symptoms that we manage along while continuing the drug.



Dexamethasone

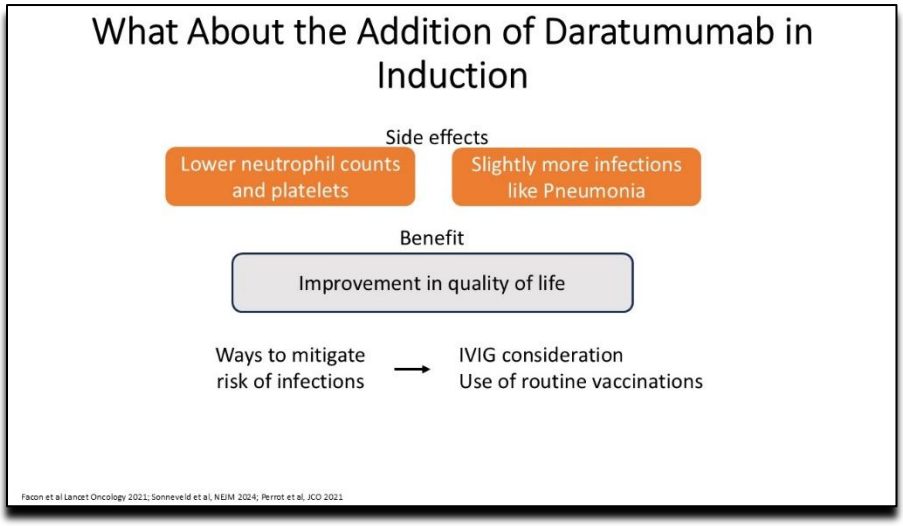
And lastly, well, not entirely last but almost lastly, want to talk about dexamethasone (Decadron®). So, dexamethasone is a drug either people love or people hate. Because there's a variety of side effects. You might not get any. You might get the benefit of having a lot of energy, or you might have the benefit or not

have the benefit and have too much energy and anxiety, insomnia, and then this actually leads to fatigue the next day. So, it can go either way. But it can affect the cardiovascular system, so it can increase high blood pressure, it can increase fluid retention, so people can have leg swelling. It can cause high sugars, especially important if you have diabetes to keep close eyes on the sugars.

And these are things that happen more in the short term. There are some things that we see more long term like cataracts. So, you're not going to develop cataracts over a month or two but over many months, this can happen. Bone density loss, muscle weakness, infections. These are all kind of long-term side effects. So, it's important to recognize that.

There are some key points here I want to highlight because we all don't want to keep dexamethasone on for too long. People have looked at what happens when patients have to have dose reductions. Does it affect how they did? Does it affect how the myeloma is controlled? And they looked at that. They looked at that in older studies that used two or three drugs in induction, and they did very well. So, it didn't really affect their outcome, so it's important to recognize that if you have to have some dose reductions in dexamethasone, it should be fine.

And also, we use the dexamethasone not only as a way to kill the myeloma, we use it as a premedication for daratumumab (Darzalex®). And we actually don't need this long term. So, premedication for daratumumab is really only needed in the first month. So, if someone is on, daratumumab for months and months and months, and they're still getting the premedication, so that's a situation where I would question the provider, do you still really need this dexamethasone? Or perhaps decrease the dose from 20 to 4. You can reduce a dose and eventually taper off. It's not needed for the premedication. So really the goals with dexamethasone: we use it upfront; we use it to help fight the cancer; to get the, to get the four-drug regimen or the three-drug regimen. But we quickly kind of peel back. We want to lower doses for toxicity and minimize unwanted steroids or unneeded steroids.



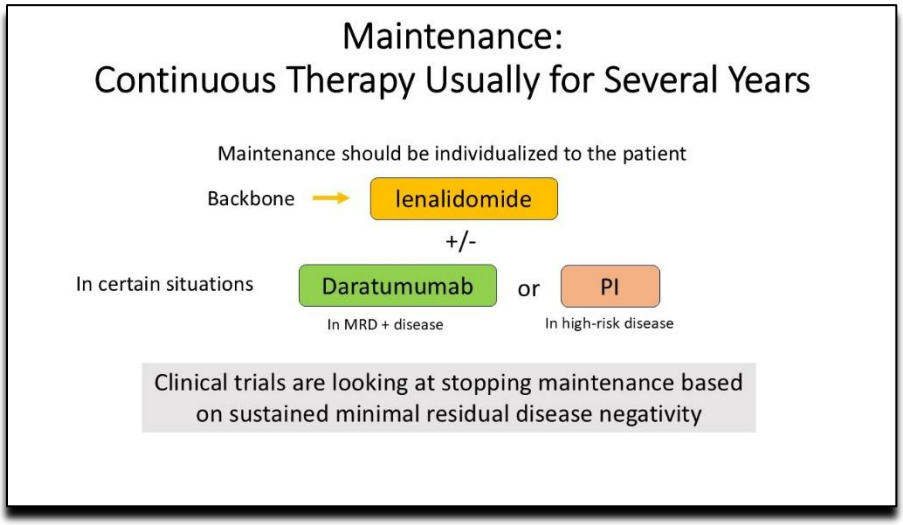
What About the Addition of Daratumumab in Induction

And what about the addition of daratumumab? I already told you it was very well tolerated, but there are some extra side effects that were seen when we added daratumumab to our backbone of the Velcade®, Revlimid®, and dex, or Revlimid® and dexamethasone. So mainly lowered blood counts, neutrophils, which are a type of white blood cells that help fight infections, were lower, and platelets, which help prevent bleeding, were lower as well.

And this result, and these are just numbers, right? But this did result in more infections like pneumonia. So, while this was going on, actually it didn't affect the quality of life, even though there were more infections seen, not a lot of infections but still more. Overall, the quality of life was better when patients got daratumumab, even with this. And we know there are ways we can try to mitigate risks for infection.

So, first is using routine vaccinations. And we do ideally want to vaccinate, to be up to date with vaccinations before we start therapy, if we can. It's not always doable, but we try to. And next, if someone has really low immunoglobulins, because our plasma cells as I showed you, normally make immunoglobulin antibodies that help fight infections.

If we do a really good job killing those cells, we are killing the good ones and the bad ones, we don't make enough antibodies. And that's important, especially for bacterial infections. So, if you have low antibodies, and you have infections, then giving back IVIG [intravenous immunoglobulin], that's basically pooled of healthy donor antibodies once a month is beneficial to prevent severe infection if this is what is going on.



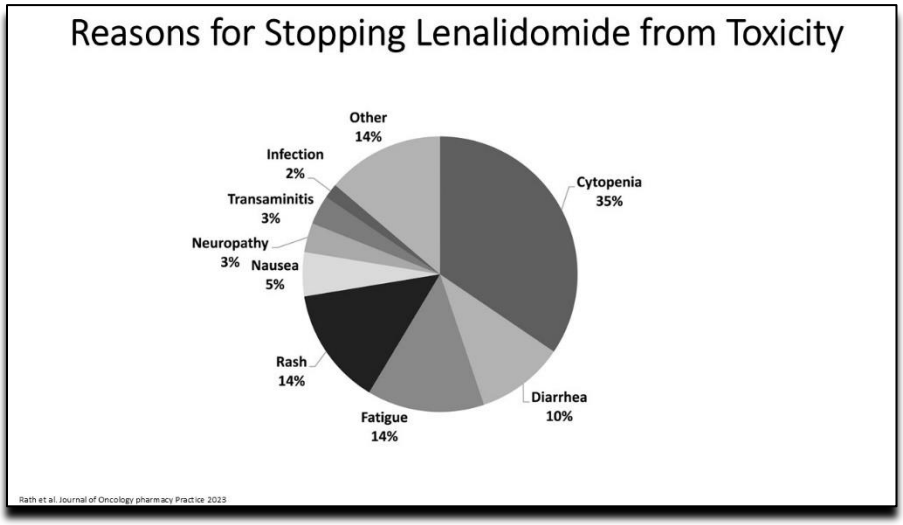
Maintenance: Continuous Therapy Usually for Several Years

Now let's focus a little bit on the maintenance. So, we kind of talked about the induction is more involved, more drugs. We didn't talk about transplant. We're not going to really talk about that today specifically. And now we're in the, taking a breath and moving onto maintenance. So, maintenance is continuous therapy, and usually for years? The average these days of how long maintenance lasts or how long patients stay in remission before they relapse is about five to six years. Again, this is an average. Some are longer, some are shorter. And we've used lenalidomide as a single agent, so just lenalidomide for many, many years. And we still use it. Now again they said things are evolving. Sometimes we use two drugs in maintenance. And this is very individual. So, maintenance really should be individualized to the patient.

So, in some situations we use daratumumab or proteasome inhibitor, more in high-risk patients. But again, there's a lot of unanswered questions and how long to keep patients on two drugs versus one. And even more interesting and important, can we stop maintenance at some point? And this is a very hot topic because again, our treatments are getting better. If we kill more myeloma cells, do we need as long maintenance? We don't know that.

These are questions that are very important and are being discussed. If someone has achieved a deep, deep remission, a deep, deep response, I mentioned this MRD negativity. And when we check it again what we

call sustained emerging MRD negativity, like a year later. That's excellent. These patients typically do better. And do we need a long maintenance? And this is important because there are reasons patients, even though they were supposed to be on maintenance, some patients can't tolerate the side effects from lenalidomide. Not every patient has the same side effects.

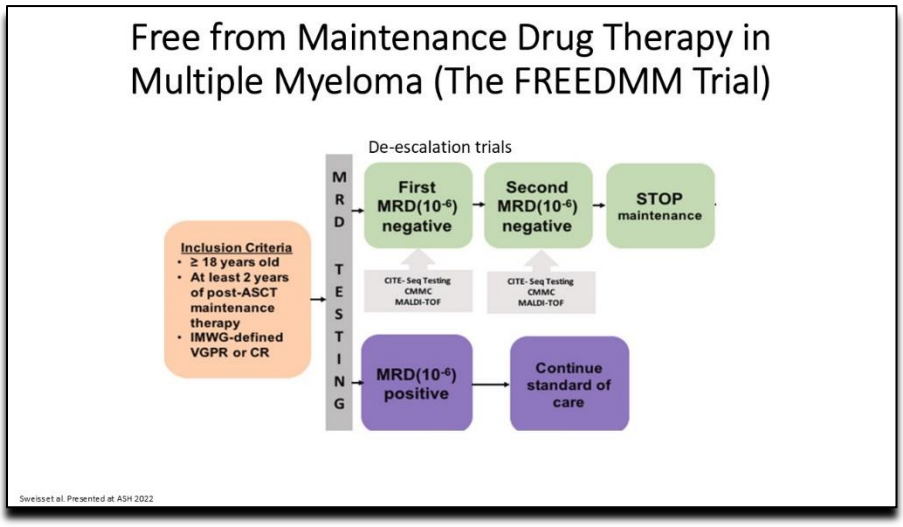


Reasons for Stopping Lenalidomide from Toxicity

So, this is a graph showing you, a pie graph, of the reasons why lenalidomide was stopped due to toxicity.

And you can see here on top, the cytopenia, that's a measurement we are monitoring. So those are low blood counts. You might not feel them, but we monitor that because it puts you at risk. Let's say the platelets to help prevent bleeding are very low, well, we don't want you to bleed, so we would hold or stop. Or the white blood cells are very low. Well, that puts you at a higher risk for infections. So, you might not feel those, but they might be a reason why your doctor wants you to stop the therapy.

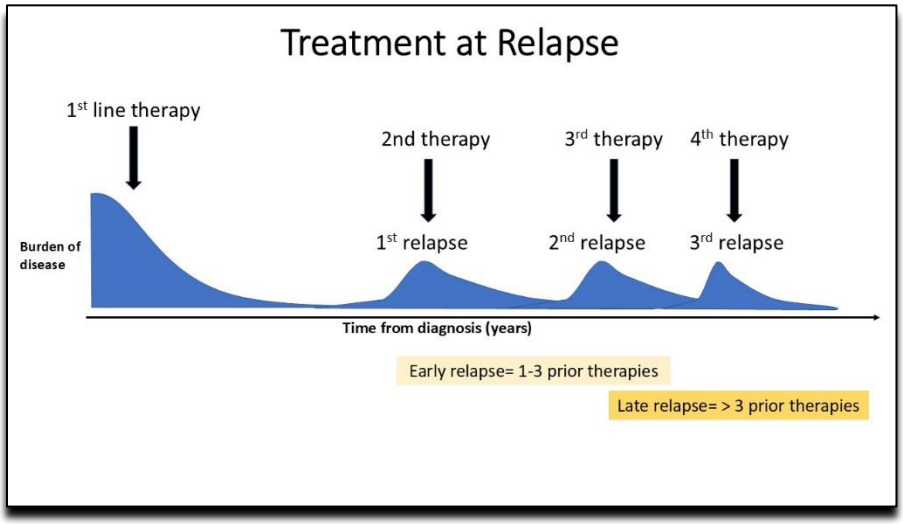
And then what you might feel you might tell us what's going on, and we say, this is not good, it's not a good drug for you. If this diarrhea is unmanageable, too much fatigue, rash, all these things that can affect your quality of life that is just not something that you can sustain for a long period of time, then we stop. So, this is why it is important to know, can we safely stop lenalidomide early?



Free from Maintenance Drug Therapy in Multiple Myeloma (The FREEDMM Trial)

And I love this study. This is the clinical trial, and it's ongoing. We do not have an answer, so I want to highlight. These are questions being asked but pointing out how we are changing our thinking about myeloma therapy because their treatments are getting better and because people are living longer. I know I've repeated that a few times because it's a good message.

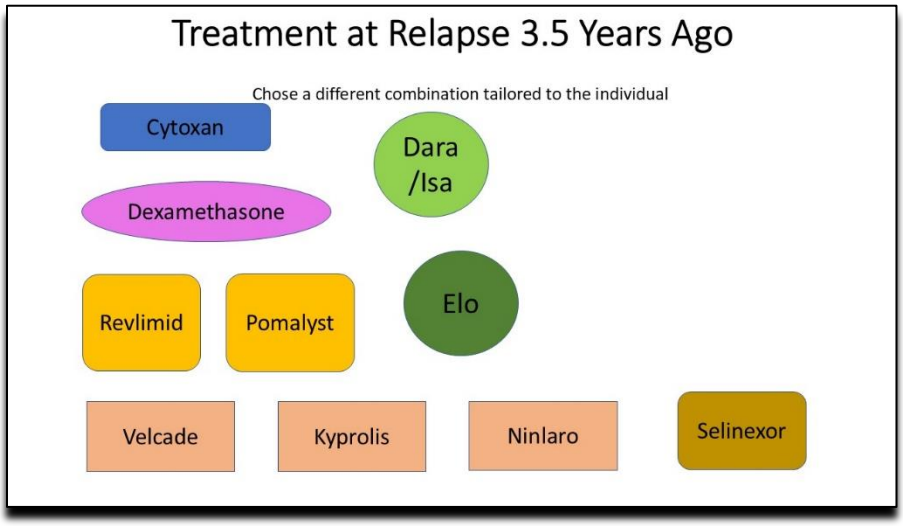
I love this. It's the freedom trial, so free from maintenance drug therapy, multiple myeloma. And it's taking patients who have had a transplant, and have had two years, at least two years of maintenance, and then checking this MRD status. And if you had two negative MRD status that sustained, then you stop. You stop maintenance. And then you get observed. So, these are what we call de-escalation studies. And hopefully in five years or maybe earlier, we'll get some information. But more to come.



Treatment at Relapse

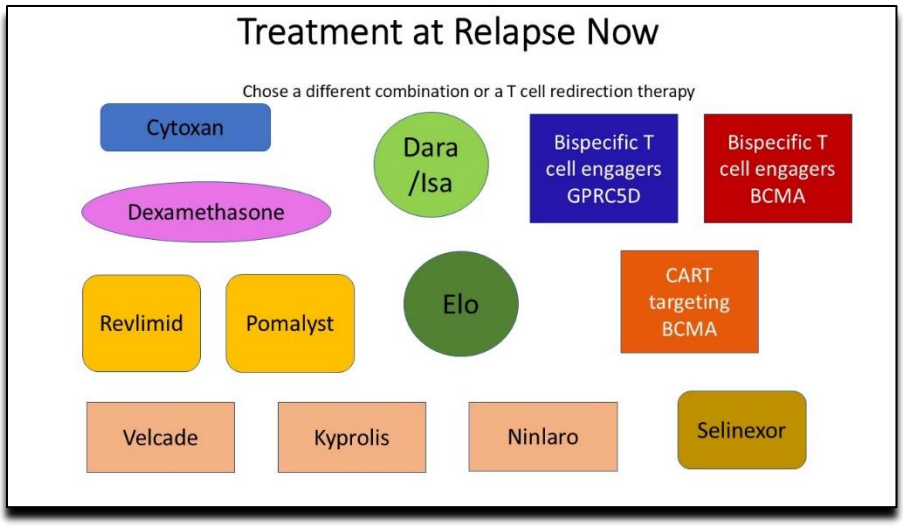
Now let's shift gears a little bit to relapse. So, as I mentioned, eventually patients do relapse because by definition it is not a curable cancer. You hope to push that out as far as possible. But it does, so this is some terminology I want to point out here. At the first relapse, then we use another therapy, which we call second-line therapy. At the second relapse, we use a third-line regimen. And at the third relapse, four-line regimen, and this pattern continues, just to give you some terminology.

And there's this early relapse, which is one to three lines of therapy versus late relapse, which is more than three lines of therapy. So, this is important because this is how the FDA [US Food & Drug Administration] approves certain drugs. So, you might be relapsed, but you might not meet the indication to get a certain drug because it's approved for late relapse, not early relapse. So, I do want to highlight this difference. And things are evolving here as well. So, again, more to come.



Treatment at Relapse 3.5 Years Ago

So, this is treatment at relapse about three, four years ago. What we do at relapse is we want to choose a different combination. We typically like three drugs in relapse. So, we pick something that you haven't had before, or depending, you might have had it before, but you weren't progressing on it. So that's how we choose. It's very individual to what you've had, what you've responded to, whether other comorbidities, whether some side effects are residual, like neuropathy, and so forth.



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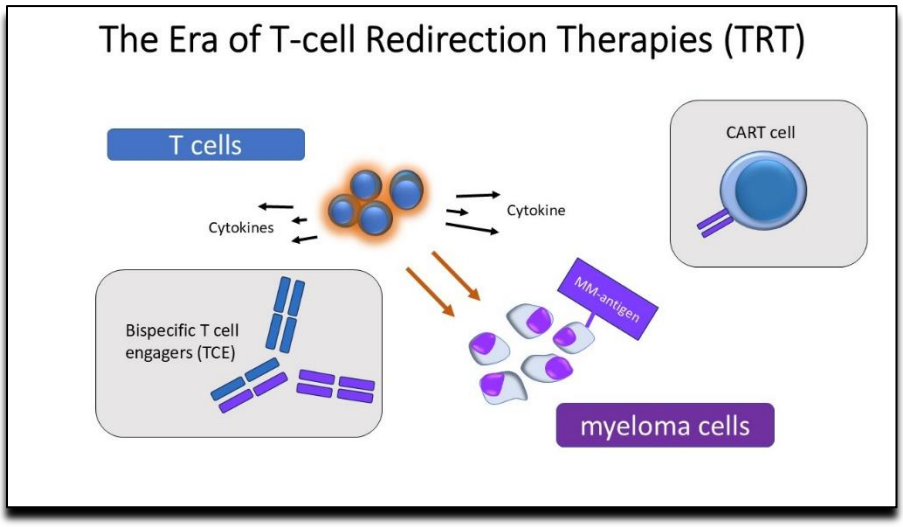
Treatment at Relapse Now

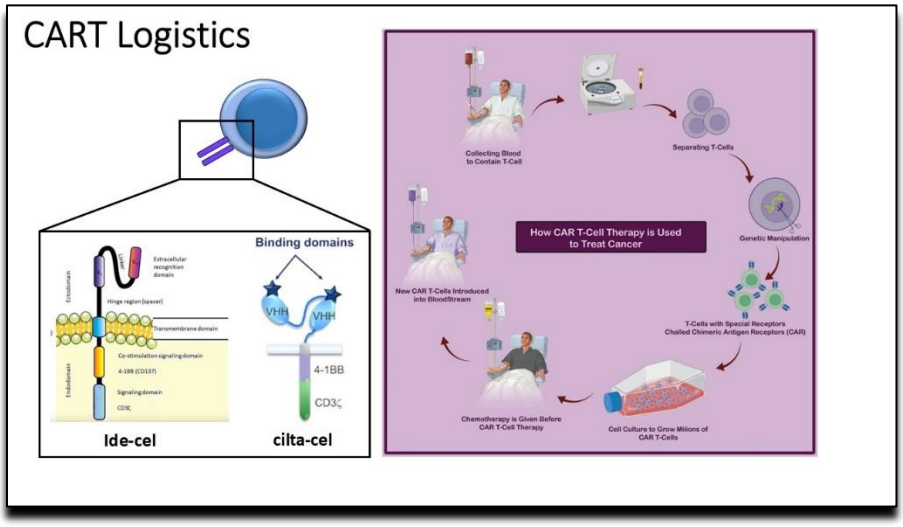
Now what do we have now at relapse. So, yes, we still have the option to choose a three-drug combination or a T-cell redirection therapy. And that could be in the form of a CAR [chimeric antigen receptor] T-cell therapy that targets a protein called BCMA [B-cell maturation antigen] or bispecific T cell engagers that targets BCMA, or bispecific T-cell engager that targets a different protein called GPRC5D.



The Era of T-cell Redirection Therapies (TRT)

And with this, we're going to talk more about really in-depth understanding of this T-cell redirection therapy because this is really exciting. So, the concept here is we want to get the T-cells to recognize the myeloma cell and kill it. So we actually know when, before myeloma, you have a precursor state called MGUS [monoclonal gammopathy of undetermined significance]. And we know that in the early states T-cells can recognize the cancer. It can recognize the MGUS. But over time, myeloma gets smarter. The immune system is more suppressed, and the T-cells can no longer recognize or are not as strong to kill the myeloma.

So, this is redirecting the T-cells, invigorating the T-cells to be able to kill the myeloma. So, this is what we are trying to do. And the T-cells recognize something they want to kill. They get activated, and then they secrete these proteins called cytokines. So, I show you that here. Now there are two ways to redirect these T-cells. One is using a monoclonal antibody like this, bispecific antibodies. Again, it looks like that myeloma protein that's being secreted. And this brings, the one arm binds to the T-cell, and another arm binds to the myeloma, based on the protein that is kind of expressed or on the cell surface. The other option is using an engineered T-cell. So, we take T-cells and genetically modify them to recognize the myeloma and make them more active.



CART Logistics

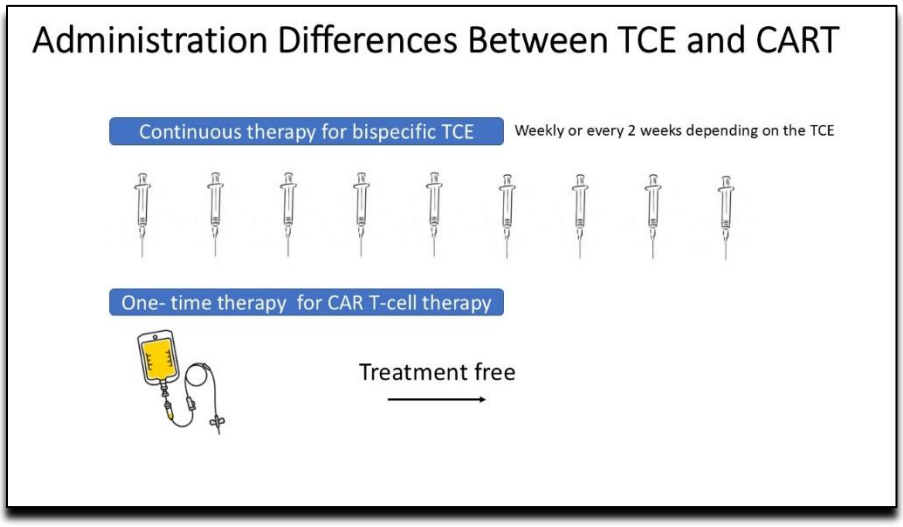
So, CAR T, because it's a genetically modified drug, are a little bit more involved. And I want to go into these steps because this is important in the decision-making and understanding what CAR T involves. So, the first step is we have to collect the T-cells from the patient. They get shipped to the manufacturer, and then they genetically modify it.

So, you can see here these T-cells now, they did not express this little receptor, which is a protein that sticks out from the cell. And now they do here. Then these grow. And then before we give the CAR T-cells infusion back to the patient, we actually give a little bit of chemo, so three days of chemo.

And this chemo's purpose is to kill the other T-cells, the other lymphocytes, because, think about CAR T as almost like an animal. So, you want it to grow and proliferate, so you want to create a niche, space. So, you kill off the other lymphocytes, so that when these T-cells come in, they have space to grow. So that's the purpose of that.

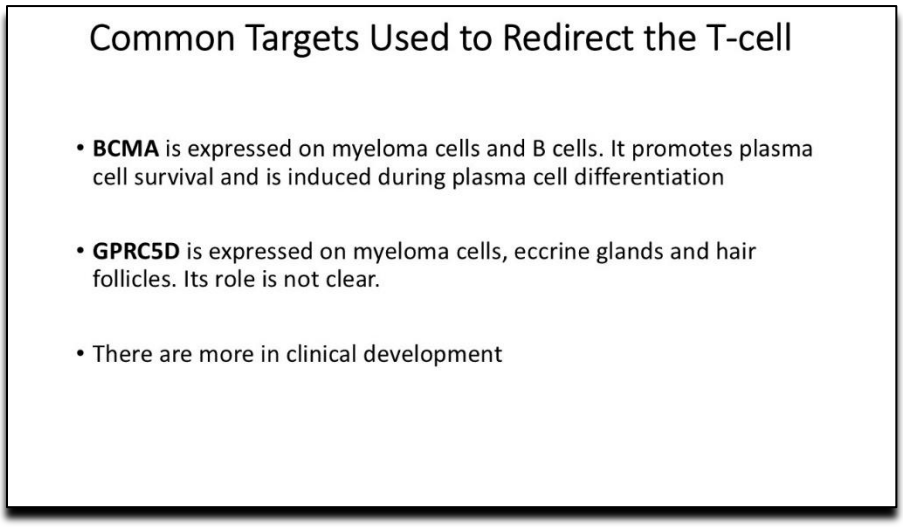
And just to show you a little bit more detail of what's going on really here is that when you're engineering in a T-cell, you have a few sections. The first is that section that is outside of the T-cell. This is up here. This is the binding domain. It's what binds and binds the myeloma cells. It's like the arm that catches the myeloma cells.

But inside the cell, there are signaling domains, basically signals to tell the T-cells to be more active. So, it kind of creates a superstar T-cell, shall we say. So, there are two CAR T-cells that are available, and one of the differences is the binding domain in cilta-cel (Carvykti®) is two. And there's one binding domain in the ide-cel (Abecma®). But this is the two CAR Ts that are currently approved.



Administration Differences Between TCE and CART

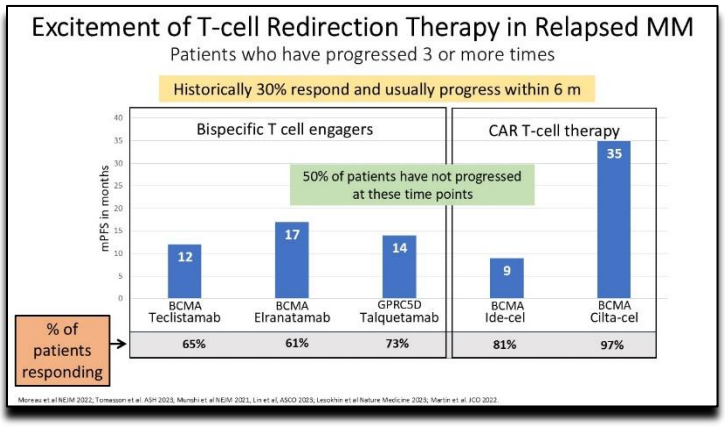
Now one of the major differences between CAR T-cells and bispecific T-cell engagers is how we give it. They are completely different drugs, of course, but a similar concept. And we give them very differently. So, the bispecifics, we give continuously. We don't really stop therapy. Depending on the bispecific, it could be weekly therapy or every other week therapy. Now for the CAR T, which is very appealing, it's a one-time infusion, so patients get the infusion and then no more myeloma treatment. That sounds like really great. There are some things that happen. It's not just you'll be given, and we let you go. But there's no more myeloma therapy. You got a treatment-free interval. So this is important to remember.



Common Targets Used to Redirect the T-cell

The targets that the myeloma, that the T-cells are targeting on the myeloma cells, there are two major ones that are being used right now, which is the BCMA. And this is a protein that is important in the survival of the myeloma cells, so we like to target those things. We don't want myeloma to survive. And the GPRC5D actually, people don't really know what it does, but it's approaching that again is on the myeloma cell. But it's also on glands and hair follicles and on the tongue. And you'll understand why I'm talking about it when we talk more specific side effects relating to that.

And these are not all the targets that are being developed, so these are targets that are proved, but there are other targets in clinical development.



Excitement of T-cell Redirection Therapy in Relapsed MM

So why are we so excited about these T-cells redirecting therapy? So, I want to give you a little bit of a historical background here. So all drugs in myeloma, when they are being developed, they always get tested in the late relapse. Some company is developing a drug, they want to see if it works, and the patients that need it most are patients that don't have any other options. That's how these drugs get approved first, in the relapse setting.

Now if they work very well, they get moved up earlier in the kind of trajectory of myeloma. So again, historically, patients who have had three or more lines of therapy usually, when they get another therapy, the chance of it working was about 30%. And we were so happy about that. That's how pomalidomide, which is

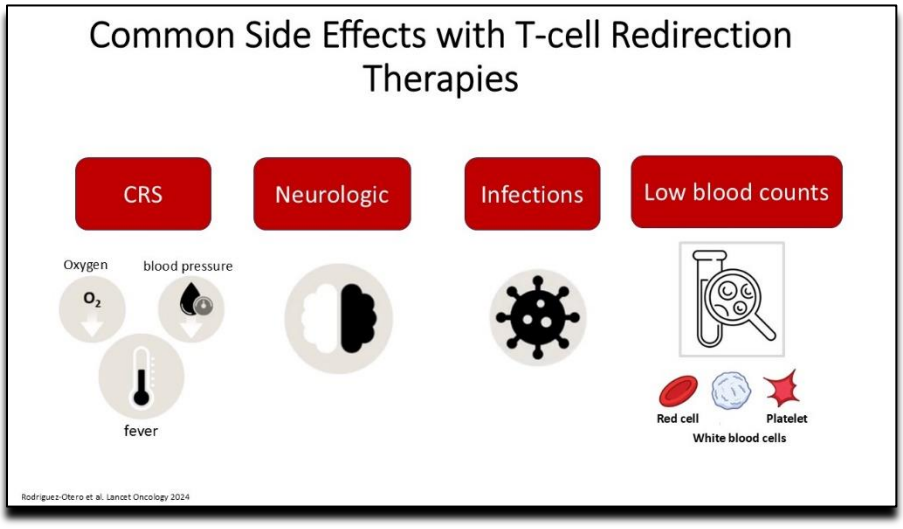
the newer generation lenalidomide, and daratumumab came to be because they had about a 30% chance of response in this particular patient population. And this was fantastic, and the FDA approved it, and so forth.

And in those patients, when you did respond, the chance of having a long duration response was very low. Most of the time, patients, even if they responded, did progress in short order, usually by six months or so. So, keep that in the back of your mind when I talk you through how these new therapies are doing. So again, I'm looking at the studies that use these therapies in the heavily pretreated, in the late relapse.

There are several of these drugs. Here I highlight three bispecific T-cell engagers. Two are directed against BCMA, one is directed against GPRC5D. There are two CAR T products available, as I mentioned before. One is cilta-cel and one is ide-cel. And they are both against BCMA. Now honing on the orange box here, let's look at the percentage of patients that responded. So, this is really fantastic.

With the bispecifics, again there are differences, and we're not comparing one to the other because it's not allowed because of different clinical trials, but just they show you that, for the most part, about 60% to 70% responses. So that's great compared to those historical 30%. And look at the CAR Ts, 80 to high 90s, 97% response rate with cilta-cel, that is unheard of. These are unprecedented, unbelievable responses. Now responses are great, we want to know how long patients remain in response in these situations. As I showed you before, historically that was about a few months, six months or so. So, the blue boxes here are representing the months, the amount of months that 50% of the patients have not progressed. So, about half the patients have progressed at that time and about half didn't progress and still in remission. So you can see, for the most part, it's a one-year, one and a half years with the bispecifics. Again, some are longer, some are shorter.

And with the CAR Ts, you see a little bit difference here, but with this cilta-cel about three years, again unheard of. So, this is really fantastic. And this is why we're so excited about this. But now let's talk about side effects.

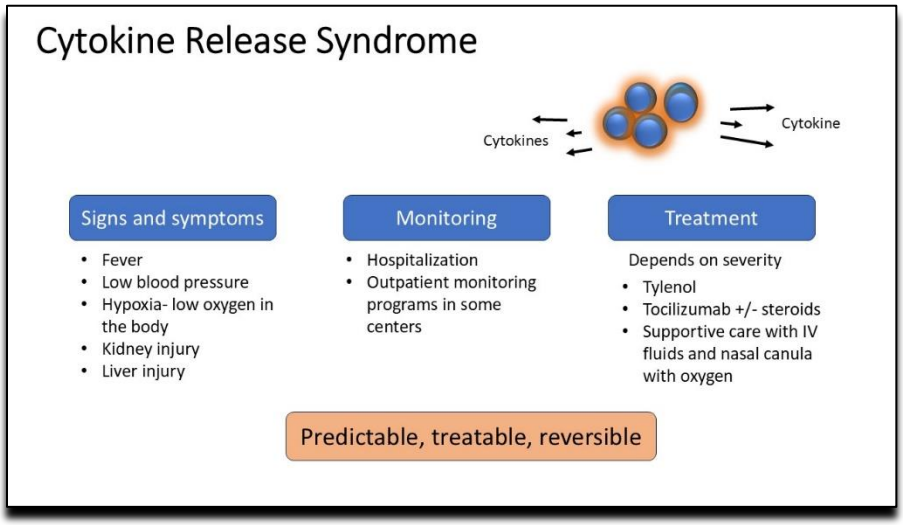


Common Side Effects with T-cell Redirection Therapies

So, I will kind of talk about general side effects with T-cell redirection therapies and point out differences between the two T-cell redirection therapies, the bispecifics and the CAR Ts. So, the most common, one of the most common side effects is this CRS, which is cytokine release syndrome.

This happens because it's an immune therapy, and T-cells are immune cells. And when they see something they don't like and want to like kill it, they get activated and release cytokines. And this causes inflammation in the body, which is why people get fevers, just like when you have any infection. The fever could just be a fever, or it can be a fever with low blood pressure or with low oxygen saturation, just like when you have a really bad infection or sepsis, similar concept here.

Now the other side effect is neurologic. And there are different flavors there, and we'll talk more details soon. The third is infections. And the fourth is low blood counts.

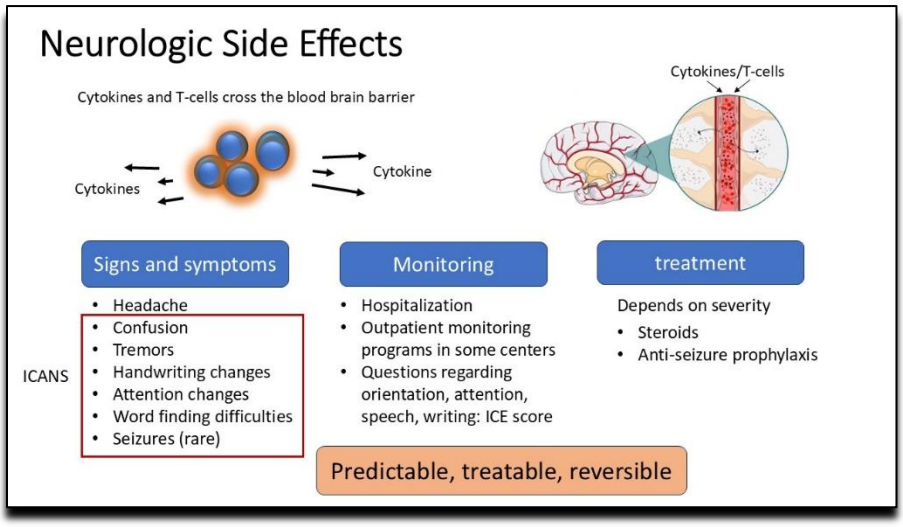


Cytokine Release Syndrome

Let's talk about cytokine release syndrome a little bit more. We talked about the signs and symptoms, this fever and low blood pressure potentially. It can also affect organs sometimes. So, when you have a lot of inflammation, sometimes that could be kidney injury or liver injury. This is reversible.

How do we monitor? How do we manage this? We need to keep a close eye on your blood pressure, the fever, the temperature. So, we hospitalize most patients. Sometimes in certain institutions, there are outpatient monitoring programs, depending on where you are, you might have an outpatient monitoring program. But otherwise, you have to be hospitalized. And what is the treatment? So, it depends on the severity. So if it's mild, meaning just a little fever, you're doing well, you could just use Tylenol® (acetaminophen). If the fever is more persistent, or you have low blood pressure, then you need something.

You need tocilizumab (Actemra®), which suppresses that immune reaction. Sometimes you also use steroids, like dexamethasone. Again, suppress the immune reaction. And, of course, supportive care. IV fluids are important, if you need extra oxygen, and so forth. Again, very rarely does this escalate to something a little bit more, that needs to have more careful attention and going to that intensive care unit for more blood pressure support. But this is much more rare. I want to highlight that this is very predictable, the cytokine release syndrome. It is treatable, and it's reversible.



Neurologic Side Effects

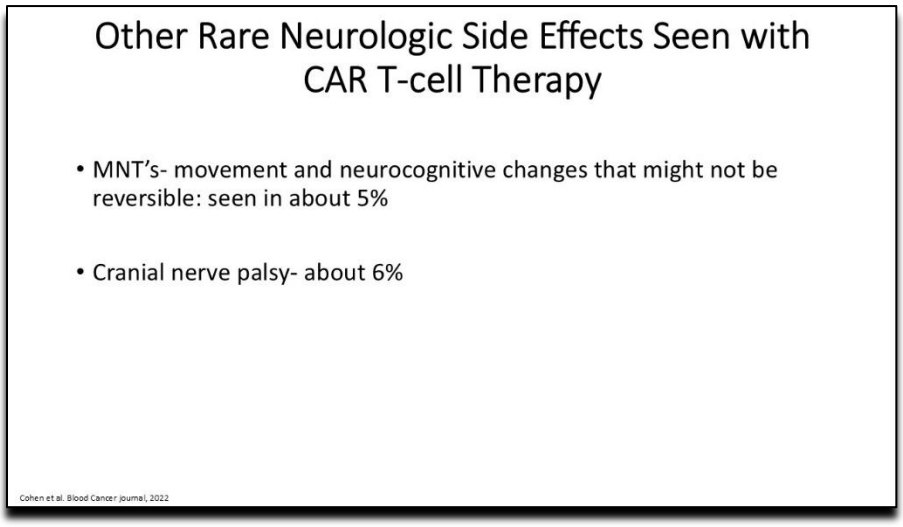
Neurologic side effects. So, the reason why we can have neurologic side effects from, more so with CAR T, and I'll show you later, is because the cytokines that are in the blood actually can cross into the brain through the blood-brain barrier, as I show you here. And T-cells can sometimes cross, too.

So, people can have confusion, tremors, handwriting changes, word finding difficulties, attention changes, and seizures, more rarely, more severe case. The term for this neurological syndrome is called ICANS [immune effector cell-associated neurotoxicity syndrome]. And you don't have to remember exactly, but I will talk to you about some other neurologic side effects. This is ICANS. And it typically happens kind of earlier on.

Headaches can happen, too, and headaches could be from the neurologic side effects or just because patients have a fever, so sometimes it's hard to tease that out. But it could be a part of this. And monitoring goes the same. You need to be hospitalized for a certain amount of time. Or if you have an outpatient program, they monitor you in that sense. But if you develop ICANS, usually you have to be hospitalized for more care.

We do ask a lot of questions every day to assess your kind of cognition and your thought process. So, we ask silly things, like where you are and what is the date and to name objects and to count backwards and we look at your handwriting. This is called the ICE [immune effector cell-associated encephalopathy] score. And we use this to assess ICANS.

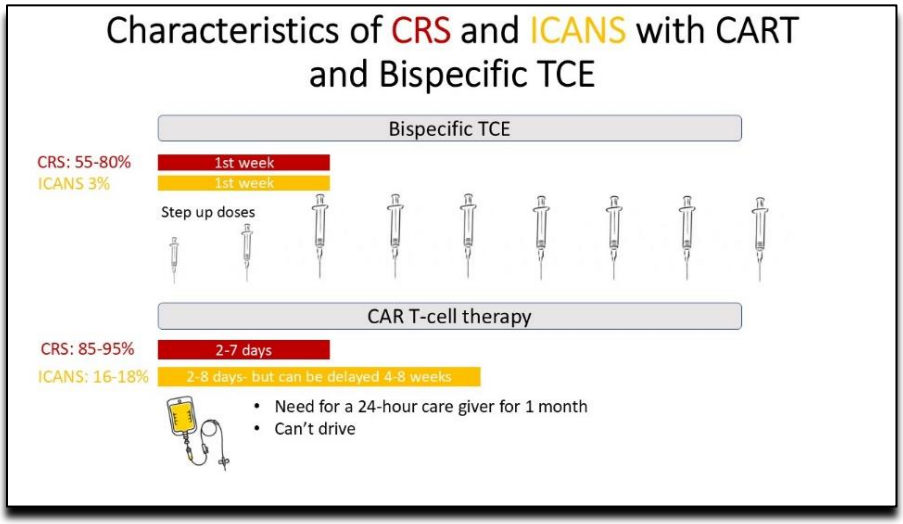
Now the treatment again, it depends on the severity. So, if it's very mild, you might not need anything. If it's more severe or persistent, then we use steroids. And we also use an anti-seizure medication called Keppra® (levetiracetam) for a lot of these. We actually in our center use it for everyone regardless of if you have ICANS. Again, predictable, treatable, reversible. So, I want to highlight, it sounds scary, but we kind of know when to expect it, and we know how to treat it.



Other Rare Neurologic Side Effects Seen with CAR T-cell Therapy

These are other rare neurologic side effects and mainly seen with CAR T-cell therapy? So, there is this MNT [movement and neurocognitive treatment-emergent events], which is movement and neurocognitive changes that resemble Parkinson's disease but is not Parkinson's disease. And this might not be reversible. No, it's not, it's very rare. In the study that looked at cilta-cel and those patients who have had multiple progression, multiple relapses, it was seen about 5% of the time.

But in the study looking at CAR T cilta-cel earlier when patients progress after the first or second therapy or third, it was about 1%. So, it's rare, but it's there. And the other side effect I wanted to highlight here is cranial nerve palsy, like Bell's palsy when you have like a facial droop. So, this was also seen, not commonly, but can be seen. And this is reversible with steroids.



Characteristics of CRS and ICANS with CART and Bispecific TCE

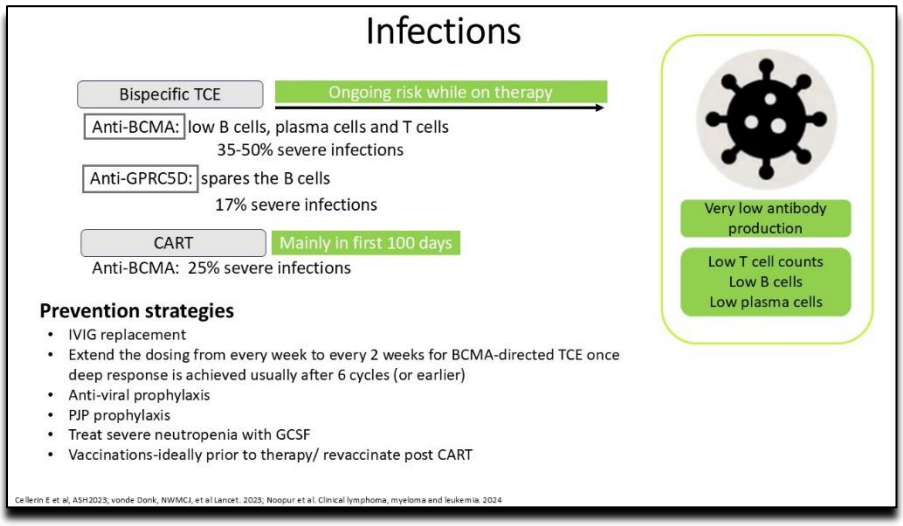
So, this is the characteristics of CRS and ICANS. And I want to distinguish the CAR T and bispecific T-cell engagers in terms of timing of such and also the risk of getting it. So just big picture, CRS and ICANS are seen more commonly with CAR T than bispecifics. But still, CRS, as you can see here, in 55% to 80% of the patients, depending on the bispecific product, where it's 85% to 95% CRS seen with the CAR T products in the

heavily pretreated patients with late relapse. ICANS really very, rarely seen with bispecifics and seen a little less than 20% with the CAR T, again in that late relapse population.

The timing with bispecific T-cell engagers, it usually happens within the first week. So, the way we give bispecifics is we give here step-up dosing, a small dose, a medium dose, and a large dose, or the target dose. And usually, we see the CRS after the first or second dose or, more rarely, after the target dose. But this is when we see it, and the ICANS in the same time frame. And it doesn't happen later, even though you continue to get the drug, it does not happen later. Very rarely does it happen, what we call delayed CRS.

With CAR T-cell therapy, the CRS timing depends on the product, actually, and happens when the T-cells expand. So, with one of them, it's about two days is the average, which is ide-cel but with cilta-cel it happens more at the seven day. So again, we know when to expect this.

ICANS usually happens with the CRS or shortly thereafter, but rarely can be delayed up to four to eight weeks. And this is why CAR T-cell therapy is more involved. And you do need a 24-hour caregiver for one month after the CAR T-cells are infused. And you can't drive for eight weeks because while it's rare, what if something happens while you are driving? We don't want an accident. And you need a 24-hour caregiver because you don't know if you're confused, so you need to be kind of watched, not watched like a hawk but be around. So, this is a little bit more involved.



Infections

Now let's talk about infections. The reason why we have infections with both of these T-cell redirection therapies, is because we, one, lower the plasma cells. We are killing plasma cells very well, so we decrease plasma cells. We actually decrease B cells for any BCMA-directed therapy. And we lower T-cell counts. So, we're injuring some of your immune system. And this is important because a patient then can't mount antibody responses.

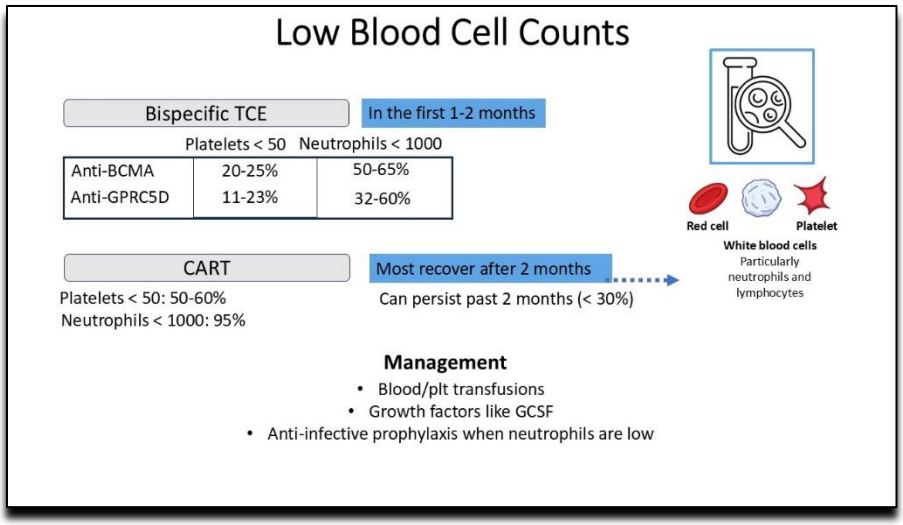
Again, I told you plasma cells make antibodies. B cells also make antibodies. Those are their two main antibody-producing cells, and they can both be very, very low, so patients have very low antibodies and are at risk for infections. Now there's a slightly lower risk of severe infections with the anti-GPRC5D bispecifics because they spare the B cells.

So severe infections were seen in 35% to 50% with anti-BCMA bispecifics but only about 17% of the GPRC5D. In general, the infection risks with the bispecifics are ongoing while on therapy, where they are mainly in the

first 100 days with the CAR T-cell therapy. So, kind of they diminish over time afterwards because you're no longer on this therapy. You kind of got it and then so your immune system is coming back.

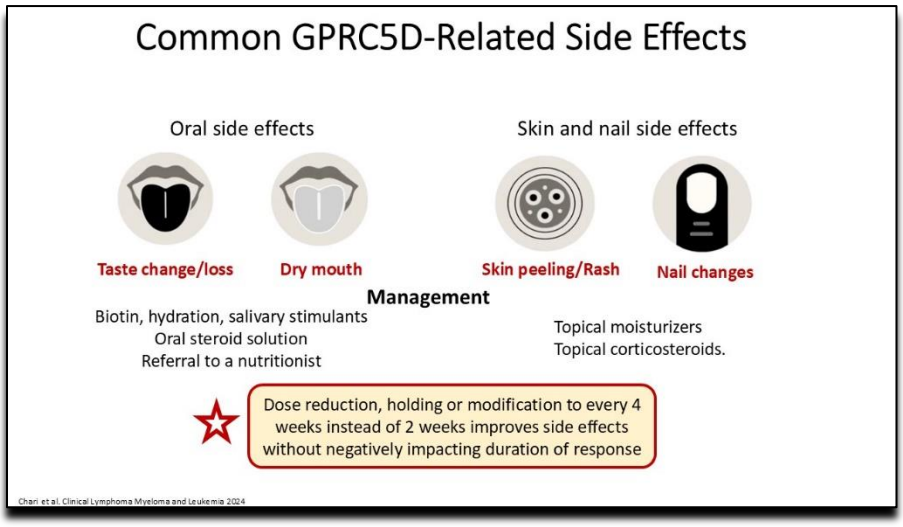
Now what can we do to prevent infections? So, there is good data, meaning we've studied this, that giving IVIG, even if he didn't have a prior infection but you give it preventatively, prevents severe infections. So, this is recommended, particularly with the bispecifics. Also considering extending the dosing from every week to every two weeks for the BCMA agents or even longer for the GPRC5D agents to every four weeks. So, these are things to consider.

And antiviral prophylaxis, we do this for most of our patients, like acyclovir. PJP [pneumocystis jirovecii pneumonia] prophylaxis, which is a particular pneumonia that patients can get when T cells are low. So, this is important. Also to consider treating severe neutropenia with G-CSF, which is a growth factor to promote neutrophil count recovery. And vaccinations, so being up to date with vaccinations. Ideally, we like to do it before therapy. But we do revaccinate post CAR T. And the reason why we like to do it before is because, again, once you get these agents, you are killing some of the cells that are very important to develop antibody responses. So, it's good to have it before if you can.



Low Blood Cell Counts

And then lastly, the low blood counts. Now, I put up some numbers here in terms of percentages of having a more severe low blood count, specifically the low platelets or the low neutrophils. And you don't need to kind of go into the details, but bottom line is we see more severe low blood counts with CAR T, and these low blood counts can persist for longer. So typically with the bispecifics we will see them in the first few cycles. But with CAR T, a small portion of patients might have persistent low blood counts longer than two or three months. And whether that means, it just means you might need more supportive care during that time, which I kind of talked about here. So, management, including blood and platelet transfusions, growth factors platelet, and, of course, anti-infective prophylaxis when neutrophils are low, like antibacterial prophylaxis.



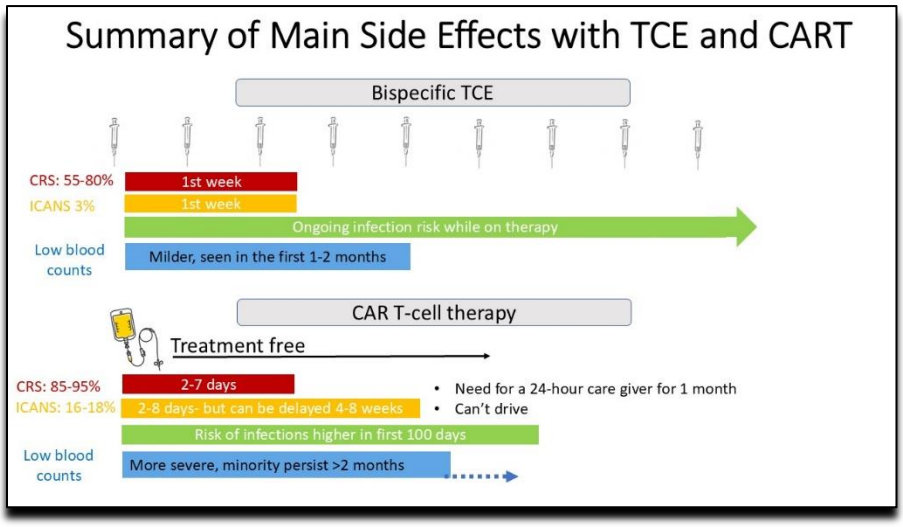
Common GPRC5D- Related Side Effects

These are very specific side effects that I want to move on to, which are really GPRC5D-related. So we're not talking bispecifics or CAR T, this is really towards targeting this protein.

So, because this protein is expressed in the tongue and glands and hair follicles, on nailbeds, it causes these side effects, what we call oral side effects which lead to dry mouth, taste change, taste loss. And you can get skin rashes, or not rash but peeling, red palms, very dry skin, nail changes. So, these are all not life-threatening but very bothersome to patients. And the management here, first line is we try to kind of improve the symptoms with hydration, salivary stimulants, Biotene® (saliva substitutes), oral steroid solution, dexamethasone solution, kind of swish and spit. We can refer to a nutritionist because you don't have a lot of taste, so kind of focusing on good nutrition, make sure you're still eating well, avoiding weight loss because we have seen weight loss with these agents.

And in terms of the skin and nail changes, a lot of creams, topical steroids, sometimes for more rash and itchy rash, antihistamines, things like that. But I'd have to say I think the most beneficial management is to either reduce the dose or hold treatment and extend the treatments from every two weeks to four weeks.

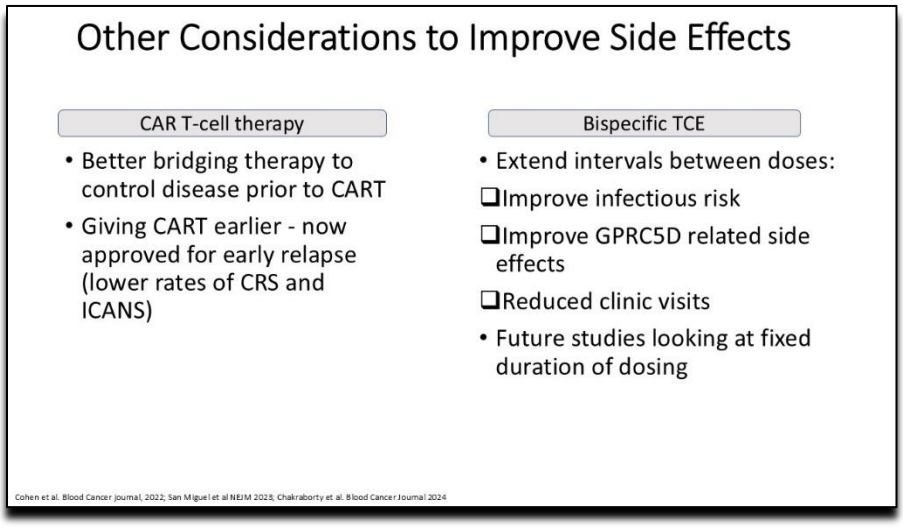
That actually was looked at, and they showed that there is improvement in these side effects, and it does not affect how well it works, which is really important. And when we dose reduce, and we modify, we want to make sure we're not affecting how well it works. It is a balancing act. But they looked at this, and it didn't affect the duration of time patients stayed in remission. So, this is something I do for all my patients who either have bad side effects or even have a really, really good response. And sometimes I would delay them to every four weeks.



Summary of Main Side Effects with TCE and CART

And this is a summary slide that is a little bit busy but just to kind of capture everything I talked about. I tried to color code it with all the common side effects that we see with both of these, kind of the timing of such. So bottom line is with CAR T, it's a one-time treatment. You have a treatment-free interval, but it's a little bit more involved. You have a higher risk of ICANS or other neurologic side effects.

You do need a 24-hour caregiver. You can't drive, so it affects your day-to-day life. The risk(s) for infections are typically actually less overall than the bispecifics. The bispecifics have, the risk continues as you are on the therapy. And the blood counts are typically more severe, low blood counts are more severe and can persist for longer.

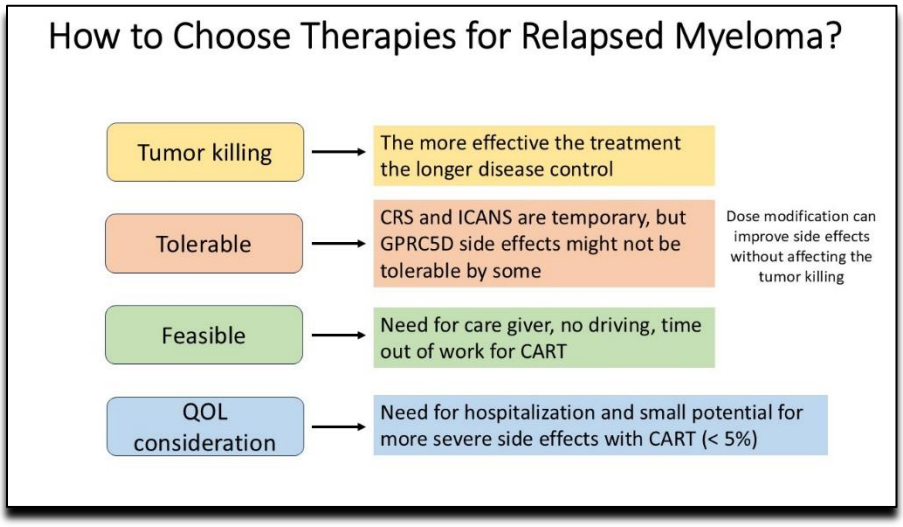


Other Considerations to Improve Side Effects

There are some other considerations to improve side effects with these drugs. Particularly with CAR T-cell therapy, talking about the neurologic side effects or talking about the Parkinsonism. We do see that one of the risk factors to develop these more severe side effects, it's having a lot of disease before you go to CAR T. And that's why good bridging therapy, and what's bridging therapy? Bridging therapy is using another therapy to control a disease.

And it's important to remember that when these drugs were studied, these patients didn't have a lot of options. They might not have had good bridging therapies. But now, CAR T is approved for early relapse. So typically, we do have better options that the patient hasn't had yet, so we can try something to try to bring the disease down more before we go to CAR T. And we do see that has reduced some of the side effects, like lower rates of CRS and ICANS in those studies. And again, mitigating the risk for the unusual and rare side effect of Parkinsonism.

For the bispecifics, the duration of time or how we should give it over a long period of time is an unanswered question. We need to figure this out. So, for example, we've seen that extending the intervals does improve some of the infection risks and definitely improves the GPRC5D-related side effects and quality of life, of course, with the reduced clinic visits that's also a consideration. So, we really need future studies to hone in on how long we need to continue this? Can we give breaks for some patients? And these are all things that are being investigated.

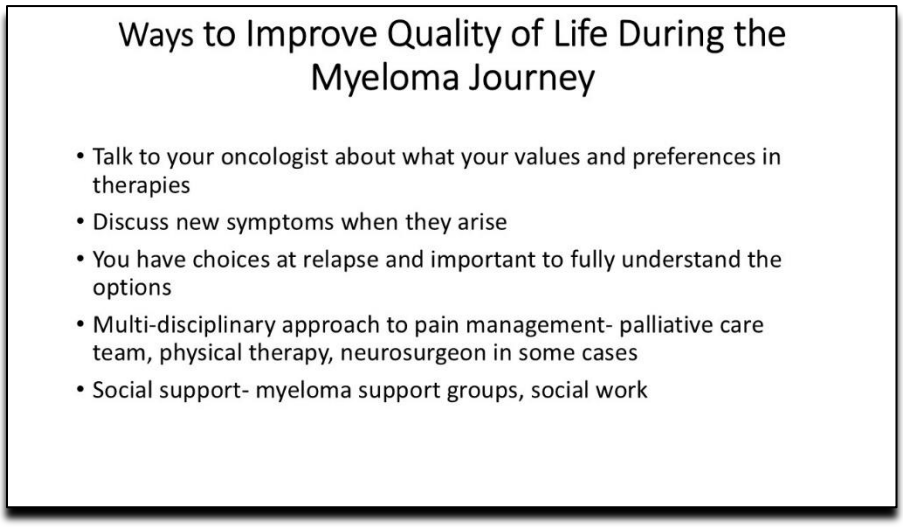


How to Choose Therapies for Relapsed Myeloma?

So, kind of to summarize how we're choosing therapies for relapsed myeloma. We, of course, want the best effective therapy, for better tumor killing, for longer disease control. So that's important. But we also need to assess the different side effects, make sure it's tolerable, make sure it aligns with your quality of life. For example, if eating and if taste is so important for you that if you did not have a good taste, if you didn't taste your food, that's just not worth it. Then GPRC5D is direct to therapy, specifically with the BITEs [bispecific T-cell engagers]. Bispecifics is not a good option. So, these are things to discuss but it's also important to remember that CRS and ICANS are manageable, are reversible. They're temporary. And with the GPRC5D we can adjust the doses.

Now the next in green here, I talk about feasibility. We have to figure out if this is feasible for you and your family. The fact that you need a caregiver for CAR T-cell therapy, the no driving aspect, all this has to be taken into account.

And then the hospitalization need. So, I am focusing on the T-cell redirection therapies. But there are other options. So, if you haven't had daratumumab, if you were diagnosed 10 years ago, and you were getting VRd without the dara, and you're progressing now, you can use daratumumab-based therapy. So, knowing the different options, depending on what you've had when you are progressing, is important. Because, yes, using these therapies does require a hospitalization for most institutions. So, these are things to talk about.



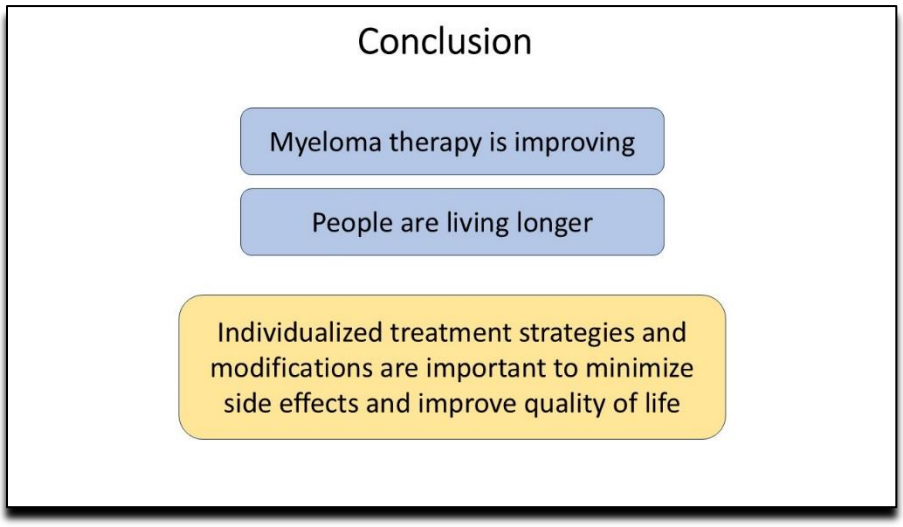
Ways to Improve Quality of Life During the Myeloma Journey

So overall ways to improve your quality of life during the myeloma therapy, there's a lot of different things to consider. So obviously good communication with your oncologist. Talk about what your values are. They get to know you. They know their family, they know your living situation, your distance from the hospital, and so forth. What are your preferences, IV versus no IV therapies, and so forth?

Discuss new symptoms when they arrive. So sometimes we see patients every four weeks. But if in the middle, there is something that comes up specifically again, something like neuropathy, something that you don't want to fall behind on, give the clinic a call and let them know.

And you have to know that you have choices; with choices, comes a lot of decision-making. And knowing and really understanding the different options, risks, benefits is important for this shared decision-making. And a multidisciplinary approach is very important to myeloma. Pain management, physical therapy is very important. I find with bony disease, sometimes it really helps stabilize the core and helps with spinal pain, mobility, muscle strength, really important.

Of course, sometimes in situations, you might need more interventions. Kyphoplasty [a surgical technique to help with back pain that involves inflating a balloon before stabilizing the area with chemical cement], so sometimes you need surgeons. And social support. This is a lot take in. And myeloma support groups are out there, social work, these societies. So, it's important to kind of know what you need at what time and know that the resources are out there.

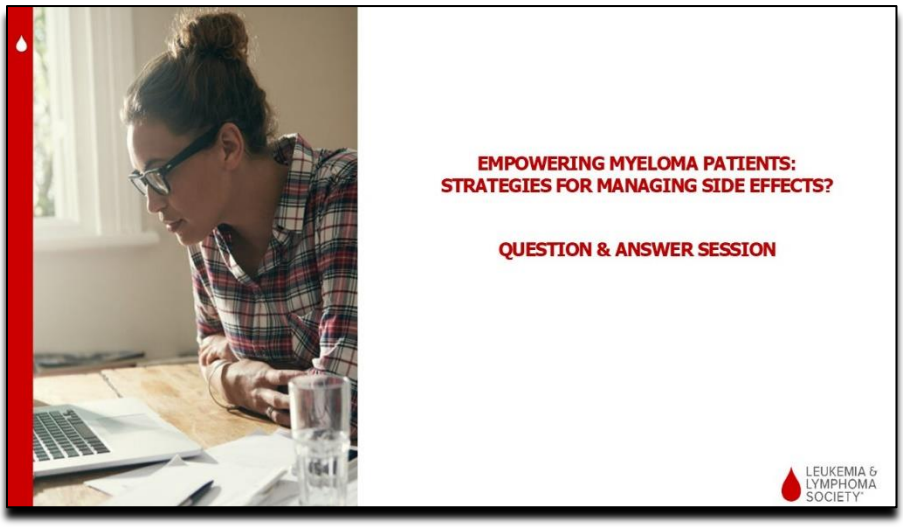


Conclusion

So, to conclude, myeloma therapy is definitely improving, and it's continuing to improve. And patients are living longer. And we need to rethink our treatment strategy, and we need to modify our treatments to really minimize side effects, improve quality of life, and think about this long term.

Thank You

So, with that, I will end my discussion, and I'll take questions.



Questions & Answer Session

Lizette Figueroa-Rivera
Thank you so much, Dr. Bar, for your very informative presentation. As you mentioned, it's time for the question-and-answer portion of our program.

And we'll start with one of our online questions. Dr. Darlene asks, bispecific antibodies are causing significant immunosuppression. Is there any research being done on the necessity of antifungals, antivirals, and antibacterial treatment, and for what duration? Also, the efficacy of vaccines on those bispecific regimens.

Dr. Noffar Bar
Yes. So that's a great question, this is a big problem. We're trying to address that obviously in the community trying to see if extending the intervals, giving their new systems a break, but using antifungals have not been shown to be beneficial. Fungal infections are extremely rare. It's mostly viral and bacterial infections. So there have been some unusual fungal infections, but it's not common, and it's not generally recommended to use ongoing antifungal prophylaxis. Antiviral definitely. At periods when neutrophils are very low, then, yes, antibacterial prophylaxis, we use like moxifloxacin (Avelox®). And in terms of vaccinations, you are 100% right. The responses to vaccinations are low with bispecific T-cell engagers. So, we do try to make sure everyone is up to date with their vaccines, pneumonia vaccine, flu vaccine, COVID booster, all these things before and again it's not always that feasible depending on the urgency of needing another line of therapy, but this is important. While you are on the bispecific it doesn't mean we don't still recommend the flu vaccine. You might not have as good a response, but we still recommend to do it. If there is some response, it's better than none.

Lizette Figueroa-Rivera
Thank you. And we'll take our next question from our phone audience, please.

Operator
The next question is from Billy in Michigan. Please proceed with your question.

Billy
Thank you, and I appreciate you, doctor. November 9th it will be a year that I had multiple myeloma cancer. And my question is, you mentioned on the neuropathy, I'm taking gabapentin, Decadron® (dexamethasone) once a week with my lenalidomide. Now my question is, I'm also a type 2 diabetic. And is there anything,

anything I can take to help. I know it's uncurable. But is there anything else out there I can take to stop the pain?

Dr. Noffar Bar
So having diabetes definitely is a risk factor for having neuropathy. So, if the neuropathy happened even before starting treatment with bortezomib, then I would say it's more likely from the diabetes, but if it, maybe you had it before, and now it's worse on the myeloma therapy, it could definitely be the relation to the myeloma therapy. But in terms of treatments is using things like gabapentin. And often when you start low, and we work our way upwards, there's a lot of room to titrate up. That means increasing the dose. And sometimes it takes a few weeks to kind of see the optimal response after you increase the dose. But the first step is using something like gabapentin, or Lyrica® (pregabalin) if that doesn't work, and also if there is balance issues, working with physical therapy. Physical therapy also helps. And if the diabetes is an aspect of this, controlling the sugars. Because if the sugars are elevated continuously, that will also aggravate the neuropathy over time.

Lizette Figueroa-Rivera
Thank you. And our next question comes from Stewart. Stewart is asking, does the presence of AL amyloidosis in any way change the severity or management of side effects?

Dr. Noffar Bar
Does it? It depends. So, we didn't really talk about AL amyloidosis [a rare disorder found in about 10 to 20 percent of myeloma patients in which an abnormal protein called amyloid is produced and deposited in tissue or organs]. The treatment is similar but a little bit different. But some patients with amyloid have a hard time tolerating IMIDs [immunomodulatory drugs] like lenalidomide. So, it's actually not chosen as a frontline therapy for amyloidosis. If how you're presenting is really with amyloidosis, we actually use Cytoxan® (cyclophosphamide) instead of the lenalidomide. So that's something to think about. Someone with ALbcan have neuropathy, so we are much more cautious about the bortezomib, starting off maybe at a lower dose and really keeping a close eye on that. So, yes, there are some things we definitely keep in the back of our minds when we make these decisions.

Lizette Figueroa-Rivera
Thank you so much. And we'll take the next question from our telephone audience.

Operator
The question is from Pamela in Nevada. Please proceed with your question.

Pamela
Yes. Hi, Doctor Bar. My question is around a new medication we're trying now called Pomalyst® (pomalidomide). And we had to decrease the dose because I did go into neutropenia. But I want to find out what the studies show as far as it helping multiple myeloma and plasmacytoma [a localized tumor of malignant plasma cells], which is a rare form that I acquired after the multiple myeloma went into remission. So, I'm wondering what you know about that and the duration that you believe is a good duration that has been seen to work for patients without going into remission, or keeping them in remission.

Dr. Noffar Bar
Yeah, that's an excellent question. So pomalidomide, Pomalyst®, is a second generation Revlimid®. And it works well in combination. So, I don't know exactly the combination that you're getting, but it can be combined with various anti-myeloma therapies. So, we do prefer to use it, not just by itself but in combination. The exact duration of time really is so variable, depending on the kind of disease you have, high-risk features typically have a shorter duration than the average.

And all the numbers we can quote, it's not super accurate at this point in time because there's so many variables. It would have to be more individualized too, kind of what you've had before, how you progressed, what's the trajectory and speed of progression and these aspects. But, yes, it is effective. It is definitely effective for relapsed myeloma. And one of the common medications we use in combination at first or second relapse.

Lizette Figueroa-Rivera
Thank you. Our next question comes from Arthur. Arthur is asking, can anything be done to slow down the process of smoldering myeloma?

Dr. Noffar Bar
That's a very good question. By the way, I love that everyone is all over the country. Smoldering myeloma is a controversial topic. It depends. Smoldering also has its risks - so low risk, high risk. So, what is high risk in smoldering? High risk in smoldering is the chance of it progressing to myeloma faster, where low risk is probably low risk to progress.

In terms of slowing down, yes. There is data using lenalidomide or lenalidomide and steroids in high-risk smoldering to decrease the progression to myeloma. There's also interesting studies using more therapies, the "curative" studies, using even transplant for smoldering. But we don't really know if that's going to make a difference or not, so these studies we have to look long term to see what it really did.

But, yes, high-risk myeloma you can discuss treatment with lenalidomide or lenalidomide and dexamethasone for a certain amount of time. The other option is just to observe closely. And again, if it's low risk or intermediate risk of smoldering, I would not treat. There's actually no studies that show that that's the thing to do.

Lizette Figueroa-Rivera
Thank you. And our next question comes from Doris. Doris is asking if you have any recommendations to control weight during the intake of steroids?

Dr. Noffar Bar
Hmm, yes. So, yes, dexamethasone can definitely increase weight through two different ways. One, it can increase your appetite, so you're actually eating more. And it can increase your weight if you have food retention. So that's a good question. I don't have a great answer to that, except for if this is a big problem, reducing the dose of steroids. I would avoid long-term steroids, so then minimizing the dose, so it won't have as much of an effect on the hunger.

Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our telephone audience, please.

Operator
The question is from Doug from Ohio. Please proceed with your question.

Doug
Oh, yes, Doctor Bar. This is Doug Zimmerman. This is a physical therapy or exercise question. Due to lesions that I have per my doctor, no matter how I exercise, low impact, namely just push-ups, one-pound weights, et cetera, my body reacts in an aching way. Is there, other than walking, is there any recommendation how to exercise to keep in shape to a certain degree?

Dr. Noffar Bar
Yes. I have like a go-to physical therapist who I refer all my patients, with these patients who have lytic lesions in the spine, pain, wear a back brace. And I've seen them work magic sometimes. It's a lot of core strengthening, proximal muscle, meaning like thigh muscle strength. I don't know. Push-ups, I would say, is more strenuous. One-pound weights are not a lot. But if you tried things like squatting by a wall and really seeing a physical therapist that specializes in cancer patients and myeloma patients would be my recommendation.

Lizette Figueroa-Rivera
Thank you. And our next question, Theresa and Don are asking if there are any holistic things that can be done instead of adding more drugs for the side effects.

Dr. Noffar Bar
Holistic things. The one thing I can think about is this chemo brain or brain fog that sometimes patients get with anti-cancer therapy, and it's not unique to myeloma. But in that situation, I do think some holistic therapy might be beneficial, like mindfulness, meditation, yoga, things that help focus your attention, kind of practicing these activities that you're losing, like attention, memory. And physical activity, yoga, movement, Tai chi, these things can be helpful.

In terms of other things with the side effects, people have done acupuncture sometimes. There is no good science that will tell you this will help or not help but something that you can do again. If something is not harmful and potentially beneficial, it is worthwhile to try.

Lizette Figueroa-Rivera
Thank you. Lot of people are asking about chemo brain and brain fog. And wanted to mention that that is something that does occur, correct?

Dr. Noffar Bar
Yes, yes, it definitely does. People, it's a type of cognitive decline. You're not really up to yourself. You can't focus as much. Memory can be affected. So definitely something we see. And even, again, in other cancers it has been seen after chemotherapy is already done. There is a lot of kind of research with the breast cancer world. So, things like cognitive exercises, physical therapy, all these things can help. There isn't really any medication that's been shown to be beneficial in studies. So, I cannot recommend anything like that.

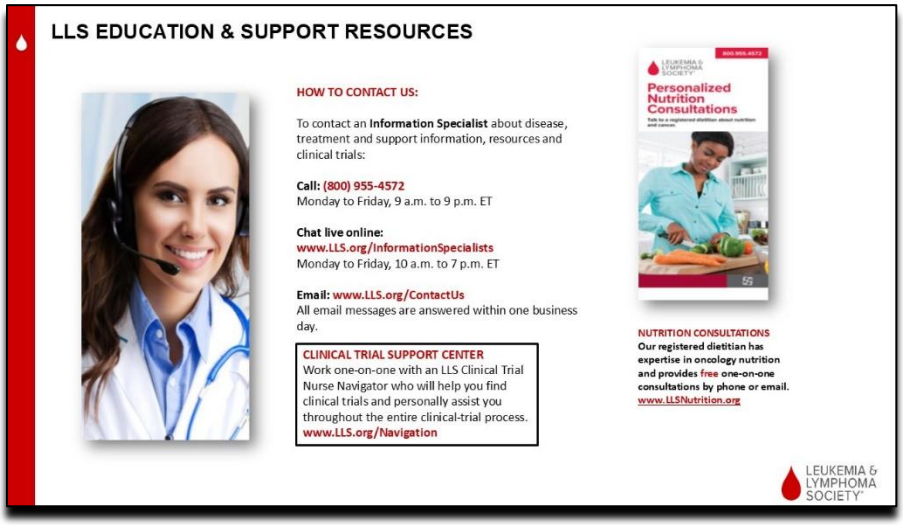
Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our phone audience, please.

Operator
The question is from Kim in Texas. Please proceed with your question.

Kim
My question was when you talk of relapse, I had a stem cell transplant. When I was first diagnosed, I had excruciating pain. And I ended up having a pathological fracture in my femur, so I have a lot of metal in my right leg plus I had bilateral knee surgery, two knee surgeries. But I don't have any symptoms of myeloma, since I had my stem cell transplant. So that's what I was wondering. Is it in regards to that if you have a stem cell transplant, would it keep you in remission?

Dr. Noffar Bar
So, yeah. So that's a good question. A stem cell transplant, autologous stem cell transplant, does prolong the time patients stay in remission, yes. And that's why we do it, exactly. And symptoms of myeloma or symptoms of relapse might not happen. We might see, so there's two types of relapse. One is that we see in the blood, we see the myeloma numbers go up. But you might feel perfectly fine. And this is relapse, that I tell you you're relapsing. It's a little bit different than coming in with, oh, I have a new pain. Then we find there's a new myeloma lesion or something like that. And then that, in that situation, you might present with pain that relapsed. But usually, when we're following the numbers very closely, we usually don't get there, but sometimes the myeloma catches us off-guard. But, yes, the transplant is meant to prolong the time patients stay in remission.

Lizette Figueroa-Rivera
Thank you so much. And that was our final question today. I know we have a lot of questions that we weren't able to get to.



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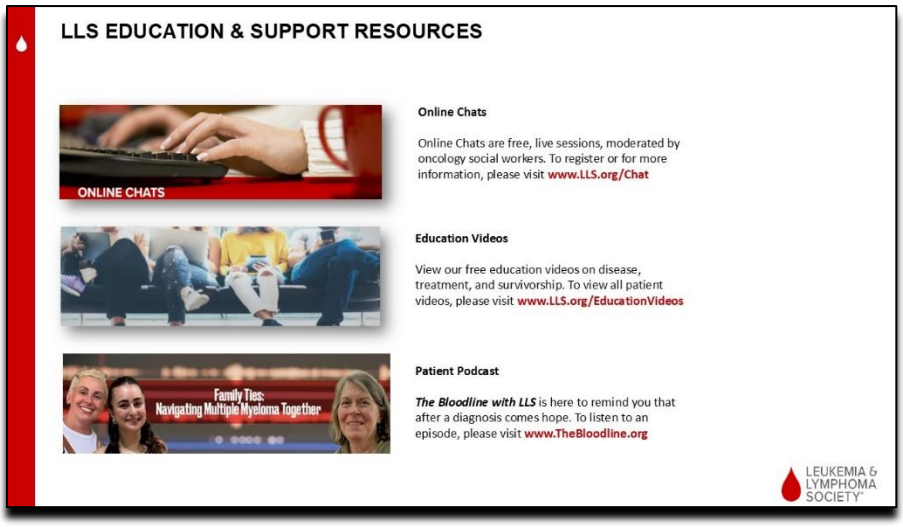

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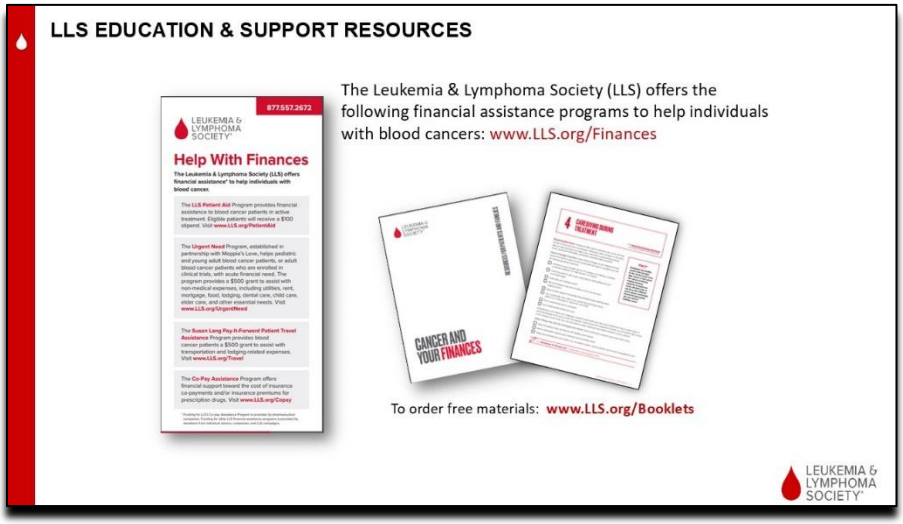

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Again, we would like to thank and acknowledge Genentech, a member of the Roche Group, for their support.

Thank You

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us on this program. Take good care and continue to provide us with your feedback and your concerns. Thank you.