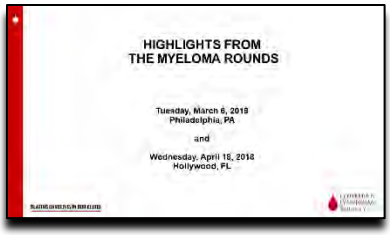
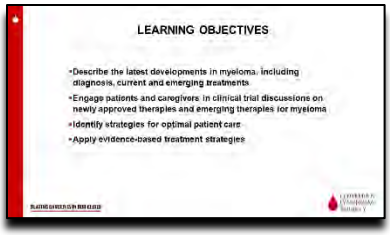


Slide 1 – Highlights from the Myeloma Rounds

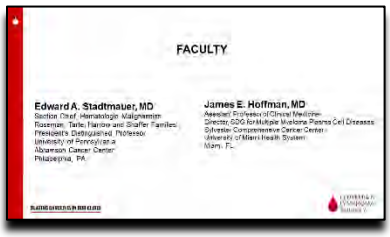
Lauren Berger: Hello, everyone. On behalf of The Leukemia & Lymphoma Society, Albert Einstein College of Medicine, and Medical Learning Institute, Inc., thank you for sharing your time with us for this continuing education program on *Highlights from the Myeloma Rounds.*



Slide 2 - Learning Objectives

The learning objectives for this program are listed on this slide:

- Describe the latest developments in myeloma, including diagnosis, current and emerging treatments
- Engage patients and caregivers in clinical trial discussions on newly approved therapies and emerging therapies for myeloma
- Identify strategies for optimal patient care
- Apply evidence-based treatment strategies



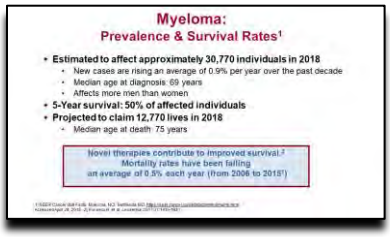
Slide 3 – Faculty

We're fortunate to have as our presenters, Dr. Edward Stadtmauer and Dr. James Hoffman, two of the nation's leading experts in myeloma. We appreciate their dedication and their commitment to caring for patients living with blood cancers.

Dr. Stadtmauer is Section Chief, Hematologic Malignancies; Roseman, Tarte, Harrow and Shaffer Families' President's Distinguished Professor, at the University of Pennsylvania Abramson Cancer Center in Philadelphia, Pennsylvania. Dr. Hoffman is Assistant Professor of Clinical Medicine; Director, SDG for Multiple Myeloma Plasma Cell Diseases, at Sylvester Comprehensive Cancer Center, University of Miami Health System in Miami, Florida.

Our special thanks to Dr. Stadtmauer and Dr. Hoffman for volunteering their time and expertise with us. Dr. Stadtmauer, I am now privileged to turn the program over to you.

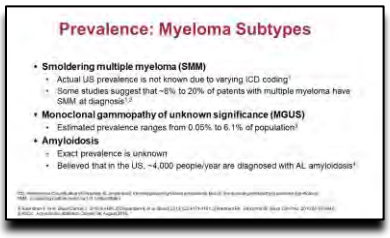
Dr. Stadtmauer: Thank you, Lauren. And it is my pleasure to give you an update on multiple myeloma.



Slide 4 - Myeloma: Prevalence & Survival Rates

As you know, myeloma affects over 30,000 people a year in the United States. The prevalence of myeloma seems to be increasing, perhaps 1% per year over the past decade. The median age at diagnosis is 69 years, men more than women, and survival has been improving tremendously so that there are over 50% of patients who are still living with myeloma over 5 years after the diagnosis.

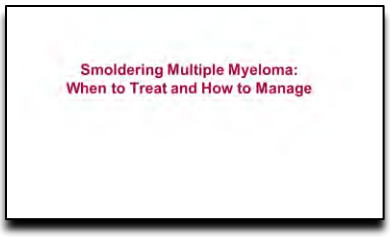
Unfortunately, it still remains a fatal disease and over 12,000 people will die of the disease a year in 2018 with a median age at death of 75. Fortunately, the newer therapies have been contributing to improved survival.



Slide 5 - Prevalence: Myeloma Subtypes

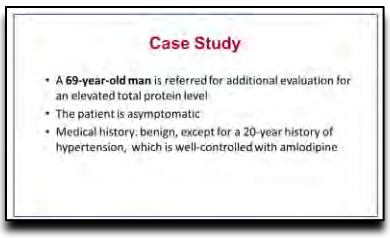
Multiple myeloma comes in a number of malignant plasma cell types. There's the monoclonal gammopathy of unknown significance. It's the most common plasma cell disorder. The estimated prevalence ranges from anywhere from less than 1% to 6% of the population. Approximately 1% of the population will have a monoclonal gammopathy if searched for.

Smoldering myeloma is really somewhat difficult to determine the prevalence, but some have suggested that it's in somewhere in the neighborhood of 10% to 20% of patients with myeloma have smoldering myeloma at diagnosis. And then amyloidosis is approximately 10% of the myeloma. Maybe 4,000 patients per year will be diagnosed.



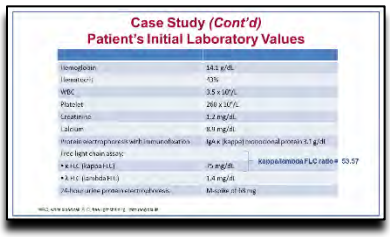
Slide 6 - Smoldering Multiple Myeloma: When to Treat and How to Manage

So, let's talk about the new definitions of smoldering myeloma and when to treat and how to manage it.



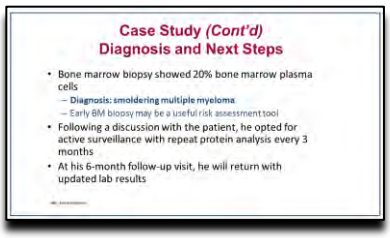
Slide 7 - Case Study

We're going to start with a case study. A 69-year-old man is referred for additional evaluation for an elevated total protein level. The patient has no symptoms. Medical history was completely benign except for a 20-year history of hypertension, which is well controlled with amlodipine.



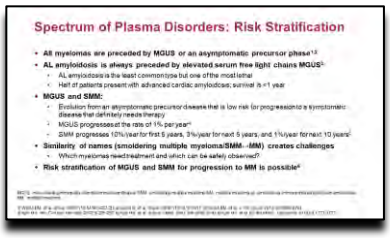
Slide 8 - Case Study (Cont'd): Patient's Initial Laboratory Values

Routine laboratory evaluation was conducted, which showed that CBC was perfectly normal with a normal white count, hemoglobin, hematocrit. The creatinine was at the upper limit of normal, normal calcium. But when a serum protein electrophoresis was conducted, an IgA kappa monoclonal spike was noted at 3.1 grams per deciliter. And further evaluation shows a kappa that's elevated at 75, a lambda of 1.4 with a ratio of 53:1. Looking at a urine protein electrophoresis also showed some Bence Jones proteinuria.



Slide 9 - Case Study (Cont'd): Diagnosis and Next Steps

Based on this monoclonal spike, a bone marrow biopsy was performed and 20% of the bone marrow were involved with light chain restricted plasma cells. And given the lack of end-organ damage, this gave the diagnosis of smoldering myeloma. Following discussion with the patient, we opted for additional surveillance, just active observation with bloodwork every 3 months and with a 6-month follow-up visit returning for updated labs.



Slide 10 - Spectrum of Plasma Disorders: Risk Stratification

So, let's look a little bit at the spectrum of plasma cell disorders and smoldering myeloma and risk stratification. There's more and more data to suggest that, ultimately, all patients who are diagnosed with active myeloma, if you look back, they have had some evidence of monoclonal protein, an MGUS or an asymptomatic precursor phase up to perhaps 30 years prior to the diagnosis of active myeloma.

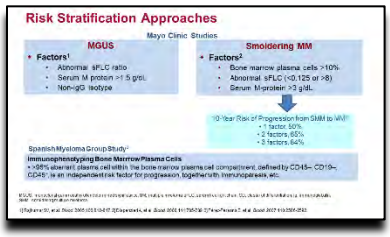
AL amyloidosis is almost always, preceded by some serum free light chain, in the blood, and unfortunately, half the patients will present with cardiac amyloidosis. And those patients have a poor survival.

The evolution from an asymptomatic precursor disease to a symptomatic disease is the major thing that we are looking for and to define whether the patient needs therapy. If you make a diagnosis of a

monoclonal gammopathy of undetermined significance, the progress of these patients averages about 1% per year, though in the first 5 years of the diagnosis of MGUS, there's probably a higher rate of evolution to smoldering or more active myeloma, and then it goes down after a number of years of monitoring.

For smoldering myeloma, this progresses – perhaps 10% of those patients a year for the first 5 years will evolve into active disease with end-organ damage. And then the number also goes down as time goes on, for the next 5 years, 3%, and over the next 10 years, 1%. There is some challenge in terms of the terminology of smoldering myeloma and myeloma, but I think that with the new definitions, this has been clarified.

So, what about risk stratification? Is there something that we can do to help us determine which patients need more closer observation and which patients perhaps need therapy?



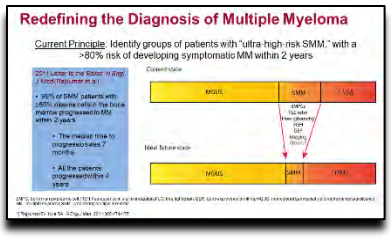
Slide 11 - Risk Stratification Approaches

There's been a number of helpful trials. The Mayo Clinic, in particular, has done a lot of retrospective analyses of their data and of intergroup data. For instance, for monoclonal gammopathy of undetermined significance, there are a number of factors that will increase the likelihood or the risk of a person with MGUS evolving into smoldering or active myeloma. The more abnormal the light chain ratio, a serum protein that's greater than 1.5 gram per deciliter, and the non-IgG isotypes seem to have a little bit more likelihood of evolving to more active disease and, therefore, should be monitored more closely.

Smoldering myeloma, we had known, even before the recent changes that I'll talk about, that bone marrow plasmacytosis greater than 10%, abnormal ratios of a serum free light chain and serum M spikes greater than 3 grams per deciliter suggest an increased risk and, in fact, the risk stratification coding, where if you have one of those factors versus two of those factors, and ultimately, if you have three of those factors, 84% of those patients will evolve to a more active myeloma within 10 years.

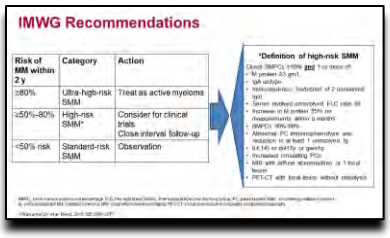
The Spanish group has done a lot of work using flow cytometry to both diagnose minimal residual disease in myeloma but also to identify a higher-risk group with various, flow cytometric characteristics such as being CD19 negative, CD45 negative, etc. What they have found is, if you have greater than 95% of the plasma cells that are aberrant using their tests, then this is an independent prognosticator for a higher-risk smoldering myeloma.

And that's important for understanding some of the European studies that I'll talk about in a second.



Slide 12 - Redefining the Diagnosis of Multiple Myeloma

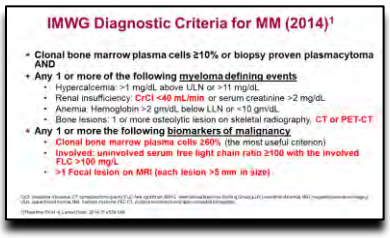
So based on observing or understanding the risk factors in smoldering myeloma, it actually has resulted in a reduction in the amount of patients that actually have smoldering myeloma because we are defining the higher and higher-risk smoldering myelomas as active myeloma, and we're identifying a group of patients with smoldering myeloma that really have much less likelihood of evolving, which are really MGUS. I think that's very helpful because what we really want to do is almost eliminate the smoldering myeloma category to either call it a completely benign monoclonal gammopathy that we can watch infrequently, or decide that this is an active myeloma, this is a malignant plasma cell disorder and, therefore, needs treatment.



Slide 13 - IMWG Recommendations

The IMWG has been really focused on this because it's clinically very important. If we can identify a group of patients that you know within 2 years have a greater than 80% chance of evolving into a symptomatic disease, then as clinicians, we don't want to treat patients 3 months after they need treatment. We want to treat patients 3 months before they need treatment but not 3 years before they need treatment.

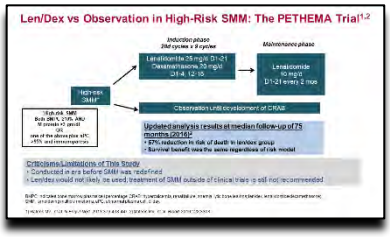
And so here are a number of characteristics that sort of categorize patients into either a standard-risk smoldering myeloma or really closer to an MGUS versus the ultra-high-risk, which really now we consider to be active myeloma versus those in the middle, which are really the ones that we need for clinical trials, those ones who have a 50% to 80% chance of evolving into an active myeloma within 2 years.



Slide 14 - IMWG Diagnostic Criteria for MM (2014)

So based on a retrospective analysis of large investigational trials, in 2014, we added a new diagnosis or new diagnostic categories to define active myeloma. Of course, we've had the CRAB criteria for a long time now – hypercalcemia, renal insufficiency, anemia, and bone lesions. What was added was the SLiM criteria, which are biomarkers of malignancies where you can define a group of patients that do not have the classic CRAB criteria but will develop those criteria within 2 years. And this a clonal bone marrow plasmacytosis greater than 60%. That is the most useful criterion and has been reproduced that this really is an important prognostic factor by a number of studies.

The other is a free light chain analysis where the uninvolved serum free light chain ratio greater than 100 with an involved free light chain greater than 100 milligrams per liter. And then recognizing that we have many much more sensitive imaging studies with our MRIs and PET scans, etc, that if you have more than one focal lesion on these more sensitive imaging studies, then that now will define the patient as an ultra-high-risk smoldering myeloma, or, as most of us consider, active myeloma.



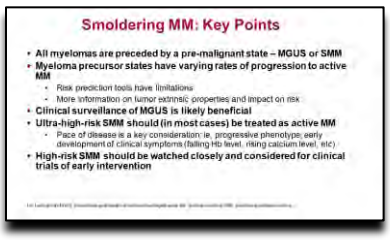
Slide 15 - Len/Dex vs Observation in High-Risk SMM: The PETHEMA Trial

One of the most noteworthy studies in smoldering myeloma, concerning whether or not this should be treated, was done by the Spanish group where they took patients with a high-risk smoldering myeloma. The problem is that they defined it not in the modern era. They defined the high-risk smoldering myeloma based on criteria that they sort of had developed internally. And probably one of the most important criteria was that flow cytometric technique that they used that I talked about earlier. But they took patients who had high-risk smoldering myeloma, which many of these patients we would call active myeloma at this time, and they randomly assigned them lenalidomide and dexamethasone followed by lenalidomide maintenance therapy versus observation.

And, obviously they looked at response rate. And, obviously, we would guess that people who get treated would respond better than people who wouldn't, but what was perhaps surprising was that not only was there a response rate difference but there was a survival difference. In fact, 57% reduction in the risk of death in the patients who received lenalidomide and dexamethasone.

And so this at least started the discussion about whether patients particularly with higher-risk features should be treated rather than observed. But, again, the definition of this group of patients does not

really meet now the modern definitions and in fact, many of these patients we now consider active myeloma and would treat nevertheless.



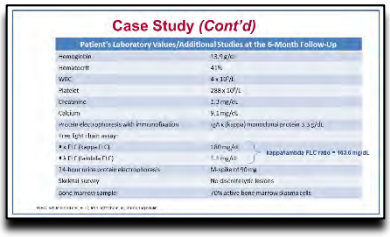
Slide 16 - Smoldering MM: Key Points

Just to summarize the key points in smoldering myeloma, I think it's important to really acknowledge that the first mutation that occurs in plasma cells in a patient who ultimately is going to develop multiple myeloma probably just leads to a benign monoclonal gammopathy or an MGUS state. And then, over time, further mutations seem to lead to a smoldering state. And then even further mutations lead to what we consider active myeloma. So, if you look back, most patients will have some precursor state.

Progression rate though varies to smoldering or active myeloma. And we now have some tools that we can use to predict this. Clinical surveillance of these patients is actually key. And it's just really what frequency should you see these patients? After observation for a number of years, perhaps once a year, observation is sufficient. But during those first 5 years of observation, it's probably a good idea to see the patients more frequently to make sure that you're not just catching someone in the earliest phase of active myeloma versus someone who truly has had a smoldering disease for a while.

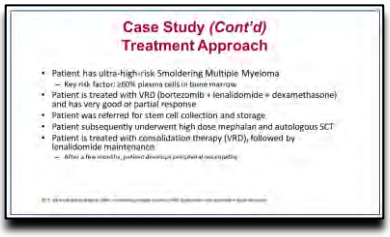
Ultra-high-risk smoldering myeloma is now treated as active myeloma. Since 80% of those patients will develop CRAB criteria within 2 years, why wait for those to occur? And it's clear that treating them is improving their survival. And so early intervention for these high-risk patients is very reasonable.

All right, and so now I guess we move on to the next phase.



Slide 17 - Case Study (Cont'd)

Dr. Hoffman: All right, with that very thorough overview of smoldering myeloma in place, we're going to move back on with our case. So, our patient comes back for the planned 6-month follow-up and we see the labs here. The hemoglobin is okay. The white cells are okay. The platelets remain normal. His kidney function and calcium are good. We see the same IgA kappa monoclonal protein; however, we're dealing with rising numbers. The M spike is 3.1, the free kappa light chains have risen to 180 with a kappa to lambda ratio that's now greater than 100 at 163. We still have the Bence Jones proteinuria, and still have no lytic lesions on our skeletal survey; however, repeat bone marrow biopsy now shows 70% active bone marrow plasma cells. And, obviously, this exceeds that threshold that Dr. Stadtmauer mentioned of 60% and kind of changes the way we would categorize this patient.

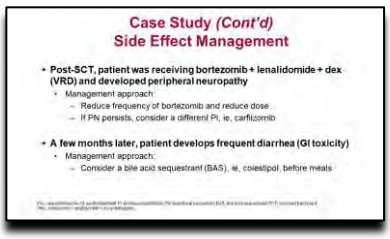


Slide 18 - Case Study (Cont'd): Treatment Approach

So, by that, by exceeding that 60% mark in the bone marrow, this patient now has what we would call ultra-high-risk smoldering myeloma, or really treatment-requiring myeloma, given the very high likelihood of developing overt CRAB criteria in the near term. As per current guidelines, the patient was started on standard induction chemotherapy with the VRD regimen, which is bortezomib or Velcade®, lenalidomide or Revlimid®, along with dexamethasone, and has a good response to that induction.

Subsequently goes on to stem cell collection and storage followed by a stem cell transplant, autologous stem cell transplant using high-dose melphalan and some additional consolidative therapy with the same VRD followed ultimately by lenalidomide maintenance. And this would be a very standard approach for a patient with treatment-requiring multiple myeloma in 2018.

Unfortunately, as is common, the patient did experience some side effects to this therapy, particularly some peripheral neuropathy.

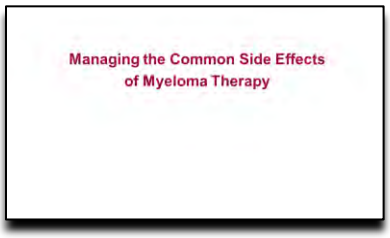


Slide 19 - Case Study (Cont'd): Side Effect Management

This I think kind of bridges us to the next thing that we're going to talk about here, which is managing some of the side effects of myeloma therapy. Myeloma therapy has become exceedingly active and effective but we still have side effects to navigate on a frequent basis.

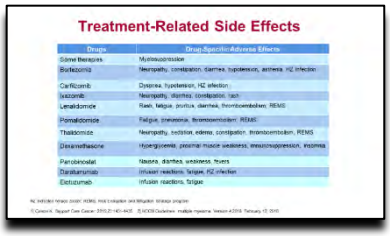
So, again, to reiterate, this patient, after the transplant, received some additional VRD, bortezomib-lenalidomide-dexamethasone, and developed peripheral neuropathy. We're going to get into this in some upcoming slides, but our management approach when a patient is dealing with a side effect of active therapy is to do our best to mitigate those side effects. And one initial move is to reduce the frequency of bortezomib and reduce its dose, as a very frequent side effect of bortezomib is peripheral neuropathy. Should the neuropathy worsen despite these mitigation strategies, we might have to stop the bortezomib and consider a different proteasome inhibitor like carfilzomib, which doesn't really cause any peripheral neuropathy or even perhaps a non-proteasome inhibitor type of therapy.

If we follow our patient along a little bit further, he then developed diarrhea, which is a fairly common side effect of lenalidomide therapy. Again, as we'll come to in some upcoming slides, one approach might be including a bile acid sequestrant like colestipol along with meals. Occasionally, if side effects like diarrhea are not mitigated, by counteractive medications, some of these treatments may need to be stopped and changed.



Slide 20 - Managing the Common Side Effects of Myeloma Therapy

So, with that, we're going to now discuss how we manage the common side effects of myeloma therapy.



Slide 21 - Treatment-Related Side Effects

So here we have a table of some of the frequent treatment-related side effects. And I'll walk through them pointing out some of those that I think are most clinically relevant. Many of the therapies for multiple myeloma cause myelosuppression. It makes some sense here because these medicines are intended to suppress plasma cells in the bone marrow, and there is some bystander effect. Many patients come into these therapies with sick bone marrows, like the patient we just discussed. Seventy percent of the bone marrow factor was occupied by the myeloma. So, coming into initial therapy with the low blood counts is very typical – low white cells, red cells, and platelets.

And then, by introducing therapies like we do that can make that worse in the near term, it's certainly something we have to navigate very carefully. Low white blood cell counts raise the risk of infection. Low red blood cell counts are obviously critical as it relates to fatigue and dyspnea, and low platelets can promote bleeding.

So, to walk through some of the major medications that we use and associated side effects, bortezomib, as we mentioned in our patient, definitely can cause neuropathy. As we'll discuss, there are different administration methods and dosings and schedules that could mitigate this.

Bortezomib can have some GI toxicity, and some patients manifest it as constipation and other diarrhea. And all the proteasome inhibitors – bortezomib, carfilzomib, and ixazomib – can be associated with herpes zoster infection, requiring prophylaxis as we'll come to.

Carfilzomib, a newer generation proteasome inhibitor, has certain advantages in terms of potency over bortezomib and it doesn't cause any peripheral neuropathy, which is a very valuable asset. However, it has a unique kind of side effect profile in that it can induce dyspnea, even fluid retention, and occasionally low blood pressure.

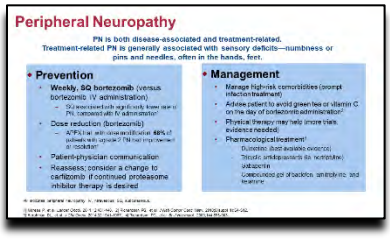
Ixazomib, which is the oral proteasome inhibitor, which is very convenient for patients, has similar effects to bortezomib in that it can cause neuropathy and GI toxicity.

When we talk about the immunomodulators, the lenalidomide, pomalidomide, and thalidomide family, there are certain side effects that overlap, for example, rash and constipation. When we talk about lenalidomide, rash is certainly a major side effect that we have to navigate. Antihistamine therapy, dose modifications are fairly common. Pruritus can precede the rash. Lenalidomide, as we discussed in our patient, can cause some initial constipation, but over time, we see a fair amount of diarrhea. All 3 drugs in this class can be associated with thromboembolism and require prophylaxis to be dictated based on risk. All 3 of these drugs our patients to enroll to the REMS program, because of the side effects related to these drugs, particularly birth defects. Patients have to receive their medicine by those mechanisms.

Pomalidomide has a similar side effect profile to lenalidomide albeit a little bit less in each category in terms of incidence of side effects. And thalidomide, the first of the drugs approved, certainly has the most neuropathy of the 3. And unlike bortezomib, this neuropathy tends to be somewhat irreversible, and so is a really critical side effect to pay close attention to.

Dexamethasone, which is a partner drug, you know, with almost all of the medicines we use in myeloma, in some ways gives the most near-term toxicity. Patients can have hyperglycemia, certainly those that are prone to it to begin with. Proximal muscle weakness with prolonged use, immunosuppression, insomnia, even agitation and anxiety are major issues for patients. And then some of the newer drugs -panobinostat is somewhat notorious for GI toxicity and doses have to be carefully adjusted.

The newest class of medication, the monoclonal antibody, daratumumab and elotuzumab, both share the risk of infusion reactions, which can be mitigated with premedication but have little in the way of longer-term side effects, although patients do require prophylaxis for herpes zoster, the same as they do with the proteasome inhibitors.



Slide 22 - Peripheral Neuropathy

So, to dive deeper into a couple of the side effects mentioned in that table, peripheral neuropathy. Peripheral neuropathy certainly can be treatment-related, as I've mentioned, but it can also be disease-associated. There's many mechanisms where monoclonal gammopathies can induce neuropathy. So, again, some of these patients come in with preexisting nerve damage either by paraneoplastic mechanisms or by amyloidosis or even cryoglobulinemia, etc.

Treatment-related neuropathy is generally sensory in nature and numbness or pins and needles, often in the hands and feet, the typical glove and stockings type sensory neuropathy that we talk about in diabetics.

The ways that we mitigate this are using... Velcade® (bortezomib) was initially approved as a twice weekly schedule, but it's been shown that using somewhat higher doses on a weekly schedule lessens

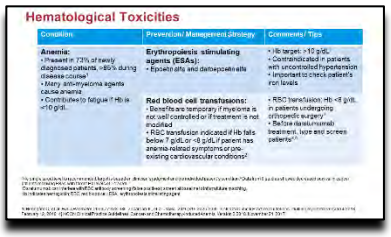
the degree of neuropathy. Also, bortezomib initially approved as an IV administration. When given subcutaneously as it is done generally in practice in 2018, is associated with significantly lower rates of neuropathy with similar efficacy.

I had mentioned earlier that bortezomib-induced neuropathy is generally at least somewhat reversible on cessation of the drug, and, therefore, really close monitoring for the evolution of neuropathy is critical. When patients develop neuropathy, dose reduction schedule adjustments can often result in improvement. At the very least, stopping bortezomib before patients have very severe neuropathy is really mandatory.

And this gets to what is extremely critical component of taking care of myeloma patients, and that's good communication. Patients need to feel open to explain the side effects that they're having so that we can react to those side effects in real time.

And, finally, as I mentioned earlier, carfilzomib, a very potent proteasome inhibitor, is associated with little to no neuropathy and is a good option for patients dealing with this issue.
A few other things to mention are that, obviously, comorbidities need to be managed as it relates to neuropathy. For example, good glycemic control is important. In myeloma, infectious risk is foremost on our minds, and we have to treat those quickly.

The activity of bortezomib is somewhat impaired with green tea or EGCG in the system, and green tea should certainly be avoided as well as high-dose antioxidant therapy like vitamin C. Makes common sense that physical therapy and exercise are valuable here. And then there are pharmacologic treatments for patients with clinically significant neuropathy including duloxetine, which has fairly good evidence; the tricyclic antidepressants; gabapentin, which is used very commonly; and then baclofen, amitriptyline, and ketamine compounded gels.



Slide 23 - Hematologic Toxicities

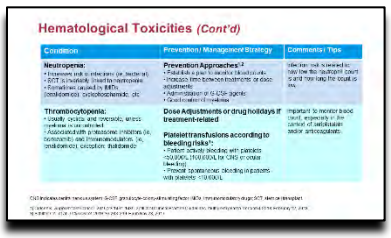
Hematologic toxicity. As I mentioned earlier, many patients come in with low counts and then we give them medicines that can lower the counts. And when we talk about anemia, this is very common, which is the A criteria in the CRAB that Dr. Stadtmauer had mentioned. And so, this is common on presentation and even more common with treatment because many of our drugs cause anemia. And, certainly, when patients have progressive anemia and fatigue, this is something that needs to be addressed. Fatigue is often multifactorial, but anemia is a potentially fixable component of that.

And how do we do that? We do that with booster shots, the erythropoietin stimulating agents (ESA) like epoetin alfa and darbepoetin, as well as transfusions when required. In modern-day medicine, we do try to limit our red cell transfusions. We typically use them when patients are below 7 grams per deciliter or below 8 grams per deciliter with associated symptoms or preexisting cardiopulmonary problems.

We use the ESA injections to keep patients' hemoglobins above 10 if at all possible. You certainly do not want to aim for targets above 12 as that has been shown to be potentially dangerous. Patients with uncontrolled hypertension are at some risk with these drugs and so blood pressure needs to be controlled. And these shots work by stimulating red cell production in the marrow, but if the marrow is iron depleted, doesn't have the resources to make those red cells, all the screaming at the marrow in the world with these injections isn't going to help, so patients really need to be iron replete.

One final note as it relates to red cell transfusions is daratumumab, a drug I mentioned earlier, the monoclonal antibody, is associated with some difficulties in terms of screening patients for antibodies in transfusing them. And patients need to have good red cell phenotyping done before their initial

infusion of daratumumab and they need competent blood banking to administer what will show up if somewhat incompatible blood because of the daratumumab.

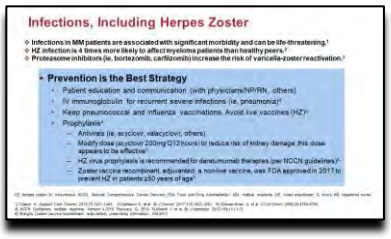


Slide 24 - Hematologic Toxicities (Cont'd)

So, moving forward with hematologic toxicities, we now have neutropenia and thrombocytopenia to discuss. Neutropenia, low neutrophil count, is associated with an increased risk of infections. Neutropenia and infection is a potentially life-threatening combination. Patients that undergo stem cell transplant are always neutropenic for a period of time afterwards and, certainly, many of our drugs, like immunomodulators and conventional chemotherapy drugs like cyclophosphamide, do this very commonly.

The way we manage patients as it relates to neutropenia is with mitigation of dose or schedule of drugs that are causing said neutropenia, or using a booster shot, a la the ESA drugs, for neutropenia we use G-CSF agents like Neupogen® (filgrastim) for patients with myeloma and high-risk neutropenia. Finally, thrombocytopenia is a very important problem that we face in the clinic. It's associated with many of our drugs, proteasome inhibitors and immunomodulators, separate from thalidomide, which is the least cytopenia-inducing in that class by a long ways.

Thrombocytopenia, obviously, at low levels, patients are at risk for bleeding. Certainly, when the counts get below 10,000, spontaneous life-threatening bleeding can occur. And this becomes a really particularly critical problem for us because, as mentioned earlier, all the immunomodulators are associated with DVT risk and patients require DVT prophylaxis. So, one can imagine a patient requiring immunomodulator therapy who develops significant thrombocytopenia, you get stuck between a rock and a hard place needing to anticoagulate to prevent blood clots but being limited in the ability to anticoagulate because of bleeding risk.

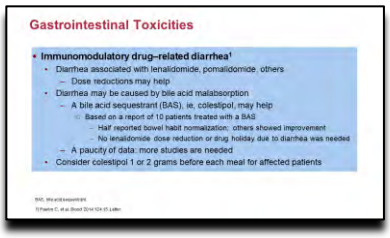


Slide 25 - Infections, Including Herpes Zoster

And then infections, which I think most of us would deem the biggest risk for our patients, certainly the most life-threatening risk. The myeloma itself increases the risk of infection. Many patients come in with their immune system significantly impaired and then our treatments impair the immune system further at very least in the beginning until the myeloma gets under better control. Herpes zoster infection is 4 times more likely to affect myeloma patients than healthy peers. We now have a zoster vaccine that is recombinant, not live, that may be a benefit to our patients although it's unclear how much this will prevent zoster in this patient population.

So particularly for patients on proteasome inhibitors like bortezomib, carfilzomib, and even the monoclonal antibodies like daratumumab, patients do require antiviral prophylaxis specifically usually acyclovir in twice daily dosing, with the dose dependent somewhat on renal function.

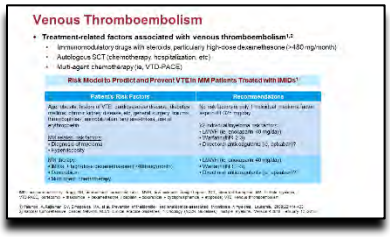
Other vaccinations like pneumococcal and influenza vaccinations, influenza being seasonal, should be done, but live vaccines need to be avoided. Some patients might benefit from IV immunoglobulin for recurrence of your infections and hypogammaglobulinemia usually defined as an IgG level of less than 500.



Slide 26 - Gastrointestinal Toxicities

Gastrointestinal toxicities are also very relevant, particularly the immunomodulators like lenalidomide can cause fairly significant chronic diarrhea. This has been found to be caused, in large part, by bile acid malabsorption and, therefore, can be mitigated by bile acid sequestrants like colestipol. And in common practice, this is often a first move for patients that are gaining significant benefit from a drug like lenalidomide but suffering from life-affecting diarrhea.

Should colestipol, often given as 1 or 2 grams before each meal, be effective, patients can be maintained on the drug. For patients that continue to have life affecting diarrhea, lenalidomide doses might need to be dropped or the drug might need to be stopped.

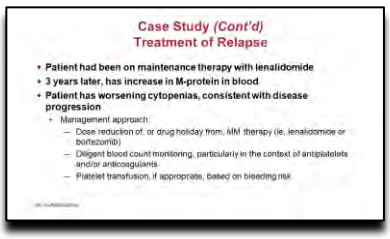


Slide 27 - Venous Thromboembolism

And then we get to venous thromboembolism, which I mentioned earlier. Certainly, all malignancies are associated with an increased risk of thromboembolism and then there are risk factors unrelated to cancer like obesity or sedentary lifestyle. However, we know that the immunomodulator drugs – lenalidomide, thalidomide, pomalidomide – particularly when combined with steroids, particularly when combined with higher-dose steroids, are associated with a significantly increased risk of venous thromboembolism. Being inpatient receiving stem cell transplants, receiving aggressive inpatient chemotherapy, like VTD-PACE (Bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide), also increase risks.

So, the way we mitigate these risks is to first assess the patient's risk factors. Should the patient have a history of venous thromboembolic disease, obesity, cardiovascular disease, be generally sedentary, have hereditary risk factors, etc, they're deemed higher risk. For patients that have no risk factors or 1 of those risk factors, an aspirin is effective in and of itself to prevent thromboembolism, doses ranging from 81 to 325 milligrams per day. Those with 2 or more of said risk factors require more aggressive anticoagulation either with low-molecular-weight heparin injection, warfarin, or direct oral anticoagulants.

I think that takes us to the end of our review of venous thromboembolism and side effects of myeloma therapy.



Slide 28 - Case Study (Cont'd): Treatment of Relapse

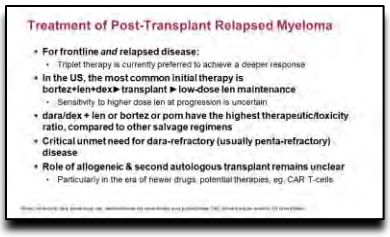
Dr. Stadtmauer: So to continue our case discussion, the patient has now been on maintenance therapy with lenalidomide and has done very well for 3 years. But then there's an increase in the serum monoclonal protein. Additionally, the patient starts having worsening cytopenias, which is somewhat common when patients are on maintenance lenalidomide, and so it's always possible it is the drug itself as you've heard from Dr. Hoffman. So, reduction of the drug, a drug holiday is sometimes useful. But in this case, the M spike is starting to rise and so more likely the cytopenias are related to disease progression.

Slide 29 - Post-Transplant Relapsed Myeloma

So, what happens after initial therapy when a patient relapses their myeloma?

Slide 30 - Multiple Myeloma: Relapse Is Inevitable

Unfortunately, for the vast majority of patients with myeloma with the current therapies that we have, relapse is expected. Sometimes it is within 3 months, sometimes it's within 3 decades, but the high likelihood is that there still are some residual malignant plasma cells in the patients. And so most of our work is how to try to prevent that relapse from happening, how to predict the patients who are going to have the highest likelihood of relapse, and, therefore treat them perhaps in a different way. In fact, given the nuances and the variabilities of various treatments and prognostic factors, every patient needs to have an individualized treatment plan.



Slide 31 - Treatment of Post-Transplant Relapsed Myeloma

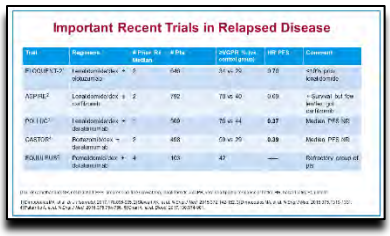
We're very fortunate though that there have been a number over the last decade of tremendously active agents for myeloma. Despite the fact that with frontline therapy with the triplet therapy of a immunomodulatory agent, a proteasome inhibitor, and a corticosteroid, and frequent high-dose alkylating agent and stem cell transplant and maintenance, disease despite using all of those agents, there still are many other agents.

We have the first-generation immunomodulatory agent thalidomide; the second-generation lenalidomide; and then the third-generation pomalidomide. We have the first-generation proteasome inhibitor bortezomib. We have the second-generation carfilzomib and an oral agent ixazomib. And then we have the monoclonal antibodies, the elotuzumab and the daratumumab. And combining all of these combinations really leads to almost a dizzying array of options for the patients with relapsed disease.

Since the most common initial therapy is now triple therapy with bortezomib, lenalidomide, and dexamethasone with or without transplantation and then a maintenance program, frequently those agents are not the initial agents that we'll use once the patient has progressed.

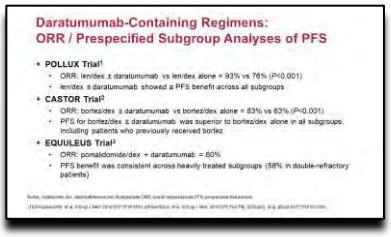
What I tend to do is sit down and look at the treatments that the patients have received in prior cycles of therapy and then just make a list every time I see a patient who is progressing of what are those options. Daratumumab-containing regimens, carfilzomib-containing regimens, and pomalidomide-containing regimens are the most common combinations that we use. And it's really mixing and matching.

There is more and more emerging data that daratumumab with either lenalidomide or bortezomib or pomalidomide have very high therapeutic to toxicity ratios and really, in many ways, the current problem is now in the patient who is refractory to daratumumab and lenalidomide and pomalidomide and carfilzomib, which we call penta-refractory disease. And then, the continuing questions of the roles of allogeneic, autologous stem cell transplant in the relapse setting and then, of course, the new therapies.



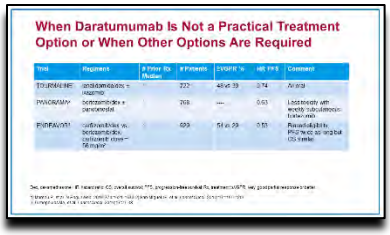
Slide 32 - Important Recent Trials in Relapsed Disease

There have been a number of very important trials in the relapse setting that have been able to inform our decision-making. We know that once a patient has progressed using just lenalidomide and dexamethasone or just bortezomib and dexamethasone, which were really our primary available agents 5 years to a decade ago, are not optimal. And it looks like triple therapy with the addition of a monoclonal antibody, elotuzumab-len-dex, is superior to len-dex. Daratumumab-len-dex is superior to len-dex. Daratumumab-bortezomib-dex is superior to bortezomib-dex. And then carfilzomib len-dex is superior to len-dex.



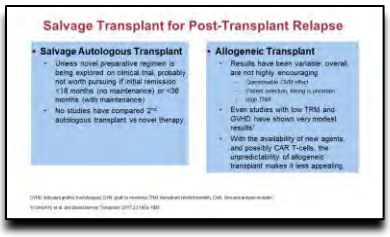
Slide 33 - Daratumumab-Containing Regimens: ORR / Prespecified Subgroup Analyses of PFS

The daratumumab-containing regimens have led to a lot of excitement, particularly with 2 trials called the Gemini trials, one POLLUX and the other CASTOR, which have compared the addition of daratumumab to either a bortezomib-lenalidomide base or I mean a bortezomib-dexamethasone base or a lenalidomide and dexamethasone base. And in both cases in randomized trial, very clear evidence of significant improvement in response rate, progression-free survival and throughout all groups of the patients that have been treated. And then further studies looking at the response rate with pomalidomide added to daratumumab also show significant response rates in very refractory patients.



Slide 34 - When Daratumumab Is Not a Practical Treatment Option or When Other Options Are Required

But daratumumab, either once it's been used and then the patients progress, or there are circumstances where the daratumumab is not a practical option, there have been other combinations in this setting, either ixazomib, lenalidomide, and dexamethasone the oral proteasome inhibitor. The, first in class HDAC inhibitor panobinostat has been shown to improve progression-free survival over bortezomib and dexamethasone. And then the combinations of carfilzomib and dexamethasone, either by itself or with the combination with immunomodulatory agents have been very active.



Slide 35 - Salvage Transplant for Post-Transplant Relapse

In terms of the use of an autologous transplant once a patient has progressed, the patients who benefit the most from consolidating a remission after relapse are the ones who've had a prolonged period of remission after their first autologous stem cell transplant. And then, it is somewhat reasonable to consider doing a second stem cell transplant after going into a remission for relapsed disease. But, for patients who have less than 18 months' worth of remission from their first transplant, then the benefits of doing a consolidative autologous stem cell transplant seem much less.

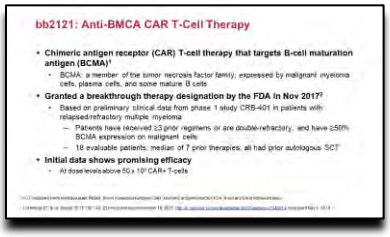
Nevertheless, it is always very helpful to have stem cells stored away because there comes a point sometimes when the disease or the treatments have caused significant cytopenias, and it's really difficult for the patient who has relapsed disease to move on to other therapies because of intolerance of those therapies. And then sometimes, and, in fact, the way I really think of it, of this setting as the salvage transplant is when you have someone who is progressing but too sick to get to other therapies. You can sometimes use high-dose melphalan and an autologous transplant to sort of right the ship and knock the disease into a remission, perhaps transient, but enough to get blood counts better and then be able to proceed with some of the other newer therapies.

In terms of allogeneic transplant, we've always had some concern about allogeneic transplant in the setting of multiple myeloma, mainly because the average age of the patient with myeloma is approximately 70 years. And so the treatment-related or regimen-related toxicities and the treatment-related mortality is high for allogeneic transplant in that setting.

However, there is a small subset of patients, particularly those who have very nasty biology and are younger patients with perfectly matched donors, where an allogeneic transplant has been very successful. And so it is a useful thing to keep in our list of potential treatments, particularly for that subset of patients. But it is true that with the emerging newer therapies that you'll hear about with CAR T-cells, etc., that perhaps creating a graft-versus-myeloma effect with your own T-cells, which will not lead to a graft-versus-host effect, may be the best approach.

Slide 36 - Venetoclax: A Promising Targeted Therapy

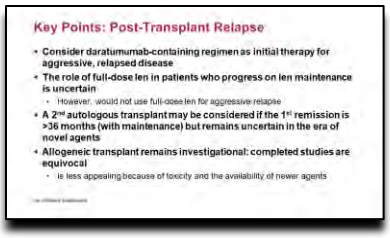
There are a couple of promising new therapies that I wanted to just highlight. One of them is venetoclax. You know, venetoclax is the oral BCL-2 inhibitor, and it has been shown to be very active in lymphoid malignancies, in chronic lymphocytic leukemia, particularly those with overexpression of BCL-2. Well it turns out that in myeloma, a subset of patients, approximately 15% to 20% of patients, have the 11;14 translocation or have overexpression of BCL-2. And there's some very promising studies that suggest that this oral agent, either by itself or in combination with proteasome inhibitors, can induce a high response rate in patients with this subtype of myeloma. And perhaps this is our first real sort of classically targeted small molecule for myeloma.



Slide 37 - bb2121: Anti-BCMA CAR T-Cell Therapy

The other major area of excitement, of course, is the CAR T-cell therapy. As you know, this therapy is now FDA-approved for children with relapsed acute lymphocytic leukemia and adults with non-Hodgkin's lymphoma. When directed against CD19, we have clear evidence that for that group of patients, there are long-term survivors. And so the next disease that has been targeted has been multiple myeloma. In general though, it has been a different target.

BCMA, the B-cell maturation antigen, is almost universally expressed on malignant plasma cells and not many other cells within the body and, therefore, is potentially an ideal target. And as you know, there have been a number of studies now that suggest a high activity. In fact, some studies, up to 100% of patients who have been infused this BCMA-directed CAR T-cells have had responses. And there are reports of patients with relapsed and refractory myeloma who are now over two-and-a-half years in strict complete remission after just the infusion of these cells. So very promising data, though the most recent data suggests that perhaps 50% of the patients will relapse within one year of this therapy. And so there remains a lot of work to be done in terms of engineering these cells to be more broadly applied to our patients with myeloma.

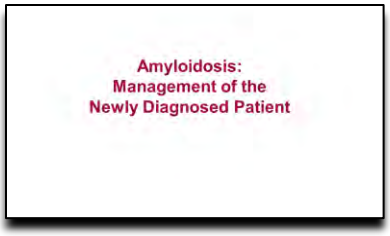


Slide 38 - Key Points: Post-Transplant Relapse

So, when the patient relapses, consider various regimens – pomalidomide-containing regimens, carfilzomib-containing regimens – but, in particular, daratumumab-containing regimens appear to be very active. And for the aggressive relapsed disease, if a patient has more of an indolent or biochemical progression, sometimes just adjusting the dose of lenalidomide and perhaps adding some steroids can right the ship and bring the patients back into remission. But many of those patients require a real alteration of therapy soon.

I think a second autologous transplant could be considered for the patients who've had long remissions, or as a true salvage therapy to right the ship and bring the patients eligible for other therapies.

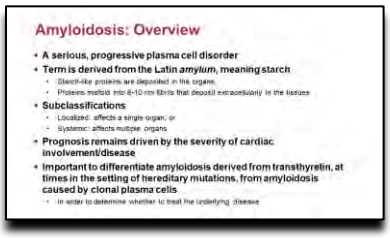
And allogeneic transplant – remains unclear, the broad benefit for that modality, but there still remains a select group of patients, particularly younger with bad biology, where this may be a very effective therapy.



Slide 39 - Amyloidosis: Management of the Newly Diagnosed Patient

Okay, so with that, we're going to move on to talk a little bit about a sister plasma cell disease to multiple myeloma and a condition that afflicts a percentage of myeloma patients over the course of their disease, namely, amyloidosis.

And we're going to talk about diagnosis and management.

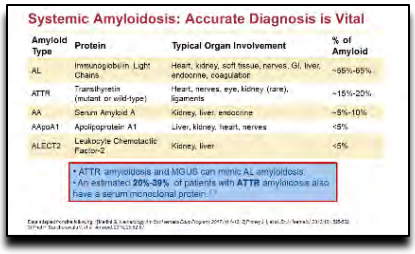


Slide 40 - Amyloidosis: Overview

So, what is amyloidosis? Well, amyloidosis, at least the form that we're going to focus on here, which is light chain or primary amyloidosis, is a serious, progressive plasma cell disorder. The word amyloid is derived from the Latin amylum meaning starch. And what occurs is this starch-like kind of a waxy protein gets deposited in multiple organs – heart, kidneys, liver, nerves. On a microscopic analysis, what you find is very small 8 to 10 nanomolar fibrils that deposit extracellularly in the tissues of these organs, causing dysfunction.

We do subclassify patients. A few will have what is called localized amyloidosis affecting a single organ, sometimes the pharynx, the bladder, or the lungs, often not even requiring total body therapy. Or the more common that we're going to focus on, which is systemic amyloidosis, where this waxy protein is deposited widely, affecting multiple organs.

The prognosis of this disease primarily hinges on the severity of the organ damage, most importantly the cardiac involvement. And it's extremely important to make sure the diagnosis is correct because there are other forms of amyloidosis that we'll touch on. One in particular is called transthyretin amyloidosis and differentiating the 2 diseases can be tricky. And treatment and management, in general, is very different.



Slide 41 - Systemic Amyloidosis: Accurate Diagnosis is Vital

So here we have an overview of the major forms of systemic amyloidosis. And, again, I'll highlight that accurate diagnosis is vital and misdiagnosis is somewhat rampant. The sister disease to multiple myeloma, the plasma cell disease, the blood disorder is AL amyloidosis. In this disease, abnormal plasma cells, not unlike the spectrum of MGUS, the smoldering myeloma to myeloma that we've been talking about, produce an abnormal protein and an immunoglobulin light chain, kappa or lambda light chains. These light chains then misfold into that waxy material called amyloid and land in the heart, kidneys, soft tissues, etc. This is the most often diagnosed form of amyloidosis certainly in the developed world.

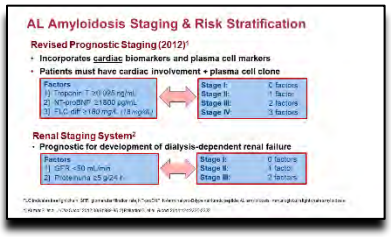
Amyloid from transthyretin, whether hereditary in nature, meaning inherited from mother or father, or wild type in nature, meaning without a hereditary mutation, is the second most common diagnosed form in the developed world. There are different subsets of this disease where different organs are involved preferentially. However, multi-organ system involvement can occur the same as in AL. The cardiac involvement is the most important here as well.

The other 3 forms listed here are more rare. AA or secondary amyloidosis is more common in areas of the world where chronic infections aren't as well treated and chronic inflammatory diseases aren't as well treated. Much more rare to see in the United States. For example, this disease most commonly affects the kidneys, causing nephrotic range proteinuria. And then other, more rare hereditary disorders like apolipoprotein A1 and others, and ALECT2 often affecting the liver, are more rarely seen.

In clinical practice, it's often most important to differentiate AL from ATTR. And this gets tricky because many patients with hereditary mutations in transthyretin can also have monoclonal gammopathies. Some of those monoclonal gammopathies can be incidental and benign and some of those monoclonal gammopathies can be responsible for an abnormal light chain, causing AL amyloidosis. A patient who may have ATTR or may have AL requires a very careful evaluation.

I'd go on to say that monoclonal gammopathies are more common in African Americans and ATTR, or TTR mutations, rather, are more common in African Americans as well. So, again, accurate diagnosis here is vital.

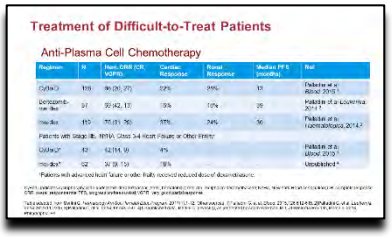
One further point in this regard, ATTR is a disorder of abnormal protein folding. It is not a blood disease. It is not a plasma cell disease. It's not treated with chemotherapy. AL is a blood disorder, like multiple myeloma, treated with medicines like we use in multiple myeloma, as we will come to, and so, therefore, the treatments could not be more different, even though under the microscope the amyloid material is the same.



Slide 42 - AL Amyloidosis: Staging & Risk Stratification

So, let's focus on AL amyloidosis 'cause this is the related disease to multiple myeloma. There are prognostic staging systems with this disease, like in many blood disorders and cancers, but here most of the prognosis hinges on organ dysfunction and less so on variables associated with the plasma cell disease. Particularly, the cardiac patients' troponin, NT-proBNP, and the free light chain differential can stratify patients into 4 stages with widely different prognoses.

In the renal staging systems, we can predict the likelihood of developing dialysis-dependent renal failure by looking at GFR and the amount of proteinuria. I'll make the point that in amyloid renal disease, you see albuminuria. You see nephrotic range proteinuria with the associated clinical sequelae of that including edema and high cholesterol. In multiple myeloma when we talk about proteinuria, we're usually talking about light chains in the urine or the Bence Jones proteins.

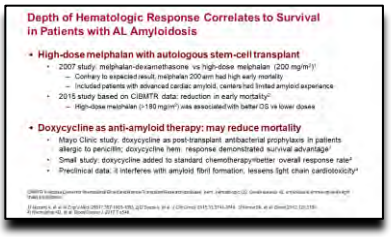


Slide 43 - Treatment of Difficult-to-Treat Patients

So how do we manage AL amyloidosis? Well, in this disease, the problem is abnormal malignant plasma cells, the same as with multiple myeloma. It's a more rare disease than multiple myeloma and trials have been conducted in a much slower pace and so, therefore, many of the meds are simply borrowed from the treatment of multiple myeloma as seen here on this table.

Commonly in practice, we use cyclophosphamide, bortezomib, and dexamethasone, which is the CyBorD regimen, which has very high hematologic response rates. When patients have hematologic response, meaning a drop in their abnormal light chains and M spike, etc, organ responses can follow, cardiac and renal in particular.

Melphalan and dexamethasone either orally, or melphalan given in high doses in the setting of autologous stem cell transplant, are also certainly still used, although high-dose therapy with autologous stem cell transplant is applicable to a smaller percentage of these patients than in myeloma because they tend to be more sick at the time of diagnosis.



Slide 44 - Depth of Hematologic Response Correlates to Survival in Patients with AL Amyloidosis

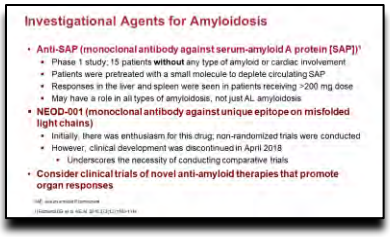
So, the principle of managing patients with AL amyloidosis is not very different from that in multiple myeloma which is you want rapid and deep reduction in the abnormal antibodies. It's been shown in this disease, in particular, that depth of hematologic response has a direct correlation to survival. And this makes sense because it's those pathologic light chains that are forming the amyloid which cause continuous organ damage. So, the more rapidly and deeply you can get those removed from circulation, the more organ recovery you can see.

So, in terms of high-dose melphalan with autologous stem cell transplant, which is still a very commonly used upfront therapy in this disease, there was one randomized trial with oral melphalan and dexamethasone versus high-dose melphalan in the setting of stem cell transplant. The results of this study showed that the melphalan at high doses with stem cell transplant had a very high early mortality, and the study favored oral melphalan and dexamethasone.

There are some criticisms of this study because around 25 percent of patients on the transplant arm suffered transplant-related mortality. And this is far higher than when currently applied to selected patients. So still 2018, most of the major amyloid myeloma centers consider high-dose melphalan but are selective about the patients that they take into that treatment. Lowering the dose of melphalan is one of the ways that we can make this safer for more borderline patients.

Interestingly enough, separate from lowering the pathologic light chains with anti-plasma cell therapy, a gentle antibiotic, namely doxycycline, has been shown to have anti-amyloid properties. And it's been shown to do this in a preclinical model, which it would show that it interferes with amyloid fibril formation and lessens light chain cardiotoxicity.

And there are some nonrandomized placebo-controlled trials but still compelling data that shows that giving doxycycline is associated with improvements in survival in patients that are post-transplant, and when added to standard chemotherapy, associated with improved outcomes.



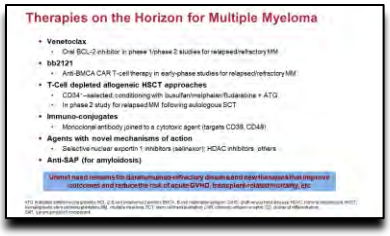
Slide 45 - Investigational Agents for Amyloidosis

As you have seen, the typical approach for AL amyloidosis is targeted on the hematologic portion of this disease, namely, the plasma cell disease, a la multiple myeloma. However, patients commonly will ask, "Well, doctor, you are going to treat the blood disease and stop further damage, but what can you do to improve my heart, my kidneys, my liver, and my nerves that have already been affected?" And we have entered an era where anti-amyloid therapies mechanisms to help remove amyloid from organs are at least being tested.

There's an anti-SAP drug, a monoclonal antibody against serum amyloid, a protein, that has been shown in clinical trials to be associated with improvement in amyloid burden. And this would not be specific for AL but potentially applicable to other forms of amyloid as well.

NEOD-001, which is a monoclonal antibody targeting a unique epitope on misfolded light chains, had a lot of promise, and there was a lot of enthusiasm in the patient population with this as well as in the amyloid-treating community. But, unfortunately, recently, it has been declared that the phase III randomized trial showed no benefit to this drug and the production of the drug was discontinued. Ultimately, we need to be able to wage this battle on 2 fronts, the blood disease and the organ dysfunction. We're optimistic that continued trials with novel anti-amyloid therapies will continue and, ultimately, some drugs will be approved in that setting.

Slide 46 - Emerging Therapies for Patients with Myeloma
And then, finally, we're going to move on to emerging therapies for patients with multiple myeloma. Dr. Stadtmauer did an excellent review of many of these things, but we're going to talk about them on a single slide.



Slide 47 - Therapies on the Horizon for Multiple Myeloma
These are some of the most exciting treatments for multiple myeloma, looking forward.

As Dr. Stadtmauer mentioned venetoclax has been shown to have very exciting efficacy in patients with a translocation of 11;14. It is certainly already being considered in off-label use for this patient population and, more importantly, in clinical trials. Hopefully, we can get the indication to use this potentially even earlier in the course of disease for those patients.

I think many of us in the field would say that the CAR T therapies, possibly the anti-BCMA CAR T therapies, are amongst the most exciting developments in the field of multiple myeloma and give some hopefulness, potentially, into the curability of this disease at some point in the future, hopefully the near future.

It was mentioned that allogeneic stem cell transplant continues to be looked at, potentially with modifications in T-cell depletion to make it a safer approach. However, historically the lack of clear efficacy and certainly the high toxicity has dampened enthusiasm that this will be broadly applied to our patients.

Immunoconjugates are also a very exciting related approach where monoclonal antibodies targeting antigens on plasma cells are joined to cytotoxic agents. Drugs in this field have already been approved in other malignancies like lymphoma, and there are many being tested in multiple myeloma. And agents with novel mechanisms of actions like selinexor, targeting nuclear export proteins, other HDAC inhibitors are also being tested. The more weapons that we have for this disease, the better. The complexity of how we combine these medicines and how we order them is a pleasant complexity to have because it implies that we have many more options for our patients. And then finally on the amyloid front, I had mentioned anti-amyloid therapies will hopefully join anti-plasma cell therapies for that patient population. And still, going forward certainly for patients that failed daratumumab-based salvage regimens, the conventional options that we have are somewhat limited. So the hope is with some of the above, particularly perhaps the CAR T approach, we're going to have more compelling options for our patients that fit into this category.

Slide 48 - Discussion / Conclusion
And I'll offer a few of my thoughts as we conclude and then Dr. Stadtmauer I am sure will want to do the same. Those of us that treat myeloma patients in the clinic are really excited with where things are and where things are headed.

We've seen myeloma come from a disease with a prognosis measured in a few years to a disease where it's really hard to tell patients what the prognosis is looking forward because we haven't seen the full survival benefits of drugs like daratumumab, which was approved only a few years ago. And we can only imagine how CAR T-based approaches and other targeted approaches are going to improve prognosis going forward. It's certainly my hope that myeloma in a relatively near term, at least for most patients, can become a chronic managed illness or perhaps even a curable condition.

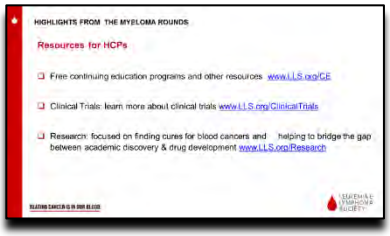
And with that, I'll allow Dr. Stadtmauer to voice some of his thoughts about the future directions in multiple myeloma.

Dr. Stadtmauer: Thank you, Dr. Hoffman. I agree completely that this career in treating patients with multiple myeloma has been a very rewarding and exciting time over the last decade or so. We've seen patients with very limited options and very low likelihood of long-term survival go, to now we expect patients with the initial therapies to respond beautifully to therapy and to have prolonged remissions and prolonged life.

Unfortunately, we still have the vast majority of patients progress. And there have been just a myriad of new therapies with both novel chemotherapies, as well as immunotherapies, as well as cellular therapies for this group of patients. And much of the work over the next few years is going to be defining the best sequence and the best combinations of these agents and really looking at the role of these novel cellular therapies and other immunotherapies and how it all mixes in. But I think there's a very bright future for our patients with myeloma.

Slide 49 – Thank You

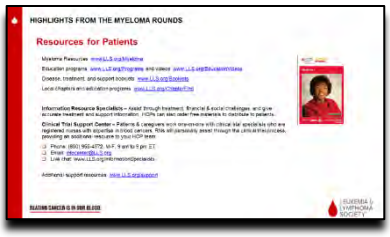
Thank you, Dr. Stadtmauer and Dr. Hoffman for your very clear and informative presentations.



Slide 50 – Resources for HCPs

I am now pleased to share information on resources for you and for your patients – all free of charge.

Please visit our website to access web based and in-person programs offering free CME and CE, as well as information on clinical trials, research and other blood cancer information.



Slide 51 – Resources for Patients

Resources for your patients are listed here and include Myeloma booklets, webinars, videos, in-person programs, financial assistance and more. We encourage you to refer your patients to the Information Resource Center to link them with services to supplement the information you provide. Staffed by master level oncology professionals they provide personalized information about resources and help patients and caregivers understand disease, treatment, side effect management and other survivorship challenges. Your referral helps patients develop the confidence to ask questions and seek information and support. Information Specialists can also send quantities of LLS booklets and other materials to your office at no charge or can send them directly to patients.

The LLS Clinical Trial Support Center provides a personalized service for patients seeking treatment within a clinical trial. Clinical Trial Specialists are registered nurses with expertise in blood cancers. They speak with patients to understand their goals, help them decide if a clinal trial is right for them, search for trials, and provide information to bring back to their healthcare team to discuss. These services are complimentary to the support you and your team provide. We hope you will reach out to LLS for these resources and that they are helpful for you and for your patients.