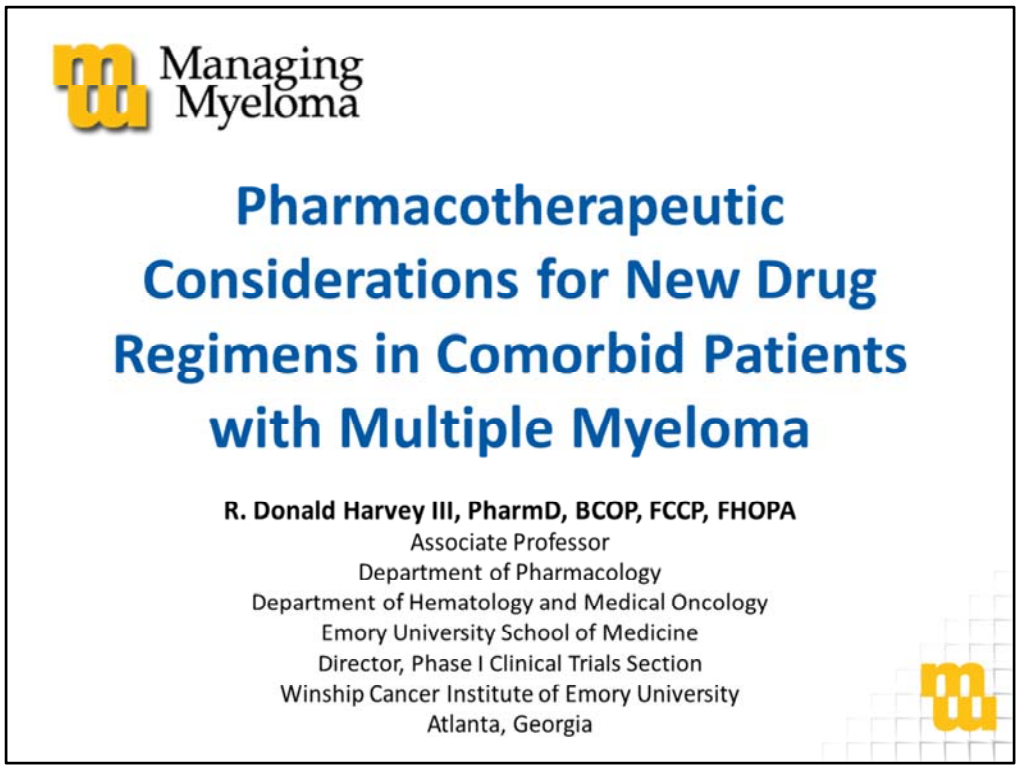
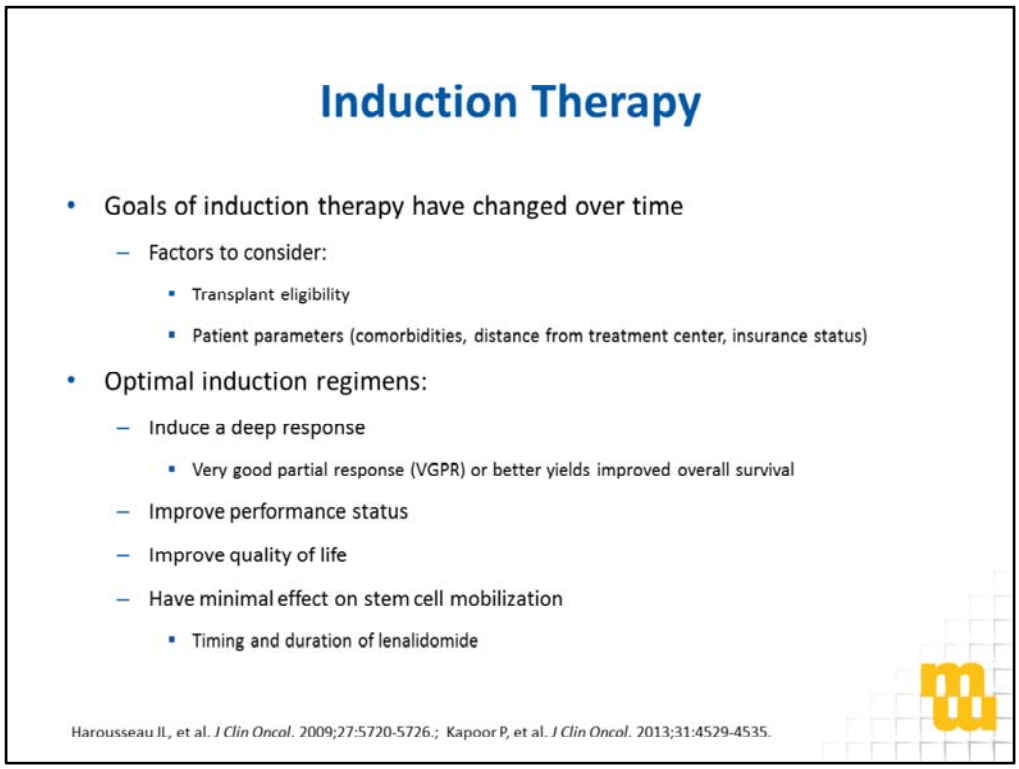
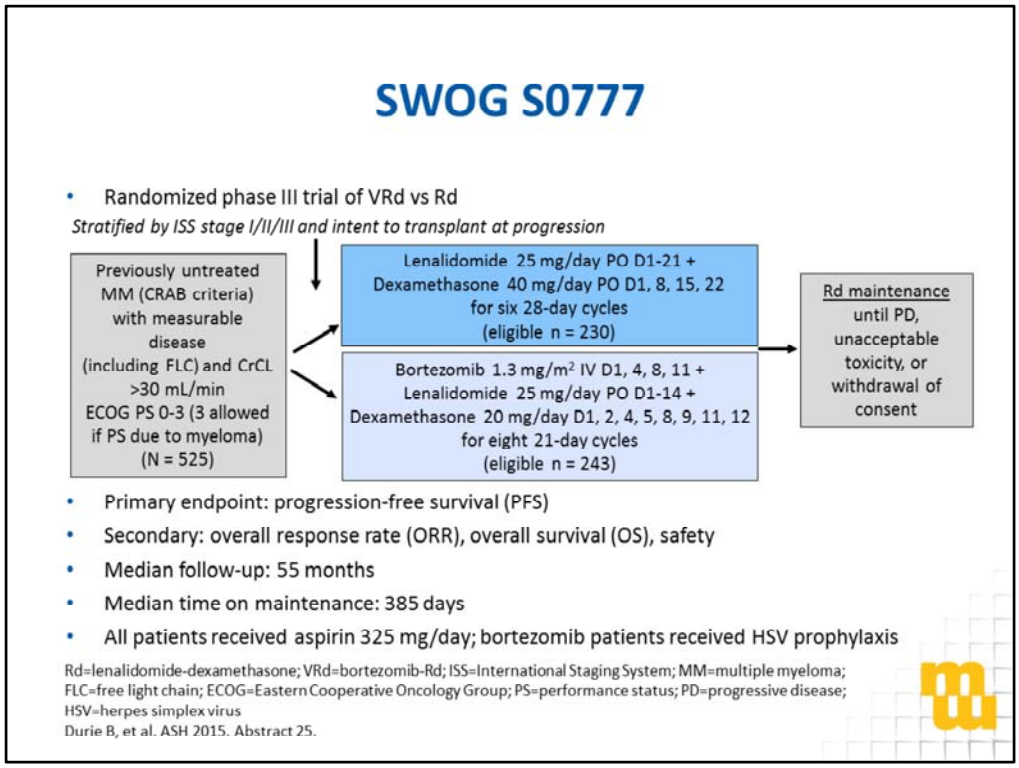
Pharmacotherapeutic Considerations for New Drug Regimens in Comorbid Patients with Multiple Myeloma



Welcome to *Managing Myeloma*. I am Dr. Donald Harvey. In today's presentation, I will review pharmacotherapeutic considerations for new drug regimens in comorbid patients with multiple myeloma. In this video, I will provide you with information and tools necessary to effectively manage treatment-related adverse events associated with newer lenalidomide- and bortezomib-based drug regimens. We will also discuss treatment considerations when using these regimens in patients with hepatic and renal dysfunction, diabetes, or cardiovascular dysfunction, all of which can require dose modification strategies, interruption of treatment, or use of concomitant medications. Let's begin.



Induction therapy in myeloma has changed substantially over the last 5 to 10 years. There are lots of patient-specific factors to consider including: transplant eligibility for autologous stem cells; patient parameters, specifically comorbidities which we will talk about today; as well as other functional issues like distance from the treatment center, insurance status, and other things we need to consider to get access to drugs. Overall, an optimal induction regimen does a number of things for the patient and for their prognosis. The first and most important thing is that it induces a deep response. An optimal regimen will induce at least a VGPR or better, because we know that that depth of response yields an improvement in overall survival. It will also potentially improve their performance status. If patients feel poorly due to their myeloma, in particular with newly diagnosed disease, then a good induction regimen will help them to remove those symptoms and hopefully feel better on therapy rather than worse. It certainly will, overall, improve their quality of life optimally. For those patients who are transplant eligible, it will have a minimum effect on stem cell mobilization, and specifically, we are referring to the timing and duration of lenalidomide. Optimally, no more than 4 cycles of lenalidomide containing therapy are used in order to maximize stem cell yield.



We know that three drugs are better than two. We know this because of the SWOG study that was performed. I really like the study for a variety of reasons, particularly in the context of today's presentation. One is that it included pretty much all patients. When you look at the eligibility criteria, these were previously untreated patients with measurable disease, including those who had free light chain only disease and from our perspective as pharmacists particularly those patients with renal insufficiency (patients who had creatinine clearances all the way down to 30 mL/minute) were included. Similarly, performance status of three patients were included if the performance status decline was due to the patient's myeloma. Overall, a little over 500 patients were randomized to either a two-drug regimen with lenalidomide and dexamethasone in six 28-day cycles, or a three-drug regimen combining bortezomib, lenalidomide, and dexamethasone. It is important to note as well that the bortezomib was given intravenously in this trial, and we will talk about why that is important in the coming slides. Patients then got those 6 months of therapy and then went on to Rd maintenance, lenalidomide and lower-dose dexamethasone alone, with the primary endpoint of progression-free survival. There were other secondary endpoints in overall response and overall survival, but again, many of these patients were eligible for transplant so they were stratified by both stage of disease as well as the intent to transplant. Median overall follow-up was over two years. Maintenance was there, and all patients received aspirin for thromboprophylaxis due to lenalidomide and venous thromboembolic risk. All patients receiving bortezomib received antiviral prophylaxis.

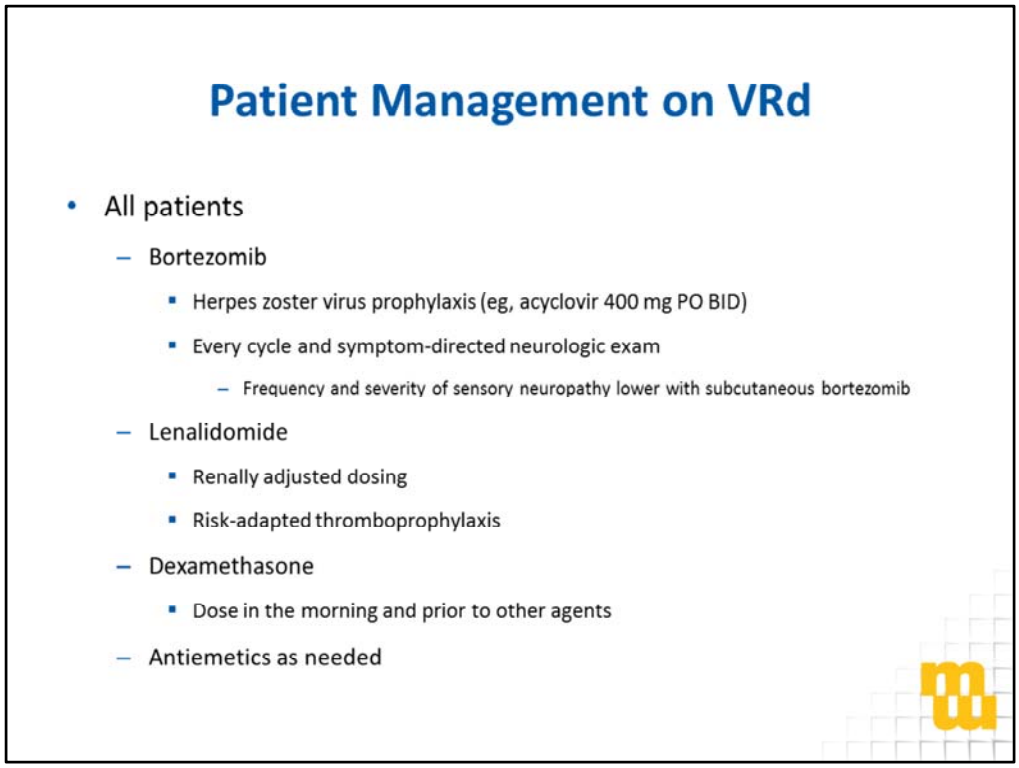
SWOG S0777: Outcomes

Survival, Months	VRd (n = 242)	Rd (n = 229)	HR	*P* Value
Median PFS	43	30	0.712 (0.560 - 0.906)	.0018
Median OS	75	64	0.709 (0.516 - 0.973)	.025

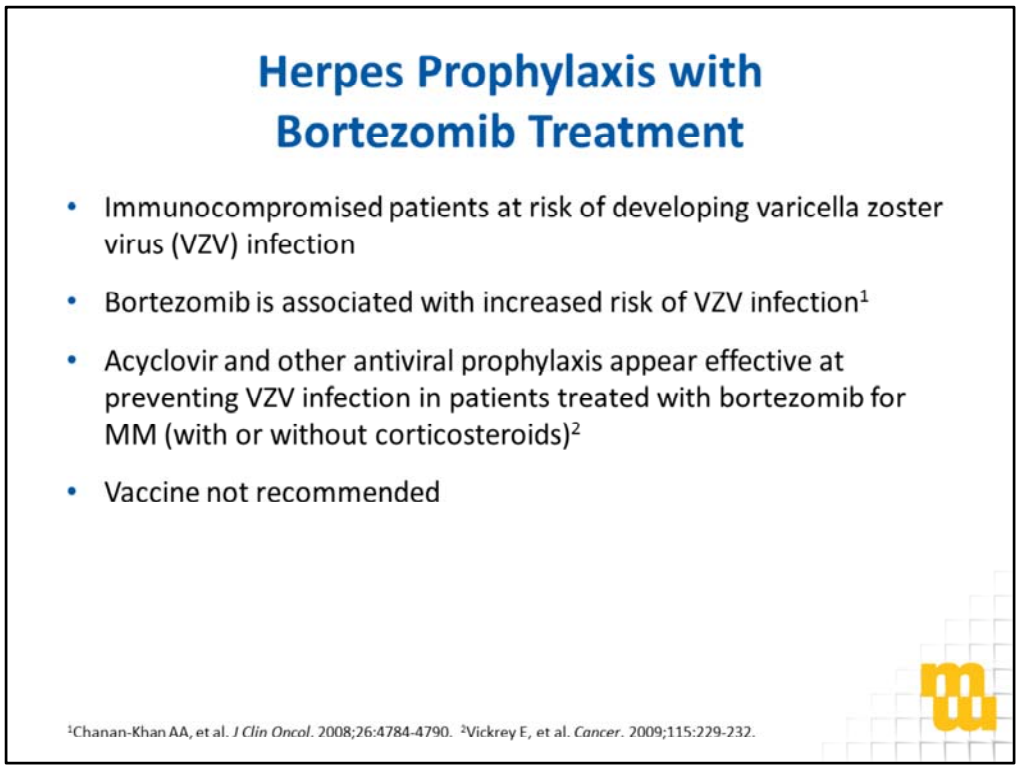
Adverse Event, %	VRd (n = 241)	Rd (n = 226)	*P* Value
Grade ≥3 adverse event (AE)			
▪ Neurologic	33	11	<.0001
▪ Pain	12	4	.0002
▪ Sensory	23	3	.004
▪ Gastrointestinal	22	8	NR
Secondary primary malignancies	4	4	

HR=hazard ratio; NR=no response
Durie B, et al. ASH 2015. Abstract 25.

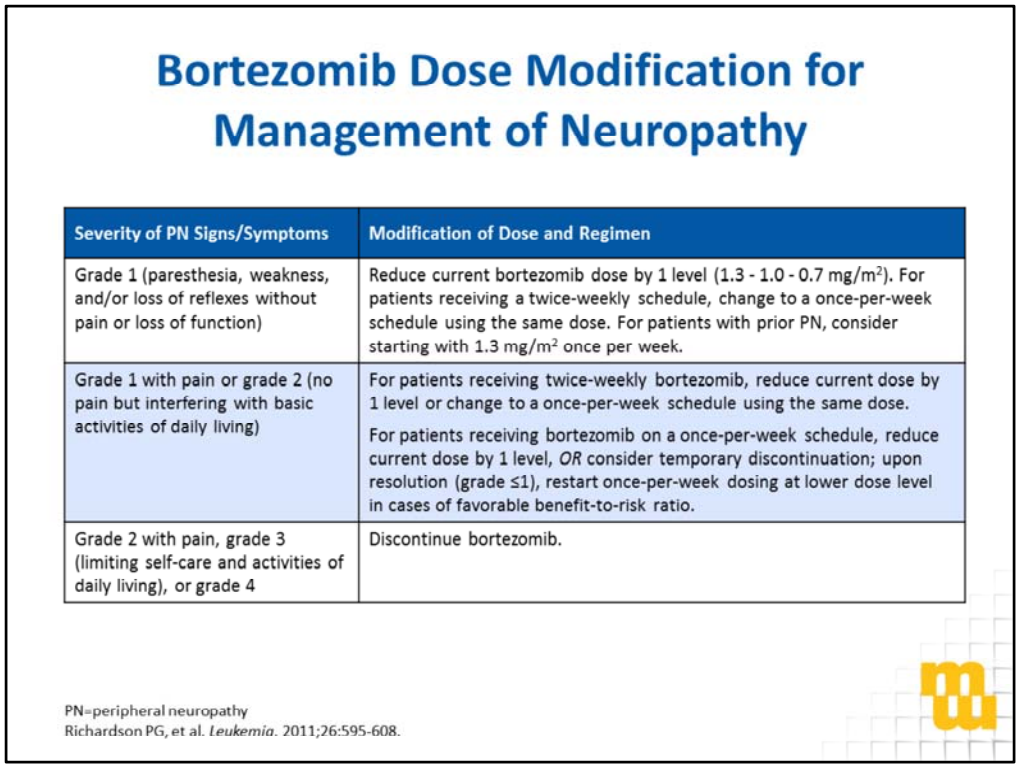
To boil it down, these are the outcomes in each arm. You can see there were significant differences in the primary endpoint of progression-free survival, with over a year difference in patients getting three drugs versus two, as well as an increase in median overall survival of about 11 months. Those were both statistically significantly different. That really cemented the idea that three drugs are better than two in a variety of patients. Again, I remind you the inclusion criteria were quite broad for this study. Adverse events are listed below. There were more neurologic and sensory neuropathy adverse events with bortezomib. Again, the bortezomib in this trial was given intravenously, and we know that subcutaneous administration is as effective as intravenous, but also reduces the issues of neurologic toxicities with bortezomib in the intravenous route. Similarly, there are gastrointestinal adverse events that I believe are underappreciated when given IV, and therefore we believe here also that subcutaneous administration reduces gastrointestinal adverse events, specifically diarrhea and nausea. Similarly, other adverse events that one might see were pretty similar between the two arms.



When we think about induction regimens, combining bortezomib, lenalidomide, and dexamethasone, we need to think prospectively about how we are going to manage patients. For bortezomib, everyone needs herpes zoster prophylaxis. For example, acyclovir 400 mg twice daily is an easy and convenient regimen but is also effective. Every patient also needs a symptom-directed neurologic exam, but very importantly a baseline neurologic exam, because we know that myeloma itself can have some neurologic implications and reduction in nerve sensory function. Lenalidomide needs renally adjusted dosing and the patient will go through that as well as well as risk-adapted thromboprophylaxis based on risk factors patients come into their treatment with. Dexamethasone should be ideally dosed in the morning prior to other agents, particularly bortezomib, because dexamethasone is an anti-emetic. It should be dosed in the morning because it has, of course, a stimulatory side effect, and so, taking it in the mid-day or evening hours is really not optimal and patients need to take it in the morning.



With bortezomib and herpes prophylaxis, we know that in patients who are immunocompromised or at risk of developing both herpes and zoster infections, bortezomib does have effects on T-cells as well as other cells and B-cells specifically. Acyclovir and other agents are effective at preventing herpes virus infections in these patients, and that is with or without corticosteroids. Any bortezomib-, or proteasome inhibitor-based treatment needs acyclovir prophylaxis or some other antiviral. The vaccine in these patients is not recommended. Not due to the fact that it might induce a herpes infection, but more that in general it is probably not going to be as effective because these patients are receiving therapy that can reduce their antigen response and long-term antibody production. They also have myeloma so their ability to stimulate a long-term memory response to a vaccine is impaired.

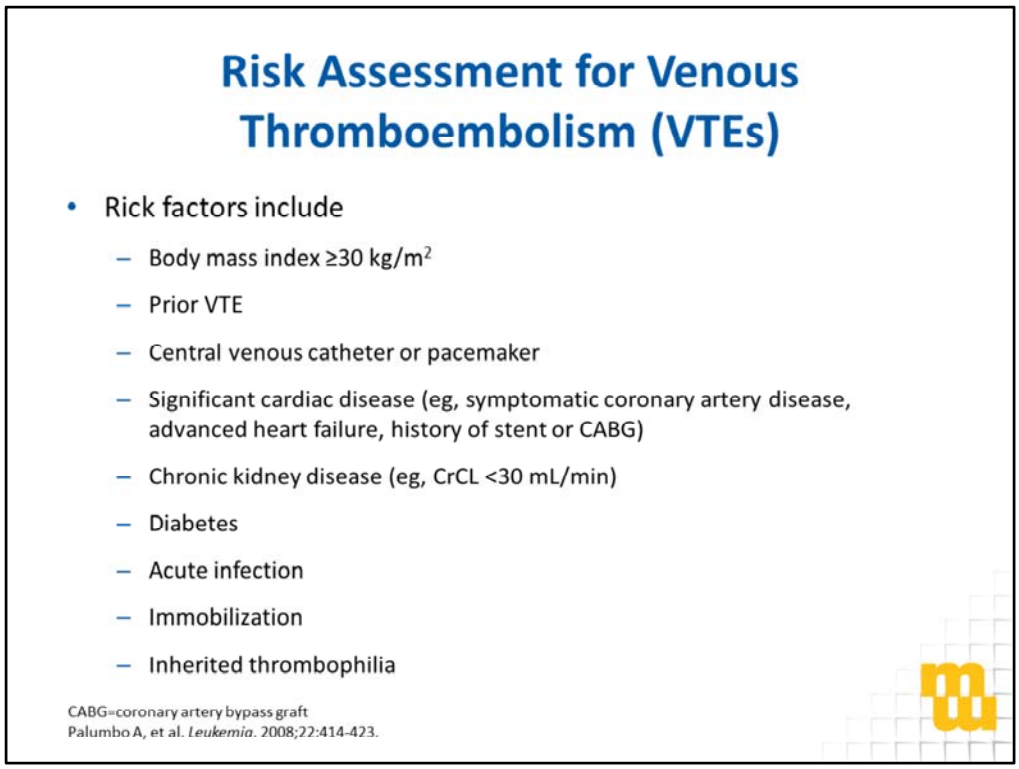


Bortezomib Dose Modification for Management of Neuropathy

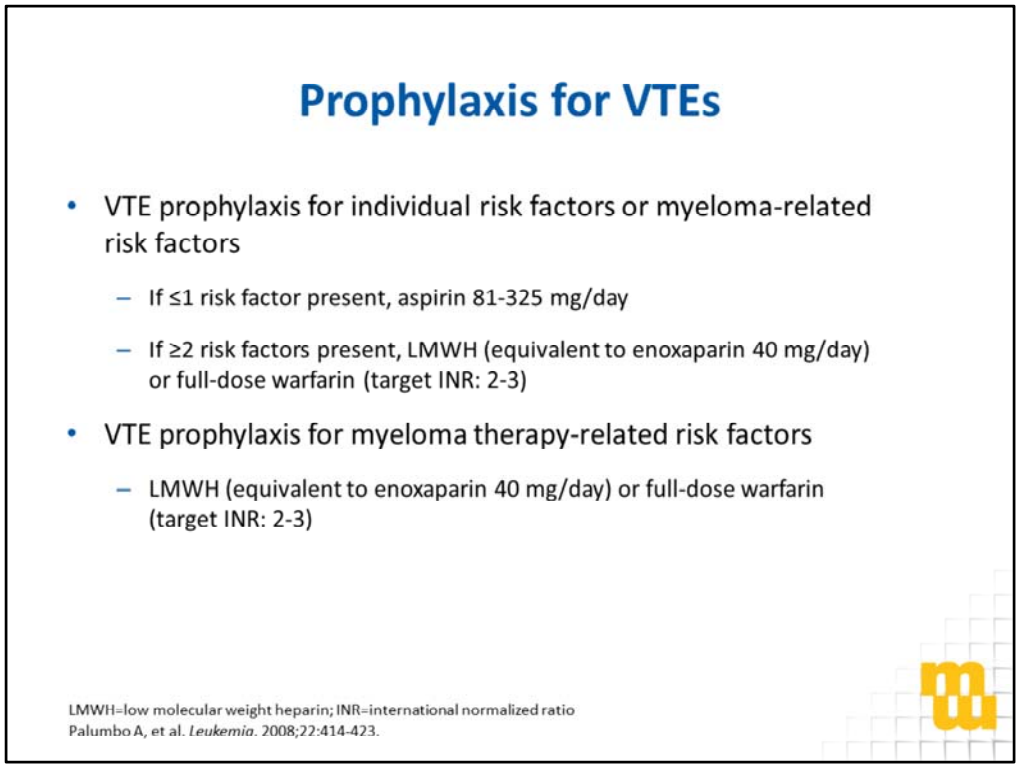
Severity of PN Signs/Symptoms	Modification of Dose and Regimen
Grade 1 (paresthesia, weakness, and/or loss of reflexes without pain or loss of function)	Reduce current bortezomib dose by 1 level (1.3 - 1.0 - 0.7 mg/m^2). For patients receiving a twice-weekly schedule, change to a once-per-week schedule using the same dose. For patients with prior PN, consider starting with 1.3 mg/m^2 once per week.
Grade 1 with pain or grade 2 (no pain but interfering with basic activities of daily living)	For patients receiving twice-weekly bortezomib, reduce current dose by 1 level or change to a once-per-week schedule using the same dose. For patients receiving bortezomib on a once-per-week schedule, reduce current dose by 1 level, *OR* consider temporary discontinuation; upon resolution (grade ≤1), restart once-per-week dosing at lower dose level in cases of favorable benefit-to-risk ratio.
Grade 2 with pain, grade 3 (limiting self-care and activities of daily living), or grade 4	Discontinue bortezomib.

PN=peripheral neuropathy
Richardson PG, et al. *Leukemia*. 2011;26:595-608.

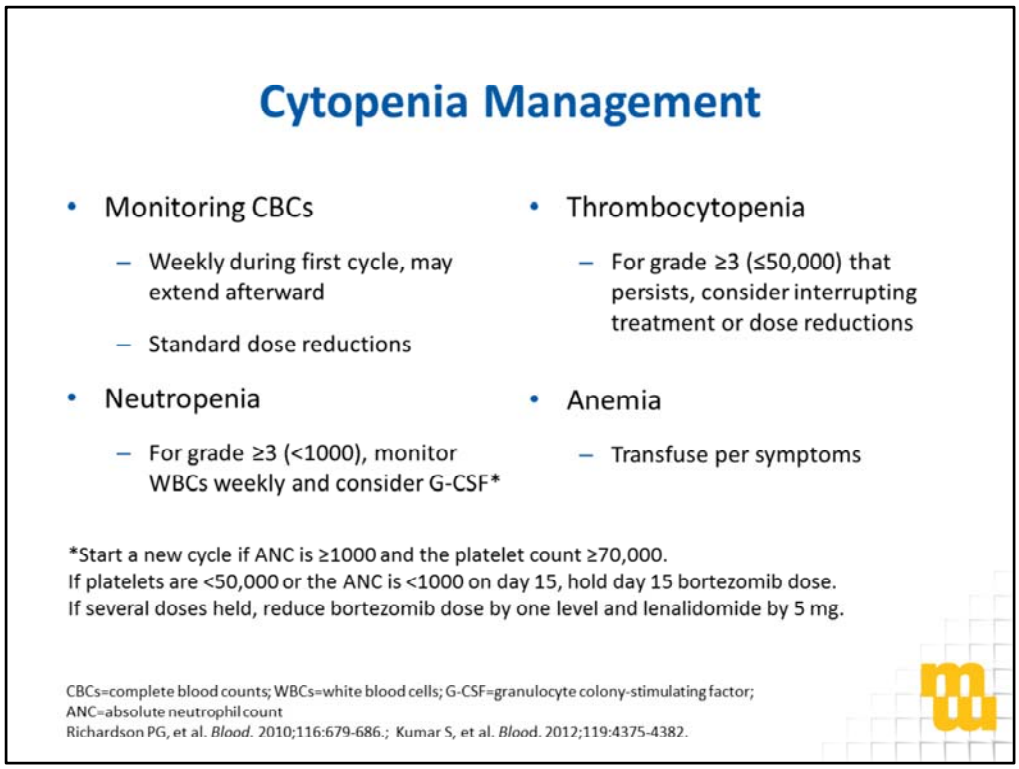
Bortezomib can cause neuropathy. These are guidelines for dose adjustment and management of patients who may develop neuropathy. Again, the subcutaneous route is associated with less neuropathy, less frequent and less severe, but regardless, it can be seen. These are dose adjustments that are recommended for patients who are receiving bortezomib and may develop neuropathy. I think the most important part to this table and most important point is that any patient who develops grade 2 neuropathy with pain or any grade 3 or grade 4 really needs bortezomib discontinuation. We do not think about that often with grade 2 adverse events, but patients who have grade 2 with pain do need to have discontinuation of bortezomib. This is important because usually we can catch these patients sooner with good cycle dependent neurologic examinations and an understanding of change in neurologic function as patients go on. In general, there are two strategies for managing these patients. One is to either reduce the dose and go, let's say, from 1.3 to 1 mg/m^2 twice weekly for 2 out of 3 weeks, or you can convert patients to weekly dosing from twice weekly dosing in order to minimize the bortezomib exposure, should they develop grade 1, or grade 1 with pain or grade 2 neuropathy.



For venous thromboembolism events (VTEs), there are risk factors patients may come into treatment with, independent of the addition of lenalidomide or IMiD-based therapy that can also increase risk. These are some of the risk factors that we know of that can increase a patient's likelihood of developing a VTE while on lenalidomide or IMiD-based therapy. Some of these are more important than others. Certainly, the history of a prior venous thromboembolic event is an important risk factor that needs to be weighed, probably more than other things on here like chronic kidney disease. Certainly, that is an issue within myeloma patients, but this is chronic kidney disease that may be due to other factors, not just myeloma. Optimally, we would induce patients and hopefully improve their renal function, but if they do have chronic kidney disease for other reasons, they may be at slightly increased risk of developing venous thromboembolic events. Similarly, acute infection, immobilization, and other risk factors that we know of in other patients increase the risk of developing a venous thromboembolic event.



The reason this is important because it changes our prophylaxis strategy. In some patients, we can use generally aspirin at full dose (typically 325 mg per day), but there is data with 81 mg per day as well. If patients have two or more risk factors for venous thromboembolic events, then a low-molecular weight heparin may be used, at the equivalent of prophylactic doses of enoxaparin, for example, or full-dose warfarin. Then, adding on for the idea of IMiD-related therapy, and then other therapies, less used therapies these days like pegylated liposomal doxorubicin can increase the risk, but in general, we are discussing IMiD-based venous thromboembolic events with this presentation. In the newer anticoagulants, for example the Xa inhibitors, there has really been no prospective data. However, one would think that based on the mechanism of clot formation in these patients and the mechanism of action of these drugs that there would be adequate and probably more than adequate prophylaxis for patients should they be on them when they are beginning induction therapy.



Moving now to cytopenias and thinking about monitoring patients as they begin induction therapy, the first part of their induction treatment may be the most monitored time because that might be the time you would see more cytopenias (thrombocytopenia, neutropenia particularly) and so, in that first cycle, weekly monitoring should be performed. It may extend the interval between, as patients show how their cytopenias may or may not develop. There are standard dose reductions that are needed, certainly bortezomib and lenalidomide have those within their product information. Specifically for neutropenia, if patients develop grade 3 or higher, you need to make sure you are measuring their complete blood counts weekly for neutrophil counts, and consider G-CSF which can be given in combination with lenalidomide and bortezomib. For thrombocytopenia, if the thrombocytopenia is thought to be due to bortezomib – again it's a relatively elastic thrombocytopenia, meaning platelet counts can go down and bounce back up – you may be able to treat through those. In patients who have grade 3 or higher, which is a platelet count of 50,000 or lower that persists – meaning it lasts for say 48, 72 hours, or longer – then you may want to consider dose reductions or holding treatment. Again, if the platelet count reduction is due to bortezomib or thought to be due to bortezomib, then you may be able to treat through it and just check and see where they are there at their next measurement. For anemia, these days erythropoietin and other growth factors are not used as commonly, and so, transfusions are more likely to be needed for symptomatic anemia, and that may be different for different patients. Patients with heart failure may need transfusions and higher hemoglobins in patients who do not have comorbidities.

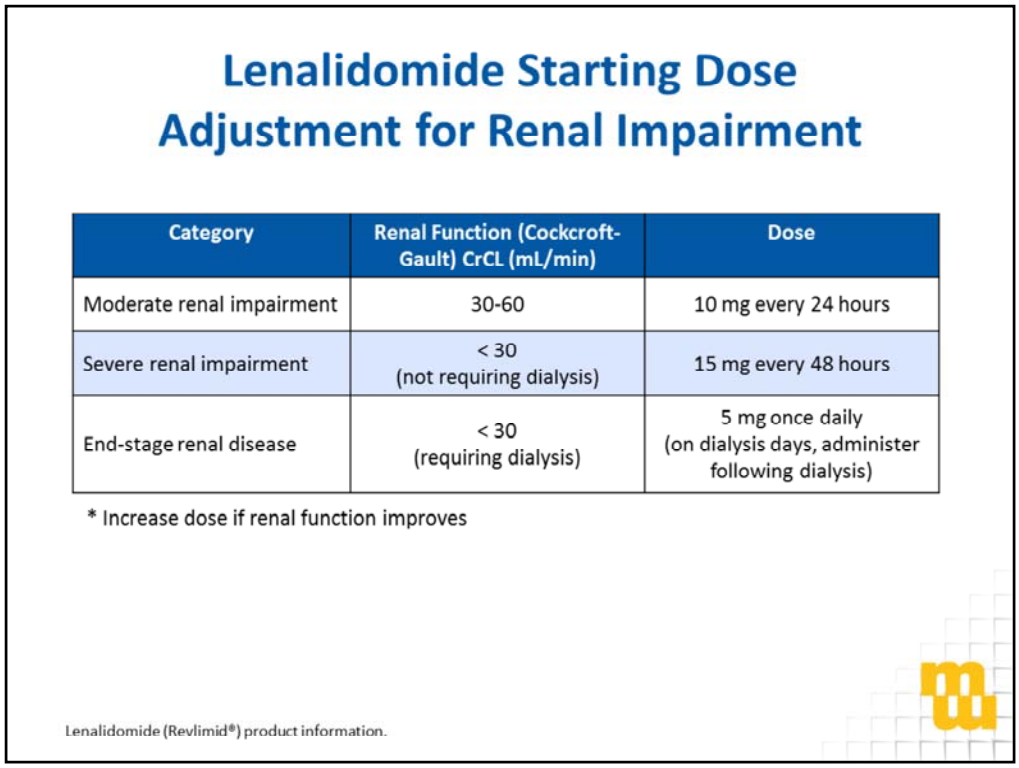
Bortezomib in Renal Dysfunction

- Subgroup analysis of patients receiving bortezomib in the phase 3 APEX trial

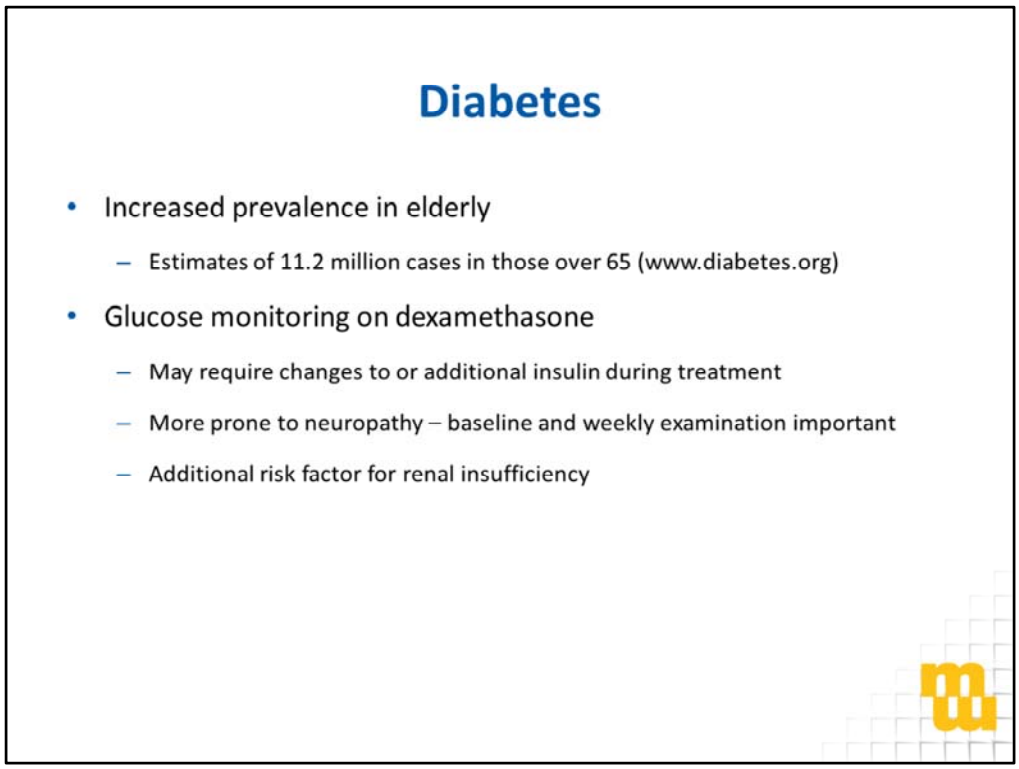
Outcome	CrCL ≤50 mL/min (n = 62)	CrCL >50 mL/min (n = 268)	*P* Value
Median time to progression (months)	4.9	6.2	0.62
Median overall survival (months)	22.8	30.0	0.07
Grade ≥3 adverse event	72%	75%	NS
Discontinuation due to adverse event	75%	75%	NS

NS=not significant
San Miguel JF, et al. *Leukemia*. 2008;22:842-849.

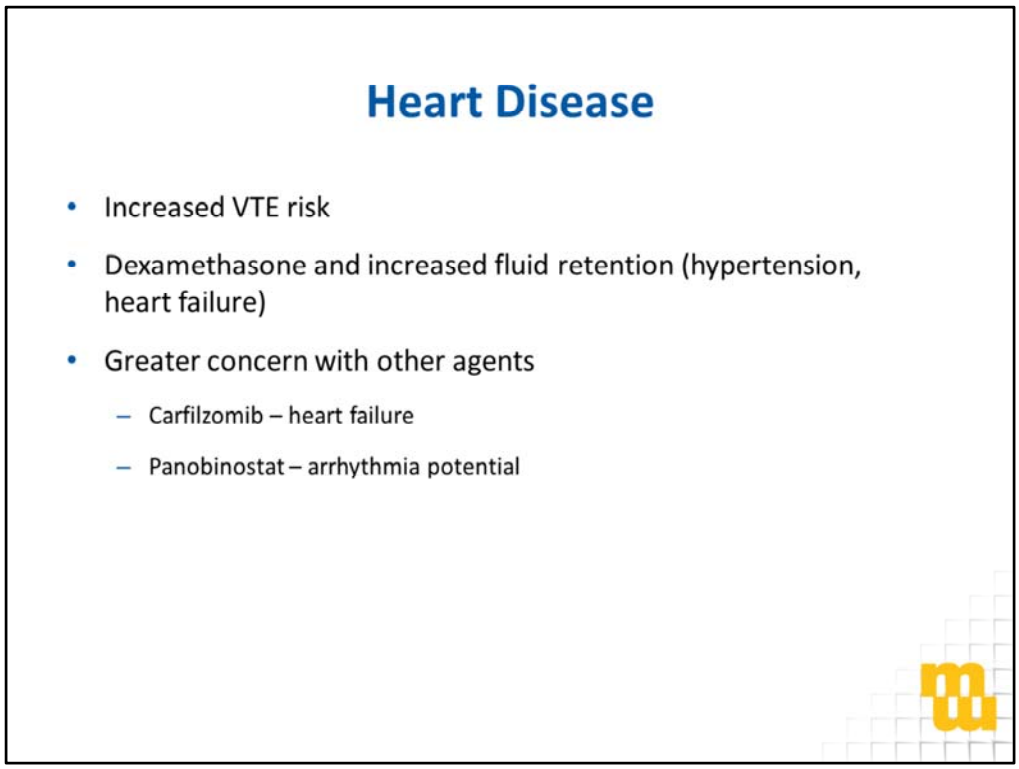
It is important to think about renal dysfunction in this population, specifically in the induction regimen setting, but also in the relapsed and refractory setting. Bortezomib has been used in many patients and certainly is not renally cleared, but has been used full dose in many patients with renal dysfunction. Data from our center and others have demonstrated this is an effective strategy. Looking at specifically the Phase 3 APEX trial of bortezomib where patients were included with creatinine clearances above 30, where those patients who had clearances between 30 and 50 were compared to those with creatinine clearances above 50, and specifically asking questions around their response as well as adverse events. If you look at the overall clinical outcomes and disease outcomes for these patients, there was really no difference in the time to progression. It was certainly numerically lower in the patients with more advanced renal dysfunction, and the overall survival was also numerically different. That really reflects the disease burden for these patients, and my belief is not that this is an issue with bortezomib or a concern with bortezomib, but more that these patients have more advanced and aggressive myeloma. Adverse events of grade 3 or higher were no different in the two populations with preserved renal function in those patients with some degree of renal insufficiency.



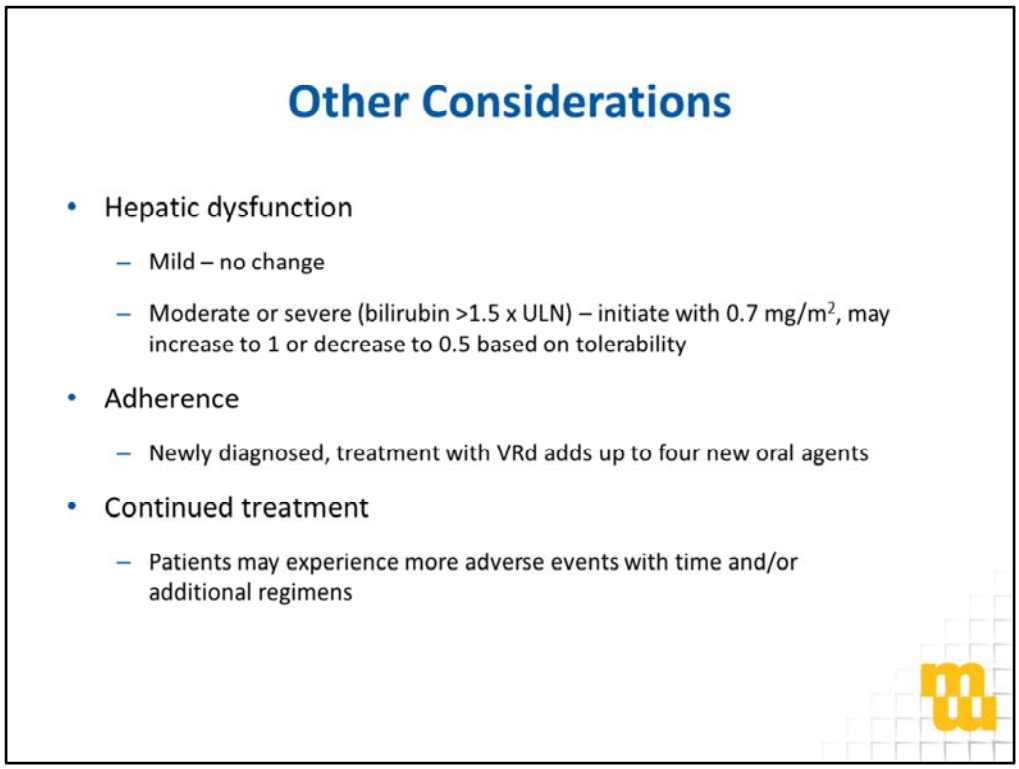
For lenalidomide, as a reminder, the starting dose is 25 mg orally. In patients who have moderate impairment, which is defined by product information for lenalidomide and FDA as 60 mL/minute or lower of creatinine clearance, it is a pretty big drop in dose. If you think about going from 25 mg to 10 mg daily, that is an over 50% dose reduction. I would think carefully about patients, for example, who have creatinine clearances above 50, because is there really a difference in clearance and area under the curve of 25 mg of lenalidomide in patients who have creatinine clearances above 50? I think it is hard to say, and particularly upfront, we really want to give good doses of drugs, and so we have tended to take a more aggressive approach in patients with creatinine clearances say above 50 and give them full dose but continue to monitor them carefully. Specifically, the product information does recommend 60 mL/minute or lower for dose reductions. The next cut point is less than 30 mL/minute, so extending the interval to every 48 hours and giving 15 mg a day in those patients who are not on dialysis but have clearances below 30. For those patients with end-stage renal disease, again 5 mg giving the drug after dialysis because it is removed by dialysis.



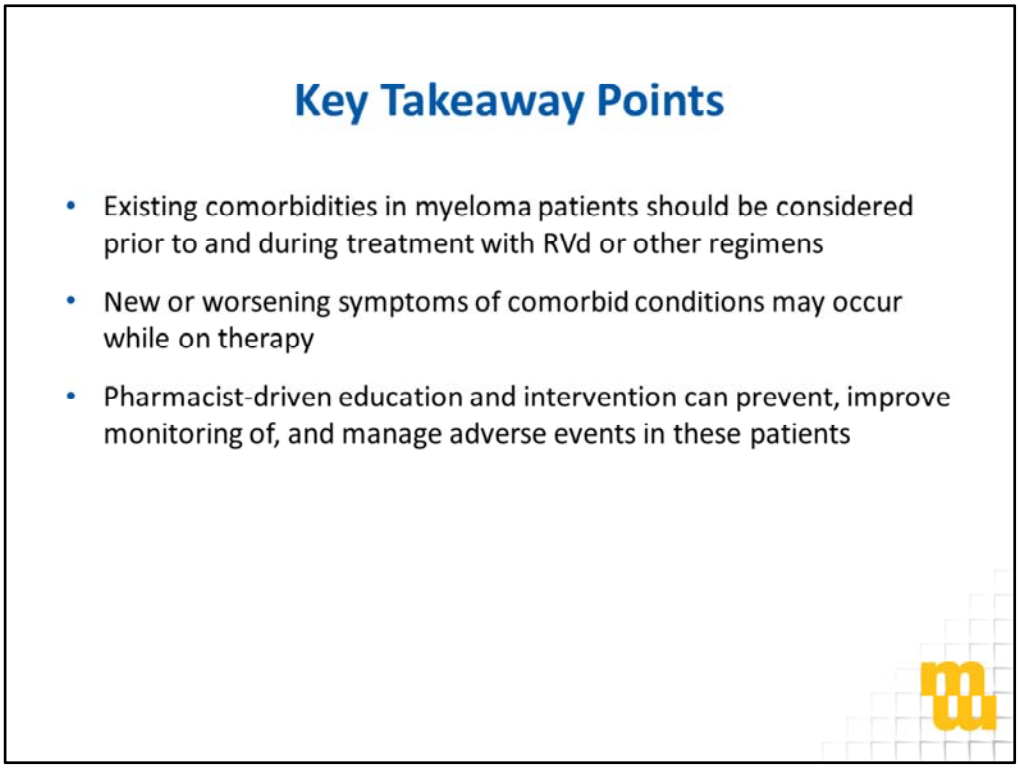
Diabetes is another important consideration in patients. Certainly, there is an increased prevalence of diabetes in the population in the US as a whole, and over 11 million cases in those over 65. For dexamethasone specifically, in patients who are diabetic, dexamethasone is still an important drug in the treatment of myeloma. It is a lympholytic and destroys plasma cells overall, and so, thinking about dexamethasone is an important factor in patients with diabetes. Glucose monitoring may need to be done more frequently. Patients may need to have add-on insulin, short-acting insulin if they are to go above 200, for example, or more aggressively as needed, but certainly, blood glucose changes can be seen in anybody taking dexamethasone, but it is of specific importance in patients with diabetes. They may also be more prone to neuropathy. That neuropathy may be the sensory neuropathy, and so, thinking about bortezomib is important, but it is also an additional risk factor for renal insufficiency. If patients have advanced diabetes and myeloma, then they sort of have two hits potentially for renal insufficiency.



For patients who come in to treatment with heart disease, specifically with lenalidomide, they may be at increased risk for venous thromboembolic events, particularly in those patients who have heart failure with ejection fractions, for example, below 40% or so. We might see increases in the risk of the development of clots, and so one needs to think carefully about those patients overall. In patients who are getting dexamethasone and who have heart failure or hypertension, it may be a concern for fluid retention. Thinking of heart disease is a greater concern with other agents we may use in the relapsed and refractory setting, or in other settings: carfilzomib and panobinostat, for example.



There are other considerations in patients with myeloma. Hepatic dysfunction in general is a pretty rare event in patients coming onto induction therapy, but in general, in patients with mild hepatic dysfunction, there is really no need for a change in any of their medications. In patients with moderate or severe dysfunction, specifically that is bilirubin above one and a half times of your upper limit of normal at your institution, you may want to initiate therapy with 0.7 mg/m^2 of bortezomib and then increase to one or decreased to 0.5 based on tolerability. Most patients will tolerate 0.7 pretty well, and so, escalating the dose is an important part of their treatment regimen. Another consideration is adherence, and as a reminder, if we start patients on bortezomib, lenalidomide, and dexamethasone, it is not just the lenalidomide and dexamethasone that patients will start to take. They will also take antiviral prophylaxis. They may also take aspirin as well or other anti-thrombotics, and so, we will really be getting patients potentially on four new drugs if they begin aspirin, antiviral prophylaxis, as well as lenalidomide and dexamethasone. That may be an issue in an elderly population that is already taking multiple medications. In general, thinking about patients in the continued treatment setting, if patients go on from induction and may go on to transplant or maintenance as myeloma continues to evolve and as their disease may relapse or be refractory primarily, then patients may start to experience more adverse events as their myeloma worsens. Specifically around renal function, renal function may not be recoverable later in the disease stage compared to the earlier stage.



So, in conclusion, I would like to leave you with these key take-away points for patients with comorbidities who are beginning therapy for induction of myeloma. Existing comorbidities in these patients should be considered prior to and during treatment with induction of bortezomib, lenalidomide and dexamethasone, or any other regimen that may be selected based on comorbidities. Those comorbid symptoms may worsen while on therapy, and so, we need to be vigilant as patients begin induction therapy, particularly in the first couple of cycles, but also as their myeloma treatment continues. Pharmacists are at critical points and junctures for education of patients as well as other health care team members for managing adverse events, predicting adverse events, and monitoring patients carefully while in therapy. So, in conclusion, I would like to thank you for viewing this activity, and hopefully, you will join other additional programs on *Managing Myeloma* in the future. Thank you.