Evolving Treatment Goals and Addressing the Barrier of High-risk Disease Improved Outcomes

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Kumar: Hello, and welcome to Managing Myeloma. Today, we are pleased to present an accredited activity in the Clinical Dialogue Series discussing the *Evolving Treatment Goals and Addressing the Barrier of High-risk Disease Improved Outcomes.*

I am a professor of medicine at Mayo Clinic in Rochester, Minnesota. I take care of patients with myeloma and related diseases, and also do clinical and laboratory-based research in these disease conditions.

Today, I am joined by Dr. Donald Harvey and Dr. Beth Faiman.

Harvey: Hello, I am an associate professor of hematology and medical oncology at the Winship Cancer Institute of Emory University. I oversee our phase 1 clinical trials program and our phase 1 unit—and as part of that, we have a number of compounds in development in early and later phases for patients with newly diagnosed relapsed/refractory disease. My research focus is on the clinical pharmacology of these and other agents, and patient disposition of drugs based on heritable and variable factors.

Faiman: Hello! I am a nurse practitioner in the Multiple Myeloma Program at the Cleveland Clinic Taussig Cancer Institute. I have a long history of taking care of multiple myeloma patients from a nursing perspective. We do run a lot of phase 1 and phase 2 clinical trials, as well as phase 3 clinical trials in the area of multiple myeloma. My research interest is focused on supportive care of multiple myeloma patients and survivorship issues.

Kumar: What we are going to do today is to discuss the various risk stratification models we currently use in multiple myeloma. Myeloma—as we have realized over time—is a very heterogeneous disease, with patients having...
very different outcomes. Some of this is determined by the various genetic abnormalities seen in the plasma cells. So today, we will go over the different genetic abnormalities, how they influence the outcome, and how they help decide treatment strategies, as well as look at what is on the horizon in terms of new therapies and how that might apply to the patients with high-risk disease. I will start off with an introduction to the concept of high-risk myeloma and how it has evolved over time, and then we can go around and specifically talk about the challenges we face with this group of patients, in terms of treatment as well as other supportive care approaches. Traditionally, we have thought about multiple myeloma as just being a single disease. They all have increased plasma cells, they all present with bone disease or renal abnormalities or anemia, but over time, we have realized that there are patients who do exceptionally well and there are patients who do very poorly with the treatments we currently have. Different prognostic factors have been described, many of which help us to identify a group of patients who tend to do poorly with the different therapies—we tend to label these patients as high-risk myeloma. Now, when we look at the survival of these patients with myeloma, it has significantly improved, but we still have about one-quarter of patients who die from the disease in the first 3 years from diagnosis (Figure 1).

Figure 1. Overall Survival Patterns from Time of New Diagnosis Observed in Era of Novel Therapies

This Mayo Clinic study included 1,038 patients diagnosed with multiple myeloma between 2001 and 2010, grouping patients into two 5-year periods by diagnosis, 2001–2005 and 2006–2010. The median estimated followup for the cohort was 5.9 years with 47% alive at last followup. The median overall survival of the patients in the more recent group (n=561) was significantly longer compared with the earlier cohort (n=477): 6.1 years (95% CI; 5.0, NR) and 4.6 years (95% CI; 4.1, 5.2), P = .002. The 6-year overall survival estimates for the earlier cohort was significantly shorter compared with the recent cohorts and were 40% (95% CI; 36, 44) and 51% (95% CI; 46, 56) respectively; P <.001.
So, these are really the patients we are thinking about when we are talking about high-risk disease. The biggest problem we face with patients with high-risk disease is that they tend to relapse very fast after the different treatments we give, and then we are always looking for other new modalities to treat them (Illustrative example provided in Figure 2).

Figure 2. Clinical course of a patient with high-risk MM

The clinical course of a single patient (MC1130) studied throughout the entire disease course is shown. Red line indicates the quantitative IgA level detected and units are shown on the left y-axis. Blue line indicates the free light chain ratio detected with units shown on the right y-axis. Alternating color regions indicate type and durations of treatment received during each interval. Red arrows highlight the time points at which BM aspirates were analyzed, the green arrow indicates the time of collection of the terminal PCL sample from peripheral blood. Dx=diagnosis; Rem=remission; R1=relapse 1; R2=relapse 2; R3=relapse 3; R4=relapse 4. The assays performed at each time point are indicated under their representative arrows.

The best way to categorize these patients or identify them upfront is based on the abnormalities that we see on FISH [fluorescence in situ hybridization] testing, the bone marrow samples at the time of diagnosis, and other laboratory markers (see Table 1 and 2).
### Table 1. IMWG Risk Stratification Work-up

<table>
<thead>
<tr>
<th>Investigation for risk stratification</th>
<th>Serum albumin and β2-microglobulin to determine ISS stage</th>
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<tbody>
<tr>
<td></td>
<td>Bone marrow examination for t(4;14), t(14;16), and del(17p) on identified PCs by FISH</td>
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<tr>
<td></td>
<td>LDH</td>
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<td></td>
<td>Immunoglobulin type IgA</td>
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<tr>
<td></td>
<td>Histology: plasmablastic disease</td>
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<td>Additional investigation for risk stratification</td>
<td>Cytogenetics</td>
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<td>Gene expression profiling</td>
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<td>Labeling index</td>
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<td>MRI/PET scan</td>
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<td>DNA copy number alteration by CGH/SNP array</td>
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PCs indicates plasma cells; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; MRI/PET, magnetic resonance imaging/posterior emission tomography; and CGH/SNP, comparative genomic hybridization/single nucleotide polymorphism.


### Table 2. IMWG Combined Genetics-ISS Risk Stratification Model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>High Risk</th>
<th>Standard risk</th>
<th>Low risk</th>
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</thead>
<tbody>
<tr>
<td>ISS I/II and t(4;14) or 17p13 del</td>
<td>ISS I/II and absence of t(4;14), 17p13 del and +1q21 and age &lt; 55 years</td>
<td>All others</td>
<td></td>
</tr>
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| Median OS | 2 years | 7 years | >10 years |

| Patients | 20% | 50% | 20% |

So maybe the first thing we can talk about is how we tailor the therapy for patients who have high-risk disease and what the unique challenges are. I will start with that question, and we can go around.

**Faiman:**
I think that, in my experience, patients could be categorized as high risk, or those who might do poorly, and then low-risk patients, who, no matter what you give them, tend to do okay for a long period of time. There is this concept that I explain to my patients about the predictive versus prognostic factors. You can have poor prognostic factors that are found on genetic testing, such as the translocation 4;14 and deletion 17p—and those biomarkers might not necessarily be predictive of you not doing as well as an individual patient, but are associated with shorter survival than those without them by FISH in clinical studies. So those are the kinds of things that I try to take into consideration at diagnosis. I also like to set the stage for goal setting at the beginning; quality of life, quantity of life, and functionality are typical things that patients really want to have and that tend to be important and meaningful to them—thus, identifying those adverse prognostics and then identifying goals at the beginning of therapy and throughout is essential.

**Harvey:**
When thinking about the high-risk patient and considering building a better regimen for them, certainly we have drugs in development, but we also are using those that are commercially available now differently. It does appear that, in those high-risk patients, more drugs with different mechanisms of action might be more effective. And we continue to see that deeper responses early do portend better longer-term outcome as longer progression-free intervals and overall survival rates. With better drugs and better approaches that we can then put together in a way that is tolerable for patients with high-risk disease, we can hopefully continue to push those numbers to higher CR [complete response] rates and longer overall survival periods.

**Kumar:**
Among the methods that we have, FISH is definitely a good way to identify some of these patients; however, even that only explains maybe 50% to 60% of the heterogeneity. We still see a lot of patients who supposedly have high-risk genetic markers who do well and patients who have standard-risk abnormalities and do very poorly. So there is still a lot of work that needs to be done in terms of being able to identify these patients accurately. Maybe some of the new methodologies like gene expression profiling and combining some of these different prognostic factors into a single model might help us to get there.

**Harvey:**
Dr. Kumar, are there specific clinical features that you tend to look at and say, “This patient is likely to be more problematic,” in terms of response to therapy than others—including plasmacytoma as a presentation, site of disease, or other source of unique characteristics that you would say tend to not do as well?
Kumar: As you mentioned, presence of myeloma cells outside the marrow, either in the form of plasmacytomas or plasma cell leukemia, can be associated with poor outcomes.3 There are certainly things that help us identify high-risk patients at diagnosis, and some of the patients declare themselves as high risk after we start the treatment by having a short duration of response. One of the goals of treatment for myeloma in general is to try to get them to the maximum response, preferably to a point at which they do not have any residual, detectable tumor left. But we also have become cognizant of the fact that myeloma—being different diseases—not everybody needs to get there to have a good outcome in the long run.37 This is important, because intense therapies can compromise the quality of life in some patients without a clear benefit. So, the challenge we are going to face in the coming years is to identify the patients whom we can treat as if they had a more indolent disease as we would do for follicular lymphoma versus somebody whom we would treat in a more aggressive fashion, like with aggressive lymphoma. So that clearly is a challenge for the future.37,38

Faiman: Oh, I was just going to say, Dr. Kumar, that we are talking about the newly diagnosed patient. But in your practice, do you typically obtain FISH testing and repeat bone marrow biopsies? For example, let’s say you have somebody who was diagnosed in 2004 and you may or may not have that FISH information available in terms of the risk. Let’s say they had standard therapy and progressed in 2010. Would you obtain FISH testing, and how would you plan your decision making in terms of the drugs that you would use to treat?

“I look at prognostication as a continuous process, so I need to keep reassessing the risk at various time points during the disease course.”
- Shaji Kumar, MD

Kumar: I think it is an important question, and our typical approach has been to repeat the FISH testing at the time of relapse.3,20 But more recently, what we have done is just look for the deletion 17p and chromosome 1 abnormalities and the myc abnormalities at the time of relapse. The primary abnormalities, such as translocations and trisomies, do not change over time,4 and we will just look for the markers that tend to evolve with disease diagnosis. It is an important question as to how we put this information into practice. I think if somebody had a diagnosis in 2004, had standard treatment, and went for 6 years without any relapse—and let’s say that patient, when we do the FISH testing, has a 4;14—I probably would not think too much about the 4;14, because the disease course suggests that it may not be that relevant. However, I would be quite concerned if I saw a deletion 17p at the time of relapse, especially since that is something that is new that comes up, and we know those patients do have very aggressive disease.”2,4,6,9,20,39
Faiman: That is our experience as well, and we try to look to the past markers, such as lactate dehydrogenase, \( \beta_2 \) microglobulin, and other characteristics that are now better defined (Table 1).\(^{3,18,20}\) But I think that continues to be one of the challenges. How do you translate the new information with the biomarkers as to whether or not they will really be predictive of prognosis? What does it mean for the patient when you find indicators of risk at relapse in the absence of this information at diagnosis? Keeping in mind that some prognostic markers may not have even been recognized or validated at the time of a patient’s diagnosis.

Kumar: I look at prognostication as a continuous process, so I need to keep reassessing the risk at various time points during the disease course. The data that we have would suggest that patients with high-risk disease need a risk-adapted strategy. I think the key is to do intense therapies and—probably over a long period of time—try to control the clone or reduce it to the least amount possible. This is supported by the data from Emory that show that patients with high-risk disease seemed to do well when you give them a combination of bortezomib/lenalidomide/dexamethasone, do a transplant, and then keep them on the same regimen continuously.\(^{22}\)

Harvey: When you look at those high-risk patients and our center’s experience with the approach that Dr. Ajay Nooka published, those three drugs for induction are typically fairly well tolerated by patients.\(^{22}\) There may be adverse events that are treatment emergent, but if one considers collection of stem cells and moving to transplant relatively quickly following the initiation of 4 cycles of triplet drugs, and then taking a maintenance strategy that continues to evolve as well, you can get deep responses. We certainly see nice, overall survival curves with a fairly intensive approach, and I think it is important to remember that the transplant certainly still has a role for those patients, particularly those with high-risk disease. We just may not expect that their disease-free interval might be as long as someone with lower-risk disease afterward, but maintenance is certainly there. I think the best and most important point is that tolerability and the maintenance phase can get a little bit challenging. Fatigue and other adverse events with lenalidomide maintenance over a long period of time can be challenging, and we need to remember that the quality of life does become important. But at the same time, those patients with high-risk disease do need more treatment. So, it can be a bit more difficult to balance, and I like the earlier point that Dr. Kumar made, that probably the most interesting group to think about are those patients with more indolent disease. Those are the folks for whom—as we get better drugs that are better tolerated over time and that we are hopefully moving to a point where we need to do a better job of identifying those with indolent disease who do not need as aggressive therapy—we can imagine a day when there are 4- and 5-drug regimens perhaps for those patients with the highest-risk disease.\(^{37,40}\) But, probably, the evolving group of interest is the group with more indolent disease course.
“I am particularly interested in the immunotherapies… elotuzumab has a unique mechanism of action and… works outside of the cells. So, because myeloma is a series of clones, and those clones will change over time, how can we lessen the impact of the actual tumor cell? Elotuzumab might be one of those agents that can help address this barrier.”
- Beth Faiman, PhD, Nurse Practitioner

Kumar:
It always reminds me of the lymphoma field—the follicular lymphoma patients may get rituximab therapy as a single agent, and then the aggressive lymphomas, which we treat with all kinds of fancy regimens. But I think intense therapy is definitely the key for some of these high-risk patients, and the data from Europeans showing that the tandem transplant may particularly benefit those people with high-risk disease, again, kind of points in that direction. Maximum eradication of the clone is probably the way to go for this aggressive disease. We need to think about mechanisms that have been described for myeloma becoming resistant to the drugs that we have now—and they are all mechanisms within the cells. For example, the cereblon expression and resistance to immunomodulatory drugs (IMIDs) drugs, as well as some of the more stem-cell-type phenotype that becomes resistant to the bortezomib therapies, have been described—which makes you wonder if new monoclonal antibodies currently in development may have a unique place for these patients. I guess that is something about which we will have to wait and see. What do you think?

Faiman:
I am particularly interested in the immunotherapies, obviously. That is kind of a hot topic of myeloma in 2015. Actually, elotuzumab has a unique mechanism of action and, as you described, works outside of the cells. So, because myeloma is a series of clones, and those clones will change over time, how can we lessen the impact of the actual tumor cell? Elotuzumab might be one of those agents that can help address this barrier. Elotuzumab targets the signaling lymphocyte activation molecule family member 7 (SLAMF7); in a group trial, we are participating in the SWOG study with elotuzumab plus or minus lenalidomide, bortezomib, and dexamethasone in high-risk populations [ClinicalTrials.gov Identifier: NCT01668719]. So I am really interested to see when the results of that trial mature, because that might reflect a difference. Up until now, we know bortezomib might have some special properties that provide benefit for patients who have select genetic markers by FISH such as t(4;14) and del17p and are consequently at particularly high risk, but the additional bortezomib does not necessarily completely overcome the poor prognosis that those patients have. It does help survival but not entirely. So the potential benefit of the immunotherapy elotuzumab in combination with bortezomib-based therapy would be one to watch. I know, Dr. Harvey, that you have experience with some of the other new agents in your phase 1 and 2 program as well.
Harvey: It has been a great time to be involved in drug development in myeloma and will continue to be for a while. Certainly, the antibodies offer nice activity, and, as Dr. Kumar mentioned, we will likely mimic the example of adding rituximab to conventional chemotherapy in lymphoma. We can see that time coming in myeloma. Elotuzumab is a fascinating drug in many ways. It has almost no activity on its own, but, clearly, it greatly enhances the activity of other agents and there is an interesting finding in which 10 mg/kg is better than 20 mg/kg. We will find more out as the phase 3 data read out over time in combination with lenalidomide and dexamethasone versus lenalidomide-dexamethasone alone. With the other antibodies that we have been involved with here, the anti-CD38 antibodies are fascinating drugs, and each of these drugs, based on their mechanism and their manufacturers, can all have their own sets of infusion reaction and may have some degree of unique adverse events. But in the end, those infusion reactions tend to be the most challenging adverse event with any of these drugs, and once you get past infusion events, they are very well tolerated over time and tend to be quite effective in early data in some patients. I think we might come to a place at which we need to identity which patients will respond better to anti-CD38 antibodies than others. It does not appear to be as simple as those who might have an infusion reaction versus those who do not. The other antibody we have been fortunate to work with is sort of a new, evolving, monoclonal-antibody, Trojan horse approach that has been seen in breast cancer with trastuzumab emtansine and brentuximab vedotin in Hodgkin lymphoma. The same concept is moving into myeloma using antibodies against the well-known plasma cell marker of CD138 which are conjugated with a maytansinoid (eg, indatuximab) much like the other maytansinoids that are currently available. Taking that approach also is intriguing in a way that can revive some of these maytansinoid drugs and deliver a toxin directly to the plasma cell. Each of these antibodies is somewhat unique; how we position them and how they come into the field of clinical practice will be interesting over the next few years.

Kumar: Clearly, though, we have learned over time that the myeloma cells are very capable of evolving under pressure of therapy with lots of clones and subclones [Figure 3], so trying to modulate things outside of the cell itself seems like a very attractive way of targeting myeloma.
The summarized results of 8 different FISH assays are shown to indicate the relative abundance of each clone defined by aCGH at the 5 time points studied. Pie charts showing the relative proportions of each indicated clone are ordered clockwise starting on the left in longitudinal order. Arrow length is proportional to the time interval. The relative ploidy of the tumor population at each time point is also indicated. The cIg FISH of relapse 4 and the PCL identified clonal cells with low levels of cytoplasmic immunoglobulin (cIg-low) and larger cells with abundant cytoplasmic immunoglobulin (cIg-high) that were scored independently.

One of the other approaches that has been quite exciting has been the chimeric antigen receptor (CAR) T-cells approach using different antigens, including CD19 in multiple myeloma, as well as other lymphoid malignancies; and B-cell antigens, are being explored in other clinical trials [ClinicalTrials.gov Identifier: NCT02135406]. This is another kind of immunotherapy approach that seems to be quite exciting. We have also been working on other modalities, such as viral therapy, measles virotherapy—at least we have had some results suggesting there might be some benefit.
Harvey: And certainly it revives the idea of immunotherapy. I think people have given up in many instances on allogeneic transplant for myeloma. Perhaps there are different ways to upregulate T-cells internally, as you mentioned. Whether it is a CAR T-cell approach or whether immune checkpoint inhibitors and OX40 will play out is also interesting to think of, but it reinvigorates this idea of immunotherapy, both from the monoclonal-antibody standpoint of targets that we know and potentially from T-cells that might be upregulated through other mechanisms, such as the CAR.68

Kumar: I think all of these therapies certainly hold promise, but the big question is going to be that we need to identify them ahead of time and do these approaches, while also kind of making sure we keep the whole quality-of-life perspective in balance. Beth, maybe you can speak to that aspect.

Faiman: Yes, and thank you. That is one other thing that I am very interested in—and the survivorship aspect of myeloma.69 These patients are living long periods of time, and so—as it is an older person’s disease—they are now putting themselves at risk for developing older individual comorbidities. So, I think that is one of the things I try to keep in mind when I am selecting and tailoring therapies for the individual is what health factors are you at risk for? So, as we do not do transplant, will that prohibit your lifestyle or other factors? Will that prevent you from being a candidate for transplant down the road? I think these are important discussions to have from the beginning, when we risk-stratify and talk about prognosis, to really enhancing the patient’s ability to stay active and live a healthier lifestyle. So, from my perspective, I think that this is important. Obviously, the laboratory research is something I am heavily involved in as well, and I think that is important. But quality of life, quantity of life, maximizing outcomes in terms of living a healthy lifestyle, and managing toxicities all are very important as well. So, immunizations, colonoscopies—those are all things that should be done.

Kumar: Right. We never used to give too much attention to those things because of the relatively short life expectancy for most of these patients. But now, you have so many more patients who you are seeing on a regular basis over a long period of time. You have to start thinking of other things that can happen to this older patient population.

Faiman: Right, and I am thinking of the individuals who might present with kappa light-chain-type myeloma with proteinuria, and they concurrently have a diagnosis of diabetes and hypertension. They do not necessarily watch their diet or exercise, and that can impact their renal function, which would prevent them from being a candidate for these clinical trials. So, those are the types of things that I am particularly interested in, and it is important. I think that is where the nurse’s role comes in as to kind of encourage the patients to look at the whole picture and elicit the support of the family as well.69
Harvey: Beth, when you have patients who come in who maybe are over the age of 65 or so, what kinds of clinical criteria do you use to sort of think about, independent of genetic risk factors by FISH? What sort of clinical characteristics do you look at and think about for selecting a regimen?

Faiman: Well, at the Cleveland Clinic, we have Care Path. So, everybody who has “standard”-risk myeloma by FISH and other criteria that take into account LDH comorbidities as well—most of the individuals who start on a doublet regimen, if renal insufficiency or high-risk features are there, then they would be driven toward the proteasome inhibitor-based regimen. If the patient wants to have a transplant earlier and that option would be provided to them—but again, we take into account more of a sheer decision-making kind of model of the clinic and try to stick to a doublet versus a triplet up front and then layering on therapies (Figure 4). If patients do not achieve a partial response after 2 cycles, then a third agent would be added on. By and large, most of our patients will participate in clinical trials, but this care path is specifically for patients who are not on a clinical trial. So when you talk about the clinical characteristics, again, it is the renal functionality, convenience, financial, all the support, all the things that most centers will take into consideration, I would say.

Figure 4. Cleveland Clinic Upfront Myeloma Care Path Pilot with Response-Adapted Therapy
Harvey: I think that is an important point in drug selection overall, as we cannot forget things like copays, insurance amounts, frequency of visits to location, and distance from the location and to an oncologist if they are referred to a center like one of our three and then want to receive treatment closer to home. Those are all pretty important characteristics—if you cannot get the drug into the patient, we cannot treat the myeloma.

Faiman: And certainly along with that, adherence, I think is important. We can recommend a 2-drug oral regimen for patients, but if they are not going to be adherent to taking the drug—and there are other barriers to filling the medications and such or forgetfulness. Those are things that, in the real world, we need to worry about. So, Dr. Kumar, you have the myeloma Mayo Stratification for Myeloma and Risk-adapted Therapy (mSMART) criteria. Do you prescribe to that, or do you have another way of selecting treatment for your patients?

Kumar: In general, we do try to stick to the algorithm [Figure 5 and 5a and 5b]. But there are clearly patients who may not quite fit in with the description there, and we may deviate. Individual patient preferences have to be taken into account as well.

Figure 5. mSMART 2.0 Risk-Stratification Criteria
Figure 5 A and B. Mayo Stratification for Myeloma and Risk-adapted Therapy mSMART-Off-Study Algorithms for Transplant Eligible (A) and Transplant Ineligible (B) Patients.
Harvey: If we initiate a patient on lenalidomide, bortezomib, and dexamethasone, we are not actually starting them on three drugs. We are starting them on five drugs because their antiviral is part of that and their thromboprophylaxis is part of that. So, considering that we are trying to get deep responses and trying to get patients on drugs for a longer period of time, if you have a 75- to 80-year-old patient with multiple comorbidities who is already on 4 to 5 medications, you are now adding at least four additional oral medicines to take—and not necessarily continuously, with lenalidomide, for example. So, these kinds of psychosocial issues do present more often than not.

Kumar: I think oral medication definitely is a plus as we try to keep patients to their normal lifestyle as much as possible. But I think—as it is already pointed out—compliance can be an issue. Drug interactions with these new, small molecules can be a big problem, especially when you think about somebody who is on multiple other drugs for hypertension or other things. Many of the oral medications are much more expensive, and the out-of-pocket expense for many of them tends to be higher than with injectables. So, these all will be challenges for us as we try to develop more patient-friendly regimens. Alright, so I think we have touched upon
many of the main points that we had outlined. Anything else you would want to add onto the whole concept of risk stratification, selecting therapy based on risk, and what is on the horizon for this high-risk patient?

Faiman: I think the only thing that we did not really touch base upon is we have a new US Food and Drug Administration–approved panobinostat, and we are using in clinical studies ibrutinib in combination with carfilzomib [ClinicalTrials.gov Identifier: NCT01962792].

So, panobinostat, in our experience—I know that the drug had delayed approval somewhat, but it does represent another treatment option. I will say my personal bias in terms of side-effect management, I am not seeing the heavily reported side effects that were in Richardson’s trial, and I think one of the reasons might be the way that bortezomib was delivered intravenously in the schedule. Hopefully, some of the newer drugs in combination with panobinostat might be a little bit more tolerable. Right now, we are using it in combination with ixazomib or MLN9708, the Takeda Oncology oral compound [ClinicalTrials.gov Identifier: NCT02057640].

Note: Adverse events (AEs) led to discontinuation in 36% in the PAN arm and 20% in the pbo arm. Common grade 3/4 lab abnormalities and AEs (regardless of study drug relationship) in the PAN vs pbo arms included thrombocytopenia (67% vs 31%), neutropenia (35% vs 11%), and diarrhea (26% vs 8%); these were generally manageable with dose reduction/supportive care. On-treatment deaths occurred in 8% and 5%, respectively.

The other agent that I have had experience with is ibrutinib in myeloma, and this is so exciting because we already know it is a drug used in chronic lymphocytic leukemia. Of course, it is an oral drug—and we just had the conversation about the compliance-and-adherence issue when you are using these newer drugs—but it tends to be pretty well tolerated as well. Hopefully, again, we still have the stage 1 dose escalation study that we are working on, but these do represent newer therapies for patients with myeloma and are added to the armamentarium [ClinicalTrials.gov Identifier: NCT01478581; NCT01962792].

Dr. Harvey, do you have any experience with those or the other drugs around the horizon?

Harvey: Yes, certainly, panobinostat. We had some work with you as well and continue with ongoing combination studies in phase 1 and subsequent evaluation. I think your point around toxicity and panobinostat’s adverse-event profiles are probably mitigated in a number of ways. I like your point around the intravenous versus subcutaneous bortezomib. I think the other idea is that some of the adverse events with panobinostat, such as thrombocytopenia, fatigue, and diarrhea—the fatigue can be very real in some patients and needs to be monitored carefully.
WARNING: FATAL AND SERIOUS TOXICITIES: SEVERE DIARRHEA AND CARDIAC TOXICITIES. See full prescribing information for complete boxed warning. Severe diarrhea occurred in 25% of panobinostat treated patients. Monitor for symptoms, institute antidiarrheal treatment, interrupt panobinostat and then reduce dose or discontinue panobinostat. (5.1)

Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving panobinostat. Arrhythmias may be exacerbated by electrolyte abnormalities. Obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated. (5.2)

INDICATIONS AND USAGE

Panobinostat, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

But for diarrhea, sometimes we are giving antiemetics with bortezomib and other drugs that perhaps were not given in the trials, or other things that may cause some slowing of the gastrointestinal tract, so the diarrhea tends to be fairly manageable pretty early on if you can get on top of it. It is nice to have another drug in panobinostat for patients who are there. We have not had much experience with ibrutinib here, but I am sure that there is more experience in Rochester and other places.

Kumar:

The good thing about this new drug is that it is a new class of drugs. I think we have been talking about the histone deacetylase inhibitors for a long time, and finally, we actually have something that is approved and in the market. I suspect there may be a limited spectrum of use, but I think it is good to have another option out there, because I think if you talk to investigators on this clinical trial, they all have been impressed by the drugs and, of course, have instances in which patients who have not done well with other drugs have achieved good benefits from this. So, I think it is good to have one more option in hand.

So, I would like to thank both of you for sharing your thoughts on this important practice topic of new therapies and modalities that may address the clinical barriers of high-risk disease. I encourage participants to view other activities on Managing Myeloma and utilize the practice resources that are provided for the professional multidisciplinary team members. Thank you.
References:


