**Sagar Lonial, MD, FACP**
Chair and Professor
Department of Hematology and Medical Oncology
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

**Heinz Ludwig, MD**
Professor of Internal Medicine
and Haemato-Oncology
Wilhelminen Cancer Research Institute
Wilhelminenspital
Vienna, Austria

**Dr. Sagar Lonial:** Hello and welcome to *Managing Myeloma*. My name is Sagar Lonial, and I am a Professor at the Winship Cancer Institute of Emory University in Atlanta. Today, I am talking with Professor Heinz Ludwig from the Wilhelminen Cancer Research Institute in Vienna, Austria, and we are going to talk about highlights from the ESH 3rd International Conference on Multiple Myeloma, and Professor Ludwig chaired a session on treatment of elderly patients. So, that is really what we are going to focus on in the next few moments. Welcome, Professor Ludwig.

**Dr. Heinz Ludwig:** Hello, thank you for having me.

**Dr. Sagar Lonial:** So, what I'd like to do is talk a little bit about some of the important updates that were presented in your session. There were three lectures, one that focused on front-line therapy for fit patients, one that focused on front-line therapy for frail patients, and then your lecture specifically on supportive care in general for myeloma patients, but we will use this as a launching pad to talk about supportive care for elderly patients. So, let's begin with the current state-of-the-art for fit patients in that presentation.

**Dr. Heinz Ludwig:** Professor Mohty from Paris made a strong point regarding transplant considering transplantation in fit elderly patients. In my opinion, the term "elderly" is an umbrella term for a very heterogenous group of patients. For fit elderly patients between 65 and 75 years of age, he recommended high-dose chemotherapy followed by autologous transplantation and stressed that this is a very effective treatment for fit elderly patients. For patients not eligible for transplant but still fit, he proposed a three-drug combination therapy. Professor Mohty mentioned several possible combinations but made a strong point for combining an IMiD with a proteasome inhibitor plus dexamethasone.

**Dr. Sagar Lonial:** So for those patients in Europe, how often are they receiving a transplant between 65 and 75?

**Dr. Heinz Ludwig:** I think this depends on the different policies of the institutions. Some centers recommend a transplant to all fit patients of this age group while others stick to an age limit between 65 to 70 years. Recently, results of two big trials comparing transplant with conventional therapy have been presented. Both studies showed a clear superiority of transplant in terms of overall response rate, complete remission rate, and MRD negativity rate as well as longer progression free survival (PFS), but at this point in time, there is no difference in overall survival. One could argue that with longer follow-up, the survival curves may still be diverge, because it is known that patients with good risk features benefit most from aggressive therapy, and so this might be seen in those patients after longer follow-up.

**Dr. Sagar Lonial:** So, that is a big, I think, point of distinction between the practice in the U.S. and the practice in Europe. There have been now a number of retrospective analyses in addition to the paper that was published recently in BMT that have demonstrated the benefit for transplant is the same independent of age, and actually, that analysis went all the way up to 78. And so for our patients, I think it is matter of picking the right patients, recognizing that patients over the age of 70 are not going to get MEL200, they are going to get MEL140. And so, by dose-reducing the melphalan, you do significantly improve the tolerance of a transplant, even for patients in their mid to upper 70s, and the best example I can give of that is the patient that I took to an autotransplant was 74, and at day 30 after transplant, he was out playing golf and walking 18 holes a day again. So, there are patients that can do remarkably well and continue to gain benefit from high-dose therapy almost independent of age. I think it is important to identify who those patients are and treat them with the appropriate induction therapy so that we do not limit their ability to collect stem cells or to have stem cell transplant as a potential option for them in the future.

**Dr. Heinz Ludwig:** Yes, but when you look at another trial which recently has been published looking at age-corrected survival curves, the benefit for transplant for patients age 70 to 75 years was smaller compared to younger patients. But I completely agree, and that was the starting point of our discussion, that there is a big variability in fitness we see in elderly patients. For transplant, you pick out those who are really fit, and those patients tend to benefit. I think that this has been shown clearly.

**Dr. Sagar Lonial:** Okay, so, let's talk a little bit about the second talk then, front-line therapy for frail patients. This has been a pretty rapidly moving target, and I suspect we are going to see data in the next 6 to 12 months that is going to make this even more challenging to sort out a little bit. What were sort of the take-home points from Dr. Larocca's talk?

**Dr. Heinz Ludwig:** Dr. La Rocca comes from the Torino team and the Torino team has established a geriatric assessment instrument which is available online on the website. Using this instrument, you can easily categorize your elderly patients into three different groups: namely those who are deemed to be fit, unfit, or who are frail. The instrument provides important prognostic information. When you apply this instrument to elderly patients, you find out that those categorized as frail have really a poor outlook, and the discrimination in outcome using the frailty index is much greater than that which you obtain when you use cytogenetic risk factors. Being frail is a significant disadvantage, of course, and the message of Dr. La Rocca's presentation makes clear that we have to adapt the treatment to the fitness of our individual patients. She recommended similarly to Dr. Mohty a triple combination for fit younger elderly patients and a very slow-go approach in those who are really frail. Patients who are frail have more complications, do not tolerate treatment as well as fit patients, and even if you reduce the dose, they discontinue treatment more often and earlier, and of course their outcome is much poorer than that of the other two groups. Due to this data, it should become common practice in my opinion to assess frailty in clinical practice. In the past, physicians believed that they were quite good in distinguishing fit and frail from unfit patients, but there are very few studies comparing the physicians' judgment with the outcome obtained using frailty instruments, and the comparison showed that these instruments enable better discrimination than physicians' judgment. This is why we need these instruments and why we need to implement these instruments in our daily practice.

**Dr. Sagar Lonial:** So, I think that the development of these instruments is really critical to appropriate triage and management and identification of potential toxicities of therapy as well. What is sort of the general thinking about treatment-wise for a newly diagnosed frail elderly patient? What are the current standards of thought?

**Dr. Heinz Ludwig:** I think the Italian Group did two trials in patients age 75 or older, and they compared two-drug combinations with three-drug combinations which were either proteasome inhibitor or lenalidomide based. Interestingly, they found that the triple-drug combinations were not superior in those elderly patients. Based on their findings, lenalidomide-dexamethasone or bortezomib-dexamethasone or a novel proteasome inhibitor plus dexamethasone, these combinations yield similar efficacy in those elderly patients with somewhat less toxicity. In addition, one has to adapt the dose and when using bortezomib, you can also modify the frequency of dosing. In very frail patients, you tend to start not only with the lower dose, but you likely will use longer treatment intervals simply switching from twice-weekly to once-weekly, and this enhances the tolerance, and in the end, you will obtain probably better results with this aggressive approach in those elderly or older patients.

**Dr. Sagar Lonial:** And just as a sort of a future consideration and thought, where do you think antibodies might fit in the management of frail patients? My sense is that that might allow us to go back to a triplet, because the antibodies are so much better tolerated potentially if we have the data obviously.

**Dr. Heinz Ludwig:** I completely agree that the antibodies are very well tolerated, and they will be moved into front-line treatment. Then, we have two drugs, let's say a two conventional drug combo plus an antibody, and that is probably the way to go in the future. For the fit elderly patients, there will be many combinations consisting of conventional chemotherapy plus an antibody. But if you think far forward, you can even think about using two different antibodies with different targets, for instance, an anti CD38 antibody plus a checkpoint inhibitor; or even two different CD38 antibodies which have different targets on the CD38 molecule.

**Dr. Sagar Lonial:** Okay, so let's get to the last section which was your talk on supportive care, that has certainly been an important part of management of all patients in myeloma given many of the comorbidities they often present with as a consequence of their disease. What is sort of new and important from your view in terms of supportive care approaches?

**Dr. Heinz Ludwig:** I think we should consider that patients with myeloma, when they are started on therapy, carry a high risk for developing infections and infection-induced mortality. When you look at mortality rates in the first 3 to 4 months after the start of therapy, you find out that roughly 10-20% die because of an infectious complication. First, we need to be proactive here because we can probably reduce the incidence of infections and thereby the outcome of our patients. Data from a Scandinavian review showed that the rate of deaths due to infections remained rather constant at 20% during the whole course of the patient's disease, and this is an alarmingly high number in my opinion, and we need to do our utmost to reduce the risk of infections. For instance, myeloma patients have a seven-fold increased risk for influenza, and they have a 10-fold increased risk for bacteria. So, every patient should be vaccinated against influenza as well as their partners and family members and, importantly, also the care team. In addition, patients should be vaccinated with pneumococcal vaccine and possibly against *Haemophilus influenzae*. When we are recommending vaccination, we should be aware the

chance to develop an excellent antibody response is low in patients with active disease. Thus, ideally, we should vaccinate patients before onset of active myeloma or while they are in very good remission.

Proteasome inhibitors inhibit T-cell activity which is important to control latent viral infections. Almost all of us have herpes viruses and many of us have CMV viruses (about 60%) and other viruses, but when patients are exposed to proteasome inhibitors, the risk of reactivation of latent viral infections increases substantially. Therefore, the patients should be on prophylaxis with acyclovir or valacyclovir, that is standard now. If the patient is on maintenance therapy with a proteasome inhibitor and if his disease is well controlled, it is unclear whether we should continue prophylactic antiviral therapy, but in my opinion, I think it is better to be on the safe side and to continue with these treatments as long as the patient is on a proteasome inhibitor. Thus, when infections occur in myeloma patients, particularly in those with poorly controlled disease, we have to be very careful and consider rapid start of antibiotic treatment even before complete diagnostic workups in order to reduce the risk of severe complications.

**Dr. Sagar Lonial:** I think the point that you brought up about infectious complications and things are really very important as the survival of patients has grown markedly because of the availability of new agents preventing common things that in the past we could not do a lot all about, such as preventable infections and prophylactic infections. Those things are really critically important. I will tell you from our practice, we believe that myeloma itself is a risk factor for developing VZV reactivation or zoster reactivation, and so, we actually put people on lifelong acyclovir prophylaxis from the time they are diagnosed, regardless of whether they are on a proteasome inhibitor or not. I think these are all certainly important discussions, and in fact, the International Myeloma Working Group is going to update their recommendations on vaccines and supportive care before the workshop in India this year. So, we will see an updated manuscript at that meeting.

**Dr. Heinz Ludwig:** There are new vaccines on the horizon, particularly for herpes zoster. Up to now only an attenuated zoster vaccine is available, and this is presently in clinical trials, it is tested in patients with hematological malignancies. More recently, a new recombinant vaccine has been shown to reduce herpes zoster incidence significantly in normal elderly people. Hopefully, these vaccines will soon be tested in myeloma patients, and these may turn out to be very helpful because if that turns out to be safe and effective, then every patient should be vaccinated with these new herpes zoster vaccines before starting proteasome inhibitor therapy. Also, we are well aware of the fact that the response to vaccines in patients with myeloma is much poorer than in normal people. Sometimes, particularly if you have time and if the patient is not really in active disease, it is worthwhile to reconsider repeating the vaccination if the antibody response is not good enough.

**Dr. Sagar Lonial:** Yes, very interesting. You are right. I think there is a lot of excitement from being able to prevent some of these common and quite debilitating complicated conditions.

**Dr. Heinz Ludwig:** Patients on long-standing lenalidomide may in rare instances develop debilitating diarrhea due to a rare syndrome called bile salt malabsorption syndrome. Some of those patients suffer really significantly from diarrhea; they are afraid to leave their home because they cannot control their bowel movements. There is a good drug which is helpful in those patients (patients with bile salt malabsorption syndrome). The drug is called Cholestagel in U.K.,

colesevelam* is the generic name. The drug is not approved for this indication to be honest, but I think if patients suffer severely from their diarrhea, it is worthwhile to give the patients a try, and use colesevelam tablets. I usually start at two tablets and sometimes I have to increase it to four tablets, and usually there is a response within 2 to 3 days. If patients do not respond, I discontinue treatment. If you want, you can of course make a precise diagnosis of bile salt malabsorption syndrome by using a radioactive bile salt and you can then test the absorption, but I think it is not needed for clinical practice because you just use it (colesevelam) and see whether it is working or not.
**Colesevelam is not FDA approved for this use in the United States.*

**Dr. Sagar Lonial:** Yes, I agree, we have been using that for about a year now. It is remarkable for the patients that are on particularly len maintenance, who have the chronic malabsorptive diarrhea. It really works very quickly, and it works in almost 90% of patients. It is really very effective. So I agree.

So, any last couple of important summary thoughts you wanted to make about your session that perhaps we have not hit already?

**Dr. Heinz Ludwig:** Yes, well, we noticed a significant improvement in outcome and this improvement in survival is much more pronounced in younger patients, but it is getting better in elderly patients as well. This increase in survival is due to novel drugs certainly, but it is also due to greater experience of specialized care teams, and due to better supportive care. Taken together, several measures contributed to the improved outcome in elderly patients, and we hope to see much more in the years to come.

**Dr. Sagar Lonial:** All right, well, thank you Dr. Ludwig for your highlights that you provided today, and thank you for joining us today. For additional resources, please view the other educational activities on *ManagingMyeloma.com*.