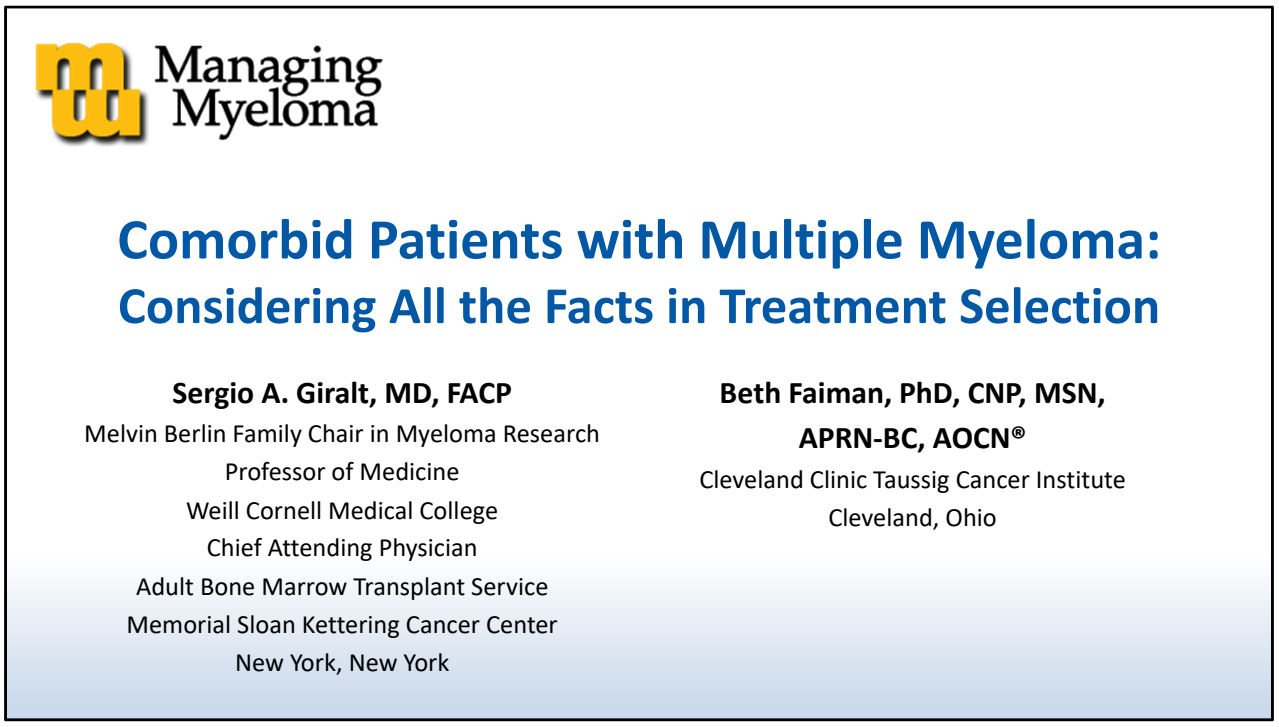
Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection



Sergio Giralt: Hello and welcome to our program, “Comorbid Patients with Multiple Myeloma: Considering All the Facts in Treatment Selection.” I am Dr. Sergio Giralt, Chief of the Adult BMT Service at Memorial Sloan Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College. I am pleased to be joined today by Dr. Beth Faiman from the Cleveland Clinic in Ohio. Together, we will share evidence and insights into the somewhat challenging and important topic. Hi Beth.

Beth Faiman: Hello, Dr. Giralt. Thank you for having me today.

Giralt: We hope by the end of our presentation you'll be able to identify how comorbidities in patients with multiple myeloma can affect treatment choices, and most importantly, the outcomes for your patients. We will review the current guidelines for standard induction regimens for newly diagnosed multiple myeloma patients, and factors you should be aware of when prescribing certain agents – or combinations of agents – in patients with comorbidities. In addition, we will spend a few minutes discussing when transplant may or may not be an option for your patients, and what drives your treatment decisions. Now, let's begin.

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Speaker Disclosures

Sergio A. Giralt, MD, FACP

- Consultant and formal advisory activities: Amgen Inc., Jazz Pharmaceuticals plc, Kite Pharma, Novartis AG, and Sanofi

Beth Faiman, PhD, CNP

- Consultant and speakers' bureau: Amgen Inc., Bristol-Myers Squibb Company, Celgene Corporation, Janssen Pharmaceuticals, Inc., and Takeda Oncology

Giralt: These are our disclosures.

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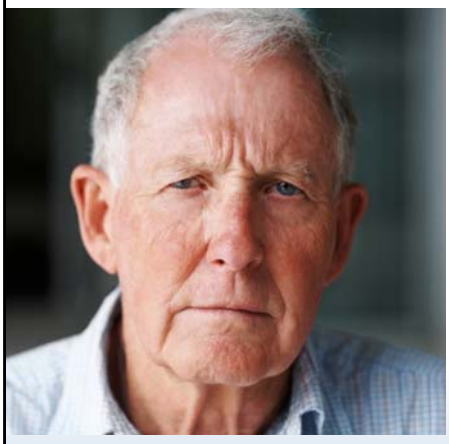
72-year-old Retired Factory Worker, Widowed, Lives Alone, Vietnam War Veteran



Past medical history

- COPD
  - Smoker x 42 pack years
- Hypertension x 20 years (controlled)

Current medical history

- Went to ER with severe back pain, fatigue
- Lumbar X-ray
  - L1 compression fracture
- MRI
  - Soft tissue mass L1

Giralt: To get started, Beth, why don't you begin by sharing a case presentation of a patient who is most likely to be seen in the clinical setting, who exemplifies what we want to discuss today.

Faiman: Thank you, Dr. Giralt. The case presentation that we selected today mirrors what you would see in your real-world practice. Here we have a retired 72-year-old factory worker who lives alone. He has a positive past medical history for COPD, who is a 42-pack-year smoker, Vietnam War Veteran, and has hypertension, although it is controlled. This gentleman went to the ER with severe back pain and fatigue. A lumbar X-ray was performed and showed an L1 compression fracture. Subsequently, due to lower extremity weakness, the ER obtained an MRI which showed a soft tissue mass at L1.

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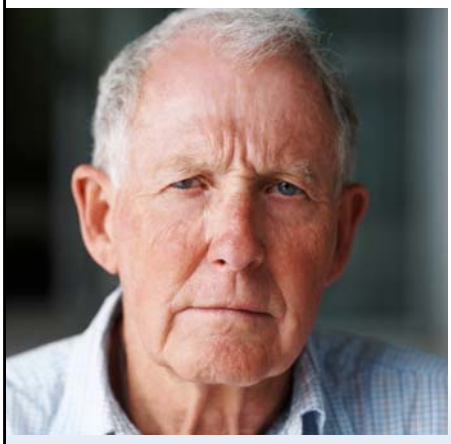
Admitted to Hospital for Pain Control and Diagnostic Evaluation



Evaluation results

- MPA: IgG 4,700 mg/dL and lambda 5,200 mg/dL
- M-spike 4.2 g/dL
- 24-hour urine <1.16 g/24 hour; mostly albumin (urine M-spike 0.3 g/dL)
- β2-microglobulin 5.6 mg/L; LDH 300; creatinine 2.4 g/dL

Bone marrow biopsy

- 20% clonal, lambda-restricted plasma cells
- Normal cytogenetics,
- No IgH translocations

Bone survey

- L1 mass and compression fracture

MPA=monoclonal protein analysis

Faiman: He was subsequently admitted for pain control and a diagnostic evaluation. His monoclonal protein analysis showed an elevated IgG and lambda and a serum M-spike of 4.2 g/dL of blood. He was secreting a fair amount of protein in his urine, about 1.16 g for 24 hours, but it was mostly albumin. His beta-2 microglobulin was elevated as well as his LDH and his serum creatinine. A bone marrow biopsy was subsequently performed and only showed 20% clonal lambda restricted plasma cells, normal cytogenetics and no IgH translocations, and the bone survey was pretty clear except for an L1 mass and a compression fracture. This bears a question, and I'll put this to you, Dr. Giralt. We have to determine: what is the diagnosis? Does this gentleman need systemic therapy? Is he a candidate for transplant if he does need therapy? What might our other concerns be regarding his comorbid conditions?

Giralt: Beth, this is an excellent case and as you said, it really reflects what we will have in practice. This patient, with what we see, obviously has a diagnosis of multiple myeloma. He has more than 10% clonal plasma cells, he has a paraprotein peak and, moreover, he has what we would call symptomatic myeloma because he has evidence of end-organ damage. We will talk a little bit more about the requirements for therapy later on. What other things could this patient have, and do we know if this patient has high-risk disease?

High-risk disease is defined by the stage – an ISS stage 3 with a beta-2 microglobulin of over 5 would be considered high-risk disease – or based on chromosomal abnormalities. A patient with a 4;14 translocation, deletion 17, gain of chromosome 1 or 14;16 translocations are all considered high-risk. Now, they are not high-risk because they won't respond: these patients respond to initial induction therapy. They are considered high-risk because the duration of response is generally less than two years. Whether he is a candidate for transplant or not is too early to say. A full staging evaluation after induction treatment, his tolerance to induction therapy, and his psychosocial and caregiver situation will also help us decide whether transplant is the right choice for him or not. Does he need systemic therapy? The answer is definitely yes.

Beth, he had a creatinine of 2.4, and I think it's important to recognize that this might be a more important emergent situation. We really want to protect two things in a patient who is presenting like this. One, we want to avoid nerve root compression, so it's worrisome that he had lower extremity weakness. If that mass at L1 was contributing to that weakness, he might require rapidly high-dose steroids or radiation. Likewise, if his creatinine from two months ago was normal, then again, obviously, his myeloma is affecting his kidneys, and rapid institution of treatment is necessary to avoid further kidney damage. Beth, what other concerns do you have regarding his comorbidities?

Faiman: I totally agree. This guy lives alone, so I worry about his safety. But going back to his comorbidities, he did have quite a bit of proteinuria. Now, that might be from the temporary renal failure, that might be from his years of hypertension, possibly underlying diabetic nephropathy, but I always worry in the lambda light chain population about kidney amyloid. He had mostly albumin secreting in his urine, so I might consider working him up for AL-amyloidosis as well.

Giralt: With a fat pad biopsy, right?

Faiman: Yes, fat pad biopsy or with a bone marrow biopsy stain (Congo red bone marrow biopsy). If I have a high suspicion based on his prior cardiac echos, I will look for cardiac amyloid as well, by checking the thickness of myocardium. These are separate from the myeloma diagnosis, but when you are thinking about doing high-dose chemotherapy in an older individual, or any systemic therapy, it is so important to look at all those differential diagnoses.

Giralt: I agree with you Beth. A lot of people are asking, what is the optimal imaging strategy for a patient with myeloma? We have traditionally used skeletal survey and that's still in the NCCN Guidelines, although we know that the International Myeloma Working Group is starting to change what they consider as the optimal imaging strategy for myeloma. At Memorial Sloan Kettering, we will either do a whole-body MRI or a PET/CT. What would happen in Cleveland Clinic, and what do you think is the optimal imaging strategy for a patient with myeloma today?

Faiman: Dr. Giralt, those are excellent questions. You were, I believe, an author on the paper from 2018 in the *Journal of Clinical Oncology* that did updates in bone this year, and so the optimal imaging is pretty much, across the board, PET/CT or MRI. There is a whole pattern of myeloma bone disease that's being described in other papers by Terpos and the International Myeloma Working Group. In my practice, we tend to start with the skeletal survey and as you mentioned, it fails to identify lesions (only about 30% to 40%); you need bone loss before you can find those lesions. Looking at the myeloma bone pattern of involvement with MRIs of the pelvis or lumbar spine or whole-body PET/CT, if you really want to quantify that burden of disease, is really important. We will absolutely do a baseline especially if there are suspicious lesions or plasmacytoma is suspected, but subsequent imaging might be more of a challenge depending on one's insurance.

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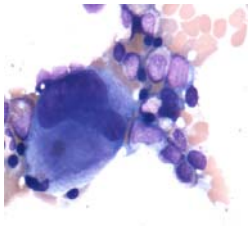
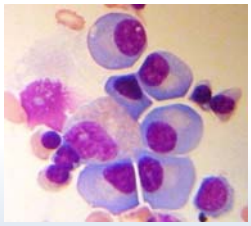
Multiple Myeloma: A Cancer of the Plasma Cells





- Healthy plasma cells produce immunoglobulins in response to foreign body invasion
- Average age at onset is 70 years
- Myeloma cells produce abnormal immunoglobulin
  - 65% IgG; 20% IgA
  - 5% to 10% light chains (monoclonal kappa, lambda light chains, Bence-Jones proteins)
  - Uncommon IgD, IgE, IgM, or nonsecretory disease

Kyle RA, et al. *Mayo Clin Proc*. 2003;78:21-33.

Giralt: Let's talk a little bit about what we know about multiple myeloma. First, multiple myeloma is a cancer of the plasma cells. The plasma cells are the cells that produce the immunoglobulins that defend us against infections in response to a foreign body (e.g. a bacteria or a virus). The average age of onset for myeloma is around 70 years. Myeloma cells produce an abnormal immunoglobulin. Two-thirds of them are IgG, 20% of them are IgA, and 5% to 10% of them do not produce a heavy chain, they produce light chain only. This is what will call light-chain-only disease and it can be either lambda light chain or kappa light chain, depending upon the light chain that the myeloma cell produces. Myeloma cells are recognized in the bone marrow because they are typical plasma cells with eccentric nuclei and a basophilic cytoplasm, but they tend to form clusters. Normal plasma cells usually are isolated. The normal percentage of bone marrow plasma cells is usually less than 5%. When we have more than 10% plasma cells, and these all are clonal, meaning that they are light chain or heavy chain restricted, we say that a patient has multiple myeloma.

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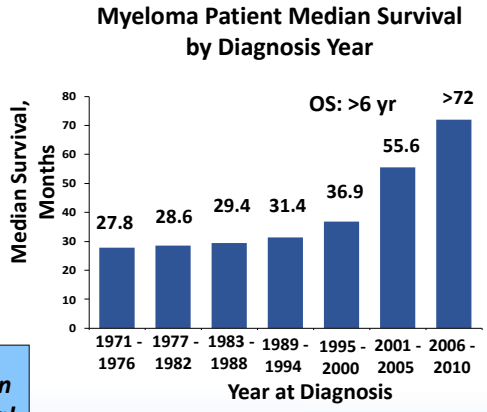
Epidemiology, Risk Factors, Survival

- Incidence
  - >50,000 currently living with MM in US
- Risk factors
  - Age
  - Gender
  - Race
  - Obesity
  - Genetics
  - Environment
- Clinical presentation
  - Back, bone pain
  - 20% asymptomatic

Patients now live more than twice as long with myeloma!



OS=median overall survival

Howlader N, et al. NCI 2016. SEER Cancer Statistics Review, 1975–2013.; Kyle RA, et al. *Mayo Clin Proc.* 2003;78(1):21-33.; Kumar SK, et al. *Blood.* 2012;120:3972.; Kumar SK, et al. *Blood.* 2008;111:2516-2520.

Giralt: There are about 50,000 patients with multiple myeloma living in the United States today, and this number is increasing over time because the survival of patients has improved with the improvement of treatment. It happens primarily in older patients. It is more common in African Americans, and in males more than females, and it seems to be associated with obesity and environmental exposures. Interestingly, our patient was a Vietnam veteran, and we know that there is an increased incidence of myeloma in Vietnam veterans that were exposed to Agent Orange. We also now know that first responders to the 9/11 attacks, as well as individuals who were in downtown New York who were exposed to the dust that was created when the towers collapsed also have a higher risk of myeloma. Traditionally, myeloma had presented with back pain, bone pain, fatigue because of anemia, and pathologic fractures. It's interesting that in the United States at least, the number of patients who are being diagnosed without any symptoms is starting to increase, because we're diagnosing it early. I think one of the most important things to recognize is that more and more patients are being diagnosed with multiple myeloma because we are looking for it more frequently, and these patients are living longer because treatment has improved significantly over the last decade. Beth, in light of our patient's presentation and our discussion, let's review the definition of active myeloma in the 2014 International Myeloma Working Group Updated Criteria.

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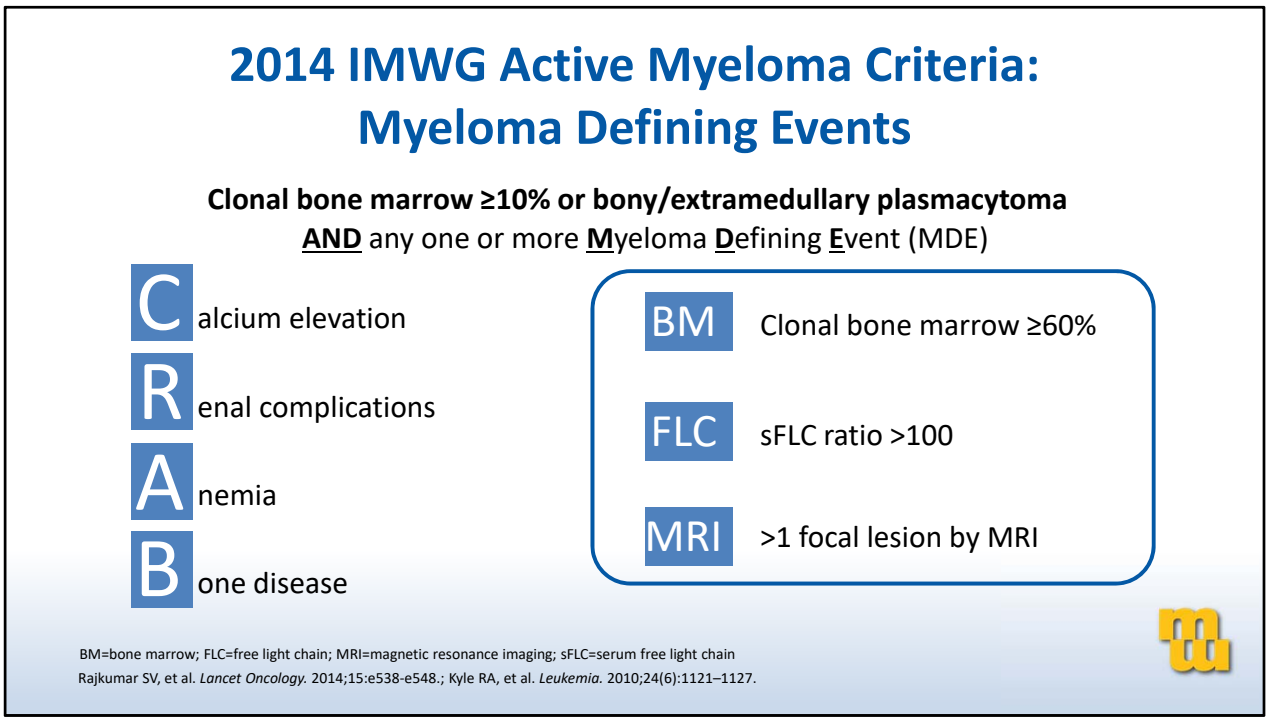

Faiman: This was new and hot off the presses a couple of years ago, but now, it's 2018, 2019, and this is kind of old news. Historically, we have this CRAB acronym. In the early 2000s, we identified these CRAB criteria by the International Myeloma Working Group papers, and we waited until end-organ damage. How funny that is to me these days, because why wait until somebody has hypercalcemia or kidney problems, renal complications, anemia, or bone disease? Why wait until one has damage to their bones? The working group got together and identified through meta-analysis the key features in which patients were likely to require treatment, and they include clonal bone marrow plasma cell percentage of greater than 60%; an elevated kappa to lambda, serum free light chain ratio of greater than 100; and an MRI with more than one focal lesion. Again, that goes to the myeloma pattern of bone involvement, and that lesion has to be greater than 5 mm. Basically, we are trying to identify patients earlier and intervene earlier prior to them having myeloma-defining events, or MDE.

Giralt: It's interesting, and I think we have to put things in historical perspective because a lot of the fellows in training and junior faculty always wonder so why were you waiting for patients to have renal complications, anemia, or bone disease? It has to do with the fact that at that time we did not have a lot of treatments and the treatments were not very good. Now, with all the treatments we have that are extremely effective, I agree with you, we should not wait for patients to fracture, and these new myeloma-defining events go a long way to preventing patients from progressing to symptomatic disease. More importantly, the whole field of high-risk smoldering myeloma is also starting to come aboard. There are now a lot of clinical trials looking at patients with high-risk smoldering myeloma who do not have myeloma-defining events, and whether these patients should be considered for treatment too, to prevent them from developing multiple myeloma in the future.

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Key Assessment Measures

History and physical

- History of bleeding and clotting disorders (risk of DVT and bleeding on anticoagulants)
  - GI bleeds
  - History of DVTs
- Comorbidities (cardiac, renal, metabolic)
  - Diabetes
  - Prior stents
  - History of CVA
- Other malignancies
- Signs of dysautonomia or amyloid
- History of dental extractions and dental examination. Consider dental clearance before starting bisphosphonates

Laboratory

- Iron and vitamin studies in patients with anemia
- Stains for amyloid in marrow and consideration for fat pad biopsy or renal biopsy in patients with nephrotic range proteinuria (particularly if lambda light chain)
- Beta-2 microglobulin
- Quantitative immunoglobulins include IgD
- Use of heavy-light chain assay
- 24-hour urine assessment

Faiman: Along those lines, we went over the history and physical exam of our patient. Again, he was a Vietnam vet, he had the typical hypertension, hyperlipidemia, COPD: common things that you would see in clinical practice. But at diagnosis and throughout – this is fluid, people change and treatment changes them – look at his history of bleeding. Does he have any GI bleeds or history of DVTs that might put him at risk for bleeding if he is placed on aspirin, or risk of thromboembolic events? Regarding comorbidities, we talked about the cardiac and renal status concerns. In respect to diabetes, I think we underestimate that many of these patients will require corticosteroids, and for those who have an underlying diabetes, this could be a real big deal with severe high diabetic ketoacidosis, or that nonketotic state; I have seen that quite a few times.

Looking at other malignancies: signs of amyloid we mention that as a possible differential diagnosis of our case study. We also have to make sure we do an effective diagnostic workup, and that workup is at baseline and throughout. You want to make sure that you obtain the correct baseline studies and then that needs to be repeated on a monthly basis for most of our patients. There are numerous papers to guide us as to what to order. For example, ruling out other signs of anemia may be not in our case study, but in the typical patient with this monoclonal gammopathy or MGUS, is the iron or vitamin B12 deficiency playing into whether or not they have anemia? Are they bleeding? We discussed using stains for amyloid in their bone marrow, or a simple fat pad biopsy, especially if they have nephrotic-range proteinuria.

Our patient's proteinuria was less than 4 g/dL, so it is not in that range, but it's high enough to warrant suspicion. The beta-2 microglobulin and LDH are very important for prognosis, and LDH outside of the normal range can be considered high-risk in addition to the cytogenetics. Of course, there are the quantitative immunoglobulins and don't forget IgD. The 24-hour urine assessment – the monoclonal protein as well as the total protein – is also very important as well.

Giralt: We are currently not using the heavy light chain assay, Beth. Are you using that in Cleveland Clinic?

Faiman: No, not yet. I feel like we have enough tools in our toolbox to appropriately diagnose and monitor our patients and we don't reliably have that test to date in our institution.

Giralt: We need to tell our audience also not to forget that it's always important to look back at medical records to see what the tempo of the disease is. It is different to approach a patient who has had chronic renal failure because of diabetes or hypertension, as opposed to somebody who had a normal renal function three months ago. In one, you can say that this patient the myeloma is probably not contributing to the renal failure, and in the other one, you have to say the myeloma is contributing to the renal failure, and rapid institution of treatment is absolutely necessary.

Giralt: Beth, as you think about this patient and with all your experience, what comorbidities of this particular patient, and what in his social situation, make you worry about what treatment may or may not do to him? You mentioned diabetes, which I think is important because at the moment we start high-dose dexamethasone, these patients need to be followed carefully to prevent them from hitting the emergency room with a blood sugar of 300. What other things can a practicing physician or their team take into consideration to make the beginning of treatment easier?

Faiman: Correct, and I think one of the most important things we forget about are the mood swings that are associated with those corticosteroids. The doses of dexamethasone are high and so you think about the metabolic concern with the hyperglycemia that might be poorly controlled, but I also worry about mood swings. This is a Vietnam vet, he might have a history of posttraumatic stress disorder or depression, so he needs a thorough psychologic evaluation in my opinion, and we try to do at least a brief one with most patients. The kidney disease and diabetes in his case will be the most important, but again in the back of my mind for all of these newly diagnosed older individuals, I'd look at his lung function knowing he has the COPD diagnosis, and try to get at least a baseline echo and EKG (or one within the last couple of years) to rule out that idea of cardiac amyloidosis.

Giralt: It's also extremely important that the patient is 70 years old, as you pointed out, he may be at risk for steroid-induced diabetes or steroid-induced mood swings, and that now with other drugs that are so potent, we really don't need to give the 40 mg of

dexamethasone to this patient. The NCCN Guidelines would recommend giving 20 mg of dexamethasone as part of the induction treatment. Beth, do you think it is important to reach out to the primary care doctor, the pulmonologist, or the cardiologist (if he has one) and kind of make a group decision of what the situation is?

Faiman: Absolutely. This gentleman was admitted in the hospital, so I'm hopeful that in his case he had the benefit of a multidisciplinary team, the nephrologist was likely consulted, as well as his primary care provider, at least in some of the larger institutions. You might be faced with having only the internist at hospitalization at the time of diagnosis pushing all these buttons, but absolutely involving the whole treatment team – and that takes us back to the team of the nurses, nurse practitioners, physician assistants, pharmacists – and bringing in everybody's expertise to help arrive at the best care possible for the patient is very important.

Giralt: I think in practicing guidelines in a patient like this, you would say that with cardiopulmonary disease and COPD, carfilzomib may not be the first drug of choice because of the problems of hypertension, and cardiopulmonary toxicity. His creatinine was elevated, so starting with an IMiD like lenalidomide might produce severe myelosuppression, so that might not be our first course of induction. Whether he has neuropathy or not, might determine how we are going to dose the bortezomib, whether we will give it twice a week or once a week. Any other hints or comments that we should be giving our audience about how we would approach a patient like this?

Faiman: I think by keeping in mind, Dr. Giralt, those key things on the previous slide, and by getting a good baseline. What is his overall DVT risk? He had 42-pack-years of smoking but is he still smoking, or did he start smoking once he learned that he has multiple myeloma? Keeping in mind those comorbid conditions are super important and by the way, this gentleman does not have peripheral neuropathy. That's the one thing he does not have, so keeping that in the back of your mind.

Giralt: So, Beth, how would we approach this patient with multiple myeloma?

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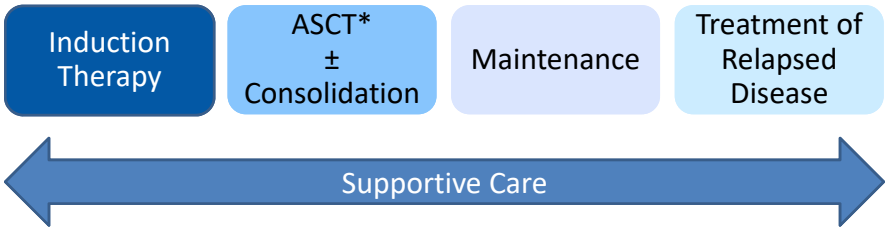
Standard Approach to Multiple Myeloma



- Refer patients (including older patients) to transplant center early, by second cycle
- Eligibility for ASCT is dynamic and should be assessed throughout the course of treatment

*All patients should be evaluated at a tertiary care center
NCCN. Multiple Myeloma Guidelines.

Faiman: As Dr. Giralt likes to describe how he thinks about treatment and describe treatment: he thinks about it in buckets. Describing the induction phase, where you want to get that individual into the best remission that you can, generally giving them anywhere from two to four or more cycles of chemotherapy or novel therapy. Again, thinking of clinical trials because we haven't gotten to where we are with myeloma without using clinical trials, so that's important. Inducing a response is important. Then we will talk about the role of transplantation in multiple myeloma, and that would be the second phase. The transplant plus or minus a consolidation phase. Then there is maintenance. You can get through the induction chemotherapy and then lower that same type of treatment that induced that remission into the maintenance, and we will discuss that. Then there is the treatment of relapsed disease. Throughout this is supportive care. One of the things that we have identified in our clinical practice is that we probably don't start bone-modifying agents early enough. In review of our charts – and this is not yet published data – for one reason or another, even though the guidelines for the International Myeloma Working Group support the starting of bone-modifying agents, we don't start those early enough. Other supportive care would be minimizing the risk of thromboembolic events and infectious complications. There was a paper in Europe that was published at ASH last year that looked at starting levofloxacin within the first few months of induction therapy to minimize the risk of early death. Keeping these things in mind is really important, so again, the standard approach to myeloma is a continuum as well.

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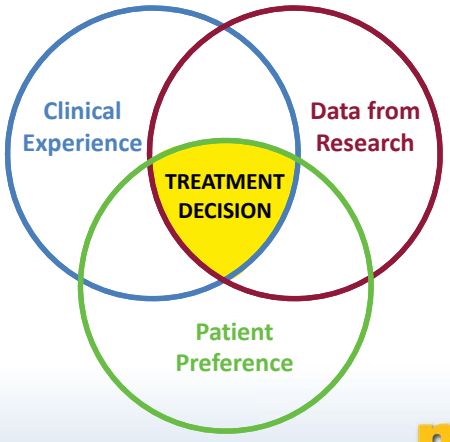
To Treat or Not to Treat…That Is the Question And with What? Shared Decision-making

- Numerous excellent choices
- Goals of care should be discussed with patient, caregivers, and the treatment team
- Balance financial, physical implications of treatment
- Fitness and frailty
- Transplant or no transplant
- Role of the team approach



Moreau P. *Blood*. 2015;126:727.

Giralt: So, should we treat or not treat, and how would you discuss this with this patient?

Faiman: We balance the clinical experience and then we would take data from clinical research, the study results and then, obviously, the patient preference. If this individual does not drive a car or have resources for transportation, he might not want to come to the clinic twice a week for an infusion, maybe an oral therapy (if he is adherent) would be best. Discussing the risks and the benefits and working with the patient is important: balancing the financial and physical implications and of course, the comorbid conditions as well. We will talk more about transplant or not coming up.

Giralt: So, you agree it's essential to have a multidisciplinary approach, particularly in the places where you have access to geriatricians or access to social workers and psychiatrists. We really have to approach them as a team to make the journey. We might not be able to make it easy, but we could try to make it less difficult.

Giralt: Beth, when you think about this, for the community physician, who should they access? Their families, caregivers, social workers, and other members of the support system, correct?

Faiman: Absolutely, so accessing the social workers and the family members is important, but I encourage my patients to get an opinion from a qualified myeloma physician who does this every day. We are not trying to steal community physicians' patients, but that will provide an extra layer of support for that patient, and we do this all the time in our practice. We will go back and forth: they will see us annually and then they will be able to receive their care locally. I think it benefits the patient, it benefits us, and it definitely benefits the knowledge gained in the community physician who might only see one or two myeloma patients in a year.

Giralt: I think that's an excellent recommendation. There are myeloma centers of excellence throughout the country. We're always willing to see patients and send them back to their community but give them what we think is the best approach for that individual patient. There are resources in many of the myeloma centers of excellence that in the community may not be available and may help the practicing physician and the team to take better care of the patient and avoid complications from happening in the future.

Faiman: I think of funding support as the big thing that our patients will have access to and it's worth the trip for most of my patients I think.

Giralt: We've talked a lot about whether this patient be considered for transplant or not. I think we have already made the decision this patient needs treatment, and the goal of treatment is always the same. We want to give all our patients the longest life, with the best quality of life, with the least amount of treatment necessary. In myeloma, we know that depth of response is important, and when we look at a patient like this 72-year-old who otherwise is fit, and is independent (he does all his activities of daily living), we should really try to look for the deepest response possible. Initially, a complete remission and then we'll talk towards the end about measurable residual disease (or minimal residual disease as it was previously known) as a surrogate endpoint for treatment. As for the question of whether this patient should proceed to transplant or not, in the early phase, I usually mention it to the patient, but I don't go too much into detail because a lot of it will be informed by the response to treatment and the tolerance to initial induction therapy. Do you think that's a correct way of approaching it, Beth?

Faiman: Absolutely. I see a lot of our patients have what I call the deer in the headlight approach. It is often the diagnosis you were not expecting to hear and delivering little pieces of information within the first few months is important; and getting in your nurses and social workers, as well as getting an extra set of ears from caregivers, if they have one available.

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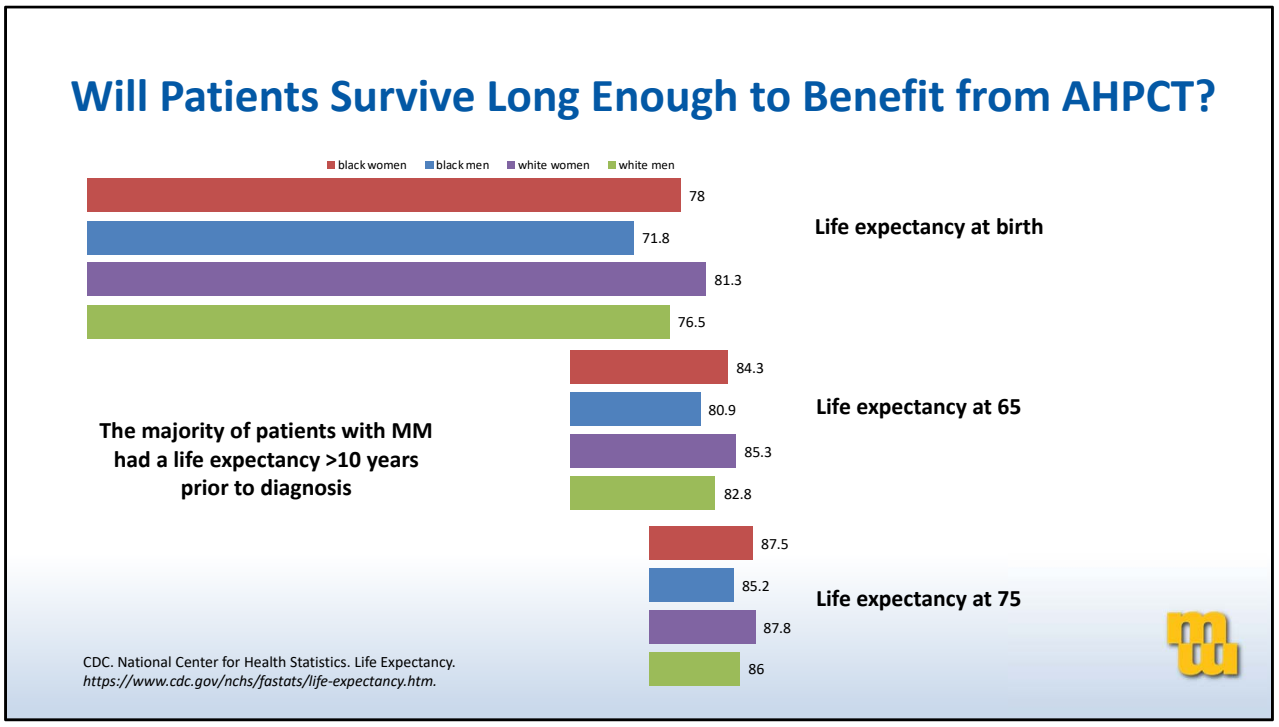

Giralt: The question is always asked to me, why are you talking about transplant in the patient who is 70 years old? If a patient is 70 years old, their life expectancy is more than 10 years, and as we will hear in younger patients, high-dose melphalan and autologous transplantation has a significant impact on progression-free survival and there are some trials that actually have a survival benefit. I tell patients, even in patients 70 and 75 years of age, there may be a significant benefit for aggressive therapy with the intent of achieving the deepest remission possible.

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Geriatric Assessment

ASCO Practice Guideline Addressed (Four Questions)

1. Should geriatric assessment (GA) be used in older adults with cancer to predict adverse outcomes from chemotherapy?
2. Which GA tools should clinicians use to predict AEs, including chemotherapy toxicity and mortality?
3. What general life expectancy data for community-dwelling patients should clinicians consider to estimate mortality and patient specific treatment decisions?
4. How should GA be used to guide management of older patients with cancer? What general life expectancy data for community-dwelling patients should clinicians consider to estimate mortality and patient?

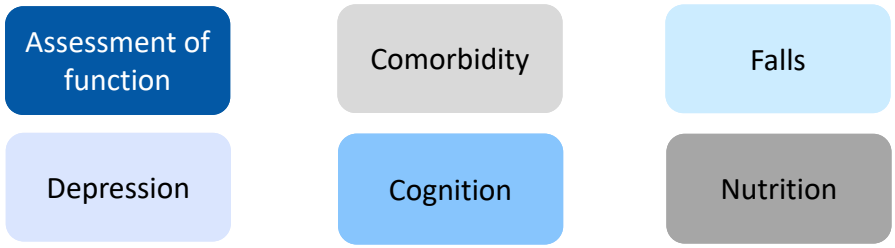
Mohile SG, et al. *J Clin Oncol*. 2018;36(22):2326-2347.

Giralt: We look at patients now who are over the age of 70, and we have ASCO practice guidelines looking at how should we address chemotherapy and oncologic therapy for older patients. These guidelines ask us “Should geriatric assessment be used in older patients to predict adverse outcomes?” The answer is definitely yes. There are multiple geriatric assessment tools that can let us predict what adverse events may occur, and whether we should dose adjust chemotherapy. In reality, what we tell older patients, is if you're fit, we should go for the full treatment. If you're frail, we should avoid treatment that will cause excessive toxicity. We also think that it's important to consider the life expectancy of a specific patient. The way we approach an 85-year-old is totally different than the way we approach a 75-year-old. The way we approach an 85-year-old who has congestive heart failure is also different as opposed to a 75-year-old. The way we approach a 70-year-old who has severe comorbidities, coronary vascular disease, and two strokes also is different. The American Society of Clinical Oncology is trying to tell all of us practicing physicians that age is just a number. That when we look at older patients, we have to look at their comorbidities, their life expectancy, and there are now multiple tools that will help us decide whether we should treat a patient aggressively with the intent of long-term disease control, or whether we should treat patients with more palliative intent.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Recommendations in Patients ≥65 Years of Age Receiving Chemotherapy

- At minimum, the following assessments are recommended which are not routinely captured in an oncology assessment



Mohile SG, et al. *J Clin Oncol*. 2018;36(22):2326-2347.

Giralt: At minimum, I think all patients who are over the age of 60 should be assessed for function and comorbidities. Have they fallen lately? Are they depressed? What is their cognitive function and what's their nutritional status? If you do not have a geriatrician close by or if it's inconvenient, all of these tools are available in the ASCO guidelines. They are relatively easy to administer, and they can be administered by a nurse, a nurse practitioner, physician assistant, or the physician in a relatively short period of time. They should be considered part of the standard evaluation of any myeloma patient over the age of 65 in whom you are getting ready to administer chemotherapy. Beth, what do you think are the other real-life considerations?

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Real-life Considerations

- Consider one's overall health status, comorbid conditions and how these impact treatment selection
  - Acute on chronic kidney disease (dose modifications, risk stratify)
  - COPD, smoking history (risk of lung infections, shortness of breath)
  - Hypertension (hypotension with bortezomib, drug interactions)
  - Diabetes (corticosteroid use)
- Living situation/support systems, physical distance from clinic
- Ability to drive back and forth or remember to take the recommended medications
- Clinical trial participation may provide more resources (transportation assistance, parking reimbursement, dedicated nurse)

Comorbidity index? Is this used in clinical practice? Other considerations?

Faiman: One of the things we use is the eyeball test: if they look good, then they are fit for chemotherapy. First I want to comment on those guidelines: as onerous as it seems to administer those tests, it's really important, but also important is one's overall health status. We have reiterated during this discussion the acute and chronic disease of the kidney. As Dr. Giralt mentioned, this gentleman might have had a creatinine of 1.3 last year and now it's elevated, but what if it was always 2.3 or 2.4? So taking into consideration historical values is very important. He must have sought medical care from time to time if his hypertension is controlled. As we mentioned, the COPD and smoking history, whether or not the hypertension is still controlled, and then the diabetes risk because of the corticosteroid use. We also reiterated the importance of his living situation. Maybe he lives alone but he has a very supportive neighbor or a significant other. Can he drive back-and-forth to treatments or access public transportation? And what's important to assess is many insurances will have transportation assistance that can be set up as part of their medical benefit. Clinical trial participation is also very important to consider, especially in a center of excellence. The functional assessment: again, if they are up and moving around,

Comorbid Patients with Multiple Myeloma:
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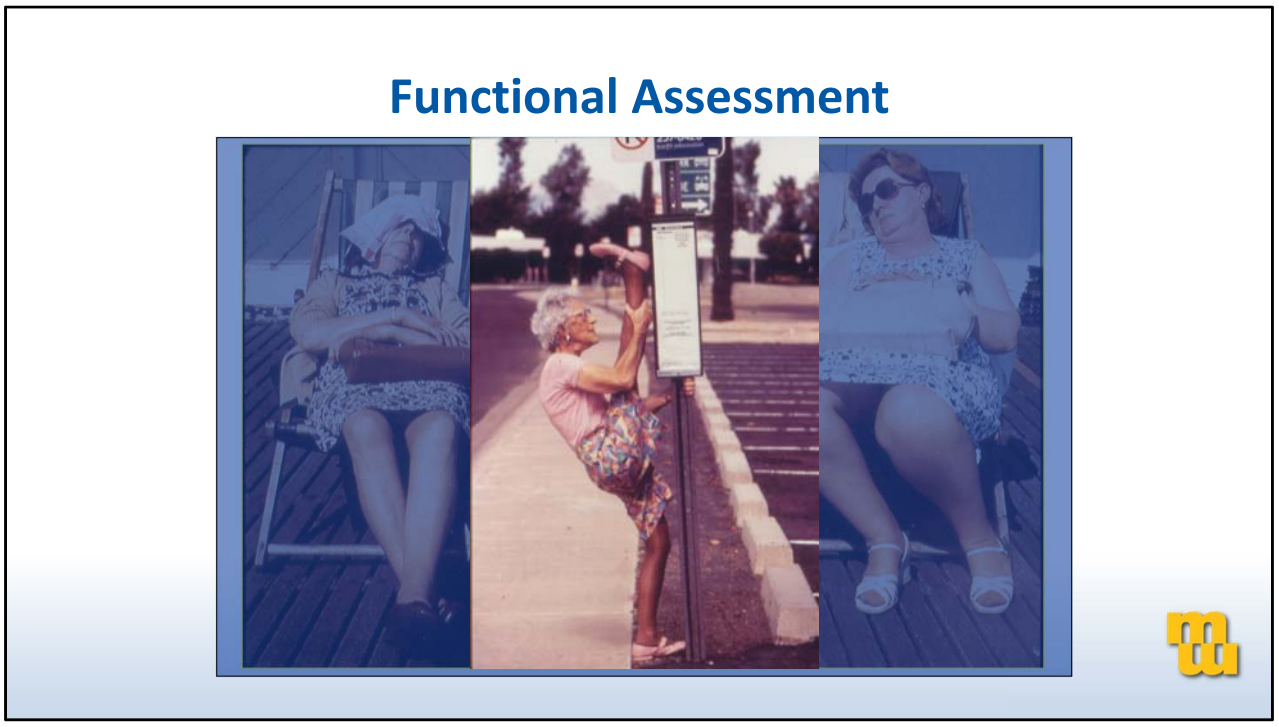


Faiman: I think it's important to assess that as well or if they are laying in a lounge chair.

Giralt: So what you're saying it's not how old you are but how you carry your age?

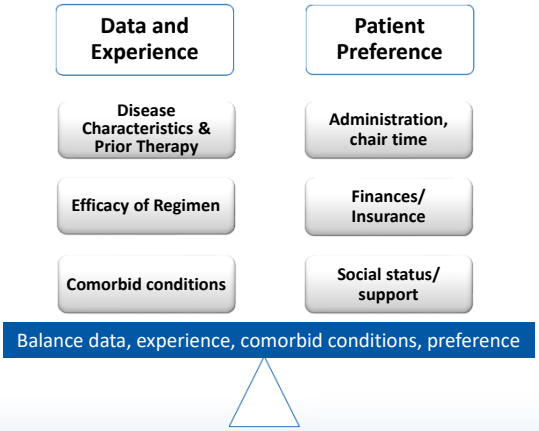
Faiman: Of course, of course, and that is a real important point.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Induction Regimens for Newly Diagnosed MM Patients

Common induction regimens

- **Transplant eligible:** three-drug induction regimen (VRd, KRd, CyBorD)
- **Transplant ineligible:**
  - Three-drug induction VRd for fit patients
  - Two-drug regimens (eg, Rd or Vd) or less intense (RVd lite) for frail or elderly patients
  - Four-drug regimen: Dara-VMP
  - Continuous Rd therapy was superior to shorter duration Rd or MPT (FIRST trial)



Dara-VMP=daratumumab-bortezomib-melphalan-prednisone; KRd=carfilzomib-lenalidomide-dexamethasone; MPT=melphalan-prednisone-thalidomide; Rd=len-dex; Vd=bortezomib-dex; VRd=bortezomib-len-dex

Faiman B, et al. *J Adv Pract Oncol.* 2016;2016:7(suppl 1):17-29.; Palumbo A, et al. *N Engl J Med.* 2014;371(10):895-905.; Attal M, et al. ASH 2015. Abstract 319.; Lentzsch S, et al. ASH 2015. Abstract 1975.; Attal M, et al. *J Clin Oncol*. 2016;34(15):8001-8001.; Hulin C, et al. *J Clin Oncol*. 2016;34:3609-3617.; Clinicaltrials.gov. Accessed April 11, 2017.

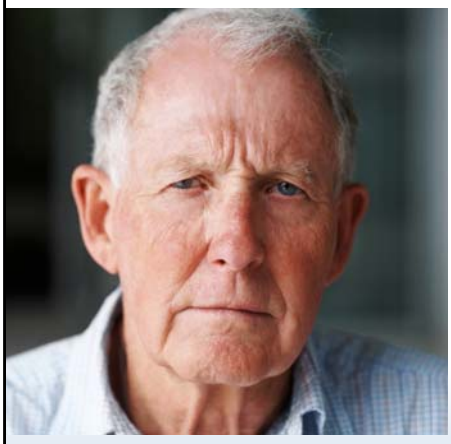
Giralt: Let's review the options for treatment at this point. We know that in somebody like him, who is potentially transplant eligible, although he has comorbidities, he is independent in his activities of daily living, he has no gross losses of his functional status, therefore we should really try to go for long-term disease control. There are three drug regimens and two drug regimens. All the randomized trials have shown that for fit patients, three drug regimens are superior than two drug regimens, and the one most commonly used in United States is the combination of bortezomib, lenalidomide, and dexamethasone (VRd). However, in this patient with a creatinine of 2.4, we would probably start with the combination of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) and if his kidney function improves after one or two cycles, we would then begin VRd. Bortezomib we would give at the standard dose of 1, 4, 8, and 11, but we would give it subcutaneously to reduce the risk of neuropathy. Would we think about carfilzomib, lenalidomide, and dexamethasone (KRd)? In this patient, I do not think it's a good choice because he has the renal dysfunction and the cardiopulmonary dysfunction. For patients who are much frailer or patients with severe comorbidities – for that 80-year-old or the patient whose life expectancy is relatively limited because of the other comorbidities – then it makes sense to do continuous therapy with the doublet such as lenalidomide-dexamethasone, or bortezomib-dexamethasone. The combination of melphalan, prednisone, and thalidomide (MPT) is something that's used in Europe but not used in the United States. You mentioned patient preference, and that is, there are all oral regimens like lenalidomide, ixazomib, and dexamethasone. You were saying Beth?

Beth I'm sorry to interrupt you, I just had a thought. You know, we, based on data from a large trial, the ALCYONE trial, daratumumab in combination with bortezomib, melphalan, and dexamethasone is now approved. Have you been using that in your practice, Dr Giralt? Or when would you consider it? Because that was a population that was transplant ineligible.

Giralt: Thank you for bringing that up. That is now approved in the United States. Melphalan, prednisone, and thalidomide are not really very commonly used. The dara/melphalan combinations are not commonly used, but remember, you don't have to use dara in combination with the MPT regimen. What I have seen from many practicing physicians for older patients is the use of daratumumab together with either dexamethasone or the addition of lenalidomide or bortezomib in the standard doses or in ameliorated doses. We do not know what the long-term data is of this regimen. It has not been published but it is being commonly used in the United States.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Initial Treatment



- The patient opts for RVd after discussing risks with his team, in light of age and kidney function
- After 4 monthly cycles, he is tolerating the regimen well and is having a nice response
  - >90% reduction in M-protein after 4 cycles (VGPR)

(RVd lenalidomide PO, bortezomib SC, and dexamethasone IV or PO)

Faiman: It makes sense to consider a standard approach for him and see if he wants to opt for transplant after psychologic evaluation and assessment of caregiver support. The transplant should not be taken lightly, and we want to make sure that he has support resources if he goes on that route. His renal function ended up improving; his GFR went to 30, so he is started at a reduced dose of lenalidomide based on the GFR, bortezomib subcutaneously and dexamethasone. After four monthly cycles, he tolerated the regimen quite well and he had a VGPR 90% reduction in his serum M-protein.

Comorbid Patients with Multiple Myeloma:
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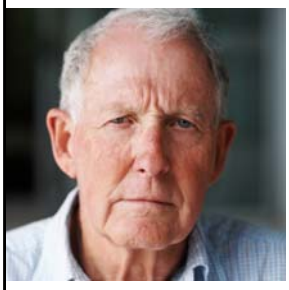
Current Status



- M-protein by SPEP: 0.3 g/dL; IgG quantification: 1.0 g/dL
- Scapular, itchy rash which spreads to both arms
  - Works with nurse practitioner to get to target lenalidomide dose 15 mg PO d 1-21 q 28 day
- Steroid-induced hyperglycemia
  - Managed initially by NP then worked with PCP to control sugars, diet education
- Creatinine improved from 2.4 g/dL at presentation to 1.9 g/dL after 4 months
- Beta-2 microglobulin: 1.4
- UPEP: no monoclonal spike seen
- UIEP: negative; FLC- kappa 42

Faiman: His SPEP remember was 4 g/dL at diagnosis, and went to 0.3 g. He had a little bit of a scapular itchy rash in both arms, but he worked with the nurse practitioner to get that target lenalidomide dose down. He had steroid-induced hyperglycemia, but again, using the multidisciplinary team members, the nurse practitioner worked with the PCP and the patient to control the blood sugars. As I mentioned the creatinine improved: he still had a reduced GFR, but his creatinine went to 1.9, beta-2 microglobulin came down, and his monoclonal spike was gone.

Giralt: I think it's important that particularly when he starts treatment initially, he should be monitored carefully to make sure that he does not have severe cytopenias, and as you mentioned, the hyperglycemia from the steroids.

Faiman: Yes, he was started on acyclovir to minimize the risk of shingles. I'm aware that there is a Shingrix vaccine that is currently available, and in the study of that live inactivated vaccine, it did include hematologic cancer patients. The vaccine at this time of this discussion is not readily available but that might be something to consider. But, Dr. Giralt, what are your thoughts regarding transplant for this patient? He is doing quite well, he had an excellent response, what would his goals be?

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Who Is Transplant Ineligible?

Absolute

- Biologic
  - Frail and poor performance status
  - Active comorbidities
- Psychosocial
  - Poor caregiver support
- Patient refusal

Relative

- Low-risk disease with major response
  - Risk/benefit ratio
- Progressive disease
- Patients over 85 years of age

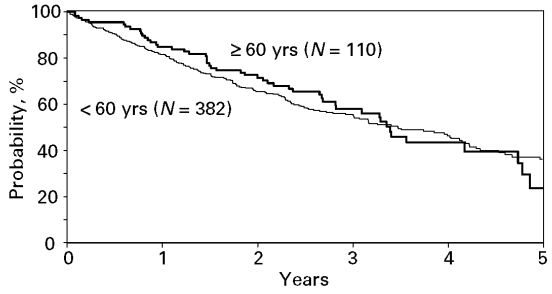
Lahuerta JJ, et al. *J Clin Oncol.* 2017;35(25):2900-2910.

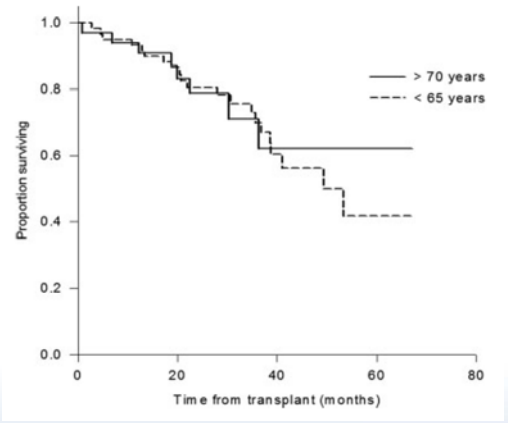
Giralt: This is a very interesting question, and again, as we look in even our younger populations, our goal is to achieve 1) a complete remission (preferably a stringent complete remission) and 2) an MRD negative complete remission . Because we know that the patients who get to this goal are the ones that do the best. The Spanish have retrospective data suggesting that only patients who get an MRD negative CR are the ones who are doing best. Our data suggest that depth of response is important and that CRs do better than PRs, and that PRs do better than people who don't respond. I think it's important to have a frank conversation with this patient at this time. Advise him that he is not in a complete remission, advise him that he is eligible for transplant.

What are the absolute contraindications? If he was frail and had poor performance status, we wouldn't consider this. If he had poor caregiver support, we would not consider this. If he had very low-risk disease like an ISS stage I with a complete remission to induction therapy, we would not consider this. Or if he was over the age of 85 or his life expectancy was not going to be 10 years, we would say, you are probably better off keeping on some form of continued therapy and enjoying your life. Also, obviously if a patient does not want to do it, we should not do it. This patient has no absolute or relative contraindications. He has failed to achieve a complete response to the best available treatment.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Age Has No Impact on Outcome in "Suitable" AHPCT Candidates

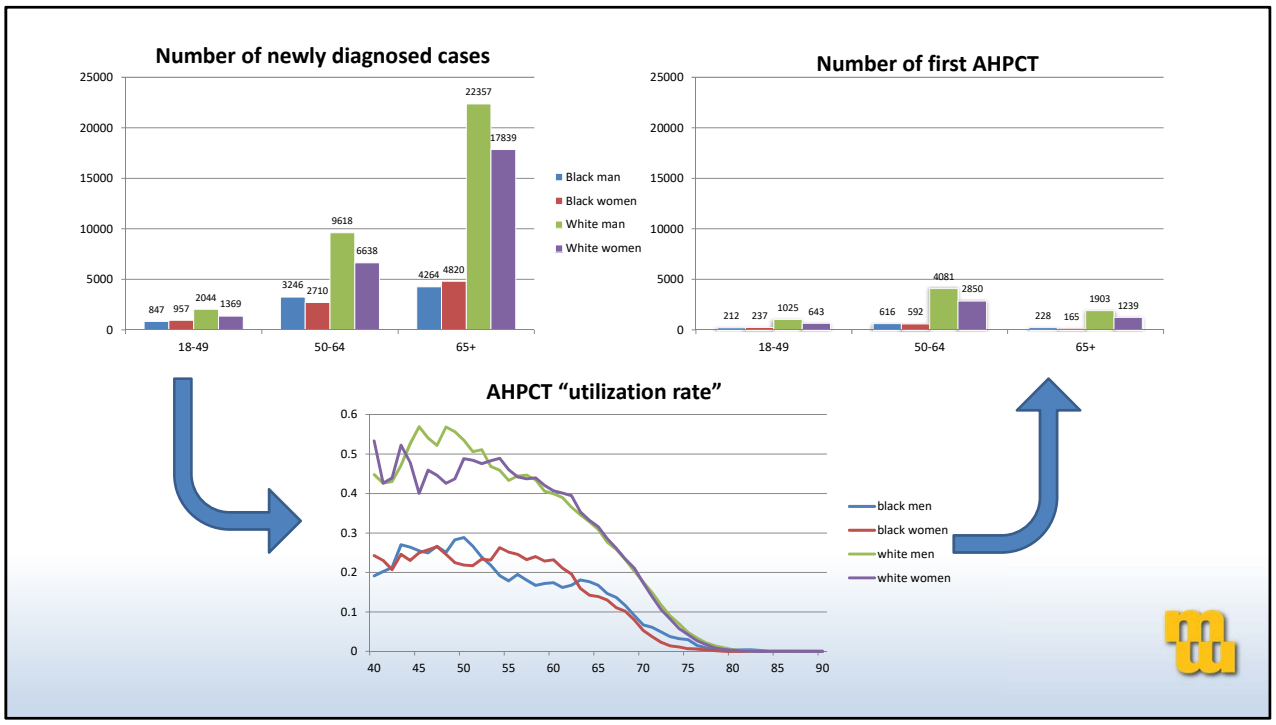




Reece DE, et al. *Bone Marrow Transplant*. 2003;32:1135.; Kumar SK, et al. *Am J Hematol*. 2008;83:617.

Giralt: I think he would benefit from high-dose melphalan. The data for patients over the age of 60 who get high-dose melphalan is the same as patients who are less than age of 60. The benefit is the same in regard to progression-free survival and potentially overall survival benefit. I think the most important thing is high-dose melphalan is the most active drug in multiple myeloma. Now, to be able to deliver high-dose melphalan safely, we need to be able to support the patient with stem-cells, and many times, we can do this as an outpatient. The transplant journey is divided in five phases: the chemotherapy phase, which is very well-tolerated: minimal nausea and vomiting. The cytopenic phase, in which the patient's white count goes to 0. They may require transfusions, they may acquire infections, but counts recover within 10 days. The early recovery phase is a transition phase, many of us transplant patients like him as an outpatient, if he had good caregiver support, with half of the patients never having to spend a day in the hospital. The early convalescent phase is a time of immune recovery where patients should avoid crowds and people who are sick, because their immune system is still recovering, and they are more predisposed to infection. After one year, the patient's immune system has recovered to the point that they should get revaccinated.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection



Giralt: Despite the fact that we know that high-dose melphalan is a very effective treatment, in older patients it is severely underutilized. Less than 20% of patients over the age of 65 are getting high-dose melphalan. Many of them are not even being referred to transplant, and if you're African American, your chances of getting a transplant if you are over 65 is almost in the single digits. We really need to do a better job of educating our community physicians as well as our patients that high-dose melphalan and autologous transplant is a valid approach for patients up to the age of 80.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Early vs Delayed: Pros and Cons

- Pros of early HCT
  - Youngest you are going to be
  - Healthiest you are going to be
  - MM is going to be the least resistant
  - Quickest return to "new normal"
- Cons of early HCT
  - 25% of patients may not need it
  - 20% of patients still relapse within two years
  - 1% risk of serious life-threatening complications
  - Three months of recovery
  - No proven impact on survival
- Pros of delayed HCT
  - Conserve QOL in the early part of disease journey
  - Minimize disruption to lifestyle
  - Hedge your bets against future relapse
- Cons of delayed HCT
  - 60-70% of patients will relapse and may need it as salvage
  - 20% of patients relapsing are unable to undergo salvage HCT
  - Recovery is likely to be harder than an upfront HCT

Giralt: What are the benefits of early transplant? Patients are as young as they are going to be, this is the healthiest they're going to be. Their myeloma is going to be the least resistant, and I think it's the quickest return to a new normal. It is true that a quarter of patients may spend five years without relapse without having received up-front transplant. The risk of complications are very low but they are not zero, and it can take three months to get back to the point where you started. The patients who opt for delayed transplant conserve their quality of life in the early part of the disease journey. A quarter of them may never have their disease relapse, so they're hedging their bets, and there is minimal disruption to their lifestyle. The main disadvantage of trying to opt for delayed transplant is two-thirds of these patients will be undergoing transplant within two years of their diagnosis, and the transplant will be as easy or as hard at that time as it was going to be early. I do think this is a personal choice. It's a choice that patients make based on the recommendations of their physicians and based on their priorities. Transplant is a choice, it's not a necessity. I happen to think that it's probably the best choice for most patients, particularly for somebody like this patient who failed to achieve a complete response to an optimal induction treatment. Beth, let's review the treatment options for non-transplant eligible patients.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Treatment of MM in Patients with Comorbid Conditions

- Steroids HDDex – still a role in relapse
- Proteasome inhibitors:
  - Bortezomib safe CrCl <13.8 mL/min, reverse RF
  - Carfilzomib can increase serum creatinine
  - Ixazomib – starting dose 3 mg
- Alkylating agents
  - Melphalan dose reduction – especially HDM
  - Cyclophosphamide dose reduction
- Immunomodulatory agents
  - Len: dose reduction or lead to myelosuppression
  - Pom: starting dose 3 mg if severe
- Monoclonal antibodies
  - Dara, ELO no dose reduction
- Corticosteroids
  - Dexamethasone and prednisone; monitor hyperglycemia
  - Illicit PCP or endocrinology assistance
- Supportive care
  - Shingles prevention (acyclovir, valacyclovir, Shingrix?)
- Bone modifying agents
  - Denosumab: no dose reduction needed
  - Bisphosphonates: pamidronate, zoledronic acid contraindicated if GFR <30
- Disease and organ health monitoring for all patients includes CBC, chem, disease biomarkers (SPEP, UPEP, serum-free light chains)

NCCN Guidelines® 2018.; Anderson K, et al. *J Clin Oncol.* 2018;36(8):812-818.

Faiman: We had a nice discussion early on that discussed the FIRST trial, which was continuous lenalidomide-dexamethasone. That's reasonable and RVd-lite is reasonable as well as the daratumumab with bortezomib-melphalan-dexamethasone. Those are the clinical trials that inform our recommendations, but I like to think of it as classes of drugs. This is particularly exciting because when I started taking care of myeloma patients in the 1990s, like Dr. Giralt, we had no idea that there would be classes of drugs in the future. The proteasome inhibitors, alkylating agents, immunomodulatory agents, and monoclonal antibodies all can be mixed and matched with corticosteroids that will provide a best optimal induction. I think what our gentleman had gotten, the RVd, he could have just continued that for 8 cycles similar to the SWOG 777 study, which showed that after 8 cycles of the RVd induction, the patients that were not up-front transplanted still had excellent outcomes. After that, they go on to lenalidomide maintenance, so that would be something to consider. We already discussed the supportive care possibility with shingles and the Shingrix vaccine. I also briefly mentioned the bone-modifying agents. We used to just call them bisphosphonates, but now denosumab is a subcutaneously injection that is FDA approved for patients with bone disease in myeloma, and what's nice is that there is no dose reduction needed. It's contraindicated to give a bisphosphonate such as medronate and zoledronic acid to individuals with a GFR of less than 30; but with denosumab, you don't have to worry about that. Of course, we need a baseline dental exam if possible and regular dental monitoring to reduce the risk of osteonecrosis. Finally, the disease and organ monitoring is also important.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Dose Modifications Are Often Necessary

- Getting the MM under control reduces the incidence and often severity of renal, hepatic impairment

Drug	Dose Modification With Renal Insufficiency (Package Insert)
Thalidomide	None
Lenalidomide*	Adjust dose with CrCl 30-60 mL/min
Pomalidomide*	Avoid with serum creatinine >3 mg/dL
Bortezomib	None
Carfilzomib	None
Ixazomib‡	Reduce to 3 mg w/ CrCl <30 mL/min or ESRD requiring dialysis; Elevated AST/ALT
Panobinostat	None
Daratumumab	None
Elotuzumab‡	None

*Primarily renal clearance. ‡Approved in combination with lenalidomide and dexamethasone

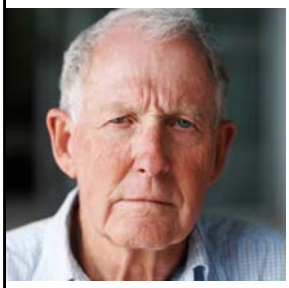
DON'T FORGET TO CONSIDER ADJUSTING DOSES OF CONCURRENT MEDICATIONS (ACYCLOVIR, ANTIBIOTICS)

https://www.fda.gov/

Faiman: When we talked about the dose modifications, if you set yourself up for success by determining the correct dose of the drug, then you're going to be okay. The IMiDs don't require a dose reduction necessarily; bortezomib and carfilzomib are safe. Ixazomib requires a dose reduction in relapsed disease (which is when we primarily use that drug at a 3 mg starting dose) as well as others, and I would refer you to the package inserts and the prescribing information primarily for those.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Case Continued



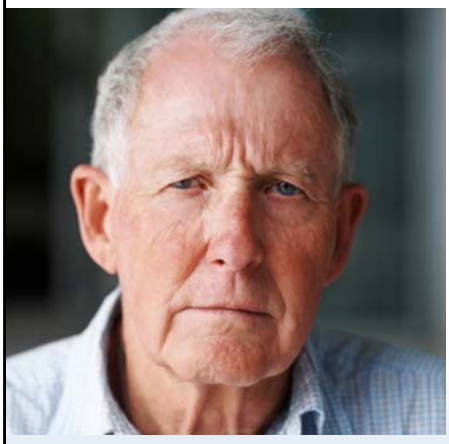
- He receives auto HCT with MEL 200 mg/m^2; three months later is in an MRD negative CR
- Question of maintenance vs no maintenance considered
- Since he had significant rash to lenalidomide and was only able to tolerate 15 mg 21/28 days during induction
  - No dose adjustment for GFR
  - IF he had concurrent amyloidosis, would treatment change?
- Other supportive care: bone modifying agents
  - Denosumab SC vs pamidronate vs zoledronic acid: What do you use?

McCarthy PL, et al. *J Clin Oncol.* 2017;35(29):3279-3289.

Faiman: He received MEL 200. It was compelling to him, he wanted to have a better remission status; that first remission is likely your best remission and the deepest remission up front will hopefully carry you. Dr. Giralt will present some data on MRD status in myeloma in just a few moments but he was MRD negative, so there was very little disease found in his bone marrow at that time. There is a big question in this gentleman of maintenance or no maintenance. There was a big meta-analysis that showed the benefit in progression free survival in patients who had lenalidomide maintenance after autologous stem-cell transplant and he said, "Okay, I did fine on the 15 mg of the lenalidomide," so he stayed on that for maintenance, continuing the supportive care with the bone-modifying agents as well. Any other thoughts with this case study, Dr. Giralt?

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Case Continued



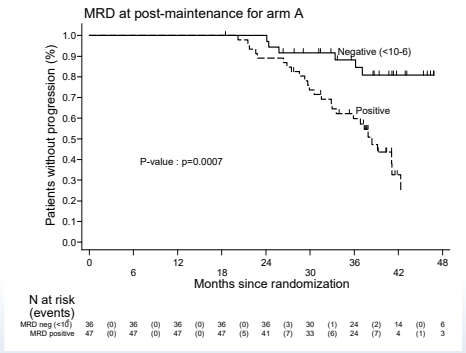
- He begins lenalidomide maintenance at 5 mg every other day and tolerates well, thus escalates to standard approved dosing 10 mg d 1-28 q 28
- Despite having an MRD negative CR 3.5 years later, has reoccurrence of M-spike with increased lytic lesions

Giralt: I'm glad that he opted for maintenance. I think the data for maintenance is very compelling. I start maintenance at the lower dose of 5 mg every other day, partly because his creatinine was still a little bit on the high side and then I escalate it. I do syncopated maintenance, which is 21 days out of 28. In spite of having an MRD negative CR, almost four years later, he has recurrence in his M-spike and now progressed with lytic lesions. I have said that this is the type of case that is disappointing because we would have expected that with an MRD negative CR, he would have had almost a seven-year time of progression free. But as we would know when we do his bone marrow, he probably has high-risk cytogenetic clones that are the ones that emerged. It also underscores the fact that these patients need to be monitored carefully because the myeloma can come back at any time, even though the majority of patients on lenalidomide maintenance actually do very well.

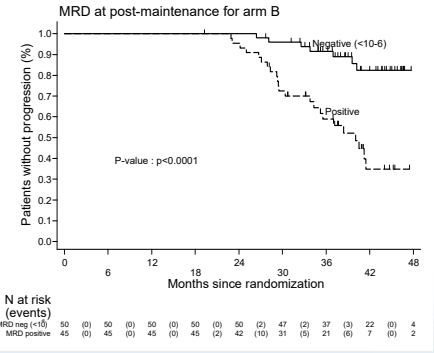
Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

IFM/DFCI 2009: Progression-free Survival According to Measurable Residual Disease (MRD) Post Maintenance

RVD Arm



Transplant Arm



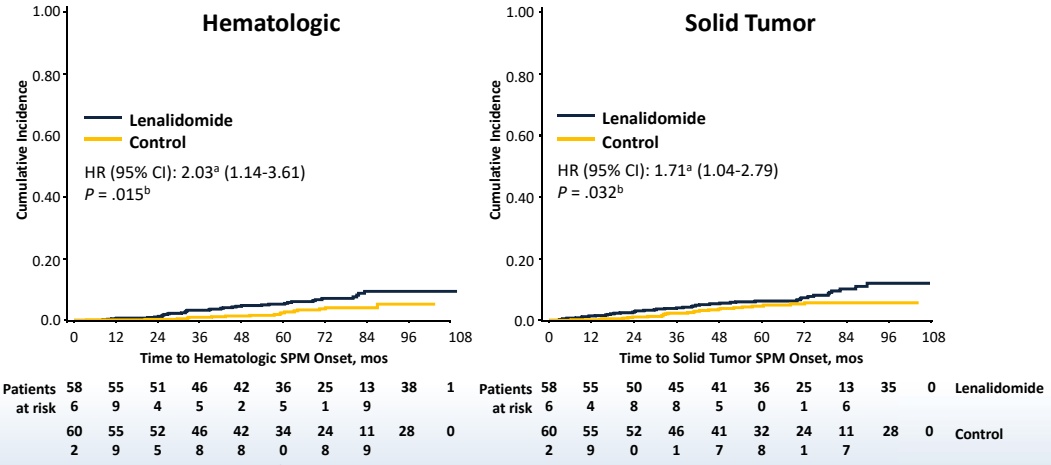
MRD previously was defined as minimal residual disease

Avet-Loiseau H, et al. *Blood.* 2015;126. Abstract 191.

Giralt: What is the data for MRD? MRD is now called measurable residual disease more than minimal residual disease. There are two assays that we can do: flow cytometry and next-generation sequencing. We know based on the French study that in an assay in which you can detect one in a million myeloma cells, that patients who have measurable residual disease negativity (less than one in a million myeloma cells) do very well. You can stop lenalidomide therapy and 20% of them will relapse within two years, but that means that 80% of them will stay in remission. However, if you are MRD positive and you stop lenalidomide therapy, based on the IFM/DFCI 2009 trial, 80% of these patients will go on to relapse within two years. The practice in the United States is lenalidomide until progression. Why? We don't have a real indication for measurable residual disease assessment at this time, but I think this is the one place where I use MRD to dictate treatment because I encourage patients to stay on maintenance therapy as long as they are MRD positive. In patients who have low-risk disease who have been MRD negative for many years, I do have a conversation about stopping treatment or stopping maintenance.

Comorbid Patients with Multiple Myeloma:
Considering All the Facts in Treatment Selection

Cumulative Incidence of Second Primary Malignancies (SPM) with Lenalidomide Maintenance



[a] HR based on Cox proportional hazards model. [b] *P* value is based on log-rank test.
SPM=second primary malignancy
Holstein SA, et al. *Lancet Haematol.* 2017;4(9):e431-e442.

Giralt: Although the meta-analysis suggested a significant survival benefit, it's important to recognize that second primary malignancies occur at a higher rate in patients on lenalidomide maintenance, 6% versus 2%, and that the increased risk of solid tumor seems to be less. These patients need to be monitored carefully, and patients who have unexplained cytopenia should have a bone marrow to rule out the emergence of either myelodysplastic syndrome or an acute leukemia. Once again, this is very rare, and the benefits of lenalidomide maintenance outweigh the risks, but we need to be monitoring and following patients very carefully. Particularly in patients who have very low-risk disease, the risk of second primary malignancies must be weighed against the benefits of lenalidomide maintenance.

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Key Points

- Patients with comorbidities can safely receive therapy to control MM
- Aggressive treatment should not be held on the basis of age
- Comprehensive geriatric assessment can help in the decision of go or no go in a older patient with MM and should be routine
- A team approach is needed to manage issues surrounding treatment with comorbid illnesses
- Patients should be encouraged to participate in clinical trials aimed to improve safety and efficacy of this procedure

Giralt: Okay Beth, let's wrap up this case and summarize. I think what we have been discussing today is that patients with comorbidities can safely receive therapy to control myeloma. Aggressive treatment should not be held based on age. Comprehensive geriatric assessment can help in the decision of go or no-go in an older patient with myeloma and should be routine. A team approach is needed to manage issues surrounding treatment with comorbid illness. Finally, all patients should be encouraged to participate in clinical trials.

Beth, thank you for joining me and let's thank the audience for joining us for this presentation. We hope this information will be useful to you in the care of your patients.