



# Treatment and Management of Multiple Myeloma

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Sean P. Cosgriff, PharmD, BCOP; and Paulette Mehta, MD

A panel discussion of the challenges and standards of care for managing patients with multiple myeloma.

The following is a lightly edited transcript of a follow-up teleconference discussion on treating patients with multiple myeloma in the VHA. For more information and the original conversation, visit [FedPrac.com/AVAHOupdates](http://FedPrac.com/AVAHOupdates).

## EARLY TREATMENT AND DIAGNOSIS

**Dr. Ascensão.** An area that is becoming very important is identifying and separating smoldering multiple myeloma (SMM) from multiple myeloma (MM) and determining when to start treatment. At the Washington DC VAMC (DCVAMC) we started early on bisphosphonates and thalidomide without much benefit, but perhaps we were treating the wrong disease.

**Dr. Mehta.** Identifying patients as early as possible is often the best way to start. Treating early disease is easier than treating late disease, and it avoids all the complications. The problem is we don't want to treat too many people because some of the people with SMM will never develop overt MM and, therefore, may not need treatment. We don't have benign treatment yet. Whatever treatment we decide to use is going to carry adverse effects and toxicity.

So the trick is identifying those patients with SMM who are likely to progress in a finite period and, therefore, can be helped by treating early to avoid the complications of late diagnosis. We know that early treatment for patients with high-risk SMM helps. In a report from *Lancet Oncology*, early treatment with lenalidomide and dexamethasone reduces time to progression.<sup>1</sup> There are other reports that treating early reduces time to progression.

So how do we identify those patients who are going

to progress? We have a few clues. We know that patients who have a myeloma spike of > 1.5 g/dL are more likely to progress than others...The more discordant the  $\kappa/\lambda$  ratio from 1:1, the higher the risk for progression. And if that ratio is 1:100 or more, that would be a risk factor for progression.

We know from the work of Mayo Clinic researchers that if there are  $\geq 60\%$  of plasma cells in the bone marrow then it is a risk factor for progression. And we know from early studies that magnetic resonance imaging (MRI) detection of bone lesions, even long before they become detectable by X-ray, also is a risk factor for rapid development to myeloma.

...Methods such as genotyping, which we do here at the University of Arkansas for Medical Sciences, even in patients with MGUS (monoclonal gammopathy of undetermined significance), can identify high-risk patients, but that is not the standard of care yet. But it may become the standard of care in the days to come.

Another thing to think about for MGUS patients: Are there ways to identify what causes MGUS patients to evolve to SMM and then to overt myeloma, and to develop means of interrupting the progression cascade? There have been clinical trials on treatments (eg, bisphosphonates, thalidomide, aspirin, and cyclooxygenase inhibitors), but we haven't found any safe, good treatment to prevent progression yet. With better technologies, we may be able to do that.

**Dr. Ascensão.** At the DCVAMC often we receive consults for a patient who had a little anemia, diabetes, renal disease, and the serum protein electrophoresis reveals a very small peak. How often should you follow patients?

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Do you do a complete workup the moment you see an MGUS or do you wait until they reach SMM?

**Dr. Mehta.** I don't think every patient needs a complete workup. If you have obviously identifiable reasons for the anemia or the renal failure, then it's less likely to be suspicious for myeloma. But patients with M spikes > 1 g/dL deserve a workup with a bone marrow aspirate and biopsy and at least bone X-rays, although MRIs would be even better.

I would differentiate based on the amount of M protein. Higher M protein patients deserve to have at least a bone marrow aspirate and bone study. Patients with M protein > 1g/dL deserve to be seen every 3 to 4 months. I see patients with tiny little peaks every 6 months. And then, after 1 or 2 years, I turn over their care to the primary care doctor to follow. If we had research protocols to look at those patients and find the methods for progression, which I had at one point, then of course, we could see them more often and try to unravel the mystery.

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### USE OF IMAGING

**Dr. Ascensão.** That's pretty close to what we do at DCVAMC. What do you think is the role for a bone survey as opposed to MRIs and positron emission tomography (PET) scans in this setting?

**Dr. Mehta.** In the real world X-rays are more accessible and much less expensive. So for the patient with very low risk who doesn't have any complaints and who has a low M spike, I think a bone survey is adequate. But you need about 30% to 40% bone destruction before you're going to find anything on the X-ray. MRIs are much more sensitive, plus they tell you about bone marrow involvement, but that should be reserved for the patient who has symptoms or a high M protein. At Central Arkansas Veterans Healthcare System we simply can't get PET scans for myeloma patients. At the myeloma center across the street from us, PET scans are used for routine evaluations.

**Dr. Chauncey.** I agree with Dr. Mehta. At VA Puget Sound Healthcare System (VAPSHCS) there isn't a problem getting PET scans, but we probably get far fewer scans than Arkansas. I still like the skeletal survey be-

## Discussion Participants

### Moderator

**João Ascensão, MD, PhD**, is a professor in the Department of Medicine and Immunology at George Washington University School of Medicine and chief hematologist and chairman of the R&D Committee at the Washington DC VA Medical Center, both in Washington, DC. He is also a clinical professor of medicine at Uniformed Services University in Bethesda, Maryland. In 2015 Dr. Ascensão served as president of the Association of VA Hematology/Oncology (AVAHO).

### Panelists

**Thomas R. Chauncey, MD, PhD**, is an associate professor of medicine and oncology at the University of Washington, and an associate member of the Fred Hutchinson Cancer Research Center. Dr. Chauncey is director of the Marrow Transplant Unit at the VA Puget Sound Health Care System, all in Seattle.

**Sean Cosgriff, PharmD, BCOP**, is the hematology/oncology clinical specialist at the VA Portland Health Care System and affiliate faculty at Oregon State and Pacific University, both in Portland, Oregon. In 2014 Dr. Cosgriff served as AVAHO president.

**Paulette Mehta, MD, MPH**, is a professor of hematology/oncology at the University of Arkansas and a physician at the Central Arkansas Veterans Healthcare System, both in Little Rock. In 2010, Dr. Mehta served as AVAHO president.

cause it directs you where to look for potential pathologic fracture. It's definitely not as sensitive as the dedicated myeloma MRI, but it's a lot easier to get at VAPSHCS, especially as a screening tool.

**Dr. Ascensão:** Right, I believe there are some issues about the number of osteolytic lesions that may drive diagnosis.

**Dr. Mehta.** For patients with high M protein, I always request MRI. But the correlation is poorer in patients who have lower M protein. I try to limit it to the patients who have symptoms or high M protein, but I

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don't have any evidence-based data to prove that's the right way.

**Dr. Ascensão.** If you were going to start treatment of SMM that you believe is evolving to a more regular myeloma, do you do anything different than you would for any of the patients that you have identified as having active myeloma? Do you have different protocols for those patients as opposed to patients who present de novo with active myeloma?

**Dr. Mehta.** Those patients should be treated with the same drugs, an IMiD and a steroid. And the question is plus or minus a proteasome inhibitor. Studies have shown that an IMiD with a steroid gets much better results than using observation alone. Whether you would get even better results with the proteasome inhibitor remains to be seen. Maybe we can do that study.

**Dr. Chauncey.** We strive to identify high-risk SMM patients and treat them accordingly. Alternatively, physicians are pulling the trigger for therapy earlier and earlier and when they come for transplant with a diagnosis of MM, it

is critical to review the initial diagnostic information.

Most transplant centers have experience with this phenomena and know that they don't want to transplant a non-high-risk SMM or any MGUS. However, by the time the patient is referred for transplantation, the initial clinical data are sometimes obscured or inaccessible.

**Dr. Ascensão:** We also look into the bone bearing areas, which allows us to make sure that if the patient has hip problems, we can work on how to approach them, whether we want to radiate those patients to prevent fractures.

**USE OF BISPHOSPHONATES**

**Dr. Cosgriff.** Myeloma metastasizes to bone, and it is one of the common sites of metastatic disease. It poses some interesting complications, whether it is from hypercalcemia due to metastatic sites, or pain syndromes. Bisphosphonates are indicated for myeloma, and they have been for years. Interestingly, unlike some of the other disease, the use of bisphosphonates induces apoptosis in myeloma. So we have seen some disease control with these agents.

The 2 bisphosphonates that are available for use are pamidronate and zoledronic acid. At the VA Portland Health Care System (VAPORHCS), we have been using pamidronate exclusively for individuals with myeloma. There was a 2003 paper that evaluated the use of bisphosphonates for skeletal-related events in myeloma and in patients with metastatic breast cancer.<sup>2</sup> In the subset analysis of myeloma patients with the bisphosphonates, there was no difference between pamidronate and zoledronic acid.

At the time, zoledronic acid was significantly more expensive than pamidronate, and so VAPORHCS opted to use pamidronate as a cost-saving measure. But there are the other reasons for picking pamidronate: Zoledronic acid has some dose recommendations and guidelines for individuals with renal failure, which is often a significant problem in patients with myeloma as well. To get around dose adjustments that need to be made for zoledronic acid, VAPORHCS switched to pamidronate, which is looser with the recommendations on renal failure.

Earlier use criteria, like the National Comprehensive Cancer Network guidelines, stated that if the renal failure was due to the disease itself and not some other outlying factor, a full 90-mg dose of pamidronate could still be used. That comment has since been removed. We still pay attention to it and reduce pamidronate dosing to

60 mg for patients with renal failure.

The prices for zoledronic acid have dropped significantly since it became a generic. The nice thing about zoledronic acid is that it has a short infusion time of 15 minutes. As chair space becomes a problem—VAPHCS has significant issues with that—zoledronic acid looks more and more attractive. The FDA label states that pamidronate should be infused over 4 hours, but VAPHCS typically has been infusing it for 3 hours.

It should be noted that denosumab (XGEVA), a monoclonal antibody that also is targeted for hypercalcemia, has been specifically excluded for myeloma. It has no FDA indication for myeloma. It does have an indication for hypercalcemia. Whether or not you can state that the patient with myeloma is hypercalcemic, and that's the reason you want to use it, it starts crossing into some gray area. The drug is still significantly more expensive and it seems to have similar efficacy rates compared with both pamidronate and zoledronic acid, so VAPHCS limits its use to individuals who would otherwise be contraindicated to zoledronic acid or pamidronate due to renal failure.

**Dr. Ascensão.** How often do you give it, every month, every 3 months?

**Dr. Cosgriff.** Currently, VAPORHCS is giving bisphosphonates every month whether in the chemotherapy unit or in the short stay unit. We are starting to reevaluate that. I have heard some emerging data that suggest we can use it once a quarter and get the same results. Those data are still emerging. It would be nice to be able to reduce the infusion frequency. But bisphosphonates adhere to bone and get incorporated into the bone matrix and stay there for an extended period of time, upwards of 6 months to a year, as with zoledronic acid.

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## OSTEONECROSIS

**Dr. Ascensão.** Do you require dental clearance prior to first dose?

**Dr. Cosgriff.** Bisphosphonates have a warning for 2% incidence of osteonecrosis of the jaw. Risk factors for the development of osteonecrosis of the jaw include poor dentition or major dental work, like extractions and ill-fitting dentures but not necessarily root canals. Ill-fitting dentures tend to rub on the gums and irritate the bone layer underneath. It's the irritation of the bone that's the

biggest risk factor for osteonecrosis of the jaw.

We require that patients see the dentist because we've had individuals develop osteonecrosis eventhough we thought they had good dentition. If a patient is seeing a dentist outside of the VA system, we ask them to notify their dentist that they're receiving bisphosphonates. Because of the risk and because we've had some individuals with good dentition develop it, VAPORHCS requires all patients, particularly those who are receiving zoledronic acid, to have dental evaluations. Denosumab also has a listed 2% incidence of osteonecrosis of the jaw, so those individuals also need to be evaluated by our dental service.

**Dr. Ascensão.** The DCVAMC has the same problem. I have a patient that presented primarily with a plasmacytoma, and we tried to get him to see the dentist. The dentist said, 'You've got to get your teeth pulled.' The patient has tried to see outside dentists and is finding all kinds of excuses because he would like to have implants.

**Dr. Cosgriff.** Anytime that you somehow damage or irritate that bone, that becomes a risk factor for the development of osteonecrosis. And for those individuals, we delay the bisphosphonate. If they're having pain syndrome, we try to support them with opiates. We would love to be able to use nonsteroidal anti-inflammatory drugs—they have really good efficacy against bone pain—but renal function and renal failures prevent the use of those in a majority of patients. We start bisphosphonates as soon as dental clears them.

**Dr. Mehta.** Isn't there a contraindication for denosumab and some evidence that it may worsen MM outcomes?

**Dr. Cosgriff.** When the drug first came on the market, it specifically stated in the package insert that it is not to be used in MM (it doesn't state it specifically anymore). There is a thought that maybe some underlying mechanism exists that might stimulate some of the myeloma problems, which is why I get a little concerned when people say, "Well, I'm using it for hypercalcemia, I'm not using it to treat or to prevent a skeletal-related event in patients with myeloma." That becomes a gray area and in that type of situation, I would recommend treating the hypercalcemia with a single dose and then switching the patient to a bisphosphonate.

**Dr. Mehta.** And of course, bisphosphonates also lower calcium. They can be used to treat hypercalcemia.

**Dr. Cosgriff.** Yes. Zoledronic acid does have limitations in renal failure, though pamidronate doesn't have quite the same limitations. The VAPORHCS tries to use exclusively for hypercalcemia as well. The data show that when using zoledronic acid compared with pamidronate, you end up with the same outcomes as far as hypercalcemia. The zoledronic acid onset of action is a little faster, around 12 to 24 hours vs 48 to 72 hours with pamidronate, but you can get around that by using calcitonin over a short period; 48 hours is typically the maximum efficacy for calcitonin in treating hypercalcemia. So we use pamidronate in place of that, supplementing with calcitonin.

The result is that at 7 days, pamidronate and zoledronic acid show the same efficacy rates for treating hypercalcemia. But the renal function sometimes prevents us from doing that. Denosumab does become an option for hypercalcemia, but again, I caution against its use for treating hypercalcemia in patients with myeloma due to the risk of advancing the myeloma.

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### BONE MARROW TRANSPLANT

**Dr. Ascensão.** Do you transplant for 1 or 2 bone marrows? What's the best maintenance regimen postallograft, and when do you start? Do you use lenalidomide the first month of the transplant or do you wait until day 100?

**Dr. Chauncey.** From my perspective, hematopoietic stem cell transplantation has never really lost prominence. It is true that the concept of marrow transplantation for MM has been around for more than 20 years for those patients with first best response (Note that I'll use best response rather than first remission). The concept was developed in an era when we had much less effective therapy, and in comparative trials, progression-free survival was consistently superior and occasionally, overall survival was better with transplantation. As treatments got better, responses got better, and there were regular questions as to whether we still needed transplantation. But the data show that as responses got better, the progression-free survivals continued to improve, and transplantation still adds something to initial therapy.

Probably the most current data are from the Dana Farber-IFM trial for which Nikhil Munshi, MD, is an investigator. The trial includes induction with lenalidomide/bortezomib/dexamethasone, which is one of the more aggressive induction regimens. When upfront transplant vs delayed transplant are compared, it seems the prelimi-

nary data still favor having an upfront transplant after initial induction therapy.

The consensus is that autologous transplantation adds to the better response that we see with better induction therapy. Overall survival has become a less accessible endpoint since the initial trials, and that's really a consequence of having better salvage therapy, and the confounding effects of subsequent treatments. We have so many options for salvage therapy that it's now very hard to look at overall survival as an endpoint in trials of initial therapy.

A sometimes contentious question when it comes to payers, and less so in the VA, is how many transplants to do as part of initial therapy? Little Rock and the French did some of the pioneering work on tandem transplants. The BMT CTN 0702–StaMINA trial looks at this directly, and is mature and should be presented soon [Editorial Note: Preliminary results were presented at the American Society of Hematology meeting on December 6, 2016].

The approach at VAPSHCS and most other transplant centers has typically been to harvest a sufficient quantity of peripheral blood stem cells to do 2 transplants. If less than a very good partial response is achieved after the first transplant, then we do a second transplant in tandem fashion.

One exception would be for plasma cell leukemia, which is very aggressive. In that case, we would routinely perform tandem transplantation. We are unlikely to ever have a randomized trial that compares 1 vs 2 transplants in that particular setting.

Another question is whether a second autologous transplantation can be useful in a nontandem fashion, and there is a large amount of retrospective data about its use as salvage treatment. In eras when there were not as many effective therapies, salvage autologous transplant was more attractive. As new therapies came along, its use has somewhat waned, but there's been renewed interest because dose-intensive melphalan with autologous rescue is relatively safe and not cross-resistant to other therapies. It also offers the option of a drug holiday after the transplant, whereas salvage drug therapy is typically continuous.

There is no universal agreement on nontandem second transplantation, there are no consistent algorithms to say when it is appropriate, but it's worth discussing with the transplant programs, especially if there is a lot of toxicity with current salvage therapy.

The last question is the role of allogeneic transplantation, and while I'm generally a proponent of allogeneic transplantation for many diseases, in spite of some really

significant efforts, the majority of allogeneic data for MM has not been very positive. The large BMT-CTN 0102 trial compared tandem autologous transplant at first response to a single autologous transplantation followed by reduced-intensity autologous transplantation from a matched sibling. This study was limited in part by enrollment bias, but the published results did not favor an allogeneic approach.<sup>3</sup> Although there was less relapse in the allogeneic setting, the mortality of allogeneic transplant was not overcome by the decrease in relapse. Neither progression-free or overall survivals at 3 years were better in the allogeneic group.

Despite small studies showing feasibility and promising results, it's currently very hard to advocate for allogeneic transplantation in MM. There are certainly centers that continue to have their own approach, with some in the U.S. that are pioneering tweaks on allogeneic regimens and graft engineering, but the data are typically small and anecdotal. That doesn't mean that there won't ultimately be a better way to do allogeneic transplantation in MM, but rather that we don't currently know the best way to approach this strategy.

#### NEXT STEPS IN MYELOMA TREATMENT

**Dr. Ascensão.** There are some people who are now starting to talk about a cure for myeloma. I'm not sure we're there yet. Certainly, it's a chronic disease that, if we can take care of the complications and maybe by starting treatment early. I'm not sure Agent Orange-exposed patients do better or worse. That's something that needs to be researched if we can find a way to compare within this group and within the type of treatment that patients get.

Is it reasonable to start looking for minimal residual disease in cells? Should we shoot for the best response? I think one of the points that Dr. Chauncey made a number of times, and I agree, is that our patient population may not be able to tolerate some of the more aggressive therapies. Perhaps we need to find a slightly different version of this algorithm for VA patients.

**Dr. Chauncey.** There's a diverse biology for both veterans and nonveterans alike. There are patients for whom a deeper response will lead to longer remission and better survival, and there are others whose disease will smolder with a lower tumor burden and not progress quickly. A lot of the early gene expression profiling data on this comes from Little Rock. Unfortunately, determination of an individual's biology is not readily accessible in the

clinic, and we are typically unable to clearly define each patient's inherent disease biology.

**Dr. Mehta.** We just don't have the answers as to exactly what to do with the information that we get except watch more closely and treat a little bit earlier. We don't even know the significance of minimal residue disease and how often to test for it and if it correlates truly with longer-term survival. These are great research questions. We need to accumulate the data and try to analyze it. We need to participate in the big data programs.

**Dr. Ascensão.** The other thing, of course, is now we have new immunotherapy approaches beyond transplant, which includes some of the checkpoint inhibitors and there's some exciting data coming out. So I think the future looks good.

**Dr. Ascensão.** We all are committed to treating our patients, our veterans, to the best of our abilities. And I think the VA has done a very good job in allowing us to do this for our patients and allowing us to provide the best treatments available out there.

#### Author disclosures

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