Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-breakthroughs-from-penn-medicine/innovative-options-for-patients-with-multiple-myeloma/7102/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Innovative Options for Patients with Multiple Myeloma

Narrator:

Welcome to "*Medical Breakthroughs"* from Penn Medicine, Advancing Medicine Through

Precision Diagnostics and Novel Therapies. Your host is Dr. Lee Freedman.

Dr. Freedman:

Multiple myeloma is a common malignancy of plasma cells. Although there have been significant advances in survival over the past 15 years, patients still often live only a handful of years after diagnosis. Understanding and developing interventions to prevent the progression from precursor states to multiple myeloma would be significant advances. I am your host, Dr. Lee Freedman, and with me today is Dr. Brendan Weiss, Assistant Professor of Medicine at the Hospital of the University of Pennsylvania at the Abramson Cancer Center. Dr. Weiss, thank you for being with us.

Dr. Weiss:

Thank you very much for inviting me.

Dr. Freedman:

Well, it is our pleasure, and I am interested to hear about the myeloma program at Penn. Can you tell us a little bit about the program and who is in the program with you?

Dr. Weiss:

We have 4 faculty members currently. The leader of the Plasma Cell Program is Edward Stadtmauer, and my colleagues are Dan Vogel and Adam Cohen. Each of us has our own specific research focus. Our leader, Ed Stadtmauer is focused on transplant-based therapies and transplant, as well as cellular therapies, immunotherapy. And Adam Cohen is also very involved and focused on immunotherapy for multiple myeloma, as well as amyloidosis which is a related plasma cell disease. And Dan Vogel is focused on new therapies and early clinical trials for relapsed multiple myeloma. My personal research interests are in the so-called myeloma precursor conditions which are known as MGUS and smoldering myeloma. As well, I lead the Penn Multidisciplinary Amyloidosis Program and am doing research in amyloidosis.

Dr. Freedman:

So, you really cover a wide range, probably the whole gamut of plasma cell diseases?

Dr. Weiss:

Yes, that is our goal at the Abramson Cancer Center in the plasma cell group, is to be able to really address all the needs of our patients, as well as address their many remaining important research questions in the plasma cell diseases.

Dr. Freedman:

So, perhaps you could enlighten me a little bit about why we need some of these newer approaches? What is the standard treatment for multiple myeloma and how successful is it?

Dr. Weiss:

That is a great question. During the intro you said that myeloma patients live about a handful of years, and what has been really remarkable in myeloma over the past 15 to 20 years, is how much progress there has been in outcomes for myeloma patients, and it has been due to the following major therapeutic advances: First, in the mid 1990s, we had high-dose melphalan and autologous stem cell transplantation, and that was the first therapy to improve survival in myeloma patients for many decades. And then, there was the introduction of thalidomide which had been around for many years, but was first found to be active in myeloma in the late 1990s. Since then, thalidomide analogues, which are also known as immunomodulatory drugs -- lenalidomide and pomalidomide -- have been developed and have become available for use. And then, another major development was the introduction of proteasome inhibitors; the first one was bortezomib and now carfilzomib. And so together, all of those new therapies, including 2 new classes of drugs, which we collectively refer to in the field as novel agents, have really dramatically improved the survival of myeloma patients, and you know, we anticipate that myeloma patients who are diagnosed nowadays probably will have average survivals of 8 to 10 years.

Dr. Freedman:

May I ask you about one of your interests that you brought up, because I am an internist and I have a number of patients that I follow who have so-called MGUS, monoclonal gammopathy of uncertain significance and we get the SPEPs and the immunofixation studies and typically don't treat until there is a significant abnormal protein spike, is that the right thing to do? Should we be intervening earlier?

Dr. Weiss:

That is a really great question, and that has been an area of interest in the field and my particular interest for some time. In 2009, I published one of the studies that established that all patients with myeloma have a preexisting monoclonal gammopathy of undetermined significance and the real challenge in the field today is to try and figure out which patients with MGUS and smoldering myeloma have really high risk of developing myeloma-related end-organ damage in the short term. With those patients, it might make sense to treat them early. And, in fact, there was a study about a year ago using lenalidomide and dexamethasone, which is an active regimen in myeloma. It was published in the *New England Journal* where they took patients with high-risk smoldering myeloma and treated them before they had any symptoms, and it did seem to show some benefit.

Dr. Freedman:

Very interesting, and are there well-established risk factors that separate the average or low-risk from the high-risk MGUS patients?

Dr. Weiss:

Unfortunately, no. That is one of the reasons the study, that I mentioned earlier, that seemed to show a benefit in treating high-risk smoldering myeloma, has not really changed our standard practice, and it is because they used a technology -- flow cytometry on bone marrow plasma cells -- that is unfortunately not widely available and has not been validated or standardized by multiple labs. And so, the current technologies that we have don't reliably identify those patients who might benefit from treatment. I have a study going on right now, here at Penn, that is trying to develop some newer biomarkers that we hope will be robust in identifying these patients, but also more easily performed throughout the general population.

Dr. Freedman:

If you are just tuning in, you are listening to Medical Breakthroughs from Penn Medicine on ReachMD. I am your host, Dr. Lee Freedman, and joining me today is Dr. Brendan Weiss, Assistant Professor of Medicine at the Hospital of the University of Pennsylvania.

Dr. Weiss, you mentioned that one of your colleagues is working on newer therapies for relapsed multiple myeloma. Can you tell us what is going on in that field?

Dr. Weiss:

Yes. There has been a lot of excitement in some of the newer therapies for relapsed myeloma. Although, as I mentioned earlier, we have made great strides with new classes of drugs such as immunomodulatory drugs and proteasome inhibitors, we still need some newer classes of drugs to continue to improve the outcomes for our patients. And so, one class of drugs are HDAC inhibitors, and there is currently an HDAC inhibitor, panobinostat, that is being evaluated by the FDA. But, my colleague, Dan Vogel, has been working with a compound, earlier in development, that is a more targeted HDAC inhibitor that does look promising. These HDAC inhibitors seem to work best in combination with bortezomib or a proteasome inhibitor. And so, it is exciting to see that possibly we will have another class of drugs to add to our armamentarium.

Dr. Freedman:

And, am I right in assuming that these newer agents work at particular points along the replication cycle of the abnormal cells?

Dr. Weiss:

The proteasome inhibitors work on the machinery that recycles the intracellular proteins. And by interrupting that process it kinds of chokes the plasma cell, which is one of the cells in the body that makes so much protein, i.e., the monoclonal immunoglobulin, and seems to be very susceptible to choking off that intracellular apparatus.

Dr. Freedman:

And then, amyloidosis is something that you are looking into and another one of your colleagues. I think of this as a disease of the elderly that really doesn't have very effective treatment. Bring me up to speed with that.

Dr. Weiss:

Yes, so amyloidosis is a very challenging disease and the challenges are really, I would say they are 3-fold currently: One is, first of all, identifying the patients before they get too sick. And that really requires an astute internist or neurologist or nephrologist who initially sees these patients with manifestations of amyloidosis, and that is a hard problem to solve. The other issue is really successfully killing the plasma cell clone that is making the immunoglobulin light chain that is causing the amyloid deposition. That area we have made advances because we have used all of these new myeloma drugs, that I mentioned, to get deeper hematologist responses; that has been encouraging. The third area is to actually go after the amyloid deposits that are already in the organs and that, so far, has not been successful but we have an early-phase clinical trial here at Penn looking at a new compound that is a monoclonal antibody to target the existing amyloid deposits. And the trial, unfortunately, is too early in its development to really comment on its efficacy but we have been encouraged to see that it is a very easily tolerated drug, which is important for these patients who are often very frail.

Dr. Freedman:

So that really sounds fascinating. I imagine you have talked about making the diagnosis early because once the amyloid plaque is in

the various organs, you see organ dysfunction. But, we may one day have something that actually breaks down the plaque in the organs after it has been deposited?

Dr. Weiss:

Exactly. That is the exact goal of this compound.

Dr. Freedman:

And are there particular symptoms that you would encourage our listeners to be watching for to, you know, think about making this diagnosis early?

Dr. Weiss:

Absolutely. Unfortunately, the symptoms are not generally specific for amyloidosis, but as an internist or cardiologist or nephrologist, if you see a patient who has unexplained fatigue or weight loss or protein in the urine, heart failure that does not respond to the typical medications that improve heart failure, neuropathy that is not otherwise explained, and another catch-phrase that some people find helpful is: If a patient looks like they have a cancer -- they are losing weight, they are tired, but no one can seem to find a cancer in the body -- that is sometimes a clue that you should look for amyloidosis.

Dr. Freedman:

And diagnosis made best by biopsy?

Dr. Weiss:

The critical diagnostic test for amyloidosis is to find amyloid deposits and it can be done at a surrogate site by using abdominal fat and having the pathologist perform a Congo red stain, or if that is negative, one can biopsy the organ that is involved, which would be, perhaps, the heart or the kidney. Sometimes, of course, that requires a referral to a specialty center that is able to perform those tests.

Dr. Freedman:

Very interesting, and very important for us to keep in mind. I have been told that there has been some success using CAR T-cells in leukemia and lymphoma. Are we doing anything with that type of therapy for myeloma at Penn?

Dr. Weiss:

Yes, so, this therapy has obviously gotten a lot of attention for acute lymphoblastic leukemia and for chronic lymphocytic leukemia and increasingly now, for some lymphomas, based on the work of Carl June and David Porter and others here at Penn Medicine, and the reason those have been successful is those T-cells have been, which are obtained from the patient, are engineered to target a protein on the surface of those cancers, CD19. And myeloma cells also express CD19 at some level and we have a pilot study ongoing at the moment looking at CD19-directed T-cells in myeloma and we hope in the near future to have an additional target identified on plasma cells to give more specific CAR T-cells to myeloma patients.

Dr. Freedman:

And then you also mentioned transplant. Is there work being done in transplant for myeloma?

Dr. Weiss:

Yes. So, for our current CAR T-cell study, we are actually giving the CAR T-cells after high-dose melphalan and autologous stem cell transplantation in patients who have very high risk of relapse, with the thought that we can control the myeloma and give some space for the CAR T-cells to eradicate any residual myeloma. And so, that is a way of improving the results of transplant for myeloma. And other studies that are being explored are studies to improve the maintenance therapy that we give after transplant with some of the newer proteasome inhibitors.

Dr. Freedman:

Well, it is clear that there have been major advances and new things on the horizon. If I could ask you to look 5, 10 years down the road, are there other things that you see coming in this field, Dr. Weiss?

Dr. Weiss:

Yes, I think the one area I didn't touch on was monoclonal antibodies for myeloma. We have participated in trials of the anti-CD38 monoclonal antibody, daratumumab, which is looking, at least based on the very early studies, looks very promising, and so we hope to have a monoclonal antibody for myeloma and hopefully this agent, or others in its class, will combine well with our existing regimens and we will be able to construct a multi-agent chemotherapy regimen including a monoclonal antibody, that will be able to control myeloma for the long term in patients, and perhaps, reduce the need for stem cell transplants early in the disease which is our current approach.

Dr. Freedman:

Well, I very much want to thank Dr. Brendan Weiss for outlining for us some of the new developments and future developments in the treatment of plasma cell disorders, particularly multiple myeloma and amyloidosis. It looks like the future is very bright, Dr. Weiss. Thank you.

Dr. Weiss:

You're welcome. Thanks for having me.

Narrator:

You have been listening to Medical Breakthroughs from Penn Medicine. To download this podcast or to access others in the series, please visit ReachMD.com/Penn and visit Penn Physician Link, an exclusive program that helps referring physicians connect with Penn. Here you can find education resources, information about our expedited referral process, and communication tools. To learn more, visit www.pennmedicine.org/physicianlink. Thank you for listening.

*Bolded words need confirmation.

End of Audio: 17:00

Transcriber: LP

Proofed: cm