Scientific & Clinical

CLINICAL TRIALS IN MULTIPLE MYELOMA

Myeloma Today in conversation with Dr. Joseph Mikhael

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Please tell us about your medical background and current affiliations.

I graduated from medical school at the University of Ottawa in Canada. My internal medicine residency at the Ottawa General Hospital was followed by hematology training in Toronto, along with a masters' degree in education at the University of Toronto - Ontario Institute for Studies in Education (OISE). In 2004, I completed a two-year multiple myeloma fellowship at Princess Margaret Hospital in Toronto, primarily under the guidance of Dr. Keith Stewart. From 2004 until starting at Mayo Clinic in January 2008, I was a staff hematologist and education coordinator for hematology at Princess Margaret Hospital.

I am a consultant hematologist at the Mayo Clinic in Scottsdale, Arizona. I specialize in plasma cell disorders: myeloma, amyloidosis, and Waldenstrom's macroglobulinemia. I am currently the principal investigator (PI) of many clinical trials, primarily in relapsed myeloma. My clinical research interests also include the transformation of MGUS to myeloma, pharmaco-economics, and supportive care in cancer. I am currently the PI of the prECOG study evaluating the use of lenalidomide (Revlimid®) in patients with renal insufficiency.

In addition, I continue to be heavily involved in education. I am an assistant professor at the Mayo College of Medicine, the Vice-Chair of Education for the division of Hematology-Oncology, the program director of the Hematology-Oncology Fellowship Training Program, and the Vice-Chair of the Graduate Education Committee at Mayo Clinic (Arizona).

How did you develop an interest in myeloma?

I was influenced by my mentor, Dr. Stewart, and I was fascinated by the complexity of this disease and by how much better we could make our patients with the novel therapies, which is what got me interested in myeloma research.

Do you work both in the clinic and in the lab?

One of the benefits of working at Mayo Clinic (Arizona) is that we have three of the best myeloma researchers – Keith Stewart, Rafael Fonseca, and Leif Bergsagel. With them in the lab, I am able to split my time between clinical research and clinical practice, as well as continue my work in education. My research work in myeloma is all clinical, be it therapeutic trials or supportive care. I follow up on what Drs. Stewart, Fonseca, and Bergsagel do in the lab. My role in the bench-to-bedside paradigm is to help bring some of what they learn in the lab into the clinic setting.

What is your approach to myeloma research?

It is a three-step process. A better understanding of myeloma leads to better drugs for this disease, which leads to better survival for patients. This requires getting samples from patients and having a sophisticated mouse model, which we have at Mayo. We can give mice myeloma, then test new drugs or test blood levels to gain knowledge about how this disease changes over a rapid period of time. This enables us to understand the pathways of the disease, so that drugs can be developed to counteract those pathways. When a new drug is developed, my role is to design clinical trials for the specific group of myeloma patients who are most likely to benefit from that particular drug. If the drug is shown to be effective, we hope that in the long run it will also be shown to improve patient survival.

What is your assessment of the current range of myeloma therapies?

There has been a major shift in the field of myeloma. Not long ago, a doctor might have said, “My standard treatment for myeloma is X.” We had very few bullets for the gun, and when the bullets ran out, they ran out. Doctors now have an arsenal of weapons to help patients fight myeloma. The reason for this is the research that has allowed us to understand myeloma on a molecular level.

How does one select the best treatment?

There are several factors to be considered, both for the disease and for the patient. We have learned that there are as many as six types of myeloma. To keep things simple, I'll break it down into the three major groups: standard-risk, intermediate-risk, and high-risk disease. We treat patients differently depending on which risk group their disease belongs to. We also consider several patient factors. Does the myeloma patient have kidney or other organ involvement? Does the patient live far away from a medical facility and, therefore, prefer an oral therapy to an intravenous one? Does the patient have specific symptoms that may eliminate some treatment options while pointing us in a different direction? We individualize the treatment based both on myeloma features and patient features.

What new treatments might become available for myeloma in the near future?

I would separate those into two categories: promising new versions of the older drugs as well as completely new mechanisms of drugs. Both of those development pipelines are very deep. Currently, the three major anti-myeloma drugs on the market are thalidomide and lenalidomide, which belong to the same drug family, and bortezomib (Velcade®). In both drug families, there are new drugs being developed.

The next-generation drug in the thalidomide and lenalidomide family that's showing a lot of promise is pomalidomide, which seems to be very well tolerated and is not associated with peripheral neuropathy (PN). It is soon to begin phase III clinical trials. Similarly, there are several next-generation proteasome inhibitors being developed. The front-runner seems to be carfilzomib, which is already under phase III investigation. In the US, it is likely to be the next drug to receive FDA approval for myeloma. The other drugs in the bortezomib family that are being developed for myeloma are either not associated with PN, can be given less frequently, or are administered orally. So the outlook in this category is very promising. In addition, there may be as many as 20 drugs being developed that are completely new to myeloma but could become a big part of what we will be able to offer patients in the near future.

Currently, drug development is less about directly attacking the plasma cell (the key cell in myeloma) and more about interrupting the bone marrow

microenvironment. We know that in myeloma the communication between the cells and their environment is very sophisticated, so we are trying to make it harder for the myeloma cells to thrive.

Also, it is important to remember that we are not looking for one silver bullet. We are learning to combine drugs, old and new, to increase efficacy and lessen toxicity. This approach also helps us counter drug resistance. There is such a complex nature to the growth and development of myeloma that we have not been able to shut it down with a single drug. One patient might have more than one type of myeloma growing in them simultaneously, and a strategic combination approach appears to be most successful at limiting the disease. Some of these therapies are only available in the context of a clinical trial.

So who is the best candidate for entering a clinical trial?

Clinical trials are available to patients at all stages of myeloma, and we encourage all patients to consider participating if there is one available to them. There is no down side. Clinical trials are not using people as guinea pigs. Clinical trials are providing patients an opportunity to be treated with either a validated therapy or a therapy that's undergoing validation. Patients always have the option to opt for standard therapy later on. Of course, as with all other important decisions, it is very important to have clear and honest discussions with the healthcare provider and the team running the trial.

Any closing comments?

Our management of myeloma – the ability to diagnose, treat, and monitor this disease – has improved tremendously. We can now detect the disease at a much lower level than ever before, both at initial diagnosis and at relapse, and we can run tests that help us stratify the patients. The use of newer drugs and drug combinations is resulting in longer and deeper remissions for many patients. Another important point is that supportive care continues to get better. We don't just treat the myeloma, we are continuing to get better at treating the whole patient.

I consider myself an optimistic realist and, overall, the future looks very optimistic. Although myeloma is still not curable, we have seen a tripling in the average

patient survival rates. Dramatic progress has been made in the field in the last decade, and our understanding of myeloma has improved significantly in the last three years. But our successes notwithstanding, we all share a very strong drive to find better and longer-lasting therapies.

In the meantime, I would stress the importance of myeloma patient education. This is a very complex disease, and knowledge is power. While scientists and clinicians seek to better understand the disease and to develop better treatments, I would encourage all patients to take a participatory role in their own care in partnership with their healthcare providers.