Lessons in Blood Cancer: How Far We Have Come – MCL (Mantle Cell Lymphoma)

TRANSCRIPT

Narrator
Doctors and researchers have been studying cancer for generations. Thanks to pioneers in science and tireless dedication, we have made great strides in diagnosis, treatment, and the quest for a cure.

But we need to understand where we started to learn how to get where we are headed.

Join us as we explore the history of blood cancer and highlight just how far we've come.

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Mantle cell lymphoma [MCL] is, among all of the B-cell lymphomas that we see, a relatively rare disease, although thankfully much is known about its biology, how we care for patients, and we have lots of data that helps support our treatment decisions. So, despite its rarity, this is a disease that we know a lot about how to treat.

What is Mantle Cell Lymphoma (MCL)?

Mantle cell lymphoma is a type of cancer that arises from a white blood cell, or an immune cell called a B cell or B lymphocyte. And there are many types of lymphomas and B-cell lymphomas, many types of B-cell non-Hodgkin lymphomas is how we categorize these types of diseases. But mantle cell lymphoma is very unique. There are upwards of 95 different lymphomas that are included in this group of diseases. And many of them can be low-grade; this means they develop over years to decades sometimes. Many are higher-grade. These are things that develop sometimes over days, but more often over weeks to months. But mantle cell lymphoma is a bit of a shapeshifter. It can behave more like a low-grade disease that develops over a longer time, or like a higher-grade disease that presents more aggressively and requires treatment much more urgently.

Discovery of Lymphomas

Lymphomas are cancers of a type of white blood cell called B cell, T cell, natural killer cells. B-cell non-Hodgkin lymphomas are cancers of B cells or B lymphocytes. We have Hodgkin lymphomas, and we have non-Hodgkin lymphomas. What does this mean?

There was a man named Thomas Hodgkin, and he identified what we now call Hodgkin lymphoma. Since that time in the early 1800s, about 95 different types of lymphomas have been identified, and we have called them all non-Hodgkin lymphomas. Now, I think that to some extent, this is kind of silly. We name all of these different diseases based on what they are not, and they have unbelievably varied biology, clinical presentations, behavior, prognosis, [and] treatments. So, we really need to think about each of these 95 or so diseases individually. Now, one way that we can do that is to think about their clinical presentations and their biology. So, we can have low-grade, indolent, slow-growing – there are all these different terms we use – these are diseases that typically come on over years to decades, although not always. No two patients are alike. On the other hand of the spectrum, we can have diseases that are very high-grade, or we'd use the word aggressive, for example. These are diseases that typically come on over days to weeks to months, usually weeks to months. Again, not always. There is a lot of variability even within these diseases. But mantle cell lymphomas can behave like a low-grade or indolent or slow-growing lymphoma – one that can present over many years and may never require therapy. And on the other end of the spectrum, I can see a patient with mantle cell lymphoma who presents with rip-roaring disease who requires chemotherapy and even admission to

the hospital that day. So, there is a tremendous heterogeneity or variability with the way that patients present to attention.

The Evolution of MCL Treatments

I think it is helpful to go back to when this disease was first named in the early 1990s. When we first called this mantle cell lymphoma. At the time, we used chemotherapy regimens like a regimen called CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]. This is a multi-agent chemotherapy regimen that had been used across a whole wide range of B-cell lymphomas and T-cell lymphomas. What they found at the time, early on, was that patients with mantle cell lymphoma unfortunately weren't doing as well as they would have liked. And so there was a lot of interest in trying to improve outcomes for patients with this disease.

For younger patients who could tolerate more intensive chemotherapies, in the 1990s they did things like adding more intensive chemotherapies like a drug called cytarabine, which if you add this to other chemotherapy components, seem to be very important for patients with this disease. They also did something in the 1990s where they did something called an auto [autologous stem cell] transplant. Now auto transplant is actually a name that can be confusing. There is actually no transplant here. This is really just what we call a consolidation treatment with just a big dose of chemotherapy. The idea is, once we have given other chemotherapies to achieve a response, an auto transplant is this big dose of chemotherapy to wipe out as many of the lymphoma cells as we can get. After this, we have to do the transplant. But what is different about a transplant in the way that we traditionally think of it (a donor transplant where say I give my immune system to somebody else or vice versa), an auto transplant is such that we actually take our own stem cells from often from just the peripheral blood that can be mobilized from the bone marrow to there where they and can be collected, put them in the freezer, and then actually get them back after the chemotherapy to repopulate our bone marrow. The idea here is to give a big dose of chemotherapy to really wipe out as much of the lymphoma as we can.

For older patients where this type of a treatment really is not feasible, we learned more about improving their treatment in the 2000s and 2010s. This was with a drug that was developed in mantle cell lymphoma across other types of B-cell lymphomas called bendamustine. Bendamustine is a chemotherapy drug that is highly, highly effective in mantle cell lymphoma and it actually seemed to be better than CHOP in this disease.

Another big development in mantle cell lymphoma in the 2000s was the development of this drug called rituximab. Rituximab is probably one of the most important advances across B-cell lymphomas. This is an antibody drug that is made to target CD20. And this is a protein that we know is on many B-cell lymphomas, but certainly on mantle cell lymphomas. This was also added to these chemotherapy regimens, be it to intensive chemotherapy for younger patients who could tolerate such a treatment, but also to less-intensive therapy like bendamustine for older patients or for folks who couldn't tolerate such a treatment. This intensification happened really from the 1990s through the 2010s.

What we have seen since then is I think really more of a de-intensification. What has allowed us to do this is the development of all of these novel targeted agents over the course of the last decade. Drugs like a drug called lenalidomide. Lenalidomide, if you combine it with rituximab, is an incredibly effective agent in this disease and can achieve responses in patients with recurrent disease after initial chemotherapy, but also has been studied even in the frontline setting, although this is really not something we typically do as a standard.

The Role of Transplantation

Even if we go back seven or eight years, when patients would receive a second line of therapy after receiving an initial chemotherapy, if they could achieve a response, we would have considered something called an allogeneic transplant (with cells from a donor). We know that this is a very effective therapy for patients with mantle cell lymphoma that can achieve curative outcomes, but comes with considerable risk as well, which is continuous. There is a continuous risk for patients who have had this type of a treatment. What we found is that over the last seven or eight years, with more and more advances in this disease, the role of a transplant in mantle cell lymphoma has diminished. We are doing this less and less and when we do it, we do it often at later lines of therapy except in very rare circumstances.

Developing Therapies: BTK Inhibitors

A whole other class of drugs called BTK inhibitors or Bruton tyrosine kinase inhibitors like the first-in-class drug called ibrutinib, a pill that was developed in the early 2010s, as well as second-generation BTK inhibitors. These were the drugs that followed it like a drug called acalabrutinib and a drug called zanubrutinib.

In the 2020s we have a very important development, which is pirtobrutinib. This is an oral therapy, it is a third-generation BTK inhibitor, and this can be effective even in patients with mantle cell lymphoma whose disease gets worse while receiving one of the first- or second-generation BTK inhibitors: ibrutinib, acalabrutinib, or zanubrutinib. It is also very safe. If you look at the side-effect profile, it is very uncommon that patients receiving pirtobrutinib have severe side effects. This is a very important addition to our treatment options for mantle cell lymphoma.

Developing Therapies: Immunotherapies

Two very important immune-based therapies have been developed over the last few years. In the 2020s, two different CAR T-cell therapies were approved for mantle cell lymphoma. The first called brexucabtagene, the second called lisocabtagene or brexu-cel and liso-cel. These are treatments that use a patient's own immune cells, their own T cells. These are different types of white blood cells from what their lymphoma comes from. These are B-cell lymphomas; these are T-cell therapies. When we use these therapies, we remove some of the T cells from patients, send them to the lab, and re-engineer them in such a way that they can be redirected to fight the mantle cell lymphoma.

This is a very complex process that requires being within two hours of a major treatment center that can do this treatment for a month after the treatment. It often requires admission to the hospital. So, this is a big step for patients with this disease. Nonetheless, this is highly effective and can achieve durable remissions with one dose of therapy.

We know that CAR T-cell therapy can be curative in other types of lymphomas when we previously did not think of them as curative in that setting. So, there is hope that in mantle cell lymphoma that this treatment could potentially achieve a more definitive, potentially curative outcome.

Developing Therapies: Bispecifics

Bispecifics are a new, emerging therapy in mantle cell lymphoma that have actually been approved in other types of lymphoma, such as diffuse large B-cell lymphoma and follicular lymphoma. These treatments work in some of the same ways as CAR T cells, but with some key differences. We don't need to make it from the patient. Bispecific therapies are manufactured. They are available in a pharmacy. You just infuse them or inject them.

In order to illustrate how bispecific antibody therapies work, I think it can be helpful to think about how normal monoclonal antibodies work. These are drugs like rituximab. Rituximab is a single antibody, and it grabs onto one target, and then it uses other cells in our immune system to come in and kill the cancer. Rituximab, for example, targets CD20 but relies on our own immune cells to come in and do it in this normal function.

Bispecific antibodies work in a very different way. It overcomes this second step by effectively having two arms. What is important about having two arms to this bispecific antibody is that one arm is critical for the latching on to the mantle cell lymphoma cancer cells. The other arm is critical for pulling in the immune cell, the T cell, that is going to go after the cancer cells to try to achieve a response.

Measuring Outcomes

MRD, or measurable residual disease, is a new type of technology that can be used to detect levels of mantle cell lymphoma at a very low level. Currently we use things like CAT [computed axial tomography] scans and PET [positron emission tomography] scans to detect disease at the end of treatment, and these are very good tools to confirm whether somebody is in a complete response or not. However, they do not detect tiny amounts of disease. MRD can get down to a level of one in a million cells. If you have as little as one out of a million mantle cell lymphoma cells in the blood or in the bone marrow, these types of technologies can potentially detect that. We have seen in clinical trials that MRD is a promising tool for predicting outcomes with mantle cell lymphoma. The question is, “Should this be used routinely in the clinic as a prognostic tool?” Meaning to tell a patient, your MRD test is this or that, and this is going to predict for this outcome or [predict for] the other in the future. Or hopefully in the future, can we use a tool like this to actually change treatment. If, say, somebody is still MRD detectable, we can still detect mantle cell lymphoma at some level. Should we do more? Or if mantle cell lymphoma is no longer detectable, can we do less?

MRD has so much potential in mantle cell lymphoma as a tool both for prognostic purposes, but also potentially in the future to be used to improve therapies. MRD is currently not approved in mantle cell lymphoma and so is only being used in clinical trials today, but my hope is that this is something that patients can use in the future.

A Hopeful Future

Look how far we have come. I'm eager to see what the future brings.

Since this disease was first named in 1991, we have witnessed dramatic improvements in patient outcomes, and this has translated to improved survival, decade to decade. What is different about the present, and I think the future, is that we are seeing this de-intensification of chemotherapies as we bring in these new therapies, these targeted treatments, and this is leading both to better outcomes, but also to improved quality of life.

Narrator
For more information about MCL and other blood cancers, please contact an Information Specialist at 1-800-955-4572 or visit www.LLS.org/InformationSpecialists.

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