Lessons in Blood Cancer: How Far We Have Come – AML (Acute Myeloid Leukemia)

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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I've been involved in the treatment of leukemia for more than 50 years. I saw my first patient as a resident, I guess in 1970 and had no idea what the disease was. So, I've been lucky in the sense of seeing what's happened to leukemia over five or six decades and a lot has happened.

What is AML?

AML or acute myeloid leukemia is an abnormal growth of white blood cells of the myeloid lineage. The myeloid lineage is the growth pattern that produces cells called neutrophils. What neutrophils do is fight infection. What happens with leukemia, and frankly all cancers, is there is a mutation or a series of mutations which makes it so that maturation no longer occurs. So, for example, instead of having neutrophils, red blood cells, and platelets like adults in a family, you have a block in what we call differentiation or growth. That leaves you almost with a society of infants. And the symptoms that occur as a consequence of that is you're missing the adults. So, you have a propensity to infection, you're weak from anemia, for example, and potentially bleeding problems because of a relative absence of platelets. And then you have the accumulation of these infants – or blasts – either in the bone marrow or the blood, and that's what we call AML.

The Evolution of AML Treatments

When I first began treating AML, a regimen, which has been called 3+7, or 7+3, that consisted of three days of a drug called daunorubicin and seven days of a drug called cytosine arabinoside or ara-C became the initial standard for treatment. It has remained the standard for most patients until this day. And you can look at that two ways: one is why are we doing the same thing? But the other is we are doing the same thing because it's of substantial benefit. And as I got older and started seeing patients over the years, one of the more satisfying things was seeing a substantial fraction of patients who were cured.

We've done literally dozens of studies to add drugs to 7+3 to see if it can be improved upon. We cured a lot of people with 7+3 and still do. Over the years, we learned a lot more about whom we cured and whom we did not. People with certain genetic patterns had a high fraction of cure, whereas people with other genetic patterns had a very, very low fraction of cure. I can't tell you how satisfying it is to see lots of people who were cured by that treatment. And that treatment was finite. It was about four to six months, and then it was done.

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The Search for New Treatments

Through the years, we have identified groups through more sophisticated laboratory studies, cytogenetics, something called flow cytometry, which can characterize proteins on the surface of cells, molecular genetics, which can more accurately define the type and also function of the mutations that cause leukemia. And then in recent years, there have been a number of drugs that have been developed that can, in a relatively precise and targeted fashion, hit the products of some of these mutations. But perhaps the home run and most interesting was the treatment of a type of AML called APL [acute promyelocytic leukemia]. APL is a very well-characterized disease. And the big break came initially from China where they reported that treatment with a drug called ATRA, all-trans retinoic acid, a vitamin A-type product, given orally can treat patients with APL first in relapse, and then as initial therapy without chemotherapy and with remarkable results that you could see that the patient has changed in just a couple of days of receiving this medicine.

It worked, as did similar trials. It took the cure rate up to about 70%. The Chinese struck again and presented data with a drug called arsenic trioxide, obviously an arsenic compound. And to make a long story short, the combination of arsenic plus ATRA – which is soon to become all oral – if done correctly, cures 80% to 90% of patients with this leukemia. You were taking patients who were in the hospital for at least a month and treating some of them as outpatients with pills, with a vitamin. Remarkable.

The Role of Transplantation

Lots of patients were cured with chemotherapy alone, but unfortunately in many, the leukemia was resistant to the chemotherapy. Allogeneic transplantation developed sort of in parallel beginning in the early 1970s. What allogeneic transplant is you take stem cells either from the bone marrow, or [in] more recent years from the peripheral blood, from donors. What's done with allogeneic transplant is the patients are given high doses of chemotherapy to both treat their residual leukemia and also suppress their immune system so that they don't reject the stem cells from the donor.

The major effect of allogeneic transplant is actually not due to the chemotherapy, but to an immune effect whereby the lymphocytes from the donor recognize the recipient, the host, as foreign and recognize the leukemia as foreign and kill the leukemia. The problem is those lymphocytes are not smart enough to distinguish the leukemia from the rest of the host and can also immunologically attack the host; something called graft-versus-host disease. There have been enormous advances in treating and preventing graft-versus-host disease at the same time maintaining the anti-leukemia effect.

Bottom line is that the initial studies showed that people with leukemia that was refractory to chemotherapy, could be cured with allogeneic transplant. [Many] transplants have now been moved from just where we treated people with refractory leukemia or resistant leukemia to much earlier stages where we have been able to identify people who are unlikely to be cured by chemotherapy, and they now receive transplant in first remission, which is when their leukemia is controlled. This has substantially increased the cure rate.

Developing Targeted Therapies Through Clinical Trials

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During the years as different therapies have been tested, we have also done laboratory evaluations of the leukemia cells. And for example, we've discovered that leukemias that have certain chromosomal changes are highly susceptible to the effects of chemotherapy alone. Now, every patient with AML also has genetic analyses attempting to identify genes that are altered in their specific type of AML. Drugs have been developed which specifically target those metabolic changes. They've all been shown to be of benefit in patients with relapsed AML.

The important lesson here is that studies in the laboratory have identified such targets, and it is likely that other such targets will be identified in the future. And of course, to reemphasize the importance of clinical trials, which incorporate these new scientific advances and these new drugs in the future.

A Cure for AML?

People who treat acute leukemia focus on cure. We obviously are aware that some patients we can't cure and offer therapy that prolongs life and is more palliative. But the first thing we're thinking about when we see a new person with leukemia is whether we can cure them and how to best cure them. What chemotherapy? Whether or not transplant is something that's going to figure prospectively in our plan [on] how to cure it. But importantly, we're thinking about cure and obviously are very happy when we see it and still have a lot of challenges because we don't see it in everybody. With the combination of targeted therapies, chemotherapy, and transplant, the cure rate in younger patients is substantial. The cure rate in older patients is not.

Treating Older Patients

The biggest challenge we face in the treatment of AML currently is with older adults. And the biology of the disease in older adults is different. Chemotherapy that cures many younger people cures fewer than 10% of people who are older. The reasons for this are the leukemia cells are resistant to this type of chemotherapy. There are more problems with tolerating chemotherapy in the older adults for obvious reasons. It is harder to apply transplant to older adults because of health issues. Although we now transplant many, many people over the age of 70 and perhaps even older. There have been changes in therapy for older adults recently. Instead of using standard 3+7, there have been combinations involving a drug called 5-azacitidine in combination with a drug called venetoclax [Venclexta®]. The latter is administered orally. It is somewhat more tolerable than 3+7, so that you could apply that therapy to a higher percentage of patients, some of whom doctors might not have considered even treating before this came along.

A Hopeful Future

It is an exciting time to be in research and to be in medicine. The changes we are going to see in the future are going to be, I think, unimaginable in terms of medicine and in cancer specifically.

As I hope I have emphasized, there have been remarkable changes in the treatment of AML in the last 50 years to the point where a substantial fraction of patients, particularly younger patients, are cured by chemotherapy and/or with the addition of transplant. There have been extraordinary advances in

supportive care, which have transformed something which may have been considered cruel to something that's tolerable even for elderly patients with AML. You can talk to patients with real optimism.

In terms of the future, when I'm talking to medical students about oncology, one of the things I say is, I can't think of a better time to be coming up to be a doctor. The advances in science are frankly breathtaking. It is amazing how many clever people there are studying cells and studying chemistry and studying immunology, which eventually becomes applicable to patient care. Frankly, this is very different than when I started. I have certainty that this will apply to patients with AML in the future as it is being applied to patients with all types of cancer.

Narrator
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