Welcome to Yale Cancer Answers

This week it’s a conversation about the care of patients with myeloid disorders with Doctor Lourdes Mendez.

Dr. Mendez is an assistant professor of medicine and hematology at the Yale School of Medicine, where Dr.
Chagpar is a professor of surgical oncology.

Dr. Mendez, maybe we can start off by you telling us a little bit more about yourself and what it is you do.

So I’m a hematologist and in the last years the patients we care for has expanded to include individuals who have something we’re calling pre disease and also clonal hematopoiesis.

So our team includes my physician colleagues who are hematologists, also very dedicated Aprn’s and nurses, as well as an incredibly talented and dedicated research team. And we provide approved treatments, but we’re also very much involved in...
00:01:19.135 --> 00:01:21.235 clinical trials and investigations
00:01:21.235 --> 00:01:24.870 as well as in trying to make
00:01:24.870 --> 00:01:27.445 new discoveries in the lab,
00:01:27.450 --> 00:01:29.823 both the wet lab as it’s called
00:01:29.823 --> 00:01:31.250 and in the dry lab.
00:01:31.250 --> 00:01:34.522 So we work together to care for
00:01:34.522 --> 00:01:36.106 existing patients and try and
00:01:36.106 --> 00:01:37.728 move the needle in our field.
00:01:39.290 --> 00:01:41.460 So let’s get through a bit of
00:01:41.460 --> 00:01:43.316 the vocabulary so you can help
00:01:43.316 --> 00:01:45.304 to define some of the terms and
00:01:45.374 --> 00:01:47.486 the kinds of patients you treat.
00:01:47.490 --> 00:01:50.794 For example,
00:01:50.794 --> 00:01:52.210 what are myeloid disorders?
00:01:53.130 --> 00:01:56.946 So if we take one further step back and
we talk about the blood and the different cell types in that are in the blood,
there are three main types.
There are white blood cells,
there are red blood cells,
and there are platelets.
And the white blood cell family further can be subdivided into myeloid cells and lymphoid cells as two subcategories.
And the myeloid cells,
I call them first responders because their role is to come to the site of infection or the site of an injury as the first representation of the immune response to that kind of insult.
And so these cells can become abnormal and
if the abnormality is profound enough, they become cancerous. And so then we refer to them as myeloid diseases or myeloid neoplasms, they’re basically myeloid cancers.

And then you mentioned a couple of other phenomena that you’ve started treating more recently. Can you tell us a little bit more about those?

Yes, and I think I should just briefly mention about leukemia before I go into the more recent predisease category. So leukemia refers to a growth of
abnormal cells in the blood and it can be further divided as acute leukemia and as chronic leukemia. So acute leukemia is termed that way because it needs really rapid attention because it refers to really uncontrolled production of cancer cells in the bone marrow and then they can also spill over into the blood. Chronic leukemias are on the other end of the spectrum and the term we use is indolent, which refers to the fact that they are kind of a slow process, something that usually we address over months and maybe sometimes even years or can just observe.
And myeloid diseases can be chronic myeloid neoplasms or chronic myeloid leukemias or there is acute myeloid leukemia. Our group actually also cares for acute lymphoblastic leukemia, which is that other subfamily of white blood cells that I was talking about within the white blood cells and the as distinct from the first responders which are the myeloid cells, the lymphoid cells, we call them the smart cells because they learn and they adapt specifically to infections and potentially also to abnormal cells like cancer cells.
So that brings us to a different condition that’s more recently been recognized that I called predisease and clonal hematopoiesis. And really this is a new entity that was only recently codified meaning it reflects our fields recognition that there is a condition that precedes myeloid neoplasms but also other blood cancers called clonal hematopoiesis. And it bears some of the genetic fingerprint of the full blown blood cancer. But it’s at the very early stages.
It’s the first hint in some ways of an abnormal cell and in the overwhelming majority of people it will never become a blood cancer. But we do know that taken as a whole, there’s about an 11 fold increased risk of developing a blood cancer if there is this predisease condition called clonal hematopoiesis. The rate of developing a blood cancer is very low, less than 1% a year, well below that actually. And so the challenge in the field is to identify those individuals that are at high risk of developing
a blood cancer down the line. And we are learning about what distinguishes people who have that high risk, but we're very much still in the midst of defining who they are and what the risk factors for progression are. We also know that this predisease condition increases the risk of dying of mortality. And surprisingly when this entity was first being described, it was found that it seems to be due to cardiovascular disease. And the increased risk of clonal hematopoiesis on cardiovascular disease is on the order of other very well established risk factors.
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00:07:52.796 --> 00:07:55.209 hematopoiesis about the need to
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diseases that we can screen for

often times we find them early

So in the case of clonal hematopoiesis,

I guess the same question applies.

I mean how do we know who gets it?

Can we screen for it?

And is there anything that we can do

that can stop it from progressing

to full blown myeloid leukemia?

So those are exactly the questions

of the moment for this condition.

And the simple answer is that we

do not screen for this condition

because we don’t have any proven

or validated interventions and
in fact we’re still defining who would need an intervention at all. So currently this is really found incidentally as a part of other genetic testing. For example, if someone has one, you know, a solid tumor as you were mentioning and underwent genetic testing for that. And there’s different kinds, some that would be more directed at characterizing the genetics of the solid tumor. Whereas other people get referred if they have a, for example,
a family history of breast cancer or ovarian cancer to genetic counseling.

And then there’s genetic testing to see if there’s an inherited risk for developing cancer.

And in the course of such genetic testing, there can be the incidental finding of a genetic mutation that best fits with this condition, clonal hematopoiesis. But we don’t screen for it.

If someone has unexplained low blood counts, then we do increasingly send a panel of genetic testing that has a capacity to identify this condition. But if someone does not have low blood
counts, if the blood counts are normal, we don’t send off such testing to screen for clonal hematopoiesis. And here I should specify the clonal hematopoiesis itself can be further subdivided into those cases where there is a blood count abnormality, like low red blood cells called anemia, low white blood cells called leukopenia or low platelets thrombocytopenia, and that’s called secus. It’s a very long name clonal cytopenia of undetermined significance and if it’s incidentally found in someone who has low normal blood counts, then it’s called CHIP, clonal.
hematopoiesis of indeterminate potential. So the goal in the field is of course for those individuals that seem to have high risk features to ultimately develop effective interventions to halt the progression to cancer. But we’re still very much at the beginning of that effort. It’s a very exciting effort however, because this condition can develop into something called MDS, or myelodysplastic syndrome or even acute myeloid leukemia. And these conditions can have...
really outcomes that are not what we would want five year survival rates in the case of a ML that on average are 30%. And so it would be very desirable to be able to cut that off at the pass so to speak and that’s really a major hope in our field. So for patients who have this premalignant condition, we don’t screen for them because there isn’t an intervention that can prevent it from becoming an invasive cancer. But is there any merit to following these patients? So let’s suppose they incidentally
were found to have a genetic mutation on another panel. And so we know that they’re at increased risk of getting clonal hematopoiesis and subsequently developing fullblown myeloid leukemia, let’s say. Is there any value to following these patients more more frequently to try to discover the leukemia when it develops? If it develops at an earlier stage, maybe we can treat it more effectively, particularly given the fact that this condition is associated with such a poor prognosis? That’s an excellent question and
the short answer is that we are following some of these individuals in clonal hematopoiesis or sometimes they’re called chip clinics now. And that is as you’re kind of alluding to, to track how things change or don’t change. The complication is that in most patients, probably more than 90%, what we’re detecting we think is an age-related phenomenon. It’s the blood system changing as people age because this is a fairly frequent condition in older individuals and a rare
condition in young individuals, let’s say less than 40 compared to 70 or older. And so we are starting, to follow these patients as I mentioned and particularly those who have low blood counts, but it’s not because we’re ready to offer them an intervention. Although clinical trials for the combination of low blood counts and this finding of a genetic fingerprint that overlaps with the net genetic fingerprint of myeloid cancers. When those two things coincide and seek us,
then there are clinical trials and interventions that are under development for these patients.

So we have a clonal hematopoiesis clinic here at Yale where we’re doing just that. We’re following these patients and the goal will be to offer a subset of them clinical trials as a part of the effort to learn and to change the disease course.

Terrific. Well, we’re going to take a short break for a medical minute, but after the break, I’d like to learn more about the research that’s been going on to potentially help these patients.
patients with myeloid disorders,

particularly in honor of Blood Cancer Awareness month.

Please stay tuned to learn more with my guest Dr. Lourdes Mendez.

Funding for Yale Cancer Answers comes from Smilow Cancer Hospital,

where their hematology program offers diagnosis and treatment of blood cancers including lymphoma, leukemia, and myeloma.

More at smilowcancerhospital.org or e-mail Cancer Answers at Yale dot Edu.

Breast cancer is one of the most common cancers in women.
In Connecticut alone, approximately 3500 women will be diagnosed with breast cancer this year. But there is hope thanks to earlier detection, noninvasive treatments, and the development of novel therapies. To fight breast cancer, women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease. With screening, early detection, and a healthy lifestyle, breast cancer can be defeated.
Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and Smilow Cancer Hospital to make innovative new treatments available to patients. Digital breast homosynthesis or 3D mammography is also transforming breast cancer screening by significantly reducing unnecessary procedures while picking up more cancers. More information is available at yalecancercenter.org.

You’re listening to Connecticut Public Radio. Welcome back to Yale Cancer Answers.
This is Doctor Anees Chagpar and I’m joined tonight by my guest, Doctor Lourdes Mendez. We’re discussing the care of patients with myeloid disorders in honor of Blood Cancer Awareness Month. And right before the break, Doctor Mendez, you were telling us about this phenomenon of clonal hematopoiesis and how this is a novel kind of discovery of essentially a premalignancy, a predisease that leads to myeloid leukemias.

So a couple of questions.
Given the fact that we’re still learning about this disease, can you shed some light on some of the research that’s going on into it and perhaps into myeloid leukemias as well? Absolutely. So in terms of the research in this space, it’s of great interest to kind of define what is the natural history of this condition. When does this start and how long is it present? Before maybe we can detect it,
or before it becomes a blood cancer, a myeloid neoplasm, for example? And one of the things that has been reported by scientists who are studying clonal hematopoiesis is that the best estimations are that in probably the majority of cases, this condition is present for decades, in maybe 30 years before it’s actually detected. Which is really, I think in my mind, startling to think that the roots of a cancer could go back so far. But again, I think it’s worth reiterating that this is a pre disease.
Maybe that's one of the best ways to call it, because in some ways it and in most people it's probably a reflection of aging more than a condition that has any significant pre-malignant potential. So even though I spoke about the fact that there's an elevenfold increased risk of a hematologic malignancy, I also mentioned that probably in 90% of individuals this is not going to lead to a significant risk of a blood cancer and that the annual risk, is under 1%.
So really maybe one of the main challenges is separating out the high risk from the low risk individuals and so there's a lot of effort to understand, to have to collect groups of these cases across academic institutions and to understand what types of mutations, how much of that mutation, what kind of other traits and in the blood count, for example. How do these things fit together to associate either with a very low risk situation or a higher risk situation? So some of the efforts in terms

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NOTE Confidence: 0.93404955
00:21:08.890 --> 00:21:12.821 which we also call targeted drugs which are
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00:21:12.821 --> 00:21:15.985 already in use for example in leukemia.
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00:21:22.183 --> 00:21:26.348 inhibitors that target IDH mutations.
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NOTE Confidence: 0.93404955
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And so there’s another clinical trial that’s going to test high doses of vitamin C and when I last checked, there’s also going to be a clinical trial even checking whether something like metformin may have some potential to change the natural progression of this condition. So there are lots of things being planned and underway and lots of collaborations that we are also participating in to do 2 things kind simultaneously, to continue to learn about the basic biology and the.
natural history of these conditions.
And also at the same time based as we learn things in real time to pull from even existing therapies and see if for people who are who are at high risk, we can start to have them benefit from what we already know. So that sounds really exciting. The other thing that you often think about is, you know when you were talking about this being a genetic condition, so you can find mutations very often these days we hear about things like CRISPR and gene editing.
Can you talk a little bit more about what exactly those are and if they have any role to play in this space?

I’m glad you bring up the point about mutations and genetics. So it I think it’s worth spending a few seconds to distinguish inherited genetic changes or mutations or variants from acquired during someone’s lifetime.

The condition I’ve been talking about, I’m referring to mutations that occurred during a person’s lifetime and not changes that were inherited from someone’s parents.

So just to make that distinction, we do have information,
increasing information in myeloid diseases as a whole, that there are people who are born with a susceptibility to myeloid diseases and really to blood cancers. So that field is really gaining more and more momentum and we now know that also true of clonal hematopoesis where there are places in our genome in our DNA that are associated with an increased risk for clonal hematopoesis. And then to your question about these technologies that were first used in the laboratory to change
genes like you were referring to

CRISPR editing tools that are now commonly used in experiments.

So these to my knowledge are not part of the kind of first round of intervention so to speak or clinical trials that are planned for clonal hematopoiesis.

But they are being applied in other blood diseases.

And it it is very tantalizing to imagine that at some point they could be applied as a precision tool to fix this acquired genetic abnormality and stop progression to a blood cancer.

When we think about the
preconditions clonal hematopoiesis, one of the nice things that you were mentioning is that trying to think about therapies that are relatively non-toxic that can potentially slow or even prevent progression to fullblown leukemias. Can you talk a little bit about some of the research and work that’s been going on in terms of leukemias themselves? I mean are we making any progress on the research front in terms of more targeted therapies for these kinds of leukemias whether that’s with the precision drugs that you were talking about or
even things like immunotherapies.

So thank you for the question because as I mentioned at the very beginning, this is a time of a lot of optimism in our field for myeloid diseases and for acute leukemias.

Our toolbox has really increased in the last several years and it’s becoming more complex in a good way in terms of decisions as to how to approach the treatment of these conditions. We are seeing improvements and outcomes for patients as a result and that really those gains are on years of research on the
molecular biology of these conditions. And to give an example of something that’s exciting in the other type of acute leukemia and acute lymphoblastic leukemia in a subtype called pH positive BALL, there’s a lot of discussion about the potential of chemotherapy free treatment now and that’s one thing that we’re very excited about is the potential to spare our patients the side effects of traditional chemotherapy. But we’re also very involved as a field and in Yale in testing.
ways to modulate the immune system against myeloid diseases and against acute leukemia in particular. And so that's a cause for a lot of optimism and excitement. Dr. Lourdes Mendez is an assistant professor of medicine and hematology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu, and past editions of the program are available in audio and written form at yalecancercenter.org. We hope you'll join us next week to learn more about the fight against.
cancer here on Connecticut Public Radio.

Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.