Support for Yale Cancer Answers comes from AstraZeneca, providing important treatment options for various types and stages of cancer. More information at astrazeneca-us.com. Welcome to Yale Cancer Answers with your host Doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it’s a conversation about pediatric cancers and lymphoblastic leukemia with doctor Aron Flagg. Doctor Flagg is an assistant professor of Pediatrics in hematology/oncology at the Yale School of Medicine, where doctor Chagpar is a professor of surgical oncology. Aron, maybe we can start off by you telling us a little bit about pediatric cancers in general. Nobody ever likes to think about cancer occurring in kids, but how common are pediatric cancers? Overall pediatric cancers are rare compared to adult cancers. The most common that we see is something
called acute lymphoblastic leukemia or ALL, and we see several 1000 cases of ALL in the United States every year. Beyond that, the next most common types of cancers are brain tumors or brain cancers, of which there are a number of types and following that there are a number of different cancers we can see elsewhere throughout the body. So tell us a little bit more about ALL. How does it present? Because if you’re a parent out there you’re kind of thinking, I never want my kid to get cancer, but Gosh darn it if I ever find a sign or symptom, I want to know what that is so that I can take appropriate next steps. Sure, this can be tough sometimes because a lot of the symptoms are nonspecific, meaning they can happen for a variety of reasons, and many of them are not cancerous. So specifically with ALL or acute lymphoblastic leukemia, many children will be very tired or fatigued.
They may look very pale. They may have bleeding or bruising for no reason, and then many children will also have pain in the bones or the joints, and so a limp is also a common symptom that patients can have. But for other types of cancers that can occur really throughout the body, the symptoms really depend on what type of cancer and where it’s occurring, so it can be very hard to list off one specific symptom that might be a sign of cancer. So from my standpoint, if a parent is worried that something is going on, if symptoms are there and not getting better on their own, they should always talk with the pediatrician. So you know when we think about ALL and the symptoms that you mentioned are really non specific. I mean kids jump around they play, they get tired, they get bruised. They may have some pain. They get pale and a lot of people go into their pediatricians. I think it can be
really tough and from my standpoint when patients finally come to see me they almost always have a diagnosis or they have a lab test that shows something is wrong. And so my job in some ways is simpler because I know there’s a problem. I think it’s much harder for an emergency room doctor or a pediatrician to take a child who’s got these symptoms where 99 out of 100 may be fine and pick out the one in 100 who really does have a severe problem. How do they do that exactly? So through careful history, a physical exam and through taking lab tests to look for things is really the best way to do it. But far and wide, the most important thing is listening to parents and looking at the child. And what exactly are they listening for? And looking for? I think when they’re listening, it’s when symptoms don’t get better. It’s something that’s been there that doesn’t seem just like a virus, which is probably the most common reason for a lot of these complaints young kids will have, and so when that symptom is there over weeks,
and instead of getting better is getting worse. Maybe children are losing weight, maybe they are having fevers for no good reason, and then again on physical exam they may be able to find something that's abnormal that they might have swollen lymph nodes, their liver or spleen might be enlarged. Something that tips them off to something going on that isn't the run of the mill problem. And you mentioned lab tests. What kind of lab tests do they get? This can be difficult because depending on what type of cancer it is, certain lab tests may or may not be a good screening test to use for leukemia. The most common lab test we would look at is a complete blood count where we can look under the microscope with the blood, look at the white blood cells, red blood cells and platelets to see if they are normal and to see if there might be leukemia cells in the blood as well. So for ALL, and we will focus our discussion on ALL because that's
the most common pediatric cancer and the one that you specialize in, what would you see in that complete blood count? So children are often anemic, meaning the red blood cell count is low. And red blood cells give your body the ability to carry oxygen. It makes the blood red and so when children are anemic, they’re often very pale as well. So again, that physical exam might clue us into the low red blood cell count. Platelets are tiny cells in the blood that help to prevent bleeding and to form clots. When you get a cut and when there’s a leukemia present, those platelets often become also very low and so we can see that very easily on a lab test. Finally, will look at the white blood cell count and leukemia cells are an early type of white blood cell, and so for many patients with leukemia, we might see that white blood cell count very elevated because of the leukemia cells in the blood, and if they see this trifecta, they get worried absolutely. And does that cinch the diagnosis of ALL?
Sometimes it does so if we can see circulating leukemia cells in the blood, there’s really nothing else that it could be, but sometimes it’s not so easy. Some kids, when they present, especially early on in the course, may not have leukemia cells in the blood, and so if we’re not able to make the diagnosis directly from a blood count, we might talk about doing a bone marrow biopsy to confirm a diagnosis. And what do you see on the bone marrow biopsy? So all of the blood is made within the bone marrow, and so when a leukemia comes on, it starts in the bone marrow. And when it’s there very early before it’s gotten into the blood, we might be able to see it in the bone marrow. So in a bone marrow biopsy, we place a small needle into one of the bones, usually in the hip bones, they take a sample to look at under the microscope, and then you see leukemia cells and that would be the definitive test.
And then they come to you, correct, with this diagnosis? And then what happens after they get over the shock of, Oh my God, my kid has cancer right? So a lot of that first meeting really is talking about, what is cancer? And where do we go from here? And really trying to get over that initial shock which can take us several days to let everything to sink in and many children, when their leukemias first are diagnosed are quite ill, and so this is usually happening in the hospital where we have time to sit down and talk outside of the constraints of an office visit. So how exactly is this treated? Is it treated through chemotherapy? It’s given in several phases, some of them more intensive, especially at the beginning. Some of them later on in the course are much easier to tolerate the beginning course. We call induction chemotherapy some of that time is spent in the hospital, especially until the leukemia starts to go into remission.
The majority of the rest of therapy is actually given in the office as an outpatient, where patients may have to come once or twice a week for several months in a row to get their therapy, and then it ends with the course of therapy that we call maintenance chemotherapy. Meaning leukemia is in remission, and we’re trying to keep it that way. Maintenance therapy is usually given on a once a month basis. Also in the office, but goes on for many years, usually two to three years from diagnosis. So these children are essentially getting chemotherapy for potentially years? Yes, if it’s a very long road and even in maintenance chemotherapy, or we think about a once a month visit to the oncology office when they’re at home, they’re often still taking chemotherapy by mouth every day or every week. And what are the effects of that? I mean, do they get sick and they still go to school? What happens to their friends and how does this affect their lives? That’s a great question. Many of our patients can lead nearly normal lives going through this.
although every patient is different. There certainly is a risk of infection, especially at the beginning when the chemotherapy is much more intensive. But really after that first month until the leukemia is in remission, after which we really advise children to try to have as normal a life as possible. We encourage kids to go to school. We encourage them to have normal relationships with friends and relatives. We really try to focus on keeping their quality of life as normal as possible. Tell me about the side effects of these chemotherapies because you know, I can imagine if you’re a kid and you’ve lost your hair and your friends are calling you bald and you’re feeling sick, it might be easier said than done to have a normal life. Yeah, absolutely. And we’re fortunate now that many children are able to be cured of their cancer. In fact, most children with ALL are able to be cured and so many years ago, our primary focus was curing the cancer. Now, because of the improvements in the chemotherapy that we can offer,
we can focus on other issues like quality of life, not just being able to get the cancer under control. We do work with psychologists to help with that transition back into normal life. You know, especially in teenagers body image is really important to be able to find ways to get through life. You know that may be different than it was before the chemotherapy in terms of side effects, Some patients may have a lot of nausea there may be infection. Many patients need transfusions because of side effects of chemotherapy. And we’re not also focusing just on the side effects that we see right at the time of chemotherapy. We’re also focusing now on the long term side effects. The late effects that might happen five years down the road, 10 years, 20 years. Whether that’s a problem with hormones affects on the heart or on bone development, really trying to find ways that we can improve upon those late outcomes and really give kids the best possible life after their therapy. So with chemotherapy, you
0:10:37.025 –> 0:10:39.355 tend to lose your hair, and I suppose
0:10:39.355 –> 0:10:41.638 that’s the case with ALL as well.
0:10:41.64 –> 0:10:44.248 But you know, with other kinds of cancer,
0:10:44.25 –> 0:10:46.539 the therapies are much shorter and we
0:10:46.539 –> 0:10:48.81 always tell people don’t worry your hair
0:10:48.81 –> 0:10:50.44 will grow back, but when they’re
0:10:50.44 –> 0:10:52.4 getting years of therapy, I mean,
0:10:52.4 –> 0:10:54.675 do they ever grow their hair back?
0:10:54.68 –> 0:10:57.288 I mean, can they ever truly feel normal?
0:10:57.53 –> 0:10:59.066 Yeah, so the hair loss tends
0:10:59.066 –> 0:11:00.09 to be reasonably temporary,
0:11:00.09 –> 0:11:01.96 again we see it at the early parts of
0:11:02.01 –> 0:11:03.93 therapy with more intensive chemotherapy.
0:11:03.93 –> 0:11:05.21 Fortunately, by the time children
0:11:05.21 –> 0:11:05.978 are on maintenance chemotherapy,
0:11:05.98 –> 0:11:07.793 the low levels of medicines that we’re
0:11:07.793 –> 0:11:09.818 giving do tend to allow hair to regrow,
0:11:09.82 –> 0:11:11.682 and so usually once you’re in that
0:11:11.682 –> 0:11:13.15 maintenance cycle for a few months,
0:11:13.15 –> 0:11:15.19 we start to see the hair come back.
0:11:15.19 –> 0:11:15.702 And interestingly,
0:11:15.702 –> 0:11:17.75 a lot of the times it comes back
0:11:17.75 –> 0:11:18.886 thicker, it’s curly,
0:11:18.886 –> 0:11:20.59 are so often it gives us something
0:11:20.642 –> 0:11:22.35 to talk about in the office in
0:11:22.35 –> 0:11:23.823 terms of comparing what their hair
0:11:23.823 –> 0:11:25.426 was before and what it is now.
0:11:26.13 –> 0:11:28.356 And one of
0:11:28.356 –> 0:11:29.946 the good things, I suppose,
0:11:29.946 –> 0:11:32.49 is that you know kids are living longer.
0:11:32.49 –> 0:11:35.026 Tell us about the prognosis with ALL.
I mean, almost all patients you mentioned are cured. A very good proportion of them are. We are now able to identify for the most part which children are going to be cured by chemotherapy and cured of their ALL early on in their therapy. And then we can also predict which kids may have a harder time to achieve remission. How do we do that? Some of its based on very simple things like age, so we know that older kids, especially adolescents or young adults, have a harder time to be cured than younger kids. That said, very young children, especially less than one year, may also have a problem getting into remission. So we can start with that. We also follow response to therapy, and what most people have been looking at the past few years is something called minimal residual disease or MRD analysis. It’s a way for us, through a bone marrow test, to see how much of a remission somebody gets into, and we know that the deeper a remission the patient enters early on predicts whether
or not they’ll be cured. And so with this information we can tell patients within a few months of their diagnosis whether or not we expect with a good certainty that they’ll be cured, or whether or not we think there may be a challenge for patients who respond quickly who are in a favorable age range. More than 95% of those children can be cured through chemotherapy. For some older children, especially young adults or patients who don’t quickly go into remission, there may be more of a struggle, and sometimes that may be more than 50 or 70% chance. I’d hate to be in that last group where you tell me that there’s going to be a bit of a challenge for me to get a cure. What do you do about that? I would be like, well thank you for telling me that I might struggle, but what are you gonna do about it right now? These are very hard conversations to have and it’s really through research that we’re trying to find better ways, especially in these high risk groups to do better to get them in remission.
So we participate in a large Children’s Hospital Consortium called the children’s oncology group that’s really doing most of the research in the country to look at how we can achieve better outcomes. And that’s using new medications that may work differently than the older types of chemotherapy, or even doing much more aggressive treatment, such as things like bone marrow transplant earlier on.

We're going to pick up the conversation looking at those newer treatments and other treatments right after we take a short break for medical minute.

Please stay tuned to learn more about pediatric cancers and lymphoblastic leukemia with my guest Doctor Aron Flagg. Support for Yale Cancer Answers comes from AstraZeneca, working to eliminate cancer as a cause of death. Learn more at astrazeneca-us.com. This is a medical minute about Melanoma. While Melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. When detected early, Melanoma is easily treated and highly curable. Clinical trials are currently underway to test...
innovative new treatments for Melanoma.
The goal of the specialized programs of research excellence in skin cancer or spore grant is to better understand the biology of skin cancer. With a focus on discovering targets that will lead to improved diagnosis and treatment, 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 Aron Flagg. We’re talking about pediatric cancers, in particular, acute lymphoblastic leukemia, which is the most common cancer affecting children. And right before the break Aron you said that we’ve done really well in terms of treating ALL and for a particular subgroup of patients those who tend to be younger children but not too young who achieve remission with induction chemotherapy that those patients have a reasonably good shot,
95% chance of achieving a cure. But then there’s another group of patients, those who may not respond so well to initial chemotherapy who may be older. who don’t have as good of a shot of cure. And so you started to mention that in that group of patients there are other things besides traditional chemotherapy that you look at. Tell us more about that. Sure, I like to think of chemotherapy as very non specific medicine that attack cells in the body that are growing quickly, like cancer cells. They also cause a lot of side effects, but as we’ve kind of plateaued with how well those medicines work we’re looking for other avenues and so we are now using many drugs called targeted agents, growing quickly, like cancer cells. the cancer cells but really to find specific targets on those cancer cells to hone in on that and make them much more effective than other drugs. We have used methods like pursuing a bone marrow transplant that allows us to give extraordinary doses of chemotherapy and give new bone marrow and then really in the past few years we’ve also used types of
interventions called cellular therapies, so we’re now able to take a patient’s own immune system to engineer cells in a laboratory, put them back in, and allow those cells to attack the cancer itself. And so we have really many new ways to treat these, to provide options for patients who previously didn’t have those.

That sounds really interesting, so let’s take each of those three in turn. Sure, so first, targeted therapies. Yeah, so we know that mutations in the genetic code of these cancer cells is really what turns them from normal cells into cancer cells. Tell us more about that approach in ALL. Yeah, so we know that mutations in the genetic code of these cancer cells is really what turns them from normal cells into cancer cells,
and many of those changes, do have medicines that might affect those and slow down the growth of those cancer cells, so we do have several of those available. In particular, there's a type of ALL called Philadelphia chromosome positive acute lymphoblastic leukemia, where there have been drugs on the market even since the 1990s, that specifically attack that Philadelphia chromosome, and so this was a disease that again 10-20 years ago, we might have recommended everybody have a bone marrow transplant, now most children don’t need a bone marrow transplant because we can give a target before that. In that case, we have targeted agents, do we give that instead of the induction chemotherapy and so on and so forth that you had mentioned before? Because it sounds like if you have a sniper, why use the machine gun, right? So right now these are really adjunctive, we give them in addition to traditional chemotherapy.
It certainly may hit a point though that as these medicines improve or we find different ones that we might not have to give the same traditional chemotherapy anymore. But we’re not there yet.

OK, so if you have a particular kind of ALL that has a particular marker, for example the Philadelphia chromosome positive ALL, then targeted therapy is something that should certainly be part of the regimen absolutely, but then you mentioned the 2nd which was bone marrow transplant and then you had mentioned the bone marrow is really the place where these cells are developed, and so in the factory that’s making all of your red blood cells and white blood cells and platelets and so on. In that bone marrow, that’s where the leukemias developed, and so with bone marrow transplant, you’re really thinking about wiping out that bone marrow, and you mentioned that the purpose of that is to give really high doses of chemotherapy. Tell us more about how that works. So right now when you give regular doses of chemotherapy,
it does attack the leukemia cells, but we can only give so much of it. And when you try to give very high doses of chemotherapy, we see so many side effects, especially to healthy bone marrow cells, that there’s really a limit to how much we can give in the setting of bone marrow transplantation or stem cell transplantation for treating a cancer like leukemia. The idea is that we give astronomically high doses of chemotherapy, sometimes radiation therapy, to try to wipe out not just the leukemia, but we might also remove the healthy bone marrow as well by giving a transplant. It allows us to restore that normal bone marrow function. So two questions, first question, if you’re going to give somebody an astronomical amount of chemotherapy, so much so that is going to wipe out their entire bone marrow, doesn’t that give them a whole lot of side effects like why do that? I mean, unless we know that the response rate is better to that, but we’re using it in people who aren’t responding anyways, right? So the
idea is that for some patients, if they have some resistance to the chemotherapy they’re getting that if we give different types of chemotherapy, and especially very high doses of chemotherapy, that we can hopefully overcome some of that resistance that’s there. But you’re absolutely right, there’s a lot of toxicity to this and one of the key areas of research right now is how can we provide similar rates of response, but without so much toxicity there. There’s definitely favorable studies on the horizon, again, some of this is targeted therapies. There’s even newer chemotherapies that are out there that can still provide we call myeloablation a strong dose of chemotherapy, but without so many side effects to the other organs. Who exactly would need a bone marrow transplant? Because it sounds right now the way you’ve described it, pretty scary. It’s absolutely something that think should be taken with caution. We use bone marrow transplant really for patients who really need it,
so we wouldn’t want to give a transplant to somebody who we think is likely to be cured through traditional chemotherapy. So for a patient with leukemia again, these are patients we anticipate to be at very high risk, maybe their cancer has already come back and we’re trying to cure it for a second time. We can use this also for a lot of other cancers that aren’t just leukemias. Sometimes we use chemotherapy and high dose chemotherapy with a rescue transplant or rescue the bone marrow for other solid tumors. Sometimes for lymphomas or lymph node cancers for a common abdominal tumor, and young children with neuroblastoma we will give chemotherapy as a way to maximize how much treatment we can give them. We also use stem cell transplant for diseases that aren’t cancer. We can use them to treat a variety of blood diseases, especially sickle cell disease or thalassemia. We can also use them to replace an immune system, so for a child that has a severe immunodeficiency,
but you can use this to restore their normal immune function, and then lastly, we can also use transplant as a way to treat certain genetic diseases or metabolic diseases where, say, a patient is missing an enzyme and we can give them a new bone marrow that can then make that enzyme from which they’re deficient so it can be used for a lot of things, but it still has a lot of side effects. And so again we are always very careful to make sure when we recommend a transplant for a patient, that we really think that is the best option compared to what else might be available for them. My second question is, you talk about wiping out the bone marrow, you need bone marrow to survive. because that’s where all of our cells are and the blood cells don’t last forever. So you need a factory continuing to make these blood cells. Where do you get the bone marrow from? So there’s a lot of places we can get it. For some diseases we can actually use the patients own bone marrow,
so again, for certain solid tumors, we might collect their bone marrow, keep it stored, and then after a high dose of chemotherapy, give it back to them to replenish their own healthy bone marrow. But for most patients, when they hear transplant, we’re really talking about somebody who’s donating a bone marrow to that patient, so that could be from a variety of people. Traditionally it’s from a sibling, so a brother or a sister whose immune system is a match to the patient, but we may also use parents. We can now use even more distant relatives, and when those people aren’t available, we can take volunteer donors from an unrelated bone marrow donor registry. And so when you do that, I mean when we think about transplant, you think it has to be a match because otherwise your immune system is going to attack that foreign stuff. Now granted, your immune system is part of your blood cells and you kind of wiped out your bone marrow, but don’t you have the risk of still attacking the new bone marrow?
If it’s not your own right?

So we definitely do need a match, and we match based on the immune system, so it’s not the same as the blood type, which a lot of people think about.

A sibling has about a 25% chance of being a match, and so if you have multiple siblings your chance of one of them being a match continues to go up the more siblings you have, but with even several siblings, many patients still don’t have a donor within the family that’s a good match, and that’s where we go to these unrelated donor registries where right now across the world there are more than 30 million people who have volunteered to potentially donate bone marrow or stem cells to patients who need it.

The most recent advance in the field is that we know parents are 1/2 match, so their immune system will be 50% the same as their children and 10 years ago that wasn’t good enough.

We now have technology that allows us to use a parent or a half match, or we call Haploidentical relative as a bone marrow donor,
and so this has hugely opened up the availability of finding a donor. Now for patients who previously didn’t have a sibling match or didn’t have a registry match, almost everybody has a family member who may be 1/2 identical who get bone marrow transplants. Do they need to be on some sort of immuno suppression for the rest of their life? Like you would be if you had a liver transplant for example? Or kidney transplant? Yeah, that’s a great question. So at least at first we do need to use immune suppression so the donor immune system runs the risk of attacking the patient and we want to quiet that donor immune system down for awhile. The really unique thing about doing a bone marrow or a stem cell transplant is because we’re giving a new immune system, that new immune system overtime actually becomes tolerant to the patient, and so with a liver transplant, patients need to remain on immuno suppression, really lifelong, to quiet the immune system, but with a bone marrow transplant
we really just need it for a brief period of time. So for many patients they are on immune suppression for three to six months after their transplants and most patients are off of immune suppression by one year after. Interesting and then the third bucket of therapies that you mentioned as something that you would consider in people who did not respond or aren’t responding well to chemotherapy, was this whole bucket of therapies you called cellular therapies? Tell us more about that. Cellular therapies are a way to leverage a patient’s immune system to recognize the cancer in their body and attack it. The first licensed cellular therapy was for acute lymphoblastic leukemia. And the way this works is that we can actually collect lymphocytes or the immune system cells from our patient in the laboratory we can teach them to recognize markers on their leukemia and then reinfuse those cells back into the patient to allow their own immune system cells that have been modified to attack their cancer. This has been really an incredible
breakthrough therapy over the past several years in almost 100% of patients who receive this therapy will go into remission within the first 30 days after receiving it. It’s really miraculous.

Wow, so a few questions. First question, when you said you harvest a patient’s lymphocytes, but your leukemia cells are part of your immune system aren’t they?

We’re able to differentiate them in the laboratory, and so really we’re able to isolate mature kind of healthy lymphocytes to be able to reinfuse back. But they made it possible that there may be leukemia cells in these cell therapy products, but the engineered cells can actually still recognize those leukemia cells to attack them, and the engineered cells will continue to attack the cancer cells and everybody gets a response.

So almost everybody responds. One of the big questions is what happens to these patients long term. So there are some patients where these engineered lymphocytes persist long term,
but for many patients the lymphocytes actually disappear over a period of about six months, and so one of the questions is how do we maintain that remission and what do we do after the cell therapy? And for many patients, that might mean still doing a bone marrow transplant once they’re in remission.

doctor Aron Flagg is an assistant professor of Pediatrics and hematology oncology 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 Yalcancercenter.org.

We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut public radio.