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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 Hematologic malignancies with Doctor Francesca Montanari. Doctor Montanari is an assistant professor of clinical medicine and hematology at the Yale School of Medicine, where Doctor Chagpar is a professor of surgical oncology.

Francesca, can we start off by you telling us a little bit about Hematologic malignancies, what they are, how common they are, and how people who have a hematological malignancy can present?

Hematological malignancies include all types of blood cancers. So these are cancers that can affect the bone marrow where the blood cells are made, blood cells, lymph nodes and other parts of the lymphatic system and
Typical hematological malignancies are leukemias, lymphomas, myelomas, and others that are rare, such as myelodysplastic and myeloproliferative disorders. These diseases represent less than 10% of all the cancers. In the United States, there are approximately 1.8 million new cases of cancer per year, and approximately 180,000 cases of blood cancers. So every 3 minutes, one person in the US is diagnosed with one of these diseases.

Approximately half of the blood cancers are lymphomas which account for 86,000 cases per year. They are further divided into Hodgkin and non-Hodgkin, which are the most common and then Hodgkin is classified into over 60 distinct subtypes. Leukemia is approximately 60,000 cases per year and less than 10% are myelomas, so symptoms and manifestation of these diseases can vary. There is a very wide range of symptoms that can be associated.
with any of these blood cancers, which depends on the specific disease and the localization. For instance, lymphoma can present with the so-called constitutional symptoms, which are very specific, fever, chills, night sweats, unintentional weight loss. But there are a lot of other symptoms which depend on the specific localization of the disease. For instance, there are lymphomas that like to affect the gastrointestinal tract, and they cause gastrointestinal disturbances. Other lymphoma can involve the eye or the structures around the eye causing trouble with vision, or they can affect the skin. And as you can imagine, depending upon the organ that is involved, you can have very different symptoms. Leukemia tends to present with symptoms related to the bone marrow involvement and the cytopenias such as fatigue from the anaemia, bleeding from low platelets, infection from low blood white cell count and multiple myeloma also
can present with fatigue from anemia, infection and bone pain. But bone pain is a more distinct sign of a multiple myeloma as it involves the bone structure and can cause pathological fractures. Lethargy and other gastrointestinal symptoms related to the hypercalcemia also can be present at presentation. That seems like just an amazing potpourri of symptoms and sites that these blood cancers can harbor in so how do patients find out that they have one of these hematologic malignancies? It seems like they can be anywhere from your bone marrow to your eyes, to your gastrointestinal tract, and the symptoms can be completely nonspecific, like a little bit of fatigue to having visual loss or gastrointestinal problems. So how is the diagnosis actually made? It depends on the various scenarios. Some of these blood cancers tend to be very slow growing and might be picked up incidentally, just performing some routine blood work by the primary care physician on occasion of the well being visit.
So finding a new presence of increased protein in the blood might raise the suspicion of myeloma and determine additional testing that eventually lead to the diagnosis. In other cases, the symptoms can be more prominent, and therefore as part of the initial investigation by the primary care physician, certain signs and symptoms might be detected that raise a flag for this condition, and further evaluation include imaging studies and more in depth blood work. Eventually, valuation by a blood cancer specialist and so once that happens, once they come to you as a blood cancer specialist, what’s the next thing that happens? So typically we do really need to run a little bit more of a work up, and that includes imaging studies, which can be anything from MRI or CT scan, even a newer form of CAT scan that is called PET Scan where we use glucose to track down in the body where there is an increase in the metabolic activity that may
reveal the presence of a cancer.
And ultimately the diagnosis is made through a pathology, so we would need a tissue sample either from a lymph node or from the bone marrow. Or sometimes a blood sample is sufficient where we do run specific tests to detect these diseases and once we have a pathological confirmation other tests might be warranted depending on the nature of the disease and typically this test helps us with prognostication and with staging. Let’s talk about that. How do we determine prognosis? And in general, what is the prognosis of these hematological malignancies, understanding, however, that this is a varied group of diseases that are lumped into this basket term. Right, so there is a lot of variability in the behavior of these diseases, and as we have improved our knowledge in the biology and mechanism that drives these diseases, we have a very complex way to assess prognosis and prognosis typically depends on very general information such as the burden of
disease at presentation, and the performance status of the patient plays a big role.

The presence of comorbidities or end organ damage from the disease, and then there are other markers that we gather from the pathology evaluation and from the genetic makeup through molecular studies and based on each disease as a specific list of features that we pay attention to when we determine the risk stratification and ultimately based on all this information, we determine what is the best treatment approach.

What is the treatment approach for these cancers in general? The type of approach is very variable.

So first of all, the most important point that I’d like to make is that, as I mentioned, the behavior of blood cancer is very variable. There are blood cancers that are very indolent and slow growing. And we don’t necessarily start treatment upon diagnosis. These diseases are considered generally not curable, but very, very manageable and treatable.
with certain drugs.
And the most important thing upon diagnosis is determining if a patient requires treatment or can be watched. We call that watchful monitoring, and once there is an indication when therapy is warranted, then the decision of which kind of therapy depends on the specific type of disease. The staging of the disease, and the predicted behavior, which is usually based on the genetic makeup of the specific blood cancer. Another important factor that helps the decision about the best strategy is based on patients characteristics such as the age, the performance status, the presence of medical conditions which might have an impact on the tolerability of the treatment and if transplant can be used for that specific patient, as part of the treatment strategy. Another factor that is very important is a patients preference now that we have multiple therapy options which offer similar results.
0:11:39.6 –> 0:11:42.81 in the long term but differ in
0:11:42.81 –> 0:11:44.83 terms of administration
0:11:44.83 –> 0:11:47.07 modality and side effects profile.
0:11:47.07 –> 0:11:49.46 Patient preference might play a
0:11:49.46 –> 0:11:52.21 big role in the final decision.
0:11:55.26 –> 0:11:58.49 During the past year there is another
0:11:58.49 –> 0:12:01.81 factor that has played
0:12:01.81 –> 0:12:05.03 a big role in our decision making,
0:12:05.03 –> 0:12:07.82 which has been the COVID pandemic.
0:12:07.82 –> 0:12:10.89 So having an aggressive blood cancer
0:12:10.89 –> 0:12:13.85 that requires treatment and has not
0:12:13.85 –> 0:12:16.72 had any variation.
0:12:16.72 –> 0:12:18.98 But because of the presence of the COVID pandemic,
0:12:18.98 –> 0:12:21.35 for those diseases that are
0:12:21.35 –> 0:12:23.73 more indolent and not immediately
0:12:23.73 –> 0:12:25.17 life threatening,
0:12:25.17 –> 0:12:28.18 we have been shifted away from
0:12:28.18 –> 0:12:30.91 using certain drugs or certain
0:12:30.91 –> 0:12:34.66 strategies to maintain the disease in
0:12:34.66 –> 0:12:38.06 remission for longer period of time.
0:12:38.06 –> 0:12:40.50 Unless there was an overall survival
0:12:40.50 –> 0:12:43.14 benefit in order to minimize the
0:12:43.14 –> 0:12:45.94 risks of increasing the severity and
0:12:45.94 –> 0:12:48.33 mortality from the infection.
0:12:50.61 –> 0:12:53.79 There’s a few points there that you
0:12:53.79 –> 0:12:56.51 mentioned that I want to pick up
0:12:56.51 –> 0:12:59.79 on and the first is that some of
0:12:59.79 –> 0:13:01.84 these diseases are fairly indolent
0:13:01.84 –> 0:13:04.12 and may not require treatment.
0:13:04.12 –> 0:13:05.81 This kind of expectant
0:13:05.81 –> 0:13:07.08 watchful waiting approach.
How do you determine whether that's the case for patients, particularly when you mentioned that many of these cancers are not curable but they are manageable? And do patients get some anxiety over the idea that they may have a cancer that were simply watching?

It's very important to have that clear communication with the patient that initiating treatment earlier for this kind of cancer does not necessarily translate in a prolongation of their life expectancy and the goal of the treatment in their case is to minimize the toxicity related to the use of certain agents and maximizing the effect in terms of allowing them to live their normal life without having any side effects from either the treatment or the disease.

So important to have good communication.

We're going to learn a lot more about hematological malignancies right after we take a short break for a medical minute. Please stay tuned to learn more with my guest Doctor Francesca Montanari. 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 head and neck cancers, although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancer and their treatment. Clinical trials are currently underway to test innovative new treatments for head and neck cancers, and in many cases less radical surgeries are able to preserve nerves, arteries and muscles in the neck, enabling patients to move, speak, breathe and eat normally after surgery. 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 Francesca Montanari. We’re talking about the care of patients with hematologic malignacies and Francesca right before the break we were talking about the fact that these...
Hematologic malignancies are so varied, varied in terms of where they present, some being in the bone marrow, some being in the lymph nodes, some being organs like eyes and GI track and bone and other places, they are varied in terms of their clinical presentation and the symptoms that they cause. In terms of their clinical course, some being very indolent and slow growing such that they wouldn’t even warrant necessarily treatment and others being far more aggressive. Can you tell us a little bit more about the cancers, specifically what you treat? Is there a certain type of hematologic malignancies that you specialize in? My research interest has always been on the lymphoma side. They are approximately half of all the blood cancers, but they are very diverse themselves. They are half of all the blood cancers, and we do typically divide them into big categories.
Hodgkin and non Hodgkin, and then furthermore into aggressive and indolent in the non Hodgkin lymphoma type and so the focus of my research has been in trying to better understand the biology of the rare of these lymphoma types. And based on the insights in the biology to develop new treatment strategies that are targeted for these less known subtypes. In particular, the focus of my research over the past decade or so has been on posttransplant lymphoproliferative disorders, which are a rare lymphomas that arise as potentially life threatening complication of solid organ transplant. These are lymphomas that arise in the setting of reactivation of infection due to the immunosuppressive treatment or due to the chronic dysregulation of the immune system in the setting of chronic immunosuppression, and historically, the prognosis of these lymphomas have been very poor because of inability to deliver full dose treatment. And due to the frailty and risk of infectious complication.
that this patients experience with a regular conventional chemotherapy, the risk of dying of infection during treatment in this population has been estimated around 30%, which is extraordinarily high and in order to try to minimize the complication from the treatment, I developed the risk stratified treatment adapted strategies which are based essentially on induction phase where we do not use cytotoxic chemotherapy but more a targeted antibody approach. And then we do reserve escalation to chemotherapy only to patients that do not achieve a full response on the least invasive treatment. And with these strategies we have been able to limit the use of cytotoxic agent to less than half of the patient population that we do treat. Another area where I’ve been conducting research is in T cell lymphoma. Those are also very rare lymphomas. They are much rarer than the B cell lymphoma which are the most common non Hodgkin lymphoma out there
and unfortunately historically we have been using a treatment that has been extrapolated from the B cell counterparts, so not really specific to these subtypes of lymphomas and the results are not as optimal as in the B cell counterpart’s.

Over the past few years, 4 new drugs have been approved in the space for this, specifically for T cell lymphoma and one of the challenges that we have now are trying to identify what is the best sequencing of this agent and what is the best way to combine them to improve the outcome of patients with additional malignancies. It sounds like in both of those scenarios the overarching theme is really personalizing treatment to the patients individual disease, so I wanted to just take a step back and talk a little bit more about the intricacies of each of these.

With regards to the post transplant lymphoma, help us to understand again how these lymphomas occur, ’cause certainly there are listeners who may have gone through a solid organ
transplant or may know someone who has and
these patients are on immunosuppressives.
So does that immunosuppressive therapy automatically increase their risk of lymphoma?
And is there anything that they can do to reduce their risk of developing lymphoma in that setting?
That’s a really good question,
so we do after the transplant patient received different immunosuppressive treatment which are related to the different kind of transplant that they have received.
For transplant, such as intestinal transplant,
immunosuppressive treatment is much tougher and much deeper than a patient that receives renal transplant where immunosuppresant treatment required for the recipient to accept the graft is much less.
And the reason we do see as a consequence of the immune suppression reactivation of common infection, and most important, is the Epstein Barr virus, which is the virus that causes mononucleosis. Most of the adult population has been exposed by adulthood to the virus, and the virus is dormant in a silent state in our body,
and is kept at bay by our immune system. So conditions such as immunosupression where our immune system defenses are lowered allow the virus to thrive again and replicate and this particular kind of virus, in the absence of an immune system that fights it and keeps it at bay, is able to transform the blood cells into lymphoma cells so typically in the first year after the transplant, most of the lymphoma that we do see are related to Epstein Barr. The lymphoma that arise after one year still can be linked to the Epstein Barr virus, but approximately half of them happen without a reactivation of Epstein virus, and they do not hardwire the genetic material of the virus and are thought to arise in the setting of a chronic immune dysregulation due to the longstanding immunosuppression. Is there anything that people can do to limit that reactivation of Epstein Barr virus? You mentioned that most adults have already experienced Epstein Barr virus,
and so should have some degree of natural immunity to the virus, although they’re on immunosuppressants. So has anybody looked at ways that people who are on immunosuppresants can prevent that reactivation? That is a really good question, and indeed, a part of these strategies in the period after transplant include close monitoring of the EBV presence in the blood. So after a solid organ transplant, depending on the kind of solid organ transplant there are algorithms and there is a monitoring of the EBV which is done in certain cases twice a month. Other cases once a month, depending on the nature of the immunosuppression and preemptive strategies to intervene. Treating the EBV before the lymphoma appears has been attempted, but the results are not optimal because there is a lot of variation in the levels of EBV that is noted in patients post transplant and not everybody that experience a reactivation of the virus end up developing a
lymphoma and therefore there is not good guidance out there regarding who to treat preemptively and who to observe.

When I was at Columbia University prior to joining the group here at Yale I was leading the effort to come up with guidelines to help clinicians in the solid organ transplant team to troubleshoot these problems, meaning want to check the EBV at what intervals and what is the threshold of the virus to consider potentially leading to a lymphoma and when to utilize treatment to reduce that virus level and it is still a discussion and a work in progress.

And do we know what factors kind of trigger that EBV to turn into a lymphoma?

Because potentially that’s another place to intervene in thinking about is there a way to potentially mitigate that transformation.

That is an excellent question, and unfortunately the reason why EBV can turn in vitro into malignant cells is because one side triggers the proliferation of these cells and
the other side blocks an important mechanism that is called apoptosis, by which the cells die but alone is not able to induce lymphoma in vivo. And the thought is that there are, like in all the other kinds of cancer, a multi step process where the cells progressively gain additional mutation and overtime the addition of this mutation together sort of cause the transformation into cancer, but we are not able in 2021 to predict which mutation and when these mutations are acquired. Doctor Francesca Montanari is assistant professor of clinical 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.