Hello. My name is Tapan Kadia. I'm an assistant professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston. And today, we're going to be talking about hematologic malignancies. In this first module, we'll discuss not only normal hematopoiesis in the normal hematologic system, but we'll also briefly go over leukemias and myelodysplastic syndrome as the first two malignancies as --- as part of the hematologic malignancies.

As part of this particular module, we'd like participants to be able to discuss the normal hematologic systems; how blood is produced with the normal components of blood; as well as the common signs and symptoms of hematologic malignancies. We'd also like to --- the participants to be able to discuss general concepts on how to initially diagnosis and stage leukemias and myelodysplastic syndromes, lymphomas, and multiple myeloma. As I described in this first module, we'd be going through the leukemias and the myelodysplastic syndrome.

So just to begin this module we're going to review the normal hematologic system or normal hematopoiesis which means the development of blood within the bone marrow. And then we'll discuss the presentation and diagnosis and staging for the most common leukemias including acute myelogenous leukemia also referred as AML, acute lymphoblastic leukemia also known as ALL, chronic myelogenous leukemia or CML, and chronic lymphocytic leukemia or CLL. At the end we'll also talk about myelodysplastic syndrome which is a very common disorder of the bone marrow and has sometimes been called pre-leukemia and we'll dis dis --- distinguish this from acute myeloid leukemia and how one can transform into the other.

So first we'll start very simply with blood. What is blood? So blood is a mixture of plasma and cells. Plasma can be thought of as a proteinaceous fluid or liquid. It's a medium where the cells, which we'll describe in a minute, sort of float around in your body and tr --- and deliver not only nutrients, but also oxygen and carbon dioxide. So blood cells which are an important component of the blood are made in the bone marrow which is essentially a factory for all of your blood cells. The three general major types of blood cells in your --- that make up your blood are white blood cells, red blood cells, and platelets.

So first we'll talk about red blood cells. So red blood cells are what give your blood the red color that you see. They're packed with a molecule called hemoglobin, which is structurally designed by nature to carry oxygen and also carry carbon dioxide. And so the function of the red blood cells is to transmit or transport oxygen from your lungs to the rest of your body and your organs and to transmit car --- carbon dioxide from your organs back to the lungs so you can breathe them out. So red blood cells are very important in in --- in carrying oxygen and carbon dioxide between your lungs and the rest of your body and, therefore, allow these organs to function appropriately in the environment.
The next cells are platelets, which theoretically are not actually cells, but are pieces of a larger cell called a megakaryocyte. A megakaryocyte can be thought of as a platelet factory. It’s a large cell that’s in the bone marrow and pieces of the megakaryocyte break off and these pieces become platelets. Platelets are very important in providing hemostasis and preventing bleeding. So when people develop cuts or --- or--- or --- get injuries the platelets go there and they stop the bleeding or they p --- initiate the process of hemostasis or the slowing down of b --- bleeding. The platelets are kept at a standard range by the body’s hormones and bone marrow throughout life to prevent bleeding, bruising, and other complications.

White blood cells are the cells in your body that are specialized to fight infections, to cause inflammation, and also to surveil against other types of cancer. There are many different types of white blood cells and those are listed here. So the types of white cells are neutrophils, lymphocytes, eosinophils, monocytes, and basophils. These cells were initially described by their appearance under a microscope. And we now know that many of these cells have different specific functions that are important for the human body, important in fighting infection, causing inflammation, allergic reactions, and even cancer surveillance.

So the first type of cell --- white cell that we’ll talk about is a neutrophil. Neutrophils are also known as granulocytes or segs (that's short for segmented neutrophils), also known as PMNs or polymorphonuclear neutrophils which is the same or most simply polys. You will hear many of these words used to be --- to describe the word neutrophil. Neutrophils are the first line of defense against infection. They fight common bacterial infections most commonly, by phagocytosis. And essentially all that means is that the neutrophil eats up or swallows offending bacteria or pathogens that are within the tissues of our body. It can also elaborate toxic oxygen and metabolites. And what that means is that it produces species, such as hydrogen peroxide or oxygen free radicals to kill bacteria, fungi, viruses, and other things that are causing problems in our body. It all --- The neutrophils also produce enzymes within themselves or act --- antibacterial enzymes which can also degrade bacteria. Neutrophils are known as the first line of defense because they’re usually the first to appear at the sites of inflammation or infection. It’s important to remember that white cells not only occur --- neutrophils not only present themselves in infectious problems but also can occur in places of inflammation such as gout or other arthritis which involve inflammation. Neutrophils are taught to be nonspecific. They can attack almost any pathogen and most target antigens, need to be coated with specialized proteins within our blood called antibodies or complement to help direct neutrophils for more efficient killing.

The next type of white cell is a lymphocyte. Lymphocytes as opposed to neutrophils are very specific and more targeted in their approach. So where neutrophils would be the first line of defense against many of our infections lymphocytes come in a little bit later and they’re usually targeted to specific antigens with or --- or antibodies that been coated on these --- on these pathogens. There are two major types of lymphocytes. We'll call them T-cells or T-lymphocytes and B lymphocytes. Natural killer cells are another component that may be considered lymphocytes, but they are very specialized
and attack in a special way. The T-cells can be subdivided into CD4 or T-helper lymphocytes and CD8 or cytotoxic T-lymphocytes. These are involved in cell-mediated immunity meaning that the T-cells actually look out for specific antibody-coated pathogens. They go after the cells in a very specific manner and kill the cells by cell-to-cell contact. So they can actually release enzymes which can make holes in the target cell. And T-cells are also important in surveilling for cancer cells or pre-cancerous cells to do what’s called immuno --- immunosurveillance to prevent the progression of cancer. T-cells can also release certain hormones called cytokines which allow other immune cells to come to their location of infection to help kill the infection. The second type of lymphocyte is a B-lymphocyte. B-lymphocytes produce antibodies and are often known to be associated with what’s called the humoral immune system. As I mentioned previously, antibodies are specialized proteins that specifically target different antigens or different tags on bacteria and viruses. Once these proteins stick to these tags or antigens the T-cells and other immune cells are directed towards it. So B-cells almost work as --- by tagging the bad pathogens and then allowing the rest of the immune system to see them and attack them. B-cells are also important in what’s called immune memory. So when patients --- people who have been either infected with a pathogen in the past or people who receive vaccines for things like measles, mumps, and rubella, the B-cells produce antibodies against these antigens. And then the B-cells remain with you for the rest of your life and produce antibodies whenever you should encounter the same pathogen again. So as a result, people who have chicken pox once don’t get it again, because these B cells have produced cells which produce antibodies against these pathogens and they remain with you lifelong to give you immunity. And as the last lymphocyte type cell, we’ll talk about natural killer cells which are a specialized group of cells which kill and --- cells that are infected with viruses and kill cancer cells and are often important in the immune surveillance as I described previously.

Monocytes and macrophages are related cells. They play a role in killing yeast, fungi, and unusual bacteria, such as listeria, which can be intracellular or inside a cell. They can also make things --- something called a granulomatous reaction in diseases such as tuberculosis. And what a granulomatous reaction essentially means is that the macrocytes and the mon --- the monocytes and the macrophages form a wall around the pathogen and wall it off from the rest of the body so as to prevent it from progressing or causing any problems. People who have been infected with tuberculosis or other diseases that cause granulomas are often found to have granulomas for many, many years after their diagnosis because these --- these granulomas persist and keep the organism walled off from the rest of the body. Macrophages are essentially monocytes that are in the tissue. And they do the same job as monocytes do in the blood where the phagocytosis and they form granulomatous reactions.

The next cell we’re going to talk about is eosinophils. Okay, so eosinophils are called eosinophils because underneath the microscope their com --- cytoplasm is composed of red granules often called eosinophilic granules. The eosinophils are a very specialized type of white cell and they are very involved in allergic reactions. So when people have allergic reactions to either drugs or even from the air like allergic rhinitis, the eosinophils
go up and --- and --- and respond to this. Eosinophils are also responsible for immune reaction to certain parasites, such as roundworms, that are often encountered outside the United States in underdeveloped nations.

The next type of cell is called a basophil. And the basophils were named this way because of the basophilic granules which are present in the cytoplasm and basophilic granules are essentially dark blue or even purplish. And the basophils are another type of specialized cell which are also involved in the allergic response as well as parasitic response. And they're often also seen sometimes in malignant conditions such as CML, which we'll describe a little bit later. They also work by releasing their granules into the bloodstream or against pathogens and these chemical mediators can either disrupt the pathogens or kill them outright.

So the next --- let's touch base a little bit on the lymphatic system. So if you'll remember, lymphocytes are one of the type of white cells that we previously described that is produced through the bone marrow and is one of your white blood cells. The lymphocytes not only reside and mature in the bone marrow, but also reside in many different organs throughout the body called lymphoid organs which are listed here. So first the bone marrow is where the lymphocytes are produced and where they can mature. The thymus is an organ where the T --- T-lymphocytes specifically migrate to and they can mature. Lymph nodes are specialized sites throughout our body where the lymphocytes reside and can react to different pathogens. The spleen is an organ in the left side of our abdomen which --- where lymphocytes can reside and also act as sentinels to evaluate and --- and screen the bloodstream for any pathogens. The tonsils are specialized lymph nodes that are present in the oropharynx. And the lymphocytes can also reside in special patches or areas in the digestive system, as well as in the respiratory system. Now, in these different lymphoid organs, the lymphocytes act in their duty to surveil --- for surveillance, to look for new pathogens, to react to these pathogens, to multiply in --- in response to these pathogens, and to eventually eradicate these pathogens. There is also a system of lymphocyte circulation that is not our bloodstream, but is similar to our bloodstream where as a system of tubes called the lymphatic circulation which transmits the lymphocytes and transports them from one lymphoid organ to another.

Next, we'll go on to cytopenia. So what is cytopenia? The word cytopenia essentially means low cell count. And cytopenias are important not only in the diagnosis of --- of leukemias, but also in the diagnosis of other diseases, such as myelodysplastic syndrome and aplastic anemia. So just to define some terms: Leukopenia means low white blood cell count. And leukopenia can predispose patients to infections by opportunistic organisms as well as common every day pathogens. It logically makes sense that if your immune system, which is composed of your white cells, are low, you'll be more at risk for infections. These infections can be frequent. And they can be severe because there's nothing to defend your body against these pathogens. Anemia is a cytopenia of low red cells. So if you remember what we talked about with the whit --- red blood cells, as you become more anemic you have less oxygen-carrying capacity, so people get shortness of breath. They get fatigue. And in older folks who already
have cardiovascular disease, they get cardiovascular complications. Finally, there’s thrombocytopenia. It’s a big word, but all it means is that you have low platelets. And if you remember the function of platelets meaning to stopping of --- of bleeding and bruising, if you have low platelets, you’ll have a high risk of bruising and a high risk of bleeding and sometimes spontaneously. So it’s very important for people to watch out when they have low platelets and see --- see if they need a platelet transfusion to prevent this particular complication.

How do you evaluate a cytopenia or when someone comes to the doctor and they have low blood counts, how does one work it up a little bit further? First thing to do is a peripheral blood smear where you take a drop of the blood, you smear it on a mi – on a slide and look at it under the microscope. And that can tell you a lot of information about why the blood cells are low. There also may be a role to do a bone marrow aspiration or a bone marrow biopsy. Essentially all this is is taking a piece of the bone marrow, which is where the blood cells are produced, to understand why the blood cells are low. Now the blood cells can be low or you can have cytopenias for essentially two basic big reasons. Number one, you are not producing enough blood, also called underproduction or you’re producing plenty of blood, but someplace in your body the blood is being destroyed and that’s called destruction. So first we’ll go over underproduction. So underproduction usually involves some problem in the bone marrow. You can have a disease of the bone marrow, such as myelodysplastic syndrome, aplastic anemia where there is a complete absence of bone marrow, or infiltration of the bone marrow with some other disease, such as other cancers or myelofibrosis or even lymphoma. Additionally, you can also have a viral infection that can infect your bone marrow and kill off the bone marrow producing cells also leading to underproduction and low blood counts. Finally, the most common cause of cytopenias that often needs to be worked up and ruled out is vitamin deficiencies. Just like any other factory needs raw material, your bone marrow needs the raw material of vitamins, such as iron, folate, and vitamin B₁₂ to make blood cells. And if you’re deficient in any of these vitamins, you do get cytopenias or low blood counts because your bone marrow doesn’t have the raw materials to make the blood.

As opposed to underproduction, the other cause of cytopenias is peripheral consumption or destruction. So as I said, your bone marrow is functioning fine. So if you were to do a bone marrow biopsy you might see a normal bone marrow producing normal blood or even producing more than what’s necessary blood, because the blood is being produced. But it’s being destroyed somewhere else. And so the causes of this are autoimmune destruction where the body’s immune system for some reason is killing off the blood cells, sequestration meaning that the blood is hiding in in --- in an enlarged organ usually a liver or a spleen. Something called DIC or disseminated intravascular coagulation where your blood is clotting more than it should and, therefore, using up many of the blood cells. Or something called a mechanical destruction. And this usually happens in people who have artificial valves, such as an aortic heart valve or a mitral valve where the blood is going through this artificial, often mechanical, metal valve and the blood is essentially getting crushed or destroyed as it goes through there. So this are some causes of cytopenias and this can be worked up by looking at a
peripheral blood smear as well as bone marrow biopsy as well as looking at vitamin deficiencies and other causes.

This diagram is going to take us into our next section which is going to be looking into the malignancies or the cancers that are derived from the blood, such as leukemias and myelodysplastic syndrome. So this is a very basic diagram that gives you a sort of family tree of where the blood cells come from. So in the beginning there are stem cells, which are pluripotent. All that means is that the stem cells can become any different type of cell in your body or in this case, a hematopoietic stem cell can become any different type of blood cell. The stem cell then differentiates into either a myeloid progenitor cell or a lymphoid progenitor cell. And from the myeloid progenitor cell you make red cells, you can granulocytes or neutrophils, and you can make monocytes or macrophages. On the other hand, the stem cell can also differentiate into a lymphoid progenitor and the lymphoid progenitor, as the name suggests, can make T-lymphocytes and B-lymphocytes. And so this is sort of a very simple family tree that allows us to differentiate between myeloid and lymphoid. And so when we talk about the leukemias you can see why they are a little bit different.

So leukemia is a group of neoplastic diseases characterized by abnormal proliferation of white blood cells. They are cancers of the white blood cells.

There are several common or general types of leukemias. We’ll call them acute leukemias which are characterized by the proliferation of immature precursors in the blood and the bone marrow. Chronic leukemias which are characterized by proliferation of mature precursors, myeloid leukemias which are derived from the myeloid series which we just talked about, and lymphoid leukemias which are characterized by cells with lymphoid --- from the lymphoid series like we just described. Acute leukemias tend to be very aggressive, very fast-moving, and not subtle. Whereas chronic leukemias are sometimes diagnosed by chance and they are very slow --- slow-moving, but still need to be treated.

So we’ll go into now the types of leukemia.

Four major types. We talked about ALL, AML, CML, and CLL. And we’ll go through each of these in a little bit of detail.

So the symptoms of leukemia in general are listed here. Usually the symptoms are very nonspecific. People often present complaining of just feeling bad, malaise, fatigue, fever. Blood count may show anemia or low red cell count. People may have bone pain in acute leukemias because the leukemia is dividing so fast within the bone marrow that it stretches the bone and causes pain. People may present with flu-like systems like say, “Hey doc I just --- I’m not getting over this fever and feeling bad.” They may present with infections over and over again which is not typical for a person and they may present with bleeding because their platelets may be low. And these are mostly signs of an acute leukemia which is usually not a subtle presentation. It comes on pretty quickly and people are pretty sick. This is opposed to chronic leukemia patients
where they often come in with a little bit of fatigue, maybe a little weight loss, maybe their spleen is enlarged because they may be infiltrated with leukemia. They may have enlarged lymph nodes or in many cases the patient may be incident ---may be asymptomatic and the CLL or the CML may be --- may be found in an incidental finding on a routine blood test in an annual physical. So this is how the acute leukemia and chronic leukemia presentations differ slightly.

So the diagnosis of leukemia can be performed by several interventions. First, the peripheral blood will show an elevated white blood cell count. Since leukemia by definition is a cancer of the white blood cells, we often see elevated white cells. And they can be mature white cells in the case of chronic leukemias or immature forms in the case of acute leukemias. You’ll also see cytopenias. Because the leukemia starts in the bone marrow and often replaces the normal bone marrow with an aggressive infiltrate of --- of cancer cells, the bone marrow will not be able to produce the normal red cells and platelets and so you often see anemia and thrombocytopenia. The diagnosis is confirmed not only by a peripheral blood smear, but also by performing a bone marrow aspiration or biopsy since that’s where the leukemia usually starts. In the bone marrow you may see the normal hematopoiesis has been replaced by a monotonous infiltrate of immature blasts in the case of acute leukemias or mature white cells in the case of chronic leukemias or sometimes a mixture where you see a --- a ---a --- leukemia in transformation. You may see some chronic forms and some immature forms.

So the first leukemia we’re going to talk about is acute lymphocytic leukemia often also called acute lymphoblastic leukemia or ALL. Patients often present with sign and symptoms of pancytopenia so they may come with infections. And they come with fatigue. And they may come with bleeding complications. They may have bone pain because I me --- as I mentioned previously, a rapidly growing leukemia within the bone marrow can stretch the bone and cause bone pain. Unlike acute myeloid leukemia which we’ll discuss in a little while, acute lymphoid leukemia is commonly seen to have organomegalic or big organs. And this is because, if you remember, many of the lymphoid organs, such as the lymph nodes, the spleen, and the bone marrow contain lymphocytes and many of the lymphoblasts which are the cells in ALL can populate the liver, the spleen, and the lymph nodes and make them enlarged and causing pain and discomfort in patients. Patients with ALL especially T-cell ALL can develop something called SVC syndrome. And what this means is that the superior vena cava, which is SVC, is often surrounded by enlarged lymph nodes from infiltration by the leukemia. This causes an obstruction in the superior vena cava and causes swelling in the patient’s face. Another unique finding to ALL is that patients can present with neurologic symptoms. ALL unlike AML commonly can go to the central nervous system including the brain and the spinal cord. And sometimes patients present with either headaches or other neurologic symptoms that sometimes look like a stroke. And the way to diagnose this is to do a spinal tap to find these cells in the cerebrospinal fluid or this fluid that surrounds your brain and spine. As I mentioned previously, you may see leukocytosis, which is an elevated white blood cell count, but you may not see leukostasis. Leukostasis essentially means that the white cells get so high that they
Leukostasis can be seen in myeloid diseases, but much less common in lymphoid diseases such as ALL. You may also see metabolic abnormalities or tumorlisis syndrome. And what this means is that as the leukemia cells are growing they are also dying at a rapid rate. As these cells die at a rapid rate, they release certain chemicals or electrolytes into the bloodstream at a rate that your kidneys cannot compensate for. And so sometimes people get elevated potassium, elevated phosphorus, and elevated uric acid which can cause heart arrhythmias and other problems, such as kidney damage.

Acute lymphoblastic leukemia is often a disease of children, but it can also be a disease of adults. In children, we have come a long way and are now able to cure over 90% of patients with acute lymphoblastic leukemia. We’re not so lucky in adults and we’re still working on better therapies and better treatments for adults to achieve that rate of cure. One way of determining prognosis in ALL is not only by age, but by looking at the chromosomes in the leukemia cells of these patients. We often see repeated chromosome abnormalities. And over the past 30-40 years, we’ve realized that certain chromosome abnormalities portend a more favorable prognosis and certain chromosome abnormalities suggest a more adverse or aggressive prognosis. So the three chromosome abnormalities listed here are just three of the many abnormalities that we usually look for in acute lymphoblastic leukemia. The Philadelphia chromosome, which we’ll talk about a little bit later in more detail, is essentially a chromosome abnormality where the 9 --- a piece of the 9th chromosome is attached to a piece of the 22nd chromosome, also called translocation 9;22. You’ll see that it carries a more adverse prognosis and it’s more common in adults and less common in the pediatric population. Hyperdiploid chromosomes or having more than 50 chromosomes, you’ll remember 46 chromosomes is normal, but having a hyperdiploid chromosome is suggested to be a more favorable karyotype and once again is seen more commonly in pediatrics and less commonly in adults. Finally, a translocation of 12 and 21 where part of the 12th chromosome is attached to part of the 21st chromosome is also considered a favorable prognosis and more often seen in kids rather than in adults.

The next leukemia we’ll talk about is acute myelogenous leukemia or AML. Again, you have rapidly worsening clinical symptoms. The bone marrow will show 20% blasts or more of which 3% or more have myeloperoxidase positivity. It’s one of the ways you distinguished AML from ALL. Again, these patients will present with complications of pancytopenia or low blood counts. So fatigue, exercise intolerance, being pale, feeling weak. They may have bleeding or bruising or even DIC or disseminated intravascular coagulation where their body --- their blood is clotting and --- and bleeding without control. And finally, they may present with infections, fatigue, fever, and neutropenia. They may also have bone pain and they also may have a high white cell count or leukocytosis. And unlike ALL patients with AML can have leukostasis if the white blood cell count is too high. Leukostasis can present as I mentioned previously with stroke-like symptoms, with severe shortness of breath, with confusion, or even kidney damage. This is why AML especially with a high white cell count is a medical emergency and should be treated by pat --- by doctors who are experienced in this disease. Rarely
AML can also present as something called a myeloid sarcoma. And what this essentially means is the AML instead of presenting as a liquid tumor, where it’s floating around in the bloodstream, can actually present as a mass, as an actual tumor in any part of the body, be it the skin, the GI tract, and sometimes even in the central nervous system.

Similar to ALL prognosis and AML is determined by age, the older you are the tougher the prognosis, as well as cytogenetics or chromosomes. We have been able to look at all the chromosome abnormalities of patients over the past 30 to 40 years. And we have divided them into three categories, what we call favorable karyotype, intermediate karyotype, and unfavorable karyotype. Just to briefly mention, there are three favorable karyotypes: translocation 8;21, inversion 16, and translocation 15;17.

To illustrate the prognostic significance of these different cytogenetic abnormalities we’ve put this chart here. This is called a Kaplan-Meier curve. And essentially what it does is it allows us to quickly look at the different categories and you’ll see on the right side favorable, intermediate, and adverse and determine their prognostic significance. So this chart depicts the overall survival of these three groups. The Y-axis depicts the percentage of patients and the X-axis depicts the time. And so you’ll see people with adverse prognosis acute myeloid leukemia by cytogenetics have a median duration of complete remission of only three to six months. Whereas those people with favorable leukemia have a median duration of remission of up --- up to two years and about half of those people can be cured. And so cytogenetics are very powerful and important and one of the primary tests that we need to check when we are diagnosing acute leukemias.

Chronic myeloid leukemias put us into the first of the chronic leukemias. Unlike acute leukemias, chronic leukemias can present as a more slow and indolent course. It’s a rare disease and its peak incidence is around age 40. CML is characterized by, again, elevated white blood cells mostly with mature neutrophils unlike the acute leukemias. You may have an elevated platelet count and not cytopenias as you may see in the acute leukemias. You may have splenomegaly and you will always have Philadelphia chromosome positivity. If you recall Philadelphia chromosome is the translocation between 9;22. And in the case of CML, it defines this disease. A patient with a myeloid disease with translocation 9;22 is known to have CML. There are different phases of CML. What’s called chronic phase which is the earliest phase which is very chronic and slow-growing. Accelerated phase which is a little bit more advanced, and finally, blastic phase which essentially is indistinguishable from an acute leukemia and is very aggressive and --- and difficult to treat.

This picture depicts what a chromosome karyotype looks like. So as I mentioned previously, we all have 23 pairs of chromosomes or 46 chromosomes. What you can see here is that part of the 22nd chromosome has been stuck onto the 9th chromosome and so this is known as translocation 9;22 which is t(9;22). And this is considered the Philadelphia chromosome and this is a hallmark for CML. But can also be seen in Philadelphia positive ALL which I mentioned previously.
So this is the hallmark of the disease. The translocation leads to the fusion of two genes, one gene located at chromosome 9 and one gene located at chromosome 22. This gives you the bcr-abl fusion gene. The reason why this is so important, how this has revolutionized the treatment of cancer is that people have developed specific targeted therapy that can block the bcr-abl gene product. So bcr-abl is a protein that signals the cell to divide and people have developed tyrosine kinase inhibitors, such as glevec or disatinib or nilotinib, which are drugs that target this protein and shut off the fusion protein and, therefore, treat the disease. These drugs unfortunately are not curable. But they have completely revolutionized the treatment of the disease and allowed people to live normal lifespans and normal lives.

Next, we’re going to talk about chronic lymphocytic leukemia or CLL. This is the most common leukemia in the western world and is often found just by chance in a doctor’s office when you present for a routine physical. The first thing you’ll see is an elevated white blood cell count and the preponderance of them will be lymphocytes, not myeloid cells but lymphocytes. The staging system of CLL is listed here. The most common staging system used in the U.S. is the Rai staging system and it’s very simple. It can be done by a physical exam and a quick CBC blood test. Rai stage 0 has an elevated lymphocyte count only. Rai stage 1 are patients who have lymphadenopathy or enlarged lymph nodes. Rai stage 2 is patients who have any evidence of splenomegaly or enlarged liver which is called hepatosplenomegaly. Rai stage 3 is any patient who has any anemia. And Rai stage 4 is a patient who has thrombocytopenia. Much like the other leukemias cytogenetics or chromosomes are also predictive of the prognosis in this disease.

Finally, I’ll touch upon myelodysplastic syndromes. Although not considered typically an acute leukemia, it’s often thought of as a pre-leukemia. It is a heterogenous group of malignant clonal stem cell disorders characterized by ineffective and disordered hematopoiesis and usually results in low blood counts. And so in the bone marrow what you’ll see is a very hypercellular bone marrow with lots of immature forms trying to mature into normal blood cells, but they cannot because of some defect. Over time, the myelodysplastic syndrome can progress to acute myeloid leukemia. By definition, if the percentage of blasts in the bone marrow reaches 20% or higher that disease is called acute myeloid leukemia, whereas if it’s under 20% and there is evidence of dysplastic changes that’s called myelodysplastic syndrome.

The clinical presentation of MDS most of our patients are above the age of 70—about half the patients above the age of 70, male and female preponderance is about equal, half of the patients come without any symptoms but just have low blood counts. The most common symptoms that do occur are due to anemia or low red cell count and they’ll come on with fatigue, transfusion requirement, shortness of breath, or even chest pain if they have cardiovascular disease. Usually you don’t really find many physical exam findings. You may notice some tachycardia or rapid heartbeat if their red cells are low or you may notice some bruising if their platelets are low.
Splenomegaly is found very uncommonly in about less than 20% of patients and some people may present with fever if they have had infections because of low blood counts.

The way you evaluate MDS, you do a normal CBC which will give you the tip-off of whether there’s low red cell count, low white cell count, low platelets or all three. But then you follow this up with a bone marrow and you’ll see a hypercellular bone marrow. Rarely you may see a hypocellular bone marrow which is called hypocellular MDS. About half the patients have chr --- chromosome abnormalities. And there is dysplasia or the cells essentially look funny under the microscope in one or more of the cell lines. And there are abnormal cytogenetics in 40 to 70% of the patients.

MDS has gone through multiple classification systems because of its difficulty in diagnosis and determining its prognosis. Some of the earlier ones are listed here. This is the FAB classification where it looked at something called refractory anemia, refractory anemia with a ringed sideroblast, refractory anemia with excess blasts, and refractory anemia with excess blasts and transformation. I won’t go into too much detail on these, but there a the --- the --- the way to diagnose these is listed in the subsequent columns looking at bone marrow blasts, peripheral blasts, and ringed sideroblasts. Why these are important is that each different category of the myelodysplastic syndrome by the FEA --- FAB gave us a prognostic significance of median overall survival as well as the risk of transforming into acute myeloid leukemia.

Now in modern times this has been mostly replaced by the WHO classification of myelodysplastic syndrome and this uses our updated knowledge in the chromosome abnormalities in MDS as well as some of the underlying molecular abnormalities of MDS. So you’ll see that the different categories are listed here and the abbreviations are also listed. Again, I won’t go into too many details, but this can be reviewed.

And we’ll end here, the first module of the hematologic malignancies section of the learning. As a summary, patients with acute and chronic leukemias have strikingly different clinical presentations which we went through in detail. Clinical staging and cytogenetic testing are essential in determining not only the prognosis but also in determining the appropriate treatment options. Finally, classification of patients with MDS can predict the risk of progression to AML which ranges from 5% in the lower risk diseases up to 50% in the higher risk diseases with adverse karyotype. So this concludes part one of the hematologic malignancies section. Please feel free to give us any comments or feedback. Thank you.