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An Overview of Acute Myeloid Leukemia

Ryan Durkee

Honors College Senior Thesis

Abstract

Acute Myeloid Leukemia is a rare disease with an estimated 20,830 new cases in the U.S. in 2015.⁴ Although it is a rare disease it is crucial to understand the history, pathophysiology, and epidemiology of AML. Comprehending the steps behind treating AML is another crucial aspect in appreciating the care that must be put into AML and the patients that suffer from it. A comprehensive look into these two aspects of AML will give a better understanding for what causes AML, how it is treated, and what these patients experience. Through this comprehensive study the future of this field will also be considered.

Introduction

The human body is a complex structure of tissues, organ systems, and biochemical pathways. It's these systems and pathways that keep us alive and functioning properly. There are a variety of complications that can occur though, and when these problems occur it can cause a broad spectrum of malfunctions in the body, anywhere from diseases to deficits in a certain nutrient, or organs working improperly. These issues can be harmless, can be detrimental to day-to-day affairs, they can even cause death.

One prevalent group of diseases that occur within our society is cancer. Nearly 14.5 million Americans still alive have a history of cancer as of January 1, 2014.¹ This ranges from diagnosed to undergoing treatment, to in remission. It is estimated that throughout the course of 2015, 1,658,370 Americans will be diagnosed with some form of cancer and 589,430 Americans will die of cancer during 2015.¹ This means that cancer is the second most common cause of death in the US, only exceeded by heart disease.¹ In our society there is a major push for research and development in the treatment of cancer. The National Institute of Health (NIH) alone has budgeted approximately \$4.9 billion per year over the last 6 years for cancer, and is projected to do the same for the upcoming years.² There are over 1,400 facilities in the U.S that are accredited by the Commission on Cancer (CoC).¹ There are more than 65 cancer centers that take part in the National Cancer Institute (NCI) Cancer Center Program.¹ This program focuses on research to help reduce cancer rates and deaths from cancer.¹ This alone is a staggering field, for there are multiple forms of cancer that can occur within the body. These cancers are grouped based on where the cancer initially started in the body. There are cancers of the stomach, lung and bronchus, prostate, liver, pancreas, colon and rectum, skin, and blood. Within these groupings are then sometimes sub-groupings based on how the cancer formed, and the stage of the cancer. For example there is breast cancer, but basal-like breast cancer is a subtype of breast cancer, the other main subtypes are luminal A, luminal B and HER₂-positive breast cancer.³

To be able to study cancer it is necessary to narrow the field of study down to the groupings and sub-groupings of this large disease. Leukemia is broadly defined as the cancer of blood forming agents, and this serves as a grouping of cancer, and the focus of this paper will be on the subgrouping of acute myeloid leukemia. The history, pathophysiology and epidemiology of this diseases will be studied. In pairing with the research of acute myeloid leukemia, stem cell and bone marrow transplants will be covered also, for these treatments have been found and utilized as effective treatment of acute myeloid leukemia.

Acute Myeloid Leukemia

As stated before Leukemia is defined as the cancer of blood forming agents, but this is a very general and broad definition, and to better understand this disease, it is important to comprehend the basic components. A great point to start is understanding some elements that are involved in blood and blood forming agents. Bone marrow is found in the inner cores of long bones such as the femur. Bone marrow consists mostly of blood stem cells, more mature blood-forming cells, fat cells, and supporting tissues that help cells grow.⁴ The role of the bone marrow is to aid in the development of blood stem cells.⁴ In the bone marrow these blood stem cells can develop into a large array of new blood cells. During the maturation process the blood stem cells can become either lymphocytes, which are a kind of white blood cell, or they can become a variety of different blood-forming cells, otherwise called myeloid cells (myeloblasts).⁴ These myeloblasts can develop into red blood cells, platelets, or a variety of non-lymphocytic white blood cells.⁴ The basic function of red blood cells in the body is to deliver oxygen from the lungs to all the tissues within the body, and to take carbon dioxide back to the lungs to be expelled.⁴ Platelets are fragments of a cell made by the bone marrow called a megakaryocyte.⁴ Platelets are important in stopping bleeding. These platelets are crucial in plugging up holes in vessels caused by cuts or bruises. Then there is the most varied group of blood cells in the body, the white blood cells. Overall, white blood cells assist the body in fighting infections. These crucial parts of the blood are important in keeping our bodies well and stable. If these components are faulty in some way, it can have devastating effects on our body, which is where leukemia has its effect on a patient with the disease.

Leukemia is a type of cancer, but within the leukemia branch there are four main types of leukemia; acute myeloid leukemia, chronic myeloid leukemia, acute lymphocytic leukemia, and chronic lymphocytic leukemia. Acute myeloid leukemia (AML) is the main focus of this paper, but to better understand AML it is important to understand the other three leukemias as well. Breaking down the different naming components of Leukemia gives easy and quick insight into the nature of the different leukemias. The “acute” and “chronic” part of the naming refers to the maturity of the affected blood cells, and how fast the disease progresses. The “myeloid” and “lymphocytic” parts of the naming refer to the types of blood forming cells that are affected by the leukemia. With Acute leukemias, the leukemia cells are immature compared to normal blast cells.⁴ These leukemias are fast growing because like normal blast cells, the leukemia cells divide quickly.⁴ The problem occurs because they do not halt their dividing when normal blast cells would. If left untreated, most patients only live a few months.⁴ With chronic leukemias, the leukemia cells are more mature, but they are still not completely normal. These more mature cells do not fight infection as well as normal white blood cells, and they survive

longer.⁴ These cells also build up and surround normal cells, which further harms the ability of the body to fight infection. Because of the nature of chronic leukemias, they tend to progress at a slower rate than acute leukemias, and patients can live many years with the disease untreated.⁴

Myeloid leukemias start in immature forms of myeloid cells. Lymphocytic leukemias start in immature forms of lymphocytes.⁴ These leukemias are not to be mixed up with a different cancer called lymphoma. The difference between these cancers is that lymphocytic leukemia develops from cells in the bone marrow, whereas lymphoma develops from cells in the lymph nodes or other organs such as the thymus.⁴ Using these nomenclatures, it can be easily pieced together that acute myeloid leukemia is a cancer that affects the myeloid cells of the bone marrow, and that these cells are immature and fast growing, and unable to perform their proper function within the body.

Since Acute Myeloid Leukemia (AML) affects the blood, there are signs and symptoms that can be observed in a patient who has AML. Leukemia cells will crowd out the normal blood-making cells in the bone marrow, this occurs because the numbers of leukemia cells start to outnumber the normal blood-making cells.⁴ This causes a patient with AML to have a shortage of normal red blood cells, white blood cells, and platelets.⁴ A shortage of red blood cells can have the symptoms of shortness of breath, fatigue, cold, and dizziness.⁵ Having a deficit of normal white blood cells means that the body cannot fight infections as well as it could when white blood cells were at a normal level. This means that individuals are more susceptible to infection.⁵ It is to be noted that some AML patients actually have an increased white blood cell count, but these are nonfunctional and do not protect against infection. Having a lack of platelets means that blood does not clot as well, and this means that bruising and bleeding can happen more frequently. Another problem that occurs because of improper clotting is having blood clots form throughout the body. In fact, there is a certain type of AML called acute promyelocytic leukemia (APL) that affects platelets. Some of the symptoms that are associated with this form of leukemia deal with calf swelling that occurs because of a blood clot that forms there, called a deep venous thrombosis (DVT).⁶ This DVT can become dislodged and move to the lungs.⁶ This is called a pulmonary embolism, and can be life threatening without treatment.⁶

With AML not only do the number of normal cells decrease, but also the number of leukemia cells increase and spread. This increase of leukemia cells can also have symptoms. Some of these symptoms are bone or joint pain caused by the build-up of leukemia cells in those tissues, and swelling of the liver and spleen which can be seen physically by a swelling of the belly.⁵ AML can spread to certain areas of the body. If AML spreads to the skin the leukemia cell can cause lumps or spots that resemble common rashes on the skin.⁵ If leukemia cells spread to the gums it can cause swelling, pain, and bleeding.⁵ AML can even spread to the central nervous system, and if that occurs such symptoms

as headaches, weakness, seizures, vomiting, trouble with balance, numbness on the face, and blurred vision can occur.⁴ These are all physical symptoms that can occur because of AML, but these do not absolutely correlate to AML, for each symptom by itself can be caused by a variety of different diseases and conditions.

AML cancer cells are bigger than normal white blood cells. This increase in size means that these cells might have trouble passing through tiny blood vessels. When these cells have trouble making it through the circulatory system, it can adversely affect the ability of normal red blood cells to get to the tissues. If the tissues do not receive normal blood flow, problems such as shortness of breath, blurry vision, or even loss of vision can occur.⁴ This becomes a major problem when there is a disturbance of the blood flow to the brain. If blood flow in the brain is affected then symptoms resembling a stroke can occur. These symptoms include headaches, weakness on one side of the body, slurred speech, confusion, and sleepiness.⁴

Since the physical symptoms of AML are so general, other causes of those symptoms need to be ruled out before a diagnosis of AML can be reached. The suspicion of AML in the first place is because of odd blood work numbers.⁷ This is not a direct diagnosis for AML though, for there are a variety of reasons for blood numbers to be low or high. From there the physician will do some x-rays of the chest to determine that an infection of the lungs or pleural cavity is not the cause for the strange numbers, then CAT scans, and MRI scans will be used to make sure no other infection is present within the body.⁷ HIV and Hepatitis testing will also be done.⁷ Once all other factors can be ruled out, then it would be likely for the physician to try some more invasive tests to determine if Leukemia is the possible culprit. These tests include drawing blood and getting a full blood count which provide numbers on red blood cells, hemoglobin, white blood cells and platelets. A lumbar puncture to analyze the cerebrospinal fluid is another test that can be utilized, along with some basic biochemical tests such as coagulation tests, and urine analysis.⁷ (See Table 1 for all diagnostic and prognostic tests)

There are a variety of tests that can make an accurate diagnosis of AML as the disease present in the patient. The initial diagnostic test for AML is dealing with morphologic identification of the leukemic myeloblasts, which are the stem cells that differentiate into granulocytes.⁷ This is done with preparations of peripheral blood and bone marrow stained with a dye called Wright-Giemsa. The presence of more than 30% leukemic blasts in a bone marrow aspirate is the number required for a definitive diagnosis of acute leukemia.⁷ The morphology that doctors are looking for is round-to-irregular nuclei, distinct nucleoli, and very little cytoplasm.⁷ One major determining morphological structure is the appearance in the cytoplasm of leukemic myeloblasts of Auer bodies, which are rods of azurophilic granules that clump together.⁷ Once acute leukemia has been determined it is very important

to be able to differentiate this acute leukemia as acute myeloid leukemia. AML must be distinguished from other diseases such as acute lymphocytic leukemia (ALL), myelodysplastic syndrome (MDS), or AML arising in the setting of MDS.⁷ This differentiation is important because each of these subtypes has a specific therapeutic strategy and prognosis that vary considerably from one another. AML can be distinguished from ALL by showing a commitment to the myeloid lineage.⁷ This is done by using morphologic, immunohistochemical, and immunologic methods.⁷ To differentiate AML from MDS or MDS-related AML requires morphologic, and genetic analysis.⁷ MDS is characterized by ineffective hematopoiesis, and although its diagnosis rests largely on morphologic evidence, there are some genetic patterns that are seen, such as the loss of all or part of chromosome 5 or 7, and the deletion of the long arm of chromosome 2, as well as the loss of Y.⁷ It only becomes MDS-related AML when myeloblasts exceed 30 percent.⁷ The reason differentiation needs to occur for MDS-related AML is because conventional AML therapy is not very effective against MDS-related AML.⁷ These are the precautions that must be taken when diseases initially look very similar to each other, but require completely different treatments and prognoses.

If AML has been established as the disease afflicting the patient, there are stages and subtypes of AML that can now be classified by the doctor through morphological and genetic identification. Since AML is a heterogeneous disease caused by a variety of pathogenic mechanisms, the morphologic level is very heterogeneous as well. The variability of the morphologies of the different subtypes is manifested by the degree of commitment and differentiation to the cells' lineage. The most common method of classification that uses this morphologic subgroupings is the French-American-British group (FAB).⁷ This divides AML into nine distinct subtypes that differ with respect to the myeloid lineage, and to what extent the leukemic-cell differentiates.⁷ (See Table 2) The leukemic-cell differentiation is determined by the blasts' reactivity with histochemical stains, including myeloperoxidase, Sudan black, and esterases α -naphthylacetate and naphthylbutyrate.⁷ Immunologic methods, such as flow cytometry, have also been incorporated into the diagnostic criteria of some of the FAB subgroups. Finally, it has been found with some leukemic blasts that nonrandom clonal chromosomal aberrations have occurred in a large percentage of patients with AML. Some of these abnormalities can even be associated with specific FAB subtypes.⁷ These cytogenetic lesions have been shown to be essential in determining effective therapeutic responses for patients with such lesions. Incorporating these three diagnostic methods: morphology, immunology, and genetics has proven to be effective to develop highly specific clinical therapies for the differing subtypes of AML.

When discussing a disease it is essential to examine the risk factors and possibilities that can increase an individual's chance of developing AML. One of the notorious proven risk factors for AML

is smoking. It's widely known that smoking is linked to cancers of the lungs, mouth, and throat, but because of the carcinogens that are prevalent in tobacco, many of those chemicals get into the bloodstream and can spread.⁸ Another major risk factor is exposure to certain chemicals. Long-term exposure to high levels of benzene is a risk factor for AML.⁹ Benzene is a solvent that is used to produce a variety of things like drugs, plastics, dyes, and petroleum. It's also a common solvent in cleaning solutions. Exposure to ionizing radiation is also a risk factor for AML; survivors of the atomic bombs in Japan had an increased incidence.⁹ Therapeutic radiation has been shown to also increase the risk of AML. It's been shown that alkylating-agent types and agents that inhibit the DNA repair enzyme topoisomerase II are two types of chemicals that increase the incidence of AML.⁹ Certain drugs such as chloramphenicol, phenylbutazone, methoxypsoralen can induce marrow damage that may progress to AML.⁹ Three other factors that affect incidence of AML are age, gender, and ethnicity. Males of European descent have a slightly higher incidence of AML.¹⁰ The Latino and Hispanic population have a higher incidence of a subtype of AML called acute promyelocytic leukemia (APL).¹⁰ The median age for AML is 65 years, so it is a disease that is shown to affect the elderly population.⁵ Genetics have also been shown to play a role, and the abnormalities that can occur on chromosomes are varied, from chromosome 5, 7, 8, 11, 16, 20, and Y.¹⁰ These are only risk factors; no one risk factor specifically causes AML, but with each one the chances of AML occurring does increase, so it's important to try to reduce the risk factors that can be managed.

Epidemiology is the study of a diseases pattern in a population, covering the statistics of incidence for the disease, from the number it affects, to the type of people that are statistically more likely to develop the disease. For AML, it is estimated that 18,860 new cases of AML and 10,460 deaths from AML will occur in the United States each year.⁵ Since AML is a varied disease with nine subtypes, records on how much each subtype accounts for all of AML is tracked. It was observed that a type of AML with a translocation of chromosome 8 and 21 accounts for about 8 percent of all AML, and an AML with an inversion of chromosome 16 accounts for 10 percent of adult AML and about 6 percent of childhood AML.⁵ The research shows that more than half of the cases are in patients that are at or over 65 years of age, and a third of all cases are in patients at or over 75 years of age.⁵ With these data we know what population to look at for the disease, and what ethnicity they might be, and what age. Their genes can be studied to see if they display any of the common genetic abnormalities that are present for a certain subtype of AML. Having these population numbers allows for health professionals to be better prepared to deal with the disease, and to understand where the disease is derived.

Hematopoietic Stem Cell Transplants

Leukemia has been defined only since the mid-19th century.¹¹ It was through the contribution of a multitude of scientists for a half a century that made leukemia a defined disease that could be diagnosed.¹¹ In its infancy, starting at the turn of the 19th century in 1801, leukocytosis was defined. It was not until 1847 that the disease itself was termed leukemia.¹¹ It took until 1869 for the physiology of leukemia to be connected to the bone marrow.¹¹ In these early years of the disease it was a death sentence to receive a leukemia diagnosis. With time, treatments became better and more effective, and an important year for the treatment of leukemia came in 1959. In this year an oncologist named Georges Mathe aimed to treat 6 physicists who were accidentally exposed to a lethal dose of radiation.¹² As a radical new treatment, Mathe attempted the first bone marrow transplant between unrelated donors.¹² Ultimately, the patients rejected their bone marrow transplants, and they experienced autologous bone-marrow recovery. It is because of this fact, the treatment was heralded as a success.¹²

A second major advance in bone marrow transplants came in the form of Dr. E Donnall Thomas. Dr. Thomas' work spanned two decades, and involved the improvement of bone marrow transplantation as treatment for cancer.¹³ In the 1960's Dr. Thomas learned about immunology and irradiation biology in dogs, and transferred this knowledge for comparisons for clinical care in human patients.¹³ During the 60's Thomas devoted his research to understand the complex system of tissue typing using dogs as his subjects.¹³ He frequently performed twin bone marrow transplants. Using identical twins is a benefit since the genes are identical, which means that the tissue and blood match are perfect.¹³ By compiling both his own research and research conducted outside his facility, Dr. Thomas's knowledge of tissue typing grew.¹³ With the advancement of knowledge on histocompatibility and with improving techniques to compare tissues, Dr. Thomas contributed major improvements in the field of transplant research.¹³ In 1990 Dr Thomas received the Nobel Prize in physiology or medicine for his work in the field of bone-marrow transplantation.¹³

Dr. Thomas took part in another major advancement in bone marrow transplants, and that was the development of second and third-generation antibiotics.¹³ These antibiotics are crucial for controlling bacterial infections in patients, for the immune system is greatly weakened during a bone marrow transplant.¹³ Because of Dr. Thomas' work, the Fred Hutchinson Cancer Center, the institute that he worked for, became a leader of cancer research and treatment.¹³ In 1968 and 1969 Fred Hutchinson Cancer Center performed their first successful non-twin transplants between siblings.¹³ In 1979 the first Hutch patient received a bone marrow transplant from an unrelated donor to treat leukemia.¹³ Without the work of these scientists, physicians, and countless others, leukemia could

possibly still be that death sentence it was nearly two centuries ago.

When performing bone marrow transplants first there is the pre-treatment, donor graft collection, and then transplants dealing with donor histocompatibility occurs. Before a transplant occurs though, it is crucial to kill all cancer cells that are present within the bone marrow. These pre-treatments utilize chemotherapy, or radiation, or both may be given in tandem. There are two methods of delivering these pre-treatments.¹⁴ Myeloablative treatment uses high-dose chemotherapy, utilizing such drugs as busulfan or cyclophosphamide, or radiation.¹⁴ This method kills any cancer cells, but it has a heavy toll on the body as well. The treatment kills all healthy bone marrow that remains.¹⁴ This vacancy of bone marrow then allows the transplanted stem cells to create new, healthy bone marrow in its place.¹⁴ Because this treatment is so severe and harmful to the body, not all patients can handle the intensity of myeloablative treatment. That is where reduced intensity treatment comes in.¹⁴ Reduced intensity treatment, also called a mini transplant, gives the patient a lower dose of chemotherapy/radiation before the transplant.¹⁴ This treatment has a less likely chance of killing all cancer cells, but it has a less cytotoxic effect on the body, and is much more tolerable than the myeloablative treatment.¹⁴ Generally mini transplants are used for older patients or patients that otherwise could not undergo transplants due to health problems.¹⁴

There are certain methods that are utilized or delivered the stem cells from the donor into the patient. Stem cells are delivered into the bloodstream of the patient, this is done usually using a tube called a central venous catheter. The stem cells then travel through the blood, and will arrive into the bone marrow, where they will implant and start forming new bone marrow. As for the donor stem cells, they are collected in two ways: bone marrow harvest, and leukapheresis.¹⁴ Bone marrow harvest is a minor surgery in which the bone marrow is removed from the back of both hip bones.¹⁴ The amount of marrow harvested depends on the weight of the person who is receiving it.¹⁴ Generally about 1 to 2 liters of bone marrow are harvested, this about 5 percent of the bodies bone marrow cells.¹⁵ Throughout the procedure the donor is under general anesthesia to insure the individual does not feel any pain during the treatment.¹⁴ After the treatment, post-operation pain can be felt by the donor at the location where the bone marrow removal occurred. Leukapheresis starts with five days of shots that promotes stem cell movement from the bone marrow into the blood.¹⁴ The factors that promote stem cell movement are cytokines, and the shots contain a glycosylated granulocyte colony-stimulating factor (G-CSF) and lenograstim which is a non-glycosylated G-CSF).¹⁶ The blood is removed intravenously from the donor.¹⁴ Using blood separation techniques the stem cells are separated from the red blood cells.¹⁴ The red blood cells are returned back to the donor after separation.¹⁴

Understanding the terminology and process of bone marrow transplants will reveal why this

process is an effective method for treating leukemia. A bone marrow transplant is a procedure that replaces damaged or destroyed bone marrow with healthy bone marrow stem cells.¹⁴ Bone marrow transplant is only one name that is used for this procedure; other interchangeable names for this procedure are stem cell transplant, hematopoietic stem cell transplant or bone marrow graft.¹⁴ There are three kinds of bone marrow transplants: autologous, allogeneic, and umbilical.¹⁴ Autologous bone marrow transplants use stem cells that are removed from the patient before they receive high-dose chemotherapy or radiation. These removed stem cells are stored in a freezer to preserve them. After the high-dose chemotherapy and radiation treatments are complete, the patient's stem cells are transferred back into their body, and the stem cells will hopefully regenerate normal bone marrow and blood cells.¹⁴ Allogeneic bone marrow transplants use stem cells that are removed from a donor that is not the patient. The aim is that the donor's genes be as close of a match to the patient's genes as possible.¹⁴ The reason for this is because there are a variety of marker proteins found on the surface of cells, and if these markers do not match up, then the body will recognize the stem cells as a foreign substance called an allergen, and the graft might be rejected by the host.¹⁴ Siblings, parents, children or other relatives are a good place to find donors that could be a good match.¹⁴ If the relative's blood cells are not close enough physically, there is a national bone marrow registry that provides the information on all bone marrow donors so that the closest match can be found.¹⁴ Umbilical cord blood transplant is an allogeneic type transplant that can also be autologous.¹⁴ Stem cells are removed from a newborn baby's umbilical cord at the time of birth. These stem cells are frozen and stored, and when the baby's blood is a match for a patient, then these stem cells are transplanted.¹⁴

With each of these different transplants there are benefits and disadvantages. The benefit of autologous transplantation is that the markers in the cell line up with the patient's body, because they are from their body.¹⁴ The disadvantage of this transplant is that because it came from the patient's body there is a risk that the bone marrow that was removed still has leukemic cells in it, thus the possibility for relapse is higher with this form of transplantation.¹⁴ The advantage of allogeneic transplantation is that if screening is done right there is an elevated chance that the stem cells the patient is receiving from the donor are not cancerous.¹⁴ The drawback of this transplant is that the histocompatibility of the donors cells may not correspond with the patient's body as well as it would with autologous transplantation.¹⁴ This means that graft-versus-host disease (GVHD) is more likely to occur, and that is a serious condition by itself.¹⁴ GVHD is where the donors cell's protein markers recognize the patient's body as a foreign substance and treats it like an allergen.¹⁷ The donors cells then attack the patient's body, and can cause some serious problems for the patient.¹⁷ The benefit of umbilical cord blood cells is that they are very immature, thus they do not have as many markers, and

this means that there is a reduced chance that the umbilical cord blood cells will be detected as allergens.¹³ The difficulty is it takes blood counts much longer to recover compared to other transplant methods.¹³ This is because the amount of stem cells that are harvested from the umbilical cord are less compared to stem cells from marrow or peripheral blood.¹⁸

After the hematopoietic stem cell transplant has been performed, there are some precautions that must be made in order to insure that the patient stays healthy. Since the patient's bone marrow has been damaged, their body's immune system is at a deficit and cannot function effectively. Because of this fact it is important to implement prophylactic anti-infectious treatment.¹⁹ This includes making sure that the patient has proper personal hygiene, dental care, and that they are protected from bacteria or fungi environments.¹⁹ Providing patients with the proper anti-fungal and anti-bacterial regimens is also a crucial part of these prophylaxes.¹⁹ For anti-fungal it has been shown that drugs with antimold activity are the most effective, some examples of these are itraconazole, posaconazole, or amphotericin.¹⁹ For bacterial prophylaxis, studies show that prophylaxis with quinolones was the most effective.¹⁹ The other major supportive treatment that can be done for patients that received a hematopoietic stem cell transplant is transfusions with platelets or red blood cells.¹⁴ Platelet transfusions help in reducing mortality from hemorrhaging, for the increase in platelets helps with clotting in the body.¹⁹ Red blood cell transfusions are used to help the patients' hemoglobin blood levels stay above 8g/dL.¹⁹

Once the hematopoietic stem cell transplant has been completed, and supportive care has been utilized, this still does not ensure that the patient will be fully healthy. This is because there are many complications that can occur, both early and delayed effects, after hematopoietic stem cell transplantation. Mucositis is the most common complication of myeloblastic preparative regimens early on.¹⁷ Mucositis can occur in a few areas of the body: oropharyngeal and intestinal.¹⁷ Oropharyngeal mucositis is painful and can involve the supraglottic area, it makes swallowing and eating very difficult for the patient.¹⁷ Intestinal mucositis causes nausea, cramping, and diarrhea.¹⁶ The second acute effect is a syndrome called sinusoidal obstruction syndrome.¹⁷ This syndrome is a combination of hepatomegaly, jaundice, and fluid retention.¹⁷ The sinusoidal endothelium becomes damaged and then it obstructs the hepatic circulation, this damages the centrilobular hepatocytes.¹⁷ In severe forms of sinusoidal obstruction syndrome, renal and respiratory failure can occur.¹⁷ This syndrome is caused by the total body irradiation, busulfan, cyclophosphamide, and other preparative agents.¹⁷

Transplantation-related lung injury can occur within four months of the procedure.¹⁷ Some of the risk factors include total-body irradiation, allogeneic transplantation, and acute GVHD.¹⁷ These risk factors suggest that the lymphocytes from the donor are targeting the lungs and are responsible for the

damage.¹⁷ Because the immune system is severely compromised, transplantation-related infections can arise even with prophylaxis. These infections usually happen because of damage to the mouth, gut, or skin, usually from preparative regimens as well as from catheters.¹⁷ The most important complication is graft-versus-host disease (GVHD).¹⁷ Acute GVHD damages the skin, gut, and liver.¹⁷ A rash can affect the palms, soles, or face and may become generalized.¹⁶ Nausea vomiting, abdominal pain, diarrhea, bloody stool, and jaundice are possibilities as well.¹⁶ The treatment for GVHD is with corticosteroids, which causes immunodeficiency. This immunodeficiency further increases the patient's chance of being infected.¹⁷ The prime risk factor is human leukocyte antigen (HLA) mismatch.¹⁷ One of the most effective treatments used to reduced GVHD is short-term treatment with methotrexate plus treatment with cyclosporine for several months.¹⁷

Most patients who survive transplantation can live a healthy life, but there are some diseases that can occur later in a delayed effect.¹⁷ The most serious of these is chronic GVHD.¹⁷ Risk increases with the patients and donor age, and if the donor was unrelated to the patient.¹⁷ Chronic GVHD can cause bronchiolitis, keratoconjunctivitis sicca, esophageal structure, malabsorption, cholestasis, hematocytopenia, and generalized immunosuppression.¹⁷ Corticosteroids are the treatment route for chronic GVHD as well, but again infection is a big risk because of this.¹⁷ After transplantation most women fail to ovulate.¹⁷ Children that are subject to transplantation have growth and development problems; growth hormone therapy can assist with height increases.¹⁷ Secondary cancer risk is increased after transplantation as well. It has been studied that after allotransplantation the incidence of cancer of the skin, oral mucosa, brain, thyroid, and bone increased.¹⁷

The procedure of hematopoietic stem cell transplantation has been discussed along with the pre- and post-operation, and the possible complications that can arise from it, and now it is important to see what the numbers look like for the patients that have received these transplants. From the U.S. Department of Health and Human Services data were collected from 2008 through 2012 on acute myeloid leukemia patients going through 1st remission. For patients that received an autologous transplant, 97.3% survived 100 days after transplant. 75.4% survived 1 year after transplant and 53.8% survived 3 years after transplant.²⁰ For patients that had an allogeneic transplant from an identical sibling 93.3% survived 100 days, 72.5% survived 1 year, and 55.0% survived 3 years.²⁰ For patients that had an allogeneic transplant from another related donor 89.5% survived 100 days, 64.0% survived 1 year, and 43.1% survived 3 years.²⁰ For patients that received an allogeneic transplant from an unrelated donor 88.3% survived 100 days, 64.8% survived 1 year, and 48.2% survived 3 years.²⁰ (Table 3) These numbers show that the best chance for survivability is either autologous transplantation or allogeneic transplantation with an identical sibling as the donor.

Relevant New Studies

As with any disease and treatment in the medical field there is always new research that is going into acute myeloid leukemia, and into bone marrow and stem cell transplants. This research aims to improve early detection methods, making diagnoses more accurate, improving the effectiveness of the bone marrow and stem cell transplants, and for finding new methods to treat AML. A few examples of literary reviews will provide some insight into where the field is heading, and what improvements have been made in the recent past for both AML and the treatment of AML.

One recent study aimed to evaluate the impact that marrow blasts at transplant had on adult patients with acute myeloid leukemia.²¹ The study analyzed 478 patients who underwent allogeneic stem cell transplantation. After a following up with the survivors of the operation, the study found that patients with higher marrow blasts at transplant showed lower overall survival, and disease-free survival. This study concluded that pre-transplant bone marrow status was an important prognostic factor for AML patients. As another addition, the higher relapse rate that was found in patients with high marrow blast count may provide insights into the tolerable blast cell burden that can be overcome by the graft-versus leukemia effect.

Another study covered a 23 year span from 1987 to 2010.²² The study observed the survival outcomes of 300 patients with acute myeloid leukemia that were treated with allogeneic hematopoietic stem cell transplantation (HSCT). The objectives were to determine the overall survival (OS) and disease-free survival (DFS), and to identify prognostic factors associated with treatments that did not go well. This was a retrospective study that used data from the Blood and Bone Marrow Transplant, National Transplant Registry, Malaysia. The overall 10 year OS and DFS was 63 and 67 percent respectively. It was found that donor gender, marrow status, and conditioning intensity were identified as important prognostic factors for OS. The significant prognostic factors for DFS were ethnic group, donor gender, marrow status, and conditioning intensity. The study concluded that HSCT for AML patients was a good treatment that should be considered as a standard therapeutic approach.

Another study published in 2012 aimed at determining the significance of terminal deoxynucleotidyl transferase (TdT) association with overall survival of 30 acute myeloid leukemia patients with minimal differentiation (AML-M0) patients after stem cell transplants.²³ It was concluded that AML-M0 can be divided into two groups based on TdT expression. The results suggest that TdT positivity in AML-M0 identifies a subset of patients that have a better prognosis after stem cell transplant. It should be noted that this is a small study group, and that further studies with broader groups should be conducted to corroborate the findings of this study, but it does serve as a good preliminary study looking into possible prognosis features of AML.

A study published in 2013 compared two drug treatments as myeloablative conditioning.²⁴ The objective of the study was to compare busulfan plus fludarabine (BuFlu) with busulfan plus cyclophosphamide (BuCy) as the conditioning regimen in allogeneic hematopoietic stem cell transplantation (allo-HSCT) for AML in first complete remission (CR1). This study took 108 AML-CR1 patients undergoing allo-HSCT. The conclusion of the study was that BuFlu as a condition regimen was associated with lower toxicities and had comparable anti-leukemic activity compared to BuCy.

In another study the researchers aimed to evaluate the efficacy of reduced intensity conditioning (RIC) prior to allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients with AML who were in first complete remission (CR1).²⁵ A second aspect was for AML patients that also had an intermediate-risk karyotype. The study was a retrospective analysis of 93 patients who received allo-HSCT following either RIC (n=37) or standard myeloablative conditioning (MAC) (n=56). These findings suggest that RIC with allo-HSCT may induce stable remission for patients with AML who received transplants in CR1. This stable remission seemed to increase for patients with an intermediate-risk karyotype, and provides evidence that RIC may be a viable option for AML patients with intermediate-risk karyotype who are ineligible for MAC following transplantation.

A study in 2008 looked at how survival rates had changed in two decades. They looked at the time periods of 1980-1984 and 2000-2004.²⁷ Patients were grouped into four groups based on age; 15-34, 35-54, 55-64, 65-74. For patients the overall 5- and 10-year survival rose from 8.4% and 5.6% to 19.5% and 17.1% respectively.²⁷ (see figure 1) The largest gain for individual gain for patients was for the 15-34 years of age, their 10 year survival increased from 13.5% to 47.9% from the 80's to the 2000's.²⁷ The least improved group was the patients aged 75 and over. Their 10-year survival rate change was close to zero, and stayed at below 5%.²⁶ The five year survival rate also climbed for the first three age groups, and the oldest age group stayed close to their 1980's numbers. (See figure 5)

Conclusion

Over the past two centuries the understanding of leukemia has undergone drastic changes. Because of these changes the treatment of the disease has steadily improved. In the 19th century leukemia was a death sentence for patients, but because of work done by physicians like Georges Mathe, Dr. E Donnall Thomas and countless others over the decades, leukemia has become a treatable disease with ever increasing survivability. The accumulation of knowledge on leukemia has led to a variety of improvements in the field, from the development of the different subtypes of leukemia such as acute myeloid leukemia, to the advances made on the treatments used to combat these leukemias. Studies are continually being made to further the knowledge of acute myeloid leukemia and other subtypes. As with any disease a cure is the goal, but until that day any improvements in the survivability and overall well-being for the individuals that are and will be afflicted by leukemias is a welcome change.

Tables and Figures

Test/procedure	General practice	Clinical
Tests to establish the diagnosis		
Complete blood counts and differential count	Yes	Yes
Bone marrow aspirate	Yes	Yes
Bone marrow trephine biopsy	Optional	Optional
Immunophenotyping	Yes	Yes
Cytogenetics	Yes	Yes
RUNX1-RUNX1T1, CBFB-MYH11, PML-RARA, or other gene fusion screening	Optional	Optional
Additional tests/procedures at diagnosis		
Demographics and medical history	Yes	Yes
Performance status (ECOG/WHO score)	Yes	Yes
Analysis of comorbidities	Yes	Yes
Biochemistry, coagulation tests, urine analysis	Yes	Yes
Serum pregnancy test	Yes	Yes
Information on oocyte and sperm cryopreservation	Option	Optional
Eligibility assessment for allogeneic HSCT	Yes	Yes
Hepatitis A, B, C; HIV-1 testing	Yes	Yes
Chest x-ray, 12-lead ECG; echocardiography (on indication)	Yes	Yes
Lumbar puncture	No	No
Biobanking	Optional	Yes
Prognostic/predictive marker assessment		
NPM1, CEBPA, FLT3 gene mutation	Optional	Yes
WT1, RUNX1, MLL, KIT, RAS, TP53, TET2, IDH1 gene mutation	No	Investigational
ERG, MN1, EFI1, BAALC gene expression	No	Investigational
Detection of minimal residual disease	No	investigational

Table 1: Complete list of diagnostic and prognostic tests for AML.⁷

FAB subtype	% of Cases	Morphology	Cytochemistry		Flow Cytometry	Cytogenetic Association
			Peroxidase / Sudan Black	Nonspecific Esterase		
M0: Minimally differentiated leukemia	2-3	Immature morphology	-	-	CD13 or 33	
M1: Myeloblastic leukemia without maturation	20	Few blasts with azurophilic granules, Auer rods, or both	3% or more	-	CD13, 33, 34, HLA-DR+	
M2: Myeloblastic leukemia with	25-30	Azurophilic granules, Auer rods are often	+	-	CD13, 15, 33, 34,	T(8;21) (q22;q22) ^e

FAB subtype	% of Cases	Morphology	Cytochemistry		Flow Cytometry	Cytogenetic Association
			Peroxidase / Sudan Black	Nonspecific Esterase		
maturation		present			HLA-DR+	
M3: Hypergranular promyelocytic leukemia	8-15	Hypergranular promyelocytes with multiple Auer rods; Variant: hypogranular	+	-	CD13, 15, 33, HLA-DR-	T(15;17) (q22;q11-12)
M4: Myelomonocytic leukemia	20-25	Granulocytic and monocytic blasts; Variant: M4Eo: increase in abnormal marrow eosinophils	+/-	+	CD11b, 13, 14f, 15, 33, HLA-DR+	M4Eo: inv(16) (p13q22)
M5: Monocytic leukemia	20-25	M5a undifferentiated; M5b differentiated	-	+	CD11b, 13, 14f, 15, 33, HLA-DR+	11q23 translocation
M6: Erythroleukemia (Di Guglielmo's disease)	5	Erythroblasts >50% of nucleated cells, myeloblasts >30% of nonerythroid cells	+/-	-	CD33, HLA-DR+	
M7: Megakaryoblastic leukemia	1-2	Megakaryoblasts >30% of all nucleated cells	-	-	CD33	

Table 2: French-American-British (FAB) AML subtyping with % of cases, morphology, cytochemistry, flow cytometry, and cytogenetic associations.²⁷

Donor Type	Number of Patients Evaluated	Survival Probability Estimate At a 95% Confidence Interval (CI) (Explain)		
		100 Days After Transplant	1 Year After Transplant	3 Years After Transplant
Autologous	329	97.3% ----- CI = 94.8 - 98.6%	75.4% ----- CI = 70.2 - 79.8%	53.8% ----- CI = 47.7 - 59.5%
HLA - identical sibling	2297	93.3% ----- CI = 92.1 - 94.2%	72.5% ----- CI = 70.6 - 74.2%	55.0% ----- CI = 52.7 - 57.3%
Other related	285	89.5% ----- CI = 85.3 - 92.5%	64.0% ----- CI = 58.1 - 69.3%	43.1% ----- CI = 36.5 - 49.5%
Unrelated	3463	88.3% ----- CI = 87.2 - 89.3%	64.8% ----- CI = 63.1 - 66.3%	48.2% ----- CI = 46.4 - 50.1%

Table 3: U.S. patient survival report for patients in 1st remission AML for different donor types.²⁰

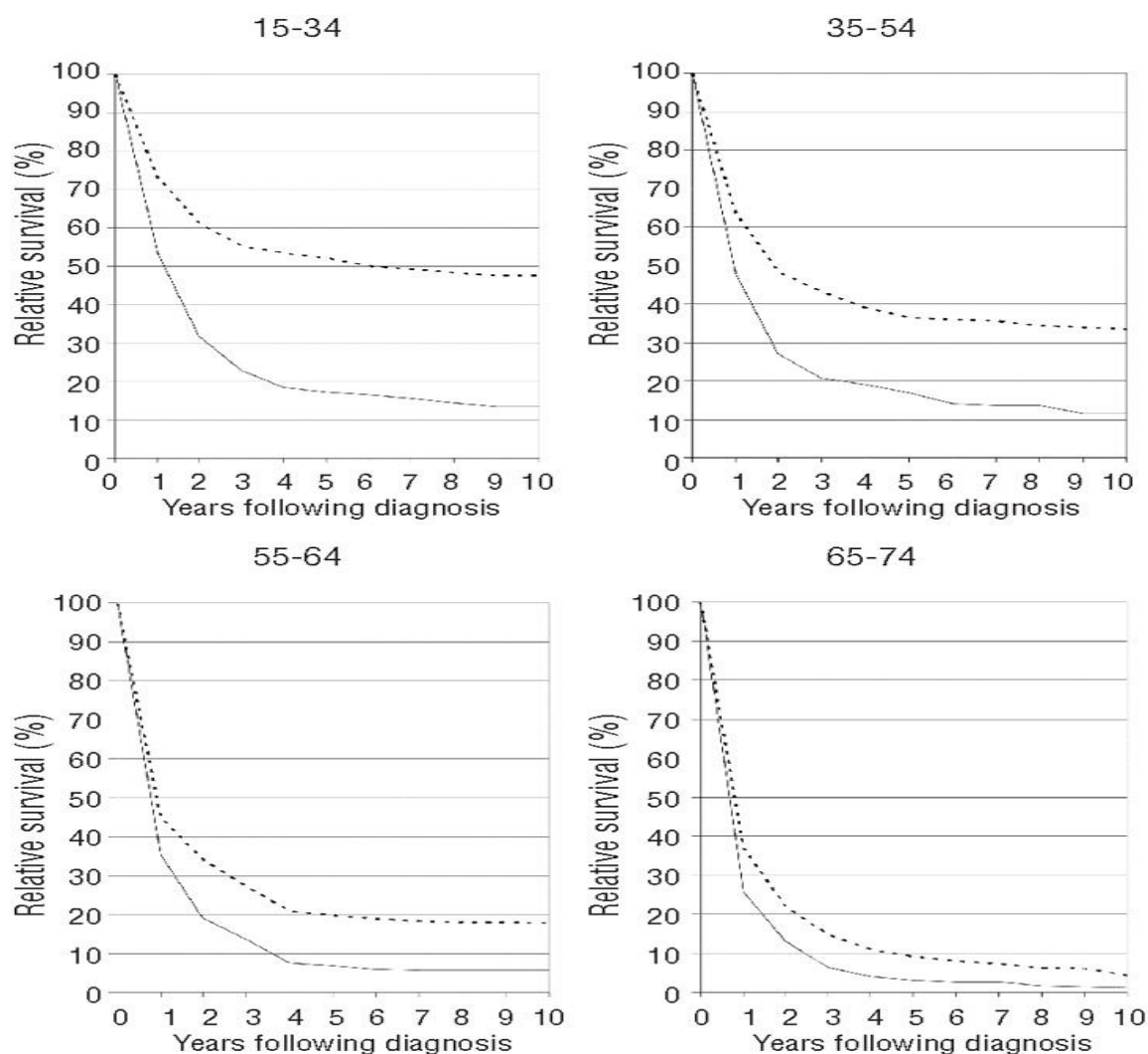


Figure 1: Ten- year relative survival curves for patients with AML by age groups. 1980-1984 solid curves and 2000-2004 dashed curves.²⁶

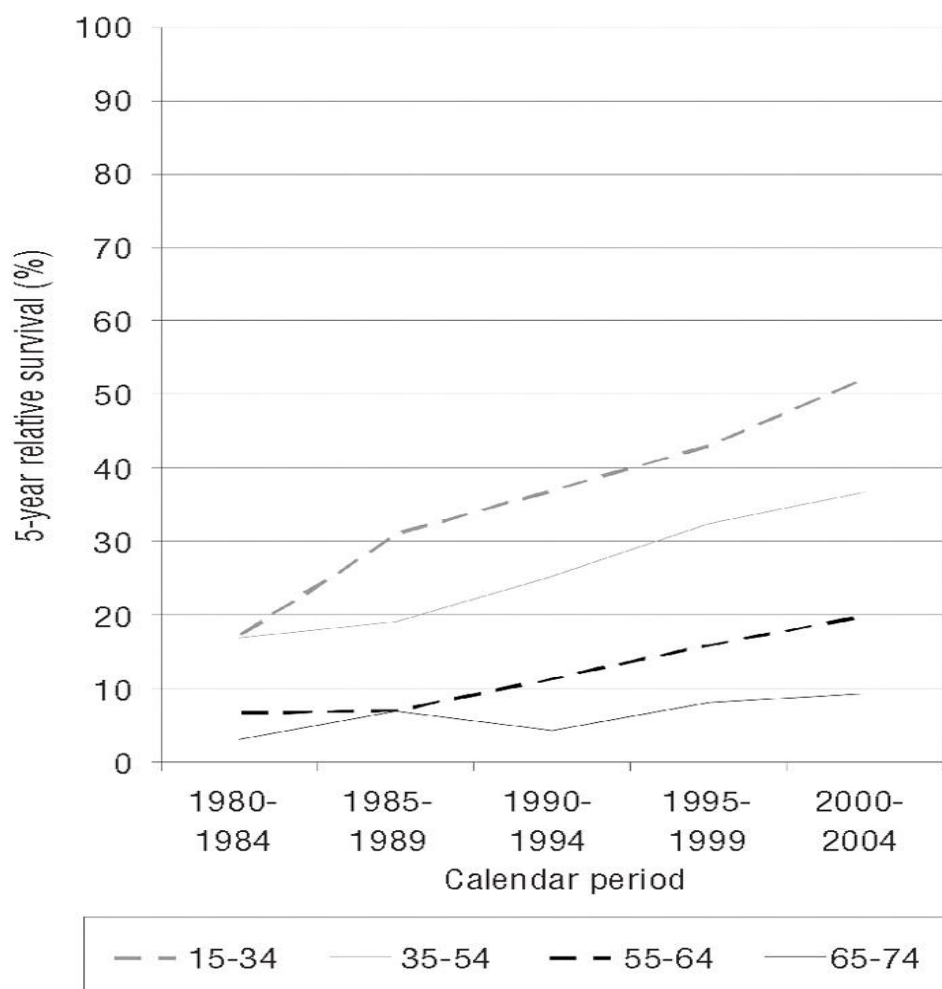


Figure 2: Period estimates of 5-year survival of patients with AML by age groups. Defined in 5 year increments from 1980 to 2004.²⁶

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