

Myeloid Leukemia: Mechanisms of Stem Cell Mutation, Proliferation, and the Ensuing Treatments

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Abstract

Myelogenous leukemia manifests as a disease in which the blood-forming cells of the body do not mature and accumulate to abnormal levels in the body, debilitating the function of healthy blood cells (NCBI, 2013). This cancer is divided into two subgroups, acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), and approximately 20,000 cases will be diagnosed in 2013 (Leukemia and Lymphoma Society, 2012). The causes of disease include chemotherapeutic drugs, organic chemicals, and ionizing radiation (NCBI, 2013). On the molecular level, each subtype has characteristic genetic aberrations as a result of inversions, translocations, and specific gene mutations that can create oncogenes or give leukemic cells a survival or proliferative advantage. Hundreds of genetic changes provide the molecular basis for AML pathogenesis, while CML is attributed to the Philadelphia chromosome, which is the translocation of chromosomes 9 and 22 (Druker & Talpaz, 2001). Blood tests, bone marrow aspirations, and cytogenetic testing allow for disease categorization; this includes classic French-American-British classification as well as favorable, intermediate, and unfavorable risk groups (Henderson, Lister, & Greaves, 2002). The disease categories for CML include chronic phase, accelerated phase, and blast phase (Phases of Chronic Myeloid Leukaemia, 2012). Treatment for AML includes chemotherapy and/or bone marrow transplants while CML is usually treated with tyrosine kinase inhibitors that target the Philadelphia chromosome (Druker & Talpaz, 2001; NCBI, 2013). Future treatment targets include the MEK/MAPK signaling pathway, specific leukemic stem cell phenotypes, and the inhibition of NF- κ B (Guzman, 2001; Jordan, 2000; Milella, Steven, & Estrov, 2001).

Introduction

Myelogenous Leukemia describes a fairly rare and debilitating cancer that can strike quickly. This disease encompasses into two types: acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). Estimates predict that 23,720 people will die from leukemia in 2013, and approximately half of those deaths will be attributed to acute myeloid leukemia. Conversely, approximately 610 will die as a result of CML in 2013; this indicates the difference in the severity of each type (American Cancer Society, 2013).

As indicated in the name, this cancer affects myeloblasts that are produced by myeloid stem cells and are precursors to granulocyte, a type of white blood cell, that aids in destroying foreign objects (WBC) (see Figure 1) (American Cancer Society, 2012).

In myeloid leukemia, too many myeloid stem cells become abnormal granulocytes (leukemic cells). These WBC's accumulate in the bone marrow and blood then negatively affect the function of healthy red blood cells, platelets, and WBC's (National Cancer Institute, 2012).

AML and CML are characterized by their differences in hematological development. In AML, myeloid cells still reproduce

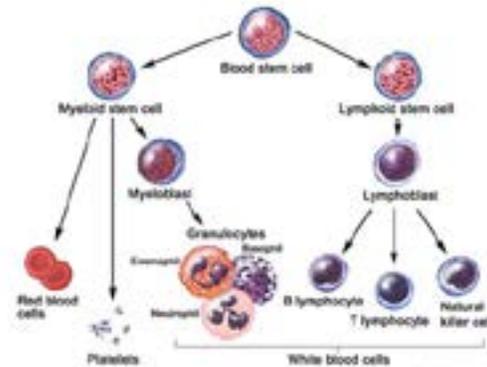


Figure 1. The normal process of blood maturation that specifically shows the myeloid cells that is affected in myeloid leukemia. Myeloid leukemia prevents myeloblasts from maturing into normal granulocytes (Childhood, n.d.).

and accumulate though they do not mature properly, creating more abnormal cells. Without treatment, most patients only survive a few months. Therefore, it is especially important for AML to be treated immediately. Conversely in CML, the myeloid cells come close to complete maturation but do not mature completely, yet they appear more morphologically normal and thereby partly functional than the cells do in the acute form (American Cancer Society, 2012). As in AML, this increased and unregulated growth crowd out these normal cells. Additionally, these aberrant granulocytes do not fight infection as well as normal WBC's do. Patients with CML tend to live for many years with treatment, while those with AML do not have such a favorable outcome.

Epidemiology

The American Cancer Society (ACS) estimates that 14,590 new cases of AML will be diagnosed while 10,370 deaths will be attributed to AML in 2013. Additionally, the ACS estimates that in 2013, 5,920 new cases will be diagnosed with CML and 610 people will die as a result of CML (American Cancer Society, 2012). In 2011, AML caused 12,950 new cases of leukemia, while 5,150 were attributed to CML for a total of 44,600 new cases (see Figure 2). The average age of an AML patient is 67, while the average age for CML is 65, indicating disease prevalence in older age groups (American Cancer Society, 2013). Within gender groups, epidemiologic studies show both AML and CML as slightly more prevalent among men when compared to women (American Cancer Society, 2012).

AML and CML affect a variety of ethnic groups, including African-Americans, Caucasians, Hispanics, Asian/Pacific Islanders, and American/Indians. Within racial groups, incidence rates were highest in Caucasians, Hispanics, African-Americans, and Asian/Pacific Islanders while American Indian/Alaskan Natives had the lowest incidence from 2005 to 2009. Death rates due to this disease during the same time were highest in Caucasians and lowest in Hispanics and Asian/Pacific Islanders (SEER Stat Fact Sheets: Acute, n.d.). During this same time frame, CML incidence rates are highest for Caucasians and African-Americans and the lowest for Asian/Pacific Islanders. Additionally, the death rates are highest in American Indian/Alaska Natives and African-Americans. The death rates are the lowest in Hispanics and Asian/Pacific Islanders (SEER Stat Fact

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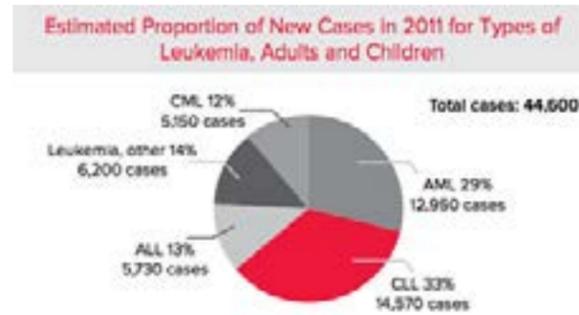


Figure 2. The total cases of leukemia in 2011 and breakdown of the proportion of individuals with AML and CLL. During that year, approximately 29% of leukemia cases diagnosed were AML while 12% were attributed to CLL (Leukemia and Lymphoma Society, 2012).

Sheets: Chronic, n.d.). Although these differences in incidence are not fully understood, increased incidence rates correspond to high-risk genetic mutations that make myeloid cells more susceptible to deleterious mutations.

Both AML and CML have been associated with certain occupations, major radiation events, and prior health conditions. Involvement in the farming and rubber film production has been connected to a predisposition for myeloid leukemia. Studies in Russia show an increase in the number of AML and CML cases after the Chernobyl disaster. This finding implicates radiation exposure as a possible cause for developing myeloid leukemia. Additionally, the Hiroshima and Nagasaki bombings caused a significant increase in AML and CML cases. While radiation exposure can cause myeloid leukemia, medical conditions give some individuals a higher risk of developing myeloid leukemia. Hematologic disorders, such as megaloblastic anemia and paroxysmal nocturnal hemoglobinuria, confer a higher risk of developing myeloid leukemia. In addition to these disorders, the Down's syndrome genetic mutations predispose individuals to AML and CML because these diseases share similar mutations (Henderson, Lister, & Greaves, 2002). Although AML and CML have a lower incidence rate when compared to other cancers, such as breast and colon cancer, AML is the second leading leukemia in mortality.

Molecular Causes and Mechanisms

Chemicals, such as benzene, some chemotherapy drugs that are classified as alkylating agents, as well as radiation have been shown to cause myeloid leukemia (NCBI, 2013). Benzene metabolites induce some of the hallmark genetic changes of myeloid leukemia, such as aneuploidy of chromosomes 7, 8, and 9 as well as the translocation of chromosomes 8 and 21 t(8;21) (Smith, 1996). Although this hydrocarbon solvent can cause deleterious genetic alterations, the most common culprits in chemically-induced leukemia are ironically the same chemicals that are commonly used to fight other cancers. The most notable chemotherapeutic chemicals are alkylating agents, such as cyclophosphamide, chlorambucil, and melphalan as well as other agents such as cisplatin and carboplatin. A fifth of those people cured of lymphoma, ovarian cancer, or Hodgkin's disease develop AML within five years of treatment with an alkylating agent. In addition to these chemotherapeutic agents, ionizing radiation has been shown to cause myeloid leukemia. Those individuals over the age of 45 that survived the bombings at Hiroshima and Nagasaki experienced higher rates of AML. Additionally, when the blast

cells of de novo leukemia were compared to that of radiation-induced leukemia, there was a higher incidence of monosomy 7 and translocation of c-myc; this suggests radiation as a cause of genetic instability (Henderson, Lister, & Greaves, 2002). Among the known causes of AML include certain chemotherapy drugs and radiation treatment (NCBI, n.d.). With cancer rates rising, and with it chemotherapy and radiation treatments, the importance of further elucidating the mechanisms and treatment of AML is increasing.

On the molecular level, 749 genetic aberrations have been identified in AML; the four most common are t(15;17), t(8;21), Inv(16), and t(6;11).

Ethnicity/Race	Survival Rate
Asian	90.7%
Non-Hispanic White	88.8%
Pacific Islander	85.6%
Hispanic	83.8%
American Indian/Alaska Native	85.6%
African American/Black	77.5%

Table 1. Four most common genetic alterations associated with AML

The t(15;17) translocation can be found in many AML cases and results in the PML-RAR(alpha) oncofusion protein. This fusion protein acts as a constitutive transcriptional repressor that interferes with gene expression programs involved in differentiation, apoptosis, and self-renewal. Yet another translocation is t(8;21), which results in the AML1-ETO oncofusion protein. AML1 is a transcriptional factor that plays a crucial role in hematopoietic differentiation. If AML1 undergoes a mutation, myeloblast will not differentiate properly into mature granulocytes and will begin to accumulate in the blood. In combination with ETO, which functions as a transcriptional repressor, this oncoprotein is thought to function as a transcription repressor. Additionally, AML is caused by inversions, such as Inv(16), which results in the CBFbeta-MYH11 oncofusion protein; this results in a transcriptional repressor. Yet another alteration comes in the form of MLL rearrangements, as a result of the translocation of chromosomes 6 and 11, and is present in at least 10% of acute leukemia patients, including AML. The MLL protein fuses to one of more than 50 partner genes, resulting in a potent, cancer-causing, protooncogene (Martens, 2010). It is possible that MLL-fusion proteins cause chromatin structure defects by altering the histones associated with the transcription start site (Martens, 2010). It has been shown that MLL rearrangements can also transform myeloid progenitor cells, that normally cannot self-renew, to have stem-cell-like renewal qualities (Huntly, 2004).

In addition to the four major genetic aberrations, the MOZ-TIF2 aberration is present in approximately 2% of those with AML. The various other mutations are present in less than 1% of AML cases (Martens, 2010). MOZ-TIF2 is the result of the inverse of (8)(p11q13). This juxtaposition is thought to modulate transcriptional activity of target genes in leukemia through the process of deviant histone acetylation (Carapeti, 1998; Lin & Sessa, 2004). MOZ-TIF2 enhances hematopoietic stem cell (HSC) and progenitor cell self-renewal capability that these cells would not normally have, allowing them to aberrantly proliferate as in the case of AML (Lin & Sessa, 2004).

In most cases, one of the partners in these fusion proteins code for a transcriptional protein and as a result, AML-fusion proteins have abnormal transcriptional regulatory activity. Although the resulting expression patterns vary and can be used to classify AML subtypes, all of the fusion proteins interfere with the process of myeloid maturation and differentiation, hallmark alterations of AML (Martens, 2010). This is indicative of a common molecular mechanism that functions to transform cells. It is suggested that aberrant regulation in signaling, apoptosis, and cell structure pathways are affected. These mechanisms that alter gene transcription, especially the function of histone acetylation, are associated with malignancies, specifically AML.

Similarly to AML, CML is categorized as a hematopoietic stem cell disease but is caused by BCR-ABL translocation, which manifests itself in a constitutively active and unregulated protein tyrosine kinase. This gives HSC's the ability to proliferate in an irregular fashion (Lin & Sessa, 2004) in their immature form. While the function of BCR is not completely understood, ABL is known to function as a protooncogene and encodes for a tyrosine kinase, which regulates the process of cell differentiation (NIH, 2012). The translocation of the long arms of chromosomes 9 and 22 create an altered chromosome 22, deemed the Philadelphia Chromosome, and encodes a constitutively active tyrosine kinase (see Figure 3) (Druker & Talpaz, 2001).

In CML, the HSC halted development at the immature stage and increased proliferation, the former that results in a loss of differentiation ability, results in the hallmarks of CML. This uncontrolled growth is partly due to BCR-ABL's activation of the Ras signaling pathway and its linkage to the Ras activator, son-of-sevenless (SOS) (Lin & Sessa, 2004; Martens, 2010).

These aberrations confer CML stem cells with a proliferative advantage in the form of preleukemic events, increasing their chances of survival. Preleukemic events include overexpression of Bcl2 and the underexpression of JunB; these changes increase proliferation and survival potential in HSC's of CML (Lin & Sessa, 2004; Passegue, 2004). Bcl2 proteins have an anti-apoptotic function and when overexpressed can lead to cancerous cells (Gene Cards), while JunB functions as a tumor suppressor by forming less effective transactivating domains (Chen). In this capacity as a tumor-suppressing agent, JunB functions as a transcription factor that regulates the number and development of myeloid cells (Passegue, 2004). Studies have shown that inactivation of JunB expands the number of leukemia HSC's as well as myeloid progenitor cells, resulting in myeloproliferative disorders, such as CML.

Although AML and CML are distinctly different cancers, leukemia associated fusion proteins that interfere with the process of hematopoietic differentiation provide the molecular basis for myeloid leukemia. This interference results in immature myeloid cells that accumulate in the bone marrow and blood stream, causing some of the classic myeloid leukemia symptoms.

Diagnosis and Disease Progression

Individuals with myeloid leukemia usually experience fatigue, fever, shortness of breath, frequent infections, weight loss and or skin rash, and upon physical examination, there may be signs of swollen lymph nodes, spleen, or liver. If a physician suspects a patient has AML the doctor will usually

Type	Name	Cytogenetics	% of Adult Patients
M0	Minimally differentiated AML		5%
M1	Acute myeloblastic leukemia w/o maturation	t(6;11)(q27;q23)	15%
M2	Acute myeloblastic leukemia, with granulocytic maturation	t(8;21)(q22;q22), t(6;9)	25%
M3	Acute promyelocytic leukemia	t(15;17)	10%
M4	Acute myelomonocytic leukemia	inv(16)(p13;q22), del(16q)	20%
M4eo	Myelomonocytic w. bone marrow eosinophilia	inv(16), t(16;16)	5%
M5a M5b	Acute Acute	del(11q), t(9;11)	10%

Table 2. The subtypes of AML as well as the cytogenetic aberration(s) that is associated with the subtype as classified by FAB classification system. It also provides an approximation of the proportion of patients with each subtype (Henderson, Lister, & Greaves, 2002; Rulina, 2010)

carry out two tests: complete blood count (CBC) and bone marrow aspiration. If it is indeed myeloid leukemia, the CBC will indicate anemia and a low platelet count (NCBI, 2013) with white blood cell counts variable. Bone marrow aspiration usually confirms the diagnosis and involves removing a small amount of marrow tissue, usually taken from the hipbone (Bone Marrow Aspiration, 2013). The aspiration samples are examined by light microscopy or flow cytometry to detect the presence of leukemic cells and hypercellularity (see Figure 4). Additionally, karyotyping or FISH testing identifies the chromosomal abnormalities, which aid in the diagnosis on CML and the classification of the AML subtype (see Figure 4) (NCBI, 2013).

The most accepted mode of disease classification is the French-American-British Classification (FAB) system, while the more clinically applicable WHO Classification system can also be used (see Table 2). The FAB classification aids in identifying which stage of the disease a patient is in, while the overall progression of AML is as follows. Myeloid stem cells progress to become immature WBC's (myeloblasts), RBC's, or platelets, all of which are abnormal. These aberrant cells are called leukemic cells or blast cells and rapidly accumulate, due to the mutations that give the cells a survival and proliferative advantage. These blast cells accumulate in the bone marrow and do not function properly, resulting in frequent infections, anemia, and easy bleeding (NCBI, 2013).

Cytogenetic testing provides information on average survival rates and post-treatment relapse of AML patients (see Table 3) (Grimwade, 2001). As the table indicates the favorable cytogenetic types have the highest survival rates while the unfavorable subtypes have significantly lower survival rates. The trend also points to inversions and translocations as favorable over whole arm losses and multiple abnormalities. It is curious that a normal karyotype does not confer an advantage over the favorable translocations listed here. More than half of newly diagnosed AML have a normal karyotype. Therefore, identifying molecular markers can aid in assessing the risk level and disease prognosis (Bienz, 2005).

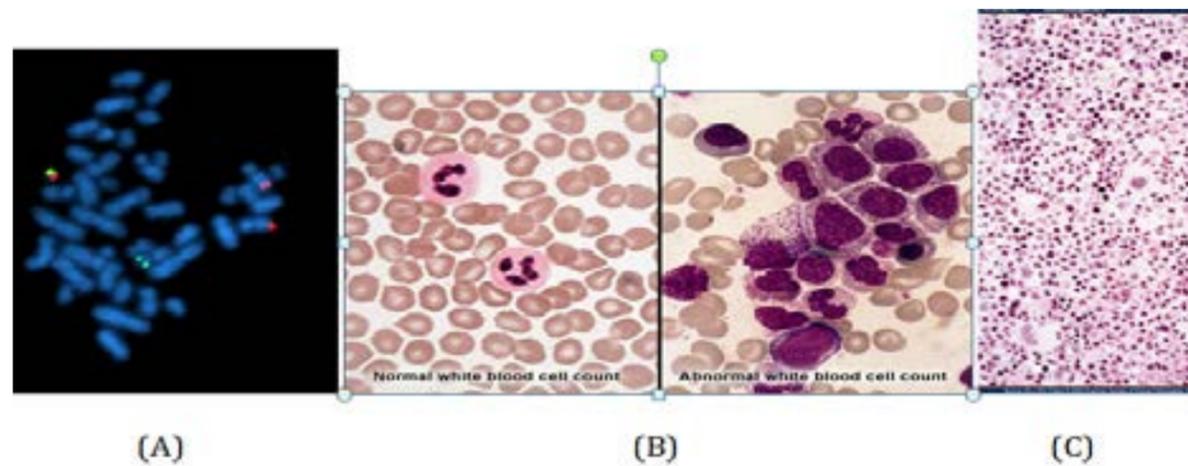


Figure 4. (A) This metaphase cell show the results of a FISH analysis on a CML patient. The green dots represent the BCR gene on a normal chromosome 22 and the red dots represent ABL gene on chromosome 9. On the left hand side, the fusion on green and red represent the Philadelphia chromosome and the fusion of BCR and ABL in CML (Philadelphia Chromosome, n.d.). (B) Normal blood smear (left) and CML blood smear (right). The CML blood smear shows an increased number of abnormal cells (large purple) (Leukemia-Acute, n.d.). (C) Bone marrow aspirate of CML patient. This aspirate shows a high concentration of cells, known as hypercellularity, which is an indicator of CML (Sibaud, 2003).

Cytogenic Subtype	Cytogenetics	5-year survival
Favorable	t(15;17)	63 +/- 4
	t(8;21)	69 +/- 4
	inv(16)	61 +/- 7
Intermediate	Trisomy 8	48 +/- 4
	Normal	45 +/- 2
	11q23	45 +/- 6
	Trisomy 21	47 +/- 7
Unfavorable	-7	10 +/- 4

Table 3. Favorable risk is indicative of a low risk of relapse post-treatment, improved response to therapy, and high-likelihood of long-term survival (Chustecka, 2008; Liao & Schiller, 2003) Intermediate risk indicates that post-chemotherapy, there is no clear high or low risk for relapse (Henderson, Lister, & Greaves, 2002; Intermediate Risk, n.d.). Unfavorable risk describes genetic changes that remain resistant to various treatments and confers a high chance of relapse (Henderson, Lister, & Greaves, 2002).

In addition to karyotype classification, there are specific mutations that help to categorize patients into risk groups and possible treatment options. Included in this group are mutations to the following genes: CEBPA, FLT3-ITD, BAALC. CEBPA (CCAAT/enhancer-binding protein alpha) functions as a tumor suppressor and is believed to disrupt the tumor suppressor function of the protein produced by the second copy of the gene. Two mutations to this gene, an inherited and a sporadic mutation, impair the DNA-binding ability of the CEBPA protein. This decreased binding ability interferes with the protein's ability to regulate gene expression and its tumor suppressor function consequently causing aberrant production of abnormal blood cells in AML (NIH, n.d.). Mutations on this gene are present in patients with an intermediate risk and are classified as M1 in the FAB classification system (Preudhomme, 2002). FLT3 (Stem cell tyrosine kinase) internal tandem duplication (ITD) mutations are also important in risk classification because FLT's normal proteins are expressed on the surface of hematopoietic progenitor cells. Additionally, its signaling plays an integral role in

the proper development on HSC and progenitor cells (Schnittger, 2005). In AML, a mutation on this gene is the most important risk factor in high-risk patients who are most likely to relapse after treatment (Kottaridis, 2001). When a CEBPA mutation is present with an FLT3-ITD mutation, the risk classification increases significantly (Preudhomme, 2002; Renneville, 2009), signifying its importance in risk classification. Yet another contributor to high-risk classification is a mutation on the BAALC (Brain and acute leukemia, cytoplasmic) gene. BAALC is expressed in normal early hematopoietic progenitor cells, undifferentiated, and differentiated myeloid cells (Huret & Senon, 2006). Normally, down regulation of BAALC expression occurs with differentiation, while in AML, overexpression is associated with disease resistance to treatment, high CIR (cumulative incidence of relapse), and inferior survival (Baldus, 2006; Huret & Senon, 2006).

While the disease classification for AML is complex, it is simple for CML; there are three phases: chronic, accelerated, and the blast phase. Each phase coincides with the number of immature leukemic or blast cells are present in the blood and bone marrow. Those in chronic phase have blast cells in concentrations of approximately 10% and have very few symptoms. In the accelerated phase, blast cells begin to accumulate in the blood and bone marrow, increasing to 10%-30% in concentration, and can be detected under a microscope (Phases of Chronic Myeloid Leukaemia, 2012). This phase includes fewer observable red blood cells and platelets as well as variations in the number of white blood cells (CML Phases, 2012). The most advanced stage, the blast phase, usually proceeds months after the accelerated phase and is characterized by blast cells in concentrations greater than 30% (Phases of Chronic Myeloid Leukaemia, 2012). This phase begins to resemble AML in severity and can be life threatening (CML Phases, 2012). The disease classifications as well as the genetic changes are important to understand because they both can help find the most suitable treatment.

Current Treatment and Success Rates

Most types of AML are treated with chemotherapeutic agents, such as daunorubicin or cytarabine and/or bone marrow transplants. While these treatments are helpful, these agents also carry with them negative side effects that include bleeding, increased risk of infection, weight loss, and mouth sores (NCBI, 2013). When administering chemotherapy, it is divided into two steps: induction and consolidation (post-remission). The purpose of induction is to reduce the number of blast cells in the bone marrow and usually involves 2 or 3 chemotherapeutic agents. The success of induction depends on the severity and subtype of AML, while multiple rounds of chemotherapy may be needed during the induction period; complete remission is achieved in 70% to 80% of adults under age 60 and in approximately 50% of adults over the age of 60. The second stage, consolidation, is required to kill the small number of remaining cancer cells and involves either more chemotherapy or a stem cell transplant; this is usually successful in gaining remission in patients under the age of 60 (LeMaistre & Shaughnessy Acute, n.d.).

Bone marrow transplants can be done in one of two ways, allogenic or autologous bone marrow transplants. Allogenic transplants are taken from HLA (MHC antigen)-identical sibling donors are usually more successful than autologous transplants, by which bone marrow is taken from the patient (Hsu, 2005; Suci, 2003; Zittoun, 1995). In patients with high-risk cytogenetics, allogenic transplants are usually performed (Suci, 2003). Together, chemotherapy and bone marrow transplants produce higher success rates than when performed alone (NCBI, 2013; Zittoun, 1995). While bone marrow transplants usually increase remission rates, the risk of death increases with this treatment (NCBI, 2013). The survival rates after transplantation for early and intermediate stages of AML are approximately 50% and drop to around 10-20% in advanced stages; this holds true for both allogenic and autologous transplants (LeMaistre & Shaughnessy, n.d.). Supportive treatments include antibiotics to treat infections, blood transfusions to fight anemia, and platelet transfusions to control bleeding (NCBI, 2013).

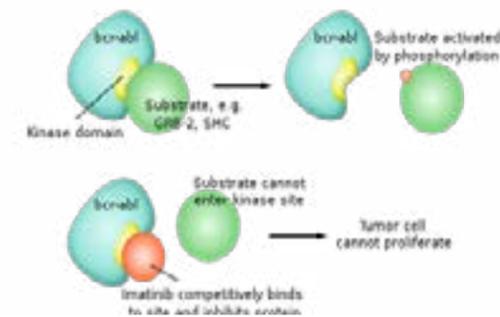


Figure 5. Gleevec functions by competitively inhibiting the active site in which leukemia related proteins would be over-phosphorylated (NIH, n.d.).

The most widely used and successful treatment for CML is tyrosine kinase inhibitors (TKI's), which function by shutting down the constitutively activated tyrosine kinase, BCR-ABL. As in AML, allogenic bone marrow transplantation can also be used to treat CML (Druker & Talpaz, 2001); it is the only curative treatment for CML but is limited to those patients that can find a suitable donor (NCBI, 2013). The lack in donor availability leads many to use TKI's, such as imatinib mesylate,

a well-accepted and tolerated CML treatment (NIH, n.d.).

Increased tyrosine kinase activity over-phosphorylates effector molecules involved in cell proliferation and survival; therefore inhibiting its activity eliminates the proliferative effects of the Philadelphia Chromosome and in many cases halts the progression of the disease (see Figure 5) (NIH, n.d.). The results of a 5-year study on Gleevec showed that after 60 months of treatment 98% of patients showed a complete hematologic response, indicative of their blood cell composition returning to normal. Additionally, the survival rate for these patients was 89% with the relapse rate only 17% (Druker, 2006). This successful therapy has contributed to the 5-year survival rate of 59.1% (SEER Stat Fact Sheets: Chronic, n.d.). Future treatment options and novel therapies should be investigated, due to the 23.4% survival rates of AML patients (SEER Stat Fact Sheets: Acute, n.d.).

Future Treatments

Future treatments that target myeloid associated signaling pathways as well as associated proteins that are expressed on leukemic cells may represent novel therapies. The MEK/MAPK signaling pathway plays a major role in cell proliferation, differentiation, and cell survival. Additionally, the constitutive activation of this pathway is one of the hallmarks of AML and can aid a cancerous cell is avoiding apoptosis, proliferation, and treatment resistance. Targeting the over-phosphorylation of this pathway presents a possible treatment for AML. Additionally, long-term cell survival of normal cells remains unaffected (Milella, Steven, & Estrov, 2001). Signaling pathways as well as leukemic stem cell phenotypes may be targeted for possible treatments. It has been previously established that leukemia stem cells of AML have a phenotypic description of CD34+/CD38- or CD34+/HLADR-. As stem cells play an integral role in AML, treatments that focus on these cells could be studied as novel therapies. CD123/CD34+ receptors have been identified as a primitive marker of leukemic stem cells and targeting these receptors may be a promising strategy for the removal of AML cells (Jordan, 2000).

In addition to signaling pathways and stem cell phenotypes, treatments that target nuclear factor kB may be advantageous in the future treatment of AML. Previous studies have found that normal progenitor cells do not express NF-kB while NF-kB is active in leukemic stem cell populations. Treatments that inhibit NF-kB may potentially induce leukemia-specific apoptosis by proteasome inhibitors, such as MG-132, a well-known inhibitor of NF-kB (Guzman, 2001).

Conclusion

Although major steps have been made in the cause and treatment of myelogenous leukemia there is still much that can be elucidated about this cancer, especially regarding AML. While there is a very successful treatment plan for CML, AML lacks a treatment that is as effective as the TKI Gleevec. Further research into the future treatments mentioned here may possibly lead to a more successful treatment than chemotherapy and bone marrow transplants. Although this cancer accounts for a small proportion of total cancer cases, a new therapy may not only affect AML sufferers. Although Gleevec was intended for CML, it has proven effective in treating advanced and metastatic gastrointestinal stromal tumors. It is possible that an AML treatment that targets a general pathway, such as MEK/MAPK pathway, may prove beneficial to other diseases. Further research into myeloid leukemia, the stem cells involved, and its molecular mechanisms is of importance because it will provide more information on developmental processes that play a role in

the regulation of the circulatory system.

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References

- American Cancer Society. (2013, January 18). Leukemia--acute myeloid (myelogenous). Retrieved March 20, 2013, from <http://www.cancer.org/cancer/leukemia-acutemyeloidaml/detailedguide/leukemia-acute-myeloid-myelogenous-key-statistics>
- American Cancer Society. (2012, June 4). Leukemia--chronic myeloid (myelogenous). Retrieved February 20, 2013, from <http://www.cancer.org/cancer/leukemia-chronicmyeloidcml/detailedguide/leukemia-chronic-myeloid-myelogenous-what-is-c-m-l>
- American Cancer Society. (2013, March 20). Leukemia--chronic myeloid (myelogenous). Retrieved January 18, 2013, from <http://www.cancer.org/cancer/leukemia-chronicmyeloidcml/detailedguide/leukemia-chronic-myeloid-myelogenous-key-statistics>
- Baldus, C. (2006). BAALC expression and FLT3 internal tandem duplication mutations in acute myeloid leukemia patients with normal cytogenetics: prognostic implications. *Journal of Clinical Oncology*, 24 (5), 790-797.
- Bienz, M. (2005). Risk assessment in patients with acute myeloid leukemia and a normal karyotype. *Clinical Cancer Research*, 11, 1416-1424.
- Bone marrow aspiration. (2013). In National Center for Biotechnology Information. Retrieved February 26, 2013, from <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004124/>
- Carapeti, M. (1998). A novel fusion between MOZ and the nuclear receptor coactivator TIF2 in acute myeloid leukemia. *Blood*, 91 (9), 3127-3133.
- Center for Disease Control and Prevention. (2012, May 21). Blood cancers: leukemia, lymphoma, myeloma. Retrieved February 19, 2013 from <http://www.cdc.gov/Features/HematologicCancers/>
- Chen, F. (n.d.). JUNB . Retrieved March 28, 2013 from Atlas of Genetics and Cytogenetics in Oncology: transactivating dimers.
- Childhood acute myeloid leukemia/other myeloid malignancies treatment. (n.d.). Retrieved March 28, 2013, from <http://www.uchospitals.edu/online-library/content=CDR258000>
- Chustecka, Z. (2008, May 1). Refinements in the risk classification for acute myeloid leukemia. Retrieved March 28, 2013, from <http://www.medscape.com/viewarticle/573844>
- CML Phases. (2012, May 3). Retrieved March 28, 2013, from: <http://www.lls.org/diseaseinformation/leukemia/chronicmyeloidleukemia/cmlphases/>
- Druker, B. J. (2006). Five-year follow-up of patients receiving Imatinib for chronic myeloid leukemia. *The New England Journal of Medicine*, 355 (23), 2408-2417.
- Druker, B., & Talpaz, M. (2001). Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *The New England Journal of Medicine*, 344 (14), 1031-1037.
- Gene Cards. (n.d.). B Cell-CLL/Lymphoma-2. Retrieved May 1, 2013, from <http://www.genecards.org/cgi-bin/carddisp.pl?gene=BCL2>
- Grimwade, D. (2001). The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood*, 98 (5), 1312-1320.
- Guzman, M. (2001). Nuclear factor-kB constitutively activated in primitive human acute myelogenous leukemia cells. *Blood*, 98 (8), 2301-2307.
- Henderson, E., Lister, T. A., & Greaves, M. F. (2002). *Leukemia (7th ed.)*. Philadelphia, PA: Saunders.
- Hsu, K. C. (2005). Improved outcome in HLA-identical sibling hematopoietic stem-cell transplantation for acute myelogenous leukemia predicted by KIR and HLA genotypes. *Blood*, 4878-4884.
- Huntly, B. J. (2004). MOZ-TIF2, but not BCR-ABL, confers properties of leukemic stem cells to committed murine hematopoietic progenitors. *Cancer Cell*, 6, 587-596.
- Huret, J., & Senon, S. (2006, February). BAALC. Retrieved March 28, 2013, from: <http://atlasgeneticsoncology.org/Genes/BAALCID739ch8q22.html>
- Intermediate Risk, Induction Therapy? (n.d.). Retrieved March 28, 2013, from <http://www.amlliance.com/questions-to-ask-about-aml.html>
- Jordan, C. (2000). The interleukin-3 receptor alpha chain in a unique marker for human acute myelogenous leukemia stem cells. *Leukemia*, 14, 1777-1784.
- Kottaridis, P. (2001). The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. *Blood*, 98 (6), 1752-1759.
- LeMaistre, C., & Shaughnessy, P. (n.d.). Acute Myelogenous Leukemia. Retrieved March 28, 2013, from [http://marrow.org/Patient/Disease_and_Treatment/About_Your_Disease/AML/Acute_Myelogenous_Leukemia_\(AML\).aspx](http://marrow.org/Patient/Disease_and_Treatment/About_Your_Disease/AML/Acute_Myelogenous_Leukemia_(AML).aspx)
- LeMaistre, C., & Shaughnessy, P. (n.d.). AML Transplant Outcomes. Retrieved March 28, 2013, from http://marrow.org/Patient/Disease_and_Treatment/About_Your_Disease/AML/Transplant_Results.aspx
- Leukemia and Lymphoma Society. (2012). Facts 2012. Leukemia-Acute. (n.d.). Retrieved May 1, 2013, from <http://www.pathologyoutlines.com/topic/leukemiaALL.html>
- Liao, M., & Schiller, G. J. (2003). The role of transplantation in favorable-risk acute myeloid leukemia. H. Lazarus, & M. J. Laughlin (Eds.), *Allogeneic Stem Cell Transplantation* (pp. 177-192). Humana Press.
- Lin, M., & Sessa, W. C. (2004 December). Chronic versus acute myelogenous leukemia: A question of self-renewal. *Cancer Cell*, 531-533.
- Martens, J. H. (2010). The molecular signature of oncofusion proteins in acute myeloid leukemia. *Federation of European Biochemical Societies*, 584, 2662-2669.
- Milella, M., Steven, K., & Estrov, Z. (2001). Therapeutic targeting of the MEK/MAPK signal transduction module in acute myeloid leukemia. *Journal of Clinical Investigation*, 108 (6), 851-859.
- National Cancer Institute. (2012 December, 12). General Information About Chronic Myelogenous Leukemia. Retrieved February 19, 2013, from <http://www.cancer.gov/cancertopics/pdq/treatment/CML/Patient/page1>
- NCBI. (2013). Acute Myeloid Leukemia. Retrieved February 2013, from <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001569/>
- NIH. (2012, April 19). BCR. Retrieved May 1, 2013, from <http://ghr.nlm.nih.gov/gene/BCR%22>
- NIH. (n.d.). CEBPA. Retrieved March 28, 2013, from <http://ghr.nlm.nih.gov/gene/CEBPA>
- NIH. (n.d.). Gleevec. Retrieved May 1, 2013, from <http://www.cancer.gov/newscenter/qa/2001/gleevecqa>
- NIH. (n.d.). Philadelphia Chromosome. Retrieved March 28, 2013, from <http://www.cancer.gov/dictionary?Cdrid=44179>
- NIH. (n.d.). Treatment options for chronic-phase chronic myelogenous leukemia (CML). Retrieved March 28, 2013, from <http://www.cancer.gov/cancertopics/pdq/treatment/CML/HealthProfessional/page4>
- Passegue, E. (2004). JunB deficiency leads to a myeloproliferative disorder arising from hematopoietic stem cells. *Cell*, 119, 431-443.
- Phases of Chronic Myeloid Leukaemia. (2012, February 1). Retrieved March 28, 2013, from <http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Leukaemiachronicmyeloid/Symptomsdiagnosis/Phases.aspx>
- Preudhomme, C. (2002). Favorable prognostic significance of CEBPA mutations in patients with de novo acute myeloid leukemia: a study from the Acute Leukemia French Association (ALFA). *Blood*, 100 (8), 2717-2723.
- Renneville, A. (2009). The favorable impact of CEBPA mutations in patients with acute myeloid leukemia is only observed in the absence of associated cytogenetic abnormalities and FLT3 internal duplication. *Blood*, 113 (21), 5090-5093.
- Rulina, A. (2010). Activated leukemic oncogenes AML1-ETO and c-kit: Role in development of acute myeloid leukemia and current approaches for their inhibition. *Biochemistry*, 75 (13), 1650-1666.
- Schnittger, S. (2005, June). FLT3 (FMS-like tyrosine kinase 3). Retrieved May 29, 2013, from <http://atlasgeneticsoncology.org/Genes/FLT3ID144.html>
- SEER Stat Fact Sheets: Acute Myeloid Leukemia. (n.d.). Retrieved February 25, 2013, from <http://seer.cancer.gov/statfacts/html/amy1.html>
- SEER Stat Fact Sheets: Chronic Myeloid Leukemia. (n.d.). Retrieved February 25, 2013, from <http://seer.cancer.gov/statfacts/html/cm1.html>
- Sibaud, V. (2003). Bone marrow histopathologic and molecular staging in epidermotropic T-Cell lymphomas. *American Journal of Clinical Pathology*, 119 (3), 414-423.
- Smith, M. T. (1996). The mechanism of benzene-induced leukemia: A hypothesis and speculations on the causes of leukemia. *Environmental Health Perspectives*, 104, 1219-1225.
- Suciu, S. (2003). Allogenic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of EORTC/GIMEMA AML-10 trial. *Blood*, 102 (4), 1232-1240.
- Zittoun, R. (1995). Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. *The New England Journal of Medicine*, 332 (4), 217-223.