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

Alexandra Reeder
Department of Biology
Lake Forest College
Lake Forest, Illinois 60045

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-κB (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 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...
In the 1980s, 15% of leukemia patients died from AML. Therapeutic approaches have not changed considerably since then. Hematopoietic stem cells are found in the bone marrow, and their activity can be evaluated with standard laboratory tests. Standard chemotherapy is based on cytotoxic drugs, such as anthracyclines and alkylating agents, which cause DNA damage and cell death. These drugs are effective against most acute leukemias, but their use is associated with significant toxicity. Targeted therapies, such as tyrosine kinase inhibitors and immunotherapies, have been developed to address the limitations of standard chemotherapy. However, further research is needed to improve treatment outcomes and reduce side effects.
normal proteins are expressed on the surface of hematopoietic (Stem cell tyrosine kinase) internal tandem duplication (ITD) in the FAB classification system (Preudhomme, 2002). FLT3 in patients with an intermediate risk and are classified as M1 cells in AML (NIH, n.d.). Mutations on this gene are present consequently causing aberrant production of abnormal blood This decreased binding ability interferes with the protein's ability of the protein produced by the second copy of the gene. Two mutations to this gene, an inherited and a sporadic 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, 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 tumors in AML (NH, 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 FLT3'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, cytotoxicity) gene. BAALC is expressed in normal early hematopoietic progenitor cells, undifferentiated, and differentiated myeloid cells (Hurst & Seren, 2004). 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 (Balduzzi, 2006; Hurst & Seren, 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 Leukemia, 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 50% (Phases of Chronic Myeloid Leukemia, 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

Increased tyrosine kinase activity over-expressing effectors 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) (NH, 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 bone marrow 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 91% (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 by leukemic cell populations have the potential to be very advantageous. 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 unaffacted (Milieu, 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 CD133+ or CD34+/CD117+. As stem cells play an integral role in AML, treatments that focus on these cells could be studied to find new treatments. CD133+/CD34+ receptors treat infections, blood transfusions to fight anemia, and platelet treatments to control bleeding (NCBI, 2013).
the regulation of the circulatory system.

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References


