ACUTE MYELOID LEUKEMIA: CURRENT AND EMERGING THERAPIES AND MARKET CONSIDERATION IN THE WORLD

AKUT MYELOİD LÖSEMİ: TÜM DÜNYADA MEVCUT VE YENİ GELİŞTİRİLEN TERAPİLER VE PAZAR ANALİZİ

Kadir GÜRSOY*

ABSTRACT

Acute myeloid leukemia (AML) is an aggressive, fast-growing cancer beginning inside bone marrow and spreading into the blood system, most often occurring in immature white blood cells. It has the lowest five-year survival rate among other types of leukemia and if left untreated, it can be fatal. Even though there have been significant improvements in the treatment of other related subtypes, AML-targeted therapy development have been limited. The current market for AML drugs cannot fill the high unmet needs in terms of drug safety and efficacy, and the growing aging population presents increased opportunities for new drugs. Considering these driving forces, it is believed that promising opportunities exist for new entrants to capture value from underserved segments of the market. It is estimated that the market size for AML drugs in 2020 will reach US$1.67 billion with an average annual growth of nearly 23%. Therefore, it is highly recommended for pharmaceutical companies to invest in this area of drug development as soon as possible in order to maximize gains from their investments as novel therapeutics enter the AML market at a rapid pace.

Keywords: Acute myleid leukemia, new therapies, market consideration, unmet needs, aging population

* Sosyal Güvenlik Uzmanı, Genel Sağlık Sigortası Genel Müdürlüğü İlaç ve Eczacılık Daire Başkanlığı, Ziyabey Cad. No: 6 Ankara, eposta:kgursoy@sgk.gov.tr Tel: 0 312 207 8730

ÖZET

Akut myleid lösemi, ilk olarak kemik iliğinin içinde gözlemlenen ve sonrasında kan sistemine yayılan, çoğunlukla olgunlaşmamış beyaz kan hücrelerinde ortaya çıkan, agresif ve hızlı bir şekilde büyüyen bir kanser türüdür. Diğer lösemi hastalıkları içinde en düşük hayatta kalma oranına sahip olan ve tedavi edilmediği taktirde ölümcül sonuçlar doğuran bir lösemi türüdür. Diğer benzer alt hastalık gruplarının tedavisinde büyük ilerlemeler mevcut iken, AML odaklı terapilerde yenilikler kısıtlıdır. Mevcut AML ilaçları, ilaçların güvenirliği ve etkililiği açısından yüksek karşılanamayan ihtiyaca cevaz verememekte ve hızla yaşlanan nüfus yeni ilaçlar için büyük bir fırsat sunmaktadır. Buna istinaden, bu alana penetre edecek olan ilaçlar için bu pazarda başarı sağlamanın çok olası olacağına inanılmaktadır. AML ilaç pazarı, yıllık ortalama %23 artış ile 2020 yılında 1,67 milyar Amerikan dolarına ulaşacağı tahmin edilmektedir. Bu yüzden, yenilikçi ilaçların bu pazara çok hızlı bir şekilde giriş yaptıkları düşünüldüğünde, ilaç firmalarının, yatırımlarından elde edecekleri kazançlarını kısa sürede maksimize etmek için bu alanda ilk ilaç geliştiren olma adına hızlı bir şekilde yatırıma yönelmeleri şiddetle önerilmektedir.

Anahtar Kelimeler: Akut myleid lösemi, yeni terapiler, pazar analizi, karşılanamayan ihtiyaçlar, yaşlanan nüfus

INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive, fast-growing cancer beginning inside bone marrow and spreading into the blood system, most often occurring in immature white blood cells. It is characterized by the over-proliferation of immature myeloid cells in the bone marrow, leading to immune deficiencies and restriction of other hematopoietic lineages. The underlying causes of AML are disruptions in the process in which myeloid progenitors differentiate into myeloid cells. The pathogenesis of AML includes chromosomal translocations (cytogenetic) and genetic mutations that result in incomplete differentiation, enhanced survival, and uncontrolled proliferation of myeloid cells and progenitors. In general, methods

of diagnosis for AML consist of light microscopy supplemented with cytochemical analysis, immunophenotyping, molecular genetics, and cytogenetic testing. Patients diagnosed with AML are treated with at least one regimen of first-line chemotherapy, called induction therapy. As the second stage of treatment for patients diagnosed with AML, consolidation therapy seeks to prevent relapse of disease. For eligible patients who have not yet received a transplant, hematopoietic stem cell transplantation is the recommended option to treat relapsed AML. There are studies to develop new novel and emerging therapeutics. AML has the lowest five-year survival rate among other types of leukemia and if left untreated, it can be fatal. Even though there have been significant improvements in the treatment of other related subtypes, AML-targeted therapy development have been limited. The current market for AML drugs cannot fill the high unmet needs in terms of drug safety and efficacy, and the growing aging population presents increased opportunities for new drugs. Considering these driving forces, it is believed that promising opportunities exist for new entrants to capture value from underserved segments of the market. It is estimated that the market size for AML drugs in 2020 will reach US$1.67 billion with an average annual growth of nearly 23%. Therefore, it is highly recommended for pharmaceutical companies to invest in this area of drug development as soon as possible in order to maximize gains from their investments as novel therapeutics enter the AML market at a rapid pace. This paper tries to summarize the background on the disease, its mechanisms and how it is diagnosed currently, then list current and emerging therapies. Afterwards, it explains the market structure and future market expectation, and finally draws a conclusion.

1. Definition and Classification of AML

AML is a cancer of myeloid cells. It is characterized by the over-proliferation of immature myeloid cells in the bone marrow, leading to immune deficiencies and restriction of other hematopoietic lineages (Lowenberg et al, 1999). As a result, other conditions that may arise

from AML include anemia, granulocytopenia, thrombocytopenia (Lowenberg et al, 1999), and patients die largely due to AML-associated complications. The mortality rate of AML is approximately 60% in adults under 65 years old and worsens with increases in age (Lowenberg et al, 1999). AML is the most common type of acute leukemia in adults (National Cancer Institute, 2012).

The underlying causes of AML are disruptions in the process in which myeloid progenitors differentiate into myeloid cells (Alcalay et al, 2001). Because the myeloid differentiation process consists of many steps in which alterations may occur, there is much heterogeneity associated with AML, leading to many AML subtypes (Renneville et al, 2008). Two types of classification system of the AML subtypes exist: the older French-American-British classification system, and the currently used World Health Organization (WHO) classification system (Tables 1 and 2, respectively).

Table 1. French-American-British Classifications of AML (Bennett et al, 1976)

M0: Acute myeloblastic leukemia with minimal differentiation
M1: Acute myeloblastic leukemia without maturation
M2: Acute myeloblastic with maturation
M3: Acute promyelocytic leukemia
M4: Acute myelomonocytic leukemia
M5a: Acute monoblastic leukemia without differentiation
M5b: Acute monoblastic leukemia with differentiation
M6: Acute erythroid leukemia
M7: Acute megakaryoblastic leukemia

Table 2. WHO Classifications of AML (Vardiman et al, 2002)

Acute myeloid leukemia with recurrent genetic abnormalities
Acute myeloid leukemia with t(8;21)(q22;q22), (AML1/ETO)
Acute myeloid leukemia with abnormal bone marrow eosinophils and inv(16)(p13q22) or t(16;16)(p13;q22), (CBF/MYH11)
Acute promyelocytic leukemia with t(15;17)(q22;q12), (PML/RAR[1]) and variants
Acute myeloid leukemia with 11q23 (MLL) abnormalities
Acute myeloid leukemia with multilineage dysplasia
Following MDS or MDS/MPD
Without antecedent MDS or MDS/MPD, but with dysplasia in at least 50% of cells in 2 or more myeloid lineages
Acute myeloid leukemia and myelodysplastic syndromes, therapy related
Alkylating agent/radiation–related type
Topoisomerase II inhibitor–related type (some may be lymphoid)
Others
Acute myeloid leukemia, not otherwise categorized
Classify as:
Acute myeloid leukemia, minimally differentiated
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute myelomonocytic leukemia
Acute monoblastic/acute monocytic leukemia
Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

2. Mechanism of Disease

The pathogenesis of AML involves chromosomal translocations (cytogenetic) and genetic mutations that result in incomplete differentiation, enhanced survival, and uncontrolled proliferation of myeloid cells and progenitors.

2.1. Cytogenetic/chromosomal abnormalities

Chromosomal translocations are particularly common in patients with AML. Chromosomal translocations result in fusion proteins that have newly gained functions. Most of the translocations associated with AML result in the fusion of a transcription factor and a gene involved in survival or apoptosis (Alcalay et al, 2001). The resulting fusion protein usually then has the added ability to serve as a transcription factor in non-regulated ways, acting on downstream genes and interfering with myeloid differentiation and proliferation (Alcalay et al, 2001). The most common fusion proteins involved in AML are: PML/RARα, AML1/ETO, CBFβ/SMMHC, and MLL/AF9 (Alcalay et al, 2001). The PML/RARα is a fusion of the RARα retinoic acid receptor with the PML nuclear protein involved in senescence and apoptosis (Zhong et al, 2000). This fusion protein is present in 95% of the M3 subtype of AML (Grignani et al, 1994). AML1 and CBFβ of the proteins AML1/ETO and CBFβ/SMMHC are both subunits of a key transcriptional regulator involved in hematopoiesis (Britos-Bray et al, 1998). Lastly, the MLL/AF9 fusion protein consists of joining of the mixed lineage leukemia (MLL) transcription factor with the AF9 transcription factor, and represents the most common MLL fusion in AML (Dimartino et al, 1999).

Studies validating the oncogenic effects of these proteins have showed that expression of the PML/RAR or AML1/ETO fusion proteins in U937 myeloid cell line prevents myeloid maturation despite the addition of various stimuli (Gelmetti et al, 1998). As well, expression of CBFβ/SMMHC or MLL-AF9 in mice leads the mice to develop AML that is preceded by defects in myeloid differentiation (Castilla et al, 1999; Corral et l, 1996). These studies suggest that fusion proteins created by chromosomal translocations disrupt normal myeloid differentiation process to enhance progenitor-like maintenance to contribute to AML.

2.2. Genetic mutations

Along with chromosomal abnormalities, gene mutations also contribute to AML onset. The common mutations associated with AML can be considered to fit into three categories: mutations affecting proliferation (FLT3, c-KIT, RAS, PTPN11), mutations affecting myeloid differentiation (AML1 and CEBPA), and mutations affecting cell cycle regulation and apoptosis (p53, NPM1) (Renneville et al, 2008). These mutations contribute to AML in accordance with the two-hit hypothesis of leukogenesis, which states that a combination of mutations (at minimum two) involved in proliferation (class I) and differentiation (class II) work together to contribute to AML (Renneville et al, 2008; Gilliland, 2001). As applied to AML mutations, class I mutations such as FLT3, c-KIT etc. enhance the proliferation and survival of blast cells, while class II mutations such as AML1 and CEBPA disrupt myeloid differentiation (Renneville et al, 2008). For descriptions of some of the genes mentioned above, please refer to Table 3.

Table 3. Descriptions of genes commonly mutated in AML

Gene	Description
FLK3	• Gene encoding a membrane receptor tyrosine kinase (Renneville et al, 2008) • Expressed by myeloid and lymphoid progenitors, involved in survival, differentiation, and proliferation; downregulated upon progenitor differentiation (Renneville et al, 2008) • Overexpressed in AML blast cells (Gilliland, 2001) • Mutation results in constitutive activation of receptor in absence of stimuli; present in 25-45% of cases of AML (Renneville et al, 2008)
c-KIT	• Proto-oncogene whose gene product activates downstream signaling pathways involved in proliferation, differentiation, and survival of cells including hematopoietic stem cells (Renneville et al, 2008)
RAS	• Encodes small GTPase that regulates signaling pathways involved in proliferation, differentiation, and apoptosis (Pylayeva-Gupta, 2011)
PTPN11	• Abbreviation for protein tyrosine standard phosphatase nonreceptor 11 • Encodes SHP2, a protein tyrosine phosphatase involved in pathways downstream of growth factors, hormones, and cell cycle regulators (Chan and Feng, 2007)
CEBPA	• Encodes for protein involved in the cellular balancing of proliferation and differentiation (Pabst and Mueller, 2009)
NPM1	• Gene product participates in cell cycle regulation; interacts with the ARF-p53 tumor suppressor pathway (Renneville et al, 2008; Bertwistle, 2004)
p53	• Encodes a transcription factor involved in initiating cell cycle arrest, DNA repair, and apoptosis upon DNA damage (Levine, 1997; Levine et al, 1991; Finlay et al, 1989)

3. Current Diagnostics

3.3. Morphology

In general, the first method of diagnosis for AML consists of light microscopy supplemented with cytochemical analysis. Bone marrow and peripheral blood samples are taken from patients and stained with Wright-Giemsa or May-Grunwald-Giemsa stains. Staining allows for an extensive morphological analysis that can provide prompt and decisive identification of myeloblastic leukemia in patient specimens. According to the WHO, a diagnosis of AML requires the presence of more than 20% myeloblasts in peripheral blood or bone marrow samples (Swerdlow et al, 2008). Myeloblasts have a number of defining traits that can be observed by visual inspection: large size, a low nucleus:cytoplasm ratio, stippled chromatin, and many nucleoli. In addition, azurophilic granules found in the cytoplasm form characteristic inclusion bodies called Auer rods that can be visualized by microscopy (Dohner et al, 2010).

In addition to microscopy, cytochemical analysis using myeloperoxidase, Sudan black B, and nonspecific esterase stains is used to detect lineage involvement in specimens from patients diagnosed with AML. When present in more than 3% of blasts, myeloperoxidase and Sudan black B staining mark the presence of myeloid lineage (Grimwade, 2001). Nonspecific esterase stains can also be used to detect monocyte lineage.

3.4. Cytogenetics

Cytogenetic testing is used to detect chromosomal abnormalities in patients with a suspected diagnosis of AML. Normal and diseased karyotypes can be determined from patient bone marrow and blood specimens. Currently, the WHO lists seven recurrent chromosomal translocations and inversions that are associated with AML (Swerdlow et al, 2008). Because 55% of adult AML cases are characterized by chromosomal abnormalities, cytogenetic analysis is an essential step in establishing a conclusive AML diagnosis (Van Dongen et al, 1999).

3.5. Immunophenotyping

Immunophenotyping using flow cytometry is used in conjunction with cytochemistry to establish lineage involvement in suspected AML cases. Patient samples are treated with antibodies that bind to a panel of antigen markers on the surface of various immune system cells. These cells are then sorted by flow cytometry based on the presence of specific surface antigens known as the CD cell markers. By evaluating the profile of surface antigens found within a given patient sample, the lineage involvement of an acute leukemia case can be determined. The determination of lineage involvement via immunophenotyping is especially useful in distinguishing AML from other subtypes of leukemia.

3.6. Molecular genetics

DNA and RNA obtained from blood and bone marrow specimens can be subjected to analysis by reverse transcriptase polymerase chain reaction (RT-PCR) for the presence of characteristic gene fusions associated with chromosomal rearrangements in AML, such as s RUNX1-RUNX1T1, CBFB-MYH11, MLLT3-MLL, DEK-NUP214 (Tallman et al, 2005). With varying frequencies, a number of somatic mutations have also been associated with the development of AML. At present, mutations in the NPM1 (nucleophosmin) and CEPBA (CCAAT/enhancer-binding protein alpha) gene are included in the WHO's classification system for acute leukemias (Tallman et al, 2005). In addition, mutations in FLT3 (fms-related tyrosine kinase-3), MLL (mixed lineage leukemia), NRAS (v-ras oncogene homolog), WT1 (Wilm's tumor suppressor gene), and RUNX1 (runt-related transcription factor 1) among other genes are being studied as potential markers of AML (Dohner et al, 2010).

4. Current Therapeutics

4.1. Induction therapy

Patients diagnosed with AML are treated with at least one regimen of first-line chemotherapy, called induction therapy. A standard course

of induction therapy is the 7+3 regimen: cytarabine is administered by infusion for 7 days followed by intravenous administration of daunorubicin for 3 days. This method of treatment has been shown to achieve complete remission in approximately 70% percent of patients within the 18-60 age group (Tallman et al, 2005).

In order to improve the remission rate achieved through induction therapy, a number of alternative therapeutic strategies have been explored. First, induction regimens have been modified by using alternative anthracyclines instead of daunorubicin. For instance, replacing daunorubicin with idarubicin has been reported to improve the remission rate in some AML clinical trials (Berman et al, 1991). Second, regimens with high-dose cytarabine have been compared to standard-dose regimens to determine whether intensifying induction therapy improves patient outcomes. The clinical trial data do not provide conclusive evidence demonstrating that such regimens enhance the complete remission rate in AML patients, but it has been suggested that a higher dose of cytabarine may extend the duration of remission (Kern and Estey, 2006). Finally, the therapeutic benefits of the addition of a third therapeutic agent to induction regimens have been investigated. During clinical trials, adding etoposide to a 7+3 regimen of cytarabine and daunorubicin improved remission duration but did not increase the complete remission rate (Bishop et al, 1990). Moreover, the addition of the purine nucleoside analog cladribine to induction regimens has been shown to result in improved remission rates for AML patients under the age of 60 (Holowiecki et al, 2004). Finally, for patients diagnosed with a subtype of AML called acute promyelocytic leukemia, anthracycline-based induction therapy is supplemented with all-*trans*-retinoic acid (Ryningen et al, 2008).

4.2. Consolidation therapy

As the second stage of treatment for patients diagnosed with AML, consolidation therapy seeks to prevent relapse of disease. For many adult patients under the age of 60, consolidation therapy can extend the disease-free survival period from 4-8 months to 2-3 years (Cassileth et al, 1998).

Consolidation therapy is prescribed in accordance with a given patient's prognosis and overall health. For instance, patients diagnosed with AML driven by cytogenetic alterations with favorable outcomes (e.g. inv(16), t(8;21), and t(15;17)) are treated with additional regimens of chemotherapy. The standard choice is high-dose cytarabine, as consolidation regimens generally consist of high-dose administrations of the therapeutic agent used during induction therapy. On the other hand, allogeneic hematopoietic stem cell transplantation is recommended for patients whose AML is driven by high-risk cytogenetic or therapy-related mutations (Phillips et al, 2012). Naturally, this recommendation is contingent upon the availability of a donor and the patient's ability to survive transplant-related complications. For AML patients who are considered intermediate-risk, the specific regimen of consolidation therapy is determined on a case-by-case basis by considering a host of health-related and personal factors.

Table 4. Drugs currently approved by the FDA for the treatment of AML (National Cancer Institute)

Name	*Brand Name(s)*	*Approval Year*	*Mechanism*	*Indications*
All-*trans*-retinoic acid	Vesanoid (Roche)	1995	Induces differentiation of leukemic promyelocytes	First-line treatment for acute promyelotic leukemia
Arsenic trioxide	Trisenox (Cell Therapeutics)	2000	Fragments DNA	Second-line treatment for acute promyelotic leukemia
Cytarabine	Cytosar-U (Upjohn), Tarabine PFS (Pfizer)	1969	Inhibits DNA synthesis	First-line treatment for most subtypes of AML
Daunorubicin hydrochloride	Cerubidine (Pfizer)	1979	Inhibits DNA synthesis	First-line treatment for most subtypes of AML
Doxorubicin hydrochloride	Adriamycin PFS (Pfizer)	1987	Inhibits DNA synthesis	First-line treatment for most subtypes of AML
Idarubicin hydrochloride	Idamycin PFS (Pfizer)	1997	Inhibits DNA synthesis	First-line treatment for most subtypes of AML

4.3. Relapsed disease

For eligible patients who have not yet received a transplant, hematopoietic stem cell transplantation is the recommended option to treat relapsed AML. In addition, the drug-linked monoclonal antibody gemtuzumab ozogamicin was approved in 2000 to treat patients over the age of 60 who suffered from relapsed AML (Giles, 2005). Although this drug appeared to offer promising results to a patient subgroup that is often ineligible for high-dose chemotherapy and stem cell transplants, it was removed from the market in 2010 due to evidence demonstrating increased patient fatalities as a result of treatment.

Standard treatment options for patients with relapsed AML who cannot receive a stem cell transplant or whose relapse occurs after a transplant are scarcely limited. Such patients may choose to enter clinical trials in order to be treated with novel and emerging therapeutics. A variety of therapeutic agents are currently being investigated to treat AML, such as FLT3 inhibitors, farnesyl transferase inhibitors, epigenetic-targeted drugs, and monoclonal antibody conjugates (Robak and Wierzbowska, 2009). Targeted therapies may provide novel approaches to treating AML in patients with relapsed disease that responds poorly to conventional treatment methods.

5. Novel and Emerging Therapeutics

5.1. Approaches to drug discovery

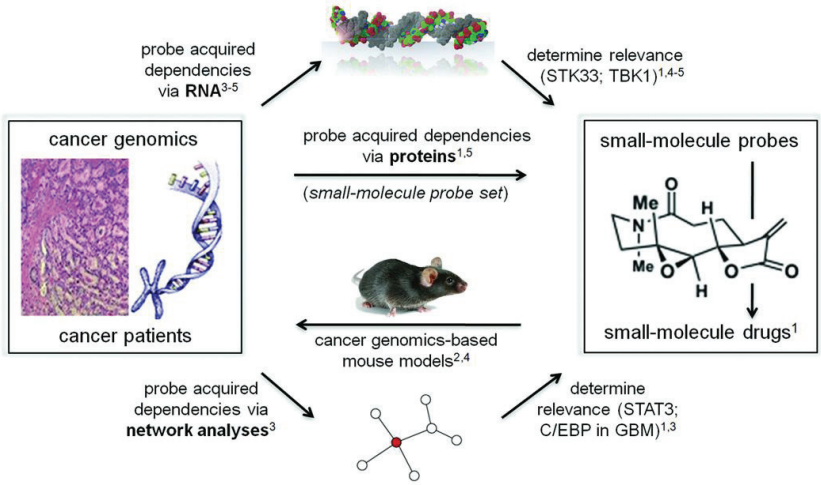
Therapeutic development efforts focus on identifying specific susceptibilities of cancer in an attempt to reduce toxic side effects of common chemotherapeutics. Screening methods are often used to identify potential therapeutic targets, including RNAi screens and functional screens of small-molecule libraries. Other methods of identifying drug targets include network analysis. The image below shows the iterative process of identifying relevant disease targets and drug discovery (Schreiber et al, 2010). Merrimack utilizes mathematical modeling to construct a network analysis of cancer in order to identify drug targets.

5.2. Epigenetics and cancer

Focus on epigenetic proteins have become of increasing interest in the study of cancer, especially of hematopoietic cancers such as AML. Epigenetics refers to heritable information independent of the DNA sequence. This often refers to histone modifications, such as methylation, acetylation, and sumoylation, and DNA methylation. The study of epigenetics is related to chromatin the complex of DNA and proteins that provide the genome structure (Feinberg, 2007).

Potential for targeting epigenetic readers for the treatment of AML is supported by studies indicating genetic mutations in epigenetic enzymes. Genetic mutations in epigenetic reader proteins have been found in AML, affecting DNMT3A, CBP, p300, MOZ, MORF, MLL1, NSD1, NSD3, and JARID1A (Dawson et al, 2012).

Figure 1. Screening methods for drug discovery. Adapted from (Schreiber et al, 2010)



5.3. Bromodomain inhibitors

One type of epigenetic reader domain that has gained recent attention - the bromodomain - binds to acetylated lysines (Prinjha et al, 2012). The importance of bromodomains to the survival of AML

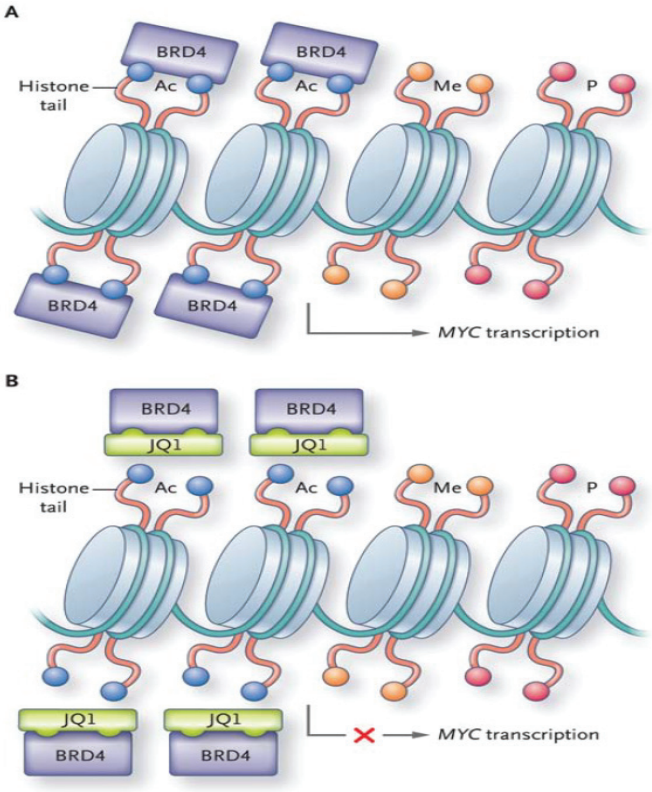
was identified through an RNAi screen. Zuber et al. conducted an RNAi screen of chromatin regulators to look for knockdowns that led to AML growth attenuation. Most potent on the list of hits was Brd4 (Zuber et al, 2011). This screen when linked with a small molecule inhibitor of bromodomains developed at the Dana Farber Cancer Institute launched inhibition of bromodomains for cancer into the spotlight for therapeutic development (Zuber et al, 2011; Filippakopoulos et al, 2010). Brd4 inhibition by RNAi and by small molecule inhibitor JQ1 caused an increase in apoptosis, differentiation into myeloid cells, as well as growth attention in human AML cell lines and in a murine in vivo model of AML (Zuber et al, 2011). Importantly, the potent effect of Brd4 inhibition is mediated through downregulation of MYC, a well-established tumor oncogene (Godley and Le Beau, 2012).

5.4. Market Interest

This work has attracted the attention of pharmaceutical companies and investors. Tensha Therapeutics is looking into bromodomain inhibitor treatment for AML, as well as BRD4-NUT midline carcinoma. They are backed by the venture capital firm HealthCare Ventures[1]. Multiple bromodomain inhibitors called I-BET have also been since developed by GlaxoSmithKline.

1 Tensha therapeutics completes $15 million series A financing to advance selective bromodomain inhibitors for cancer and other disorders. BusinessWire.

Figure 2. Brd4 is an epigenetic reader. Inhibition of bromodomains of Brd4 by small-molecule binding reduces MYC transcription in AML cells. Adapted from (Godley and Le Beau, 2012)

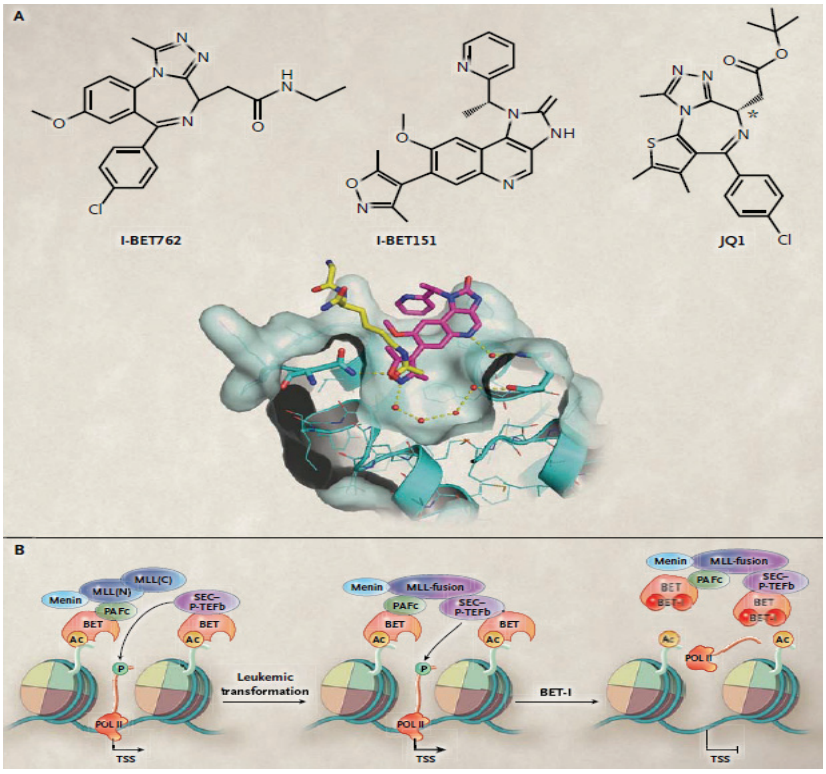


A Phase I clinical trial for a bromodomain inhibitor, OTX015, was conducted by Mitsubishi Tanabe Pharma Company[2]. OncoEthix gained approval from the US National Institute of Health to conduct a Phase I clinical trial to determine appropriate OTX015 dosages in AML and ALL patients[3].

2 OncoEthix In-Licenses OTX015, an anticancer Bromodomain inhibitor from Mitsubishi Tanabe Pharma Corporation," College hill Life Sciences, http://www.collegehill-lifesciences.com/news/2012/06/oncoethix-in-licenses-otx015-an-anticancer-bromodomain-inhibitor-from-mitsubishi-tanabe-pharma-corporation

3 A Phase I, Dose-finding Study of the Bromodomain (Brd) Inhibitor OTX015 in Haematological Malignancies, ClinicalTrials.gov: A service of the US National Institutes of Health, http://www.clinicaltrials.gov/ct2/show/study/NCT01713582

Figure 3. Small-molecule inhibitors in development for bromodomain inhibition for treatment in acute myeloid leukemia. Adapted from (Dawson et al, 2012)



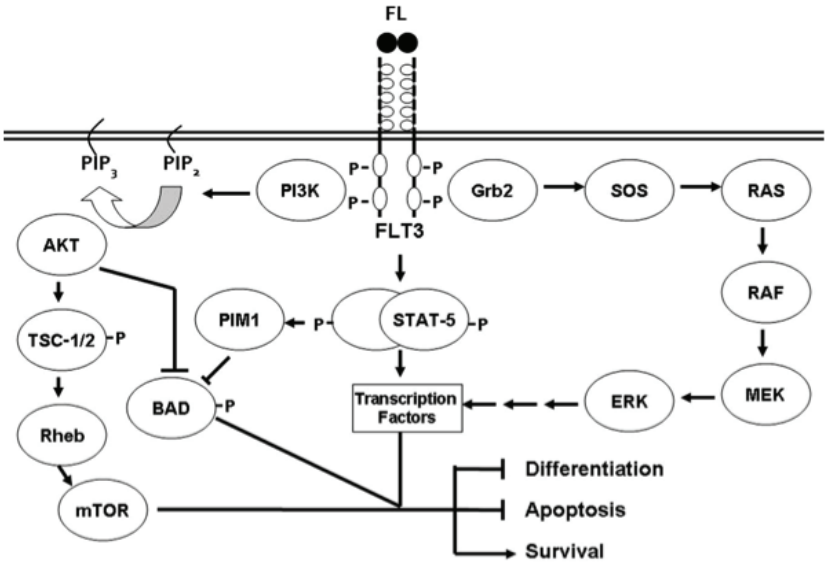
5.5. Sorafenib

Sorafenib tosylate (Nexavar®), a multi-targeted tyrosine kinase inhibitor, was developed by Bayer Pharmaceuticals and is now approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with unresectable hepatocellular carcinoma and advanced renal cell carcinoma (National Cancer Institute). Sorafenib can inhibit multiple receptor tyrosine kinases (RTKs), including FMS-like tyrosine kinase 3 (FLT3), which is mutated in approximately 15-30% of patients with AML (Fathi and Chabner, 2011).

FLT3, a member of the RTK subclass III family, is expressed in normal hematopoetic cells and plays a role in survival, differentiation, and proliferation. Wild-type FLT3 remains a monomer on the cell surface until it binds the FLT3 ligand (FL), which causes FLT3 dimerization, autophosphorylation of the intracellular tyrosine kinase domains, and subsequent activation of multiple signaling pathways (Figure 4) (Stirewalt and Radich, 2003).

Overexpression of FLT3 is demonstrated in many human AML cell lines *in vitro* (both at the transcript and protein levels). The most common activating FLT3 mutations are an internal tandem duplication (ITD) in exon 14, which encodes the juxtamembrane domain (which leads to constitutive, ligand-independent activation of the kinase) and point mutations in exon 20, which encodes the second tyrosine kinase domain (TKD2). Constitutive activation or overexpression of FLT3 can result in dysregulated cell proliferation and the suppression of apoptosis (Stirewalt and Radich, 2003; Birg et al, 1992).

Figure 4. The FLT3 RTK dimerizes upon binding of its extracellular ligand, FL, and activates pathways regulating cellular proliferation and survival, e.g. the PI3K/AKT and MAPK signaling axes (Fathi and Chabner, 2011)

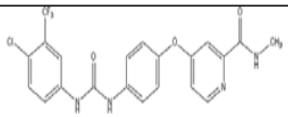
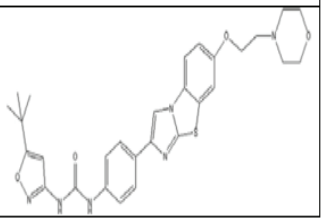


Pre-clinical studies have demonstrated that Sorafenib, a heterocyclic compound, can inhibit both wild type and mutated FLT3 enzymatic and signaling activities in AML blast cells, resulting in growth arrest and apoptosis. The IC50 of Sorafenib (concentration of drug that reduces FLT3 autophosphorylation by 50% as calculated from cell-based assays *in vitro*) is 3 nM in media and 484 nm in plasma (Table 5). Some *in vitro* studies suggest that AML blasts treated with Sorafenib upregulate pro-apoptotic Bim, while others demonstrate downregulation of anti-apoptotic Mcl-2. Many show preferential activity against components of the MAPK signaling cascade (e.g. downregulation of Mek/Erk activity) (Fathi and Chabner, 2011; Wiernik, 2010).

FLT3 mutational status can define prognosis; patients with the FLT3-ITD mutation have a negative prognostic impact (lower overall survival rates and a greater chance of relapse) when compared to patients with wild-type FLT3. Patients with FLT3 point mutations do not demonstrate the same level of negative prognostic impact as patients with FLT3-ITD. One Phase I clinical study of 15 AML patients with refractory/relapsed AML treated with single dose Sorafenib showed a reduction of bone marrow blast percentages in 6 patients; another phase I study from MD Anderson preliminarily demonstrates a reduction in bone marrow blast percentages in 11 out of 20 patients. Nine of these patients had the FLT3-ITD mutation. Due to the high tolerance of Sorafenib as a single dose, it has been used off-label for patients with advanced FLT3 AML (Fathi and Chabner, 2011).

Sorafenib has been used in combination with cytarabine and idarubicin-based induction in a Phase I/II clinical trial with 51 newly diagnosed AML patients. The investigators reported that 38 patients had complete response (CR) post induction, and 14 of 15 patients with FLT3-ITD had CR. However, a Phase II trial from a European multicenter treating elderly AML patients with Sorafenib and standard induction did not report such surprising results (as reported at an American Society of Hematology meeting). Although patients tolerated the combination well, there was no perceivable benefit in terms of CR or event-free survival, even in patients with mutational status (Fathi and Chabner, 2011).

Table 5. IC50 data for novel FLT3 inhibitors. Adapted from (Fathi and Chabner, 2011)

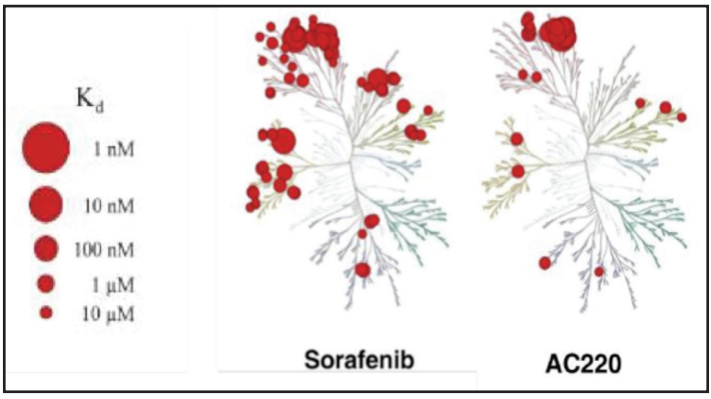
FLT3 Inhibitor	IC50, in vitro FLT3 inhibition, media	IC50, in vitro FLT3 inhibition, plasma	Chemical Structure
Sorafenib	3 nM	484 nM	
AC220	1 nM	18 nM	

5.6. AC220

AC220 is one of the second generation FLT3 inhibitors developed by Ambit Biosciences (San Diego, CA). The new generation of inhibitors has much higher selectivity for FLT3 in comparison to broader multi-kinase inhibitors (e.g. Sorafenib) (Figure 5). AC220 has higher potency and a low IC50 both in media and plasma *in vitro* than most first and second generation FLT3 inhibitors, suggesting AC220 has a high potential in maintaining potency *in vivo* (Table 5) (Zarrinkar et al, 2009).

In a phase I clinical study of 45 patients with refractory/relapsed AML treated with single agent AC220, 11 had transient clinical responses, 4 had CR, and 3 of the total had FLT3 mutational status. Phase II trials are underway at multiple institutions for patients with mutant FLT3 AML using single agent AC220 (Fathi and Chabner, 2011).

Figure 5. Compounds were screened against a KinomeScan (http://www.kinomescan.com) panel of 402 kinase assays. Red circles indicate kinases bound, and circle size indicates binding affinity. Interactions with Kd < 3 uM are shown. Adapted from (Zarrinkar et al, 2009).



6. Novel Diagnostics/Biomarkers

Due to the heterogeneity of AML, there are few efficient biomarkers available to stratify patients based on subtype and risk levels for targeted molecular therapies. Currently, molecular markers screened to determine patient treatment include FLT3-ITD, NPM1, CEBPA and CKIT mutations amongst other, but risk stratification still remains complex.

New studies aim to stratify patient populations quickly and definitively. IDH mutations were recently found in AML, although the prognostic significance of such mutations is still being investigated (Mardis et al, 2012). IDH proteins catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate (alpha-KG), but IDH mutants catalyze the reduction of alpha-KG to 2-hydroxyglutarate (2-HG). One study measured serum, urine, marrow aspirate, and myeloblast 2-HG during conventional therapy for newly diagnosed AML. The results demonstrate that patients with IDH-mutant AML have high baseline levels of 2-HG, which can be measured effectively in serum and urine as a non-invasive biomarker (Fathi et al, 2012).

Another study utilized genome-wide methylation as a method to stratify 344 AML patients into 16 groups. Five new AML subtypes were discovered with distinct clinical outcomes. The study identified a common epigenetic signature detected in the vast majority of cases, and a robust 15 gene DNA methylation classifier that could predict overall survival. The use of epigenetic profiling to define and clinically stratify AML patients into subgroups may lead to the development of novel biomarkers that can streamline clinical trial decision-making and design (Figueroa et al., 2010).

7. Market Considerations

AML is the most common form of acute leukemia diagnosed among adults, and the median age of patients with this disease is 66 years (National Cancer Institute, 2012). In addition, the overall five-year survival rate is only 23.4%, which is the lowest among other types of leukemia. According to the WHO, AML is expected to be more prevalent in the developed world due to genetic and environmental factors, and radiation exposure is the leading cause of all types of AML. Each year, the global incidence of AML is rising steadily. While a total of 62,226 new cases were recorded in 2010, the number of new cases is expected to be 95,211 and 129,837 for 2015 and 2020 respectively (Bodimeade, 2012). Below, current market analysis and future expectations on the AML market are conducted and the barriers into market entry and driving factors on the growth potential of the market are discussed.

The global pharmaceutical market grew by 4.5% in 2011 and reached a level of $839 billion USD (IMS Health, 2011). While average growth in developed markets was 2.8%, that in emerging markets such as China, Russia, Brazil, and India was over four times higher at 12% (IMS Health, 2011). The pharmaceutical spending growth rate is slowing down due to patent cliffs for some blockbuster drugs and cost containment strategies of regulatory authorities such as price cuts, reimbursement restrictions, and increase in standards for approvals of new drugs. The oncology market, constituting 7% of the global market,

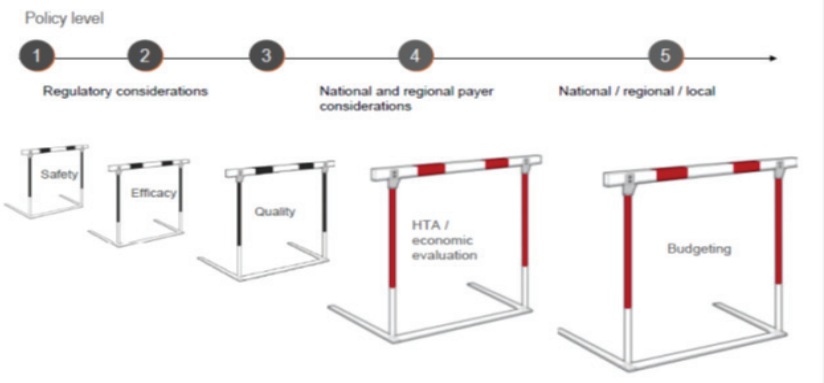
is the steam engine for growth in the overall industry. The market for AML therapeutics in G8 countries (USA, Canada, UK, Germany, Italy, France, Spain and Japan), taking only a tiny portion from the oncology market, aggregated to $216 million in 2010 and the market was dominated by the AVD regimen, accounting for more than half of total sales of AML drugs (Market and Markets Report, 2012). Furthermore, North America, US dominating with a 90% share, was the major contributor to the market, receiving nearly 70% of the market share in 2010; followed by Europe, Germany getting the highest portion.

The main motive behind the barriers into market entry rests in economic consequences. Since governments around the world are seeking to arrive at solutions for rising healthcare costs soon after the latest economic downturn, commercial environment is getting harsher. Healthcare payers are imposing new cost constraints on providers and are evaluating the value of medicines more carefully. They want new therapies that are clinically and economically better than the existing alternatives along with evidence based on real-world outcomes. Health technology assessment plays a crucial role in their reimbursement decisions (Figure 6) (Bagwell and Dujnn, 2011).

Consequently, the regulatory environment is simultaneously getting more rigorous. The European Medicines Agency (EMA) recently introduced a new three-pronged approach to the management of adverse reactions (European Medicines and Agency, 2012) and the FDA is launching an active surveillance system called Sentinel to oversee the safety of all drugs available in the U.S. market (FDA, 2012). Moreover, the FDA Amendments Act of 2007 has compelled the FDA to increase standards for new drugs, introducing mandatory risk evaluation and mitigation strategies into the drug approval process (IMAP, 2011). This illustrates a trend toward more stringent requirements for the approval of new drugs across the world. However, it should also be noted that the FDA has developed Priority Review, Accelerated Approval, and Fast Track programs to ensure new therapies addressing unmet medical need for serious diseases are available as rapidly as possible (FDA, 2012). For example, since 1996, 68 drugs for cancer therapies have received priority review and approval. Finally, the high cost of new

therapies, availability of cheaper generic cytotoxics, and the lack of a comparative Phase III study can also pose barriers to market entry.

Figure 6. Health Technology Assessment. Adapted from (Bagwell and Dunn, 2011).

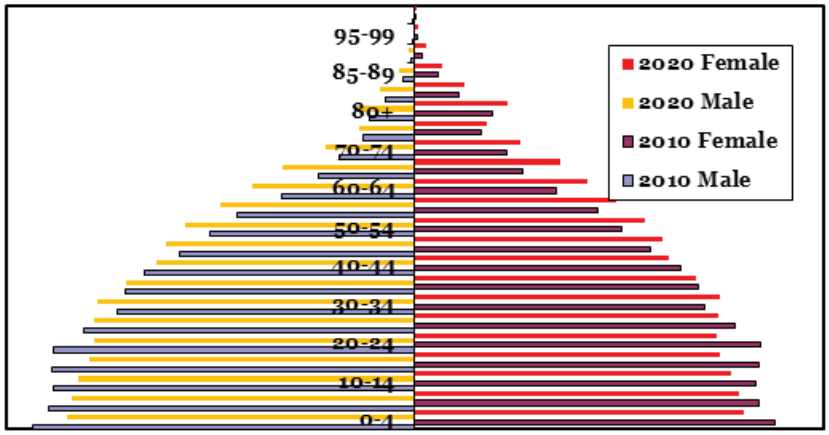


Current therapies for AML are associated with a host of various negative side effects, and some do not offer effective outcomes for elderly patients. Therefore, the market for AML drugs is presently characterized by high unmet needs in terms of drug safety and efficacy, and the growing aging population presents increased opportunities for new drugs. Provided that the yearly incidence of AML among people over 65 is 17.6/100,000 compared to 1.8/100,000 for people under 65 and approximately 300 million additional people will be over the age of 65 in 2020 than in 2010, it is clear that the greater number of AML patients seeking treatment in the next ten years will cause an expansion in the therapeutic market (Figure 7) (Bodimeade, 2012). Moreover, the entry of quality and expensive products in addition to initiatives by various regulatory authorities within the industry concerning the development of AML-targeted therapies will drive the market in the near future.

Based on a report from PwC, the global pharmaceutical market could be worth nearly $1.6 trillion by 2020 with an annual average growth of 7% (PwC, 2012). Moreover, it is estimated that the market size for AML drugs in 2020 will reach $1.67 billion with an average annual

growth of nearly 23%. Taking into account the increase in the elderly subset of the population, high unmet clinical need, and the entry of quality products in the near future, pharmaceutical companies should capitalize on the lucrative nature of the AML market by investing in the development of novel drugs to treat patients diagnosed with AML.

Figure 7. Comparison for global population in 2010 and 2020. Adapted from (United Nations, 2011).



CONCLUSION

Acute myeloid leukemia (AML) is an aggressive, fast-growing cancer beginning inside bone marrow and spreading into the blood system, most often occurring in immature white blood cells. It has the lowest five-year survival rate among other types of leukemia and if left untreated, it can be fatal. Even though there have been significant improvements in the treatment of other related subtypes such as hairy cell leukemia, chronic myeloid leukemia, and non-Hodgkins lymphoma, AML-targeted therapy development has been limited. The current market for AML drugs cannot fill the high unmet needs in terms of drug safety and efficacy, and the growing aging population

offers increased opportunities for the expansion of the therapeutic market. In addition, regulatory authorities such as the FDA and EMA have developed initiatives to incentivize pharmaceutical companies to develop innovative therapies targeting AML. Considering that these driving forces will trigger future growth in the AML market, we believe that promising opportunities exist for new entrants to capture value from underserved segments of the market. Therefore, we recommend pharmaceutical companies to invest in this area of drug development as soon as possible in order to maximize gains from their investments as novel therapeutics enter the AML market at a rapid pace.

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