

Current Management Approaches of Chronic Myeloid Leukemia

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Abstract

Chronic myeloid leukemia is a slowly progressive and clonal myeloproliferative disorder characterized by the presence of Philadelphia chromosome. Even if the global incidence is unknown, CML accounts for 15% to 20% cases of adult leukemia's in USA and is predominantly the disease of adults. It has three phases reflecting the grade of malignancy; chronic phase, accelerated phase and blast crisis phase. Initial diagnosis and monitoring of treatment response is based on hematologic, cytogenetic and molecular assessments that need to be regularly checked. The treatment in each phase had undergone a profound progress over a relatively short period of time, starting with arsenic therapy, radiotherapy, allogeneic hematopoietic stem cell transplantation, recombinant interferon- α , busulfan, and hydroxyurea, and more recently with the tyrosine kinase inhibitors. Among tyrosine kinase inhibitors national comprehensive cancer network puts imatinib, dasatinib and nilotinib as category 1 recommendation for initial treatment of chronic phase chronic myeloid leukemia. Second generation tyrosine kinase inhibitors; nilotinib, dasatinib, bosutinib and ponatinib had shown inducing higher rates of early optimal responses, although their impact on long-term overall survival remains to be determined. There are also drugs for the treatment of chronic myeloid leukemia such as histone deacetylase inhibitors, proteasome inhibitors and farnesyl transferase inhibitors which are under investigation. In addition to these vaccines are under investigation as a part of treatment for chronic myeloid leukemia which still needs further research.

Keywords: Chronic myeloid leukemia; Chromosome; Histone deacetylase

Abbreviations: ABL: Abelson; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; AP: Accelerated Phase; ATP: Adenosine Triphosphate; BC: Blast Crisis Phase; BCR: Break Point Cluster region; CCGRs: Complete Cytogenetic Response; CgR: Cytogenetic Response; CHR: Complete Hematologic Remission; CML: Chronic Myeloid Leukemia; CP: Chronic Phase; DNA: Deoxyribonucleic Acid; FDA: Food and Drug Administration; FISH: Fluorescent *In Situ* Hybridization; GCS: Granulocyte Colony Stimulating Factor; HATs: Histone Acetyltransferase; HDAs: Histone Deacetylase Inhibitors; HHT: Homohar Ringtonine; HSC: Hematopoietic Stem Cell; HSCT: Hematopoietic Stem Cell Transplantation; IL: Interleukin; LSCs: Leukemic Stem Cells; m-BCR: Minor Breakpoint Cluster Region; M-BCR: Major Point Cluster Region; MCgR: Major Cryptogenic Response; MHgR: Major Hematologic Response; mRNA: Messenger Ribonucleic Acid; OS: Overall survival; PAH: Pulmonary Artery Hypertension; PCR: Polymerase Chain Reaction; PDGF: Platelet Derived Growth Factor; Ph: Philadelphia Chromosome; PI: Proteasome Inhibitors; RINF α : Recombinant Interferon- α ; RR: Relative Risk; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; TASH: Tikur Anbessa Specialized Hospital; TKI: Tyrosine Kinase Inhibitors; VEGFR: Vascular Endothelial Growth Factor Response; WBCs: White Blood Cells; WHO: World Health Organization

Introduction

Chronic myeloid leukemia (CML) is a slowly progressive and clonal myeloproliferative disorder resulting from the neoplastic transformation of the primitive hematopoietic stem cell (HSC), which is monoclonal in origin and affecting myeloid, monocytic, erythroid, megakaryocytic, B-cell and sometimes T-cell lineages [1]. CML is characterized by the presence of the Philadelphia (Ph) chromosome which is caused by reciprocal translocation of Chromosome 9 and 22. This reciprocal translocation results in break point cluster region (BCR)-Abelson (ABL) fusion genes and thus CML can easily be delimited from other myeloproliferative neoplasms with similar symptoms or laboratory findings such as polycythemia vera, primary myelofibrosis or essential thrombocythemia [2]. As a result oncogene encodes a fusion

protein (BCR-ABL) with constitutively upregulated TK activity by phosphorylating substrates such as Ras and phosphoinositide 3 kinase, BCR-ABL which then dysregulate the proliferation, transformation, and apoptotic behavior of HSCs [1-4]. Ph chromosome is present in >90% of patients and the BCR-ABL fusion gene is seen in up to 95% of CML patients and gets translated into an oncoprotein, p210BCR/ABL, which is necessary and sufficient for malignant transformation of CML [4,5].

Little is known about the worldwide epidemiology of CML [6-9]. In the USA CML accounts for 15% to 20% of all leukemia's in adults and approximately 8220 new cases of CML were diagnosed in 2015, with an estimated five year survival and the median age at diagnosis was 63 and 64 years, respectively [10]. According to National Cancer Institute, Surveillance, Epidemiology and End result Program CML fact sheet 2016; estimated age-adjusted incidence rate is 1.8 per 100,000 populations, 0.3 deaths per 100,000 population per year and five year survival 65.1% which were based on 2009-2013 case and death reports [11]. With imatinib (Gleevec) therapy, the annual mortality has been reduced significantly (less than 2% to 3% per year, and less after the first 2 to 3 years) [8].

According to the European Treatment and Outcome Study Registry, CML occurs with an incidence rate of about 1-1.5/100,000 population across Europe [12]. According to 2013 report of Cancer Research UK; there were 714 new cases and proportion of CML among all total cancer cases were <1% and incidence rates were decreasing from the

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last 1970s [13]. There is a male predominance with the male to female ratio ranging from 1.1-1.4:1; and CML is exceedingly rare among children and the risk of the cancer rises with age with the median age at diagnosis around 60 years [7].

In South Africa, even if country wide prevalence and incidence of CML is lacking; study done at the University of Witwatersrand in Gauteng; among 119 newly diagnosed patients with CML since 2002 showed a male: female ratio of 1.17:1, with a mean age of 42 years (range 16-88) [6].

In Ethiopia, even if there is no recent published study available, among a total of 7969 medical admissions done from January 1982 to December 1987 at Tikur Anbessa Specialized Hospital (TASH), 180 (2.3%) were Leukemic patients. The age range was 14 to 80 years, with a mean of 37.6 years. The male: female ratio was 2.3:1. The commonest type of leukaemia was CML (57.8%), acute leukaemias and chronic lymphatic leukaemia (CLL) each accounted for 21.1% [14].

Even if the causes of CML are unknown there are risk factors that may increase the risk of developing Ph chromosome which are mainly responsible for the development CML. A number of risk factors have been proposed to be associated with CML. These risk factors can be environmental, chemical and diseases that result in chromosomal translocation and promote excessive Ph chromosome accumulation. By far, radiation, gender, pesticides, and body weight are the majorly discussed risk factors to be associated with CML [15].

A cohort study done on atomic bomb survivors in Japan in the Second World War during 1950-1987 showed strong evidence of radiation induced risk of developing CML [16]. People exposed to radiation from nuclear reactor accidents also showed a higher risk of developing CML. Radiotherapy for another cancer in the past could also increase risk of developing CML but this risk is very small, compared to the benefit of radiotherapy in treating the cancer [17]. The risk of getting CML increases with age and is slightly more common in males than females, but it's not known why [7].

Study results showed that those exposed to pesticides as part of their work (for example, farmers or agricultural workers) had an increased risk of developing CML compared to the general population [18]. Contact with chemical called benzene for some years may also increase CML risk [19]. Furthermore, people who are overweight or obese have a higher risk of developing certain types of cancer. For example, a case control study conducted at the University of Texas showed that obesity and adulthood weight gain play important roles in CML risk than people with a normal body weight [20].

The clinical course of CML is slowly progressive and has three phases reflecting the grade of malignancy; chronic phase (CP), accelerated phase (AP) and blast crisis (BC) phase. Untreated CML typically progresses from CP through an AP at a median of approximately 4 years, and eventually leads to terminal BC disease, with death occurring from bleeding and infectious complications. BC is characterized by a maturation arrest in the myeloid or lymphoid lineage which behaves similar to acute leukemia. The concept of a progression in phases reflects both the natural course and the course under treatment indicating treatment failure [21,22].

Initial diagnosis of CML as well as monitoring of treatment response is based on hematologic, cytogenetic and molecular assessments that need to be regularly checked. Most patients with CML (85%) are diagnosed in CP, very often (50%) as an incidental finding. There are no specific symptoms but symptomatic patients may tell about fatigue,

weight loss, complications of hyper-viscosity such as visual disturbances or priapism; and abdominal discomfort due to splenomegaly [2,21].

The management of Ph positive CML has undergone a profound progress over a relatively short period of time, starting with arsenic therapy, radiotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT), recombinant interferon-alfa (rIFN α), busulfan, hydroxyurea and more recently and most significantly with the tyrosine kinase inhibitors (TKIs) [23].

CML is extensively treated by FDA approved oral TKIs as first line therapy for newly diagnosed patients with CML and show very good treatment response and prolong survival. But the only curative therapy for CML is still allo-HSCT performed during CP [23-25]. Hence, the current article reviews the recent advancement in management of CML and forwards potential future curative therapies.

Literature Review

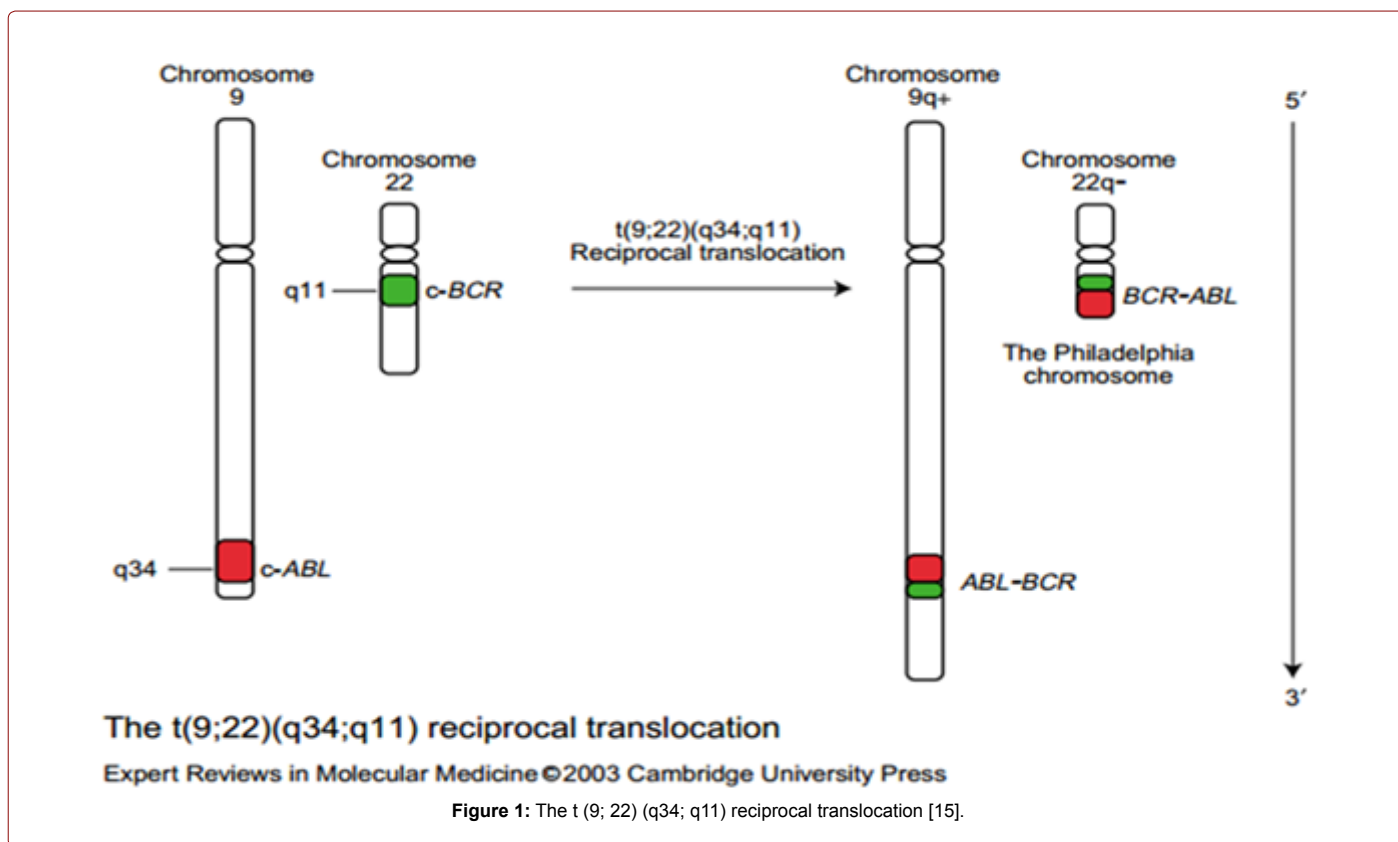
Pathophysiology and clinical pictures

Hematopoiesis is the process of producing the broad variety of all functional hematopoietic lineages including erythrocytes, leukocytes (neutrophils, basophils, eosinophils, lymphocytes, monocytes and macrophages) and platelets which happens to be delivered constantly throughout the life from HSCs [26]. It provides a mechanism of continuous damaged or aged blood cell replacement as well as rapid up-regulation of specific cell types in stress conditions like pathogen invasions [27,28]. It is estimated that maintaining the steady state cell number requires the production of 1010 cells every hour during life. This remarkable generative activity and diversity of produced cells is tightly regulated and coordinated with the current demand in the organism [28,29]. Deregulations along the developmental pathway lead to various hematological diseases like leukemia's, anemias and immune deficiencies. Therefore, elucidating the mechanisms responsible for keeping this finely tuned balance is critical for understanding of both normal hematopoietic development and pathogenesis of hematopoietic diseases [28,29].

The crucial genetic events in CML is the generation of at (9;22) (q34;q11) reciprocal chromosomal translocation in HSC. It took more than two decades until this reciprocal translocation and the resulting fusion gene to be identified. As summarized in Figure 1; the normal chromosomes 9 and 22 carry the c-ABL and c-BCR genes, respectively but the translocation between the long arms of chromosome 9 and 22 resulted in a shortened chromosome 22, commonly known as the Ph chromosome [30]. However, the exact reason for the translocation is not clear but is probably occurring because of simultaneous chromosomal breaks and repairs during mitosis, facilitated by close proximity of chromosomes 9 and 22 in the interphase nucleus. In addition, the translocation results in a longer chromosome 9 that carries the ABL-BCR hybrid gene [15,31].

The fusion of BCR and ABL genes on the Ph chromosome occurs head to tail with the 5' end of BCR coupled to the 3' end of ABL [1,31]. The molecular consequences of this translocation event are the formation of the chimeric gene BCR-ABL on chromosome 22 and a reciprocal ABL-BCR on chromosome 9. The later gene, although transcriptionally active, does not appear to have any functional role in CML and no ABL-BCR protein has, as yet, been identified [32].

Depending on the breakpoint in the BCR gene, three main types of BCR-ABL genes can be formed because of alternative splicing [15]. The first two fusion genes; b2a2 and b3a2 are the most commonly



encountered fusion transcripts in CP CML which had breakpoints in introns 1 or 2 of the ABL gene and in the major breakpoint cluster region (M-BCR) of the BCR gene, either between exons 13 and 14 (b2), or 14 and 15 (b3), respectively. This leads to an abnormal 210-kD chimeric fusion protein (P210BCR-ABL), which is essential and sufficient for the malignant transformation of CML, and responsible for the phenotypic abnormalities of CP CML [33].

In the remaining patients with ALL and rarely in patients with CML; mainly clinically characterized by the presence of the third fusion gene having breakpoints in introns 1 or 2 of ABL gene and between the alternative BCR exons e2' and e2 of minor breakpoint cluster region (m-BCR). The resultant e1a2 mRNA is translated into a 190-kd fusion protein (P190BCR-ABL) [15,34]. The other fusion gene having breakpoints in introns 1 or 2 of ABL gene and μ -BCR gene identified downstream between exons 17 and 20, giving rise to a 230-kd fusion protein (P230BCR-ABL) associated with the rare Ph-positive chronic neutrophilic leukemia, though not found in all cases [35]. Generally, a graphical view of the most common transcripts and a summary of their frequencies are given in Figure 2 and Table 1, respectively.

In contrast to ABL, BCR-ABL exhibits deregulated TK activity and are found exclusively in the cytoplasm of the cell, complexed with a number of cytoskeletal proteins. These two features appear to underlie the ability of BCR-ABL to induce a leukemic phenotype. TK are enzymes that catalyze the transfer of the phosphate group from ATP to target proteins. They play important role in diverse normal cellular regulatory processes [36].

The increased TK activity of especially p210BCR/ABL results in phosphorylation of several cellular substrates and in auto-phosphorylation of p210BCR/ABL, which in turn induces recruitment

and binding of a number of adaptor molecules and proteins. Activation of a number of signal pathways by uncontrolled TK activity of p210BCR/ABL leads to malignant transformation by interfering with basic cellular processes, such as control of cell proliferation, apoptosis, differentiation and adhesion [15,32,37]. Uncontrolled cell proliferation is related to constitutive expression by leukemic progenitors of growth-stimulating factors, notably IL-3 and GCS factor [38]. Moreover, CML cells seem to survive longer than their normal counterparts, as a result of a defective apoptotic response to stimuli that would otherwise lead to physiologic cell death [39].

Generally the BCR-ABL protein appears in two conformations: first, the catalytically inactive form with helix α in proximity to the active site and an ion binding between Lys271 and Glu286, which worsens the interaction with ATP and protein substrate, and second, a catalytically active form [40]. This is essential for the efficacy of specific inhibitors of the fusion protein as binding of commonly used inhibitors like Imatinib and Nilotinib which primarily occur in the inactive state. In the contrary, Dasatinib is able to bind to BCR-ABL in both, the inactive and the active conformation [15,41].

As summarized below in Table 2, the typical clinical course of CML has three stages: CP, AP and BC phase. The natural history of CML is a CP for three to five years followed by rapid progression to the fatal BC phase. In two-thirds of patients, the BC phase is preceded by an AP [25,42]. Common signs and symptoms of CML at CP when present are as a result of anemia and splenomegaly. These include fatigue, weight loss, malaise, easy satiety, and left upper quadrant fullness or pain. Rare manifestations include bleeding (associated with a low platelet count and/or platelet dysfunction), thrombosis (associated with thrombocytosis and/or marked leukocytosis), gouty arthritis (from

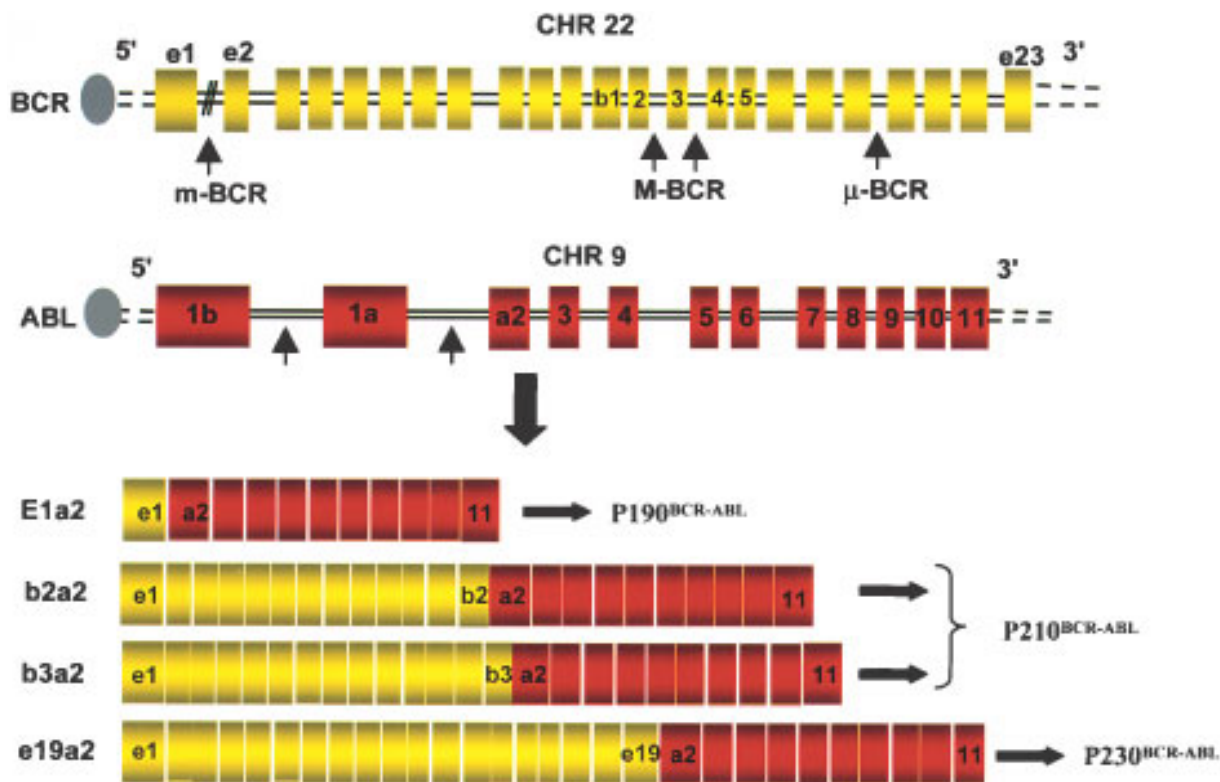


Figure 2: Locations of the breakpoints in the Abelson (ABL) and Break point cluster region (BCR) genes and structure of the chimeric BCR/ABL mRNA transcripts derived from the various breaks [30].

Molecular weight	Abbreviation	Frequency in CML
p210BCR-ABL1	b2a2	31%
	b3a2	62%
	b2a3	<1%
	b3a3	<1%
p190BCR-ABL1	e1a2	<1%

Table 1: Frequencies of break point cluster region-Abelson variants in chronic myeloid leukemia [15].

elevated uric acid levels), priapism (usually with marked leukocytosis or thrombocytosis), retinal hemorrhages, and upper gastrointestinal ulceration and bleeding (from elevated histamine levels due to basophilia) [42].

Splenomegaly is the most consistent physical sign in CML, and is detected in 50% to 60% of cases. Hepatomegaly is less common (10% to 20%). Lymphadenopathy and infiltration of skin or other tissues are uncommon. When present, they favor Ph-negative CML or AP or BP of CML. Headache, bone pain, arthralgias, pain from splenic infarction, and fever are more frequent with CML transformation [25,26,42].

The AP is defined as the presence of 10% to 19% blasts in the blood or bone marrow, basophils >20%, thrombocytosis or thrombocytopenia not related to therapy and clonal evolution in cytogenetic evaluation. The BC phase is characterized by blasts >20% of peripheral white blood cells or extramedullary blast proliferation. Most patients evolve into AP prior to BP, but 20% transit into BP without AP warning signals. AP might be insidious or present with worsening anemia, splenomegaly, and organ infiltration. AP generally leads to a rapidly fatal blast crisis

within 6 months. BP presents as an acute leukemia with worsening constitutional symptoms, bleeding, fever, and infections [25,26].

Investigations and management

Approximately 85% of patients with CML are diagnosed in the CP, of which 40% of them are asymptomatic and the diagnosis is made solely based on an abnormal blood count [25]. But it is important to exclude reactive causes of leukocytosis before embarking upon a workup of myeloid neoplasm because it could be attributable to a number of nonmalignant causes mainly infectious etiologies such as tuberculosis, chronic fungal infections, infective endocarditis, viral, and protozoal infections; connective tissue disorders such as systemic lupus erythematosus [24,42,43].

Once these etiologies have been ruled out, the diagnosis of typical CML can be made based on clinical manifestations such as unexplained leukocytosis (or occasionally thrombocytosis), differential blood count (immature granulocytes and basophilia) and presence of splenomegaly. CML diagnosis is then confirmed by the presence of abnormal Ph chromosome by routine cytogenetics, or Ph related molecular BCR-ABL abnormalities by fluorescent *in situ* hybridization (FISH) or molecular studies [24,42].

Reverse transcriptase-polymerase chain reaction (RT-PCR) amplifies the region around the splice junction between BCR and ABL. Due to this; it is highly sensitive for the detection of minimal residual disease. RT-PCR testing can either be qualitative, providing information about the presence of the BCR-ABL transcript, or quantitative assessing the amount of BCR-ABL message. Qualitative PCR is useful for

diagnosing CML and quantitative PCR is ideal for monitoring residual disease or treatment response monitoring [21,42].

As seen and summarized in Figure 3 the history of CML treatment was started by arsenic which was also the only well-documented therapy for CML in the nineteenth century. Despite some toxicity, several preparations of arsenic continued to be used for the treatment of CML until the introduction of radiotherapy in the first half of the 20th century, which was largely limited to splenic irradiation, offering pain control but no survival benefit [44].

Effective drug therapy for CML began in 1953 with an alkylating agent, oral busulfan, Busulfan's use was limited by significant myelosuppression, marrow fibrosis and prolonged aplasia but remained the preferred therapy for almost 20 years and is still in use as part of conditioning regimens in allo-HSCT. Hydroxyurea was introduced into CML therapy in 1972 and improved median survival rates over busulfan from 44 months to 58 months; however neither therapy prevented progression to AP and BC CML [45,46].

Later, in 1970s, allo-HSCT became the first therapy known to induce a state of Ph-negativity and is still considered the only therapy with the potential of curing CML but at a significant cost in mortality. Moreover, due to the unavailability of donors, allo-HSCT was only offered to a limited number of patients. IFN α was also introduced in the 1980s to patient's ineligible for transplant and was the first drug that induced a CgR and improved survival in approximately one third of the patients. IFN α progressively replaced both busulfan and hydroxyurea in the management of CML [44,46-48].

In 1998, the era of TKIs began thereby replacing the two main treatment options that existed for CML previously. The development of these targeted therapies not only overcame limitations faced by prior conventional treatments but also improve survival of patients with CML [46].

Conventional chemotherapeutic agents: Conventional cytotoxic chemotherapy is used in CP CML to reduce and temporarily control high peripheral WBC counts. Historically, the two agent's busulfan and hydroxyurea has been used for leuko-reduction but busulfan is no longer used because randomized trials have shown that hydroxyurea

treatment provides a modest survival advantage and busulfan has a risk of potentially life-threatening pulmonary fibrosis [48,49].

Hydroxyurea rapidly lowers high circulating WBCs in CP CML by inhibiting ribonucleotide reductase, which then inhibits DNA synthesis, eliminating cells in the S phase of the cell cycle, and synchronizing cells in the G1 or pre-DNA synthesis phase. Hydroxyurea can achieve a hematological response but not a CgR. Thus, nowadays hydroxyurea is used for initial or palliative cytoreduction. It is initiated at 40 to 50 mg/kg/day in divided doses until the WBC count falls approximately <20,000 cells/mm³ and may be discontinued once adequate control of WBC count is achieved and imatinib can then be initiated. Hydroxyurea will not alter the natural progression of the disease to BC because it is not active against Ph chromosome [44,48].

Recombinant interferon- α : Although exact antileukemic effects of recombinant interferon- α (rIFN- α) are still unknown, *in vitro* studies show that rIFN- α modulates gene expression, promotes cell differentiation and apoptosis, directly inhibits cell growth and proliferation, restores regulation by the bone marrow microenvironment and induces an immunomodulatory response [50].

Results from over 1500 patients randomly allocated to chemotherapy (hydroxyurea or busulfan) or rIFN α demonstrated that although both could induce hematological responses in CML, rIFN- α significantly improved patient survival, with a 5-year survival rate of 50% to 59% compared with 29% to 44% for patients receiving busulfan or hydroxyurea [51]. In a study of 1303 rIFN- α treated patients, median survival was 8.2 years for low-risk patients, 5.4 years for intermediate-risk patients and 3.5 years for high-risk patients [52].

Targeted therapies: FDA approved and commercially available targeted therapies for the treatment of CML which work specifically by inhibiting the activity of TKs; these include the 1st generation imatinib, and the 2nd generation TKIs dasatinib, nilotinib, bosutinib and ponatinib [24]. Patients who develop the T315I "gatekeeper" mutation display resistance to all currently available TKIs except ponatinib [53].

Imatinib mesylate (Gleevec) was the first TKI to receive approval by the FDA for the treatment of patients with CML in 2001. It acts *via* competitive inhibition at the ATP-binding site of the BCR-ABL protein,

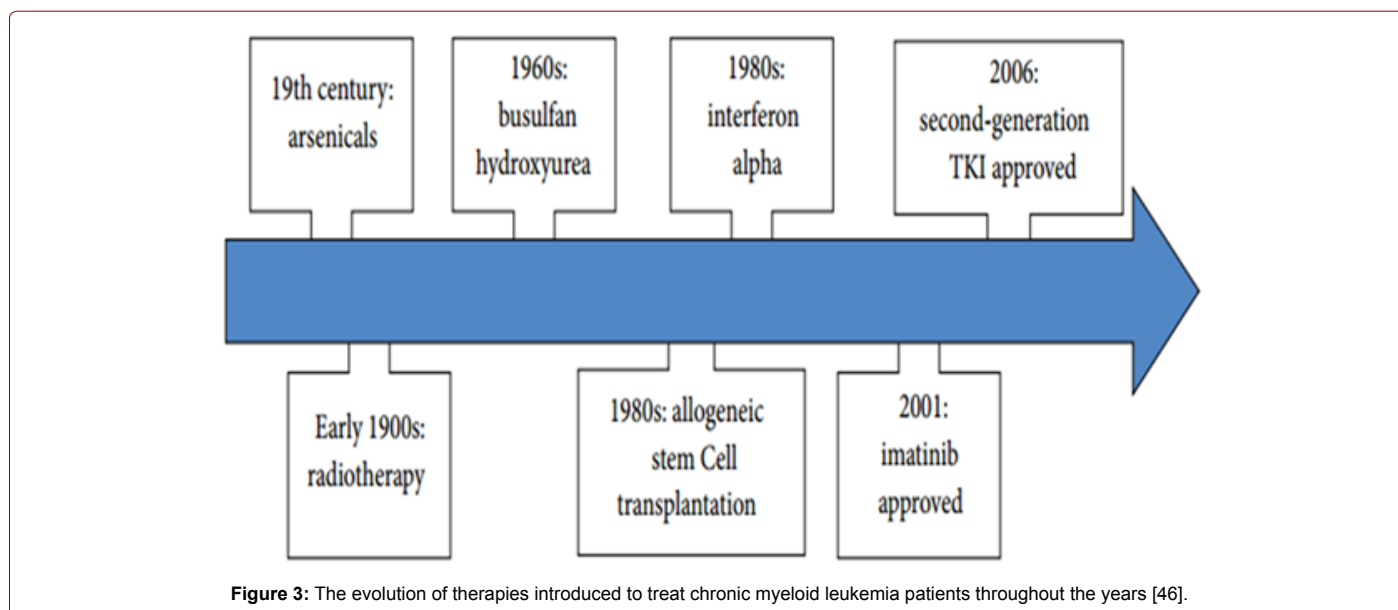


Figure 3: The evolution of therapies introduced to treat chronic myeloid leukemia patients throughout the years [46].

which results in the inhibition of phosphorylation of proteins involved in cell signal transduction. It efficiently inhibits not only the BCR-ABL protein but also blocks the platelet-derived growth factor receptor (PDGF) and mast/stem cell growth factor receptor (SCGFR) [24,44].

A result of study involving 1,106 patients who randomly assigned to receive imatinib 400 mg/day or INF α plus low-dose subcutaneous cytarabine after a median follow-up of 19 months, showed that patients receiving imatinib were significantly better than in those treated with INF α plus cytarabine, notably the respective major CgR rate and complete CgR rate for imatinib and combination therapy group were (87.1% vs. 34.7%) and (76.2% vs 14.5%). At 18 months, the estimated rate of freedom from progression to AP or BC phase CML was 96.7% in the imatinib group and 91.5% in the combination-therapy group. Imatinib was also better tolerated than combination therapy [54]. Based on this and many other IRIS study results imatinib become the initial and promising drug of choice for the treatment of CP CML over other TKIs and rIFN α in most of the countries[24,25,42] including Ethiopia.

Dasatinib (Sprycel) is an oral second generation TKI that is 350 times more potent than imatinib *in vitro*. It inhibits both ABL family kinases (BCR-ABL, PDGF and SCGFR) and SRC family of kinases (non-receptor tyrosine kinase protein) which may also be important in blunting critical cell signaling pathway. Dasatinib added advantage in that it can bind to both active and inactive conformation of BCR-ABL kinase domain. As a result it is active against nearly all BCR-ABL mutations resistant to imatinib therapy *in vitro* except T315I [42,55-57].

A multinational randomized control study involving 519 patients with newly diagnosed CP CML who randomly assigned to take either dasatinib 100 mg or imatinib 400 mg once daily, the study result showed that confirmed CCgR (77% vs 66% respectively) and MMR (46% vs 28% respectively) rates were higher in dasatinib group than imatinib after 12-month treatment follow up. Response rates were also achieved in a shorter time with dasatinib [58]. Although the results were in favor of dasatinib, progression to AP and BC phase were not significantly different between the two groups and the safety profile were similar [57,58].

Based on DASATION trial results, in October 2010, FDA approved dasatinib 100 mg orally per day for the treatment of adult patients with newly diagnosed Ph positive CP CML [24].

Nilotinib (Tasigna) another second generation TKI and a structural analog of imatinib, is 43-60 times more potent than imatinib resistant cell lines and 3-7 times more potent in imatinib sensitive cells [59]. Like imatinib it inhibits TK activity by binding to the ATP-binding site of BCR-ABL kinase, SCGFR and PDGFR and like imatinib it does not have activity against the SRC family. Nilotinib like dasatinib has activity in imatinib-resistant BCR-ABL kinase mutations except T315I [24,42,55,59].

Similar to the data with dasatinib, nilotinib has also been directly compared with imatinib in a large international ENESTnd 3-year follow-up study. In this study two doses of nilotinib (300 or 400 mg twice daily) were compared with imatinib 400 mg once daily and the results showed that the rate of MMR by 3 years was significantly higher for nilotinib 300 mg twice daily compared with imatinib (50% vs 26%) and nilotinib 400 mg twice daily compared with imatinib (44% vs 26%). There was also much less progression to AP or BP on the nilotinib arm [60]. In June 2010, based on ENESTnd trial FDA approved nilotinib 300mg orally twice daily for the treatment of adult patients with newly diagnosed Ph positive CP CML [24].

Like dasatinib, bosutinib is a dual inhibitor of BCR-ABL family and SRC family kinases. But bosutinib has minimal activity against SCGFR and PDGFR, which are nonspecific targets associated with toxicity in other TKIs. Bosutinib has activity in 16 of 18 imatinib-resistant BCR-ABL mutations, with the exceptions of the T315I and V299L mutants [61,62].

Results from 24 months follow up the BELA trial which compares bosutinib 500mg orally per day and imatinib 400 mg orally per day, the results showed that there was no significant difference of cumulative CCgR rates between the two groups (bosutinib 79%, imatinib 80%). But cumulative MMR rate and disease progression to AP or BC phase were better in bosutinib group (59% vs. 49% and 2% vs. 4% respectively). The safety profiles of bosutinib and imatinib were distinct; GI and liver-related events were more frequent with bosutinib, whereas neutropenia, musculoskeletal disorders, and edema were more frequent with imatinib [62].

On September 4, 2012 FDA, approved bosutinib for the treatment of the three phases of Ph positive CML in adult patients with resistance or intolerance to prior TKI therapy. But it is not currently recommended as first line therapy for newly diagnosed patients with CML [63].

Ponatinib is a potent multi-targeted kinase inhibitor which is active against cells expressing native or mutant BCR-ABL including T315I, VEGFR, and SRC kinases [64].

A single arm, multicenter, PACE phase II trial was done to evaluate the safety and efficacy of ponatinib (45 mg orally once daily) which involves a total of 449 heavily pretreated patients either resistance or intolerant to prior TKI therapy or with T315I mutation (267 patients with CP CML, 83 patients with AP CML, 62 patients with BC CML and 32 patients with Ph positive ALL); the results showed that among 267 patients with CP CML ponatinib induces durable MCgR, CCgR and MMR in 56%, 46% and 34% of patients respectively. The results also showed the respective response rate were higher in patients with T315I mutation [65].

Another randomized control study, phase III trial which designed to compare safety and efficacy of ponatinib (45 mg) and imatinib (400 mg) in newly diagnosed CP CML patients was terminated early due to concerns about vascular adverse events observed in patients given ponatinib in other trials. But the preliminary report showed even if the proportion of patients achieving MMR at 12 months did not differ significantly between the two groups, there might be benefit over imatinib though more arterial occlusive events (serious arterial thrombosis) than with imatinib were seen at the doses studied [64].

Even if ponatinib get accelerated FDA approval on December 14, 2012 for all three phases resistant or intolerant to the previous TKI therapy, guidelines recommend consideration of ponatinib only for patients with T315I mutation and for patients who failed multiple prior TKI therapy due to the above safety concerns [24,66].

Safety issues of TKIs: Even if the three FDA approved TKIs (imatinib, dasatinib and nilotinib) are acceptable with newly diagnosed patients with CP CML; each agent has a distinct toxicity profile that should be considered when selecting therapy over imatinib as first line since both dasatinib and nilotinib have very good efficacy in the upfront setting. In general the choice of first line therapy in a given patient may depend on risk score, physicians experience, age, ability to tolerate therapy and the presence of co-morbid conditions even though TKIs are reasonably well tolerated for patients when adequate monitoring and supportive care is given [24,57,60].

For patients at risk of developing pleural effusions, clinicians may choose to select a TKI other than dasatinib. This might be relevant for patients with a history of lung disease (e.g., chronic obstructive pulmonary disease), pericardial effusion or uncontrolled hypertension. Pulmonary arterial hypertension (PAH) is also an important complication of dasatinib, and patients with preexisting PAH may be considered for alternative TKIs in the frontline setting such as nolotinib [57,67]. Second generation TKIs have been associated with higher Grade 3/4 neutropenia and thrombocytopenia rates even if these agents were predominantly evaluated in imatinib-resistant patients who would be more likely to have impaired hematopoiesis. Example dasatinib is associated with increased risk of bleeding among patients with CML, even in the absence of thrombocytopenia, suggesting the presence of a hemostatic defect [68].

Nilotinib has been associated with hyperglycemia and hypophosphatemia, and caution should be exercised in patients with uncontrolled diabetes when initiating therapy. Nilotinib is also associated with uncommon cardiac toxicities, such as congestive heart failure, left ventricular dysfunction, ischemic heart disease and QT prolongation as compared to imatinib and dasatinib. So dasatinib or imatinib may be preferred in patients with a history of arrhythmias, ischemic heart disease, pancreatitis or hypoglycemia [59,60].

While dasatinib predisposes some patients to pleural effusions, imatinib tends to cause peripheral edema as one of its chief side effects. Patients can usually be monitored closely for this after initiation of imatinib, and intermittent use of loop diuretics helps to minimize fluid retention [69]. If patients have significant peripheral edema at baseline, nilotinib or dasatinib may be considered better first options, although the etiology of the edema should also be investigated and considered in the choice of therapy [24,57,60].

Semi-synthetic product: Omacetaxine mepesuccinate is a semi synthetic homohar ringtonine (HHT) non-TKI which is the only effective natural therapeutic agent used in patients with CML. HHT is a natural cephalotaxine alkaloid originally derived from the bark of several cephalotaxus species that are indigenous to Asia (mostly mainland China, and also Japan, Korea, and India). Historically, extracts from the bark of cephalotaxus were used in cancer patients by practitioners of traditional Chinese medicine in the Fujian Province of China [70,71].

Omacetaxine is a reversible protein synthesis inhibitor by mechanistically preventing aminoacyl-tRNA bindings to the ribosomal acceptor site and peptide bond formation at the early stage of protein elongation. But the mechanism for the antileukemic effect of omacetaxine mepesuccinate is mainly related to induction of apoptosis in leukemia cells [70]. It has also demonstrated activity against TKI-resistant BCR-ABL mutations since it acts independently of BCR-ABL kinase-binding activity. For example, in imatinib-resistant K562 cells, omacetaxine mepesuccinate caused degradation of BCR-ABL proteins by inhibiting heat shock protein 90 in a dose-dependent manner which mediates the resistance of BCR-ABL-expressing cells to apoptosis. Omacetaxine mepesuccinate also had a similar inhibitory effect on BCR-ABL T315I expressing leukemia stem cells [70,72] which is resistant to TKIs except ponatinib [64].

Omacetaxine mepesuccinate got accelerated FDA approval on October, 2012 for the treatment of adult patients with CP or AP CML with intolerant and/or resistant to \geq two TKIs. Accelerated approval was based on the safety and efficacy results from two phase II trials enrolling patients with CP or AP CML (one study involving 202

Stage	Criteria
Chronic phase	
None of the criteria for accelerated or blast phase are present	
Accelerated phase	
European leukemia net criteria*	Blasts \geq 15% and $<$ 30% in the peripheral blood or bone marrow(BM).
	Combined blasts and promyelocytes \geq 30% in the peripheral blood or bone marrow.
	Basophilia \geq 20% in the peripheral blood.
	Platelets \leq 100,000cells /mm ³ unrelated to therapy.
Cytogenetic clonal evolution.	
WHO criteria†	Blasts 10% to 19% in the peripheral blood or BM
	Basophilia \geq 20% in the peripheral blood
	Persistent thrombocytopenia ($<$ 100,000 cells/mm ³) unrelated to therapy
	Persistent thrombocytosis ($>$ 1,000,000 cells/mm ³) unresponsive to therapy
	Increasing spleen size and WBC count unresponsive to therapy
Cytogenetic clonal evolution	
Blast phase	
European leukemia net criteria	Blasts \geq 30% in the peripheral blood or bone marrow
	Extramedullary blast proliferation, apart from the spleen
WHO criteria	Blasts \geq 20% in the peripheral blood or bone marrow
	Extramedullary blast proliferation, apart from the spleen
	Large foci or clusters of blasts in the bone marrow biopsy

*Most commonly used in clinical trials. †Most commonly used by pathologists.

Table 2: Stages of chronic myeloid leukemia [25,26].

Variables	Sokal score	Hasford Score
Age	0.116 (age-43.4 years)	0.666 when age \geq 50 years
Spleen size*	0.0345 (spleen size-7.51 cm)	0.042 (spleen in cm BCM)
Platelet count $\times 10^3$ / mm ³	0.118 ((plts count/700) ² -0.563)	1.0956 when $\geq 15 \times 10^5$ / mm ³
Blood myeloblast %	0.887 (myeloblasts-2.10)	0.0584 (myeloblasts)
Blood basophil %	--	0.20399 when basophils \geq 3%
Blood eosinophils %	--	0.0413 (eosinophils)
Equation for relative risk (RR) of progression	RR=the exponential of the total obtained from the variables adjusted by weight. $\lambda_i(t)/\lambda_o(t)=EXP$ $0.0116(\text{age}-43.4)$ $+0.0345(\text{spleen}-7.51)+0.188$ $[(\text{plts}/700)^2-0.563]+0.0887(\text{blasts}-0.10)$	RR is calculated as the total obtained from the variables adjusted by weight and then multiplied by 1000.
Low risk	$<$ 0.8	\leq 780
Intermediate risk	0.8-1.2	780-480
High risk	$>$ 1.2	$>$ 1480

*Centimeters below costal margin, maximum distance.

Table 3: Prognostic scoring systems for newly diagnosed chronic myeloid leukemia based on Sokal prognostic Scoring system [77] and Hasford Scoring system [52].

patients who had failed one or more TKIs and a T315I mutation; the second study involving 203 patients who had failed treatment with two or more TKIs [73,74].

In the subset analysis of 46 patients with CP CML enrolled in the second study CHR, MCgR, CCgR were achieved in 67%, 22% and 4% of patients respectively. And also median PFS and OS were 7 months and 30 months respectively [73]. Among evaluated 62 patients with CP CML enrolled in the first study CHR, MCgR and CCgR were seen in 77%, 23%, and 16% of patients respectively. T315I clone was also reduced to below detection limits in 61% of patients [75].

Omacetaxine was also demonstrated feasible treatment option for patients with AP CML who had failed multiple TKIs as well as with T315I mutation in the two phases II trials. MHR and minor CgR were achieved in 27% and 15% of patients. MHR rates were also 32%, 40% and 50% respectively for patients with any BCR-ABL mutations, multiple mutations and T315I mutation at base line. These results were based on pooled analysis of 41 patients with AP CML [73,75].

The recommended dose and schedule for omacetaxine mepesuccinate is 1.25 mg/m² subcutaneously twice daily for 14 days of a 28 day cycle for the induction phase and 1.25 mg/m² subcutaneously twice daily for 7 days of 28 day cycle for maintenance which is continued until no longer achieving clinical treatment benefit [76].

Prognosis

Two sets of prognostic factors can be considered, namely those that can be identified prior to treatment (baseline factors) and those that can be identified during the treatment (response-related factors). The main baseline factors are the phase of disease and prognostic scoring system. Like different definitions of AP and BC have been used (Table 2), the phase of the disease also influences strongly the response, the duration of the response and overall survival (OS), with better results in CP than in AP and in AP than in BC [52,77].

The Sokal prognostic score, for example, identified four clinical variables: spleen size, blast percentage, age, and platelet count >700,000 cells/mm³ (Table 3) [77]. It predicts the cytogenetic response, molecular response and OS to 400 mg imatinib daily treatment. In the IRIS study of imatinib, the rate of 12-month molecular response among complete cytogenetic responders (CCGRs) was 66%, 45%, and 38% in low-, intermediate-, and high-risk patients, respectively. The OS at 54 months was 94%, 88%, and 81% for low, intermediate, and high Sokal risk patients. The Hasford or Euro prognostic score, which adds eosinophilia and basophilia to the calculation was developed for CML patients receiving treatment with IFN α and appears to behave in a similar manner [52].

Early cytogenetic response seems to be the most important response related prognostic factor. If no cytogenetic response (CgR) is achieved after 3 months, there is still a 50% chance of achieving a CCGR later on. If there is any (even minimal) CgR after 6 months of treatment, there is still a fair chance of achieving a CCGR but if the 6-month karyotype remains more than 95% Ph or the CgR is partial after 12 months of treatment, the probability is only 15% [24,25].

Drugs under investigation

Farnesyl transferase inhibitors: Ras proteins belong to the guanosine triphosphatase family of proteins which participate in the control of several signal transduction pathways such as cell growth, differentiation, proliferation and survival. Ras mutation is one of the most frequent aberrations in cancer and plays a fundamental role in tumorigenesis. In order to be activated, Ras requires localization to the plasma membrane. This sub-cellular localization is dependent on a post-translational modification consisting of protein farnesylation, which is a catalyzed by the farnesyl transferase enzyme (FTase) [78,79]. Based on this finding; drug development against cancer continued by probing agents that blocks FTase which finally inhibit Ras processing and consequently the growth of Ras mutated tumor [80].

In vitro studies of FTase inhibitors such as lonafarnib and tipifarnib showed synergistic activity both in imatinib sensitive and imatinib-

resistant cell lines by inhibiting the proliferation of imatinib-resistant cells and by increasing imatinib-induced apoptosis in cells from imatinib-resistant patients. Hence, it is conceivable that a combination of these agents acting through a different mechanism of action could overcome and potentially prevent the development of imatinib resistance and improve clinical outcomes. Both lonafarnib and tipifarnib are orally bioavailable nonpeptidomimetic FTase inhibitors [80]. For example; Phase I clinical trial study result showed that the combination of lonafarnib and imatinib is well tolerated and the maximum tolerated dose of lonafarnib is 100 mg twice daily when combined with imatinib at a dose of either 400 mg or 600 mg daily and treatment outcome was promising. These drugs are being studied further and are on Phase I/II clinical trial studies for the treatment of CML [81]. Another phase I clinical trial study done on combination of tipifarnib and imatinib was also well tolerated at a dose of tipifarnib 300 mg twice daily combined with imatinib 300 mg and 400 mg once daily and had activity against several Abl kinase domain mutants [82].

Histone deacetylase inhibitors: Other drugs which are under investigation in the treatment of CML are the histone deacetylase inhibitors (HDAs). Cell growth/proliferation and apoptosis are affected by post-transcriptional acetylation status of nucleosomal histones. The acetylation status of histones is determined by the co-operative enzymatic activity of the histone acetyltransferase (HATs) and histone deacetylase (HDAs) families. The balance between histone acetylation and deacetylation, mediated by HATs and HDAs, respectively, is usually well regulated. But the balance is often upset in diseases such as cancer by increasing HDAs activity (removing acetyl group) thereby modifying the degree of gene transcription [83-85].

Anticancer effects of HDAs are not only by modulating gene expression through increased histone lysine acetylation but also related to modulation of the acetylation status of non-histone proteins. In contrast to most other pro-apoptotic agents that preferentially target dividing cells, HDAs have been shown to induce apoptosis in non-proliferating cancer cell lines, which may have important implications for elimination of leukemic stem cells (LSCs) [85,86]. Imatinib induces remission in CML patients but does not eliminate LSCs, which remain a potential source of relapse. So combining HDAs with imatinib can effectively induced apoptosis in quiescent CML progenitors resistant to elimination by imatinib alone which finally reduce risk of disease progression or relapse and would increase treatment response [86,87]. Among these HDAs; panobinostat and vorinostat are under investigation for the treatment not only for CML but also for other various types of cancer in combined with other treatment modalities [88-90]. These two HDAs; panobinostat and vorinostat are FDA approved for the treatment of multiple myeloma in combined with dexamethasone and bortezomib [91] and for treatment of advanced primary cutaneous T-cell lymphoma [92]; respectively. But their role in CML treatment is still under investigation [89,90].

Proteasome inhibitors: The proteasome is an enzymatic complex that has a key role in regulating cellular processes through selective degradation of intracellular proteins, which are responsible for proliferation of cells [93]. Proteasome inhibitors (PI) are anticancer compounds that disrupt the proteolytic activity of the proteasome and lead to tumor cell growth arrest and apoptosis. Over the last decade, the proteasome has emerged as a therapeutic target in hematopoietic malignancies [93,94]. Among drugs which inhibit proteasome, bortezomib and Carfilzomib were tried for some hematologic malignancies and are FDA approved for multiple Myeloma [93,95].

As an example; for CML a pilot study done on patients with imatinib

refractory CML in CP or AP, bortezomib showed minimal efficacy and tolerable toxicity profile [93] and suppresses the cell proliferation via induction of apoptosis in CML cells by down regulation of S-phase kinase protein-2 [96] which then need further study especially in combination with TKIs as a strategy to eradicate leukemic cells [95]. Carfilzomib; another PI which also showed synergistic activity with that of imatinib for the treatment of CML and demonstrated greater efficacy and fewer side effects than bortezomib which still need to be investigated further for the treatment of CML in combination with other TKIs [79].

Allogenic hematopoietic stem cell transplantation

The number of patients undergoing allo-HSCT for CP CML has dropped significantly since TKIs were introduced, and has more of an important role when patients evolve into AP/BC. However, allo-HSCT remains an important therapeutic option for CP CML in the following situations: patients who fail at least two TKIs and potentially patients harboring the T315I mutation after a trial of ponatinib therapy. And it is the only treatment option to cure CML [97]. Generally, the place of allo-HSCT is summarized in Table 4.

Vaccines

Cancer cells are different from normal cells, so it is sometimes possible to get the body's immune system to react against them. One way to do this is to develop therapeutic strategies using vaccination against a truly tumor-specific antigen that is also the oncogenic protein required for neoplasia [98]. For example; oncogenic proteins responsible for CML are called BCR-ABL fusion oncogene which results in the expression of a chimeric protein product p210, which can be modified as a vaccine against CML [99].

Several vaccines are now being studied for use against CML.

Primary Treatment	Management of cytogenetic or molecular resistance to TKI			
	2 nd line therapy	3 rd line therapy	4 th line therapy	
Imatinib	Dasatinib	Nilotinib or Bosutinib	Poatinib	
	Nilotinib	Dasatinib or Bosutinib	HSCT	
	Bosutinib	Dasatinib or Nilotinib	Omacetaxine	
	Nilotinib			
Dasatinib	or	Poatinib HSCT Omacetaxine		
	Bosutinib			
Nilotinib	Dasatinib			
	or			
	Bosutinib			

Table 4: Summary of National Comprehensive Cancer Network guidelines Version 3.2014 for the management of chronic myeloid leukemia.

Monitoring time	Target treatment response	Suboptimal response	Resistance/ treatment failure
3 months	CHR, minor CgR (Ph+ ≤ 65%)	No cytogenetic response (Ph+ >95%)	No CHR
6 months	PCgR (≤ 35%)	No PCyR (Ph+ >35%)	No CgR(Ph+ > 95%)
12 months	CCgR (Ph ± 0%)	PCgR (Ph+ 1% – 35%)	No PCgR (Ph+ >35%)
18 months	MMR	No MMR (i.e., BCR-ABL/control gene ratio >0.10)	No CCgR(≥ 1%)
Any time		Loss of CHR	Loss of MMR
		Loss of CCyR	Evidence of BCR-ABL mutation
		Evidence of BCR-ABL mutation	

Table 5: Summary of treatment response and failure in CML patients.

Among these vaccines, a tumor specific multivalent BCR-ABL fusion peptide vaccine was tried on fourteen patients and generates specific measurable peptide-specific CD4 immune responses immune. Four patients in hematologic remission had a decrease in Ph chromosome percentage (three of them were concurrently received interferon-alpha and one on imatinib mesylate), and three patients in molecular relapse after allo-HSCT were became transiently PCR negative after vaccination. All five patients on rIFN-α were ultimately reached a CCgR [100]. A p210 multi-peptide vaccine was another vaccine which was tried on patients taking either imatinib or rIFN-α. This vaccine resulted a further reduction of residual disease and increased the number of patients reaching a molecular response [101]. Research into these and other vaccines is still continuing.

Current treatment approaches

NCCN guidelines (Table 5) recommend any of the three TKIs: imatinib, dasatinib, or nilotinib as options with a category 1 recommendation for initial treatment of CP CML. Second generation TKIs have shown inducing higher rates of early optimal responses, although their impact on long-term overall survival remains to be determined. Allo-HSCT or other chemotherapy agents are not any longer recommended as upfront treatments for CP CML given the excellent outcomes and long-term survival achieved with the TKIs [24].

Management of chronic phase chronic myeloid leukemia:

Hydroxyurea can be used as an initial management in CP CML to reduce or temporarily control symptomatic leukocytosis and thrombocytosis. Hydroxyurea may be discontinued once adequate control of the WBC and platelet count is achieved and the mean time imatinib 400 mg once daily has been initiated which is still recommended as a reasonable first line therapy for newly diagnosed patients with CP CML. Based on the recent FDA approval of dasatinib 100 mg once daily and nilotinib 300 mg twice daily, NCCN guidelines also include dasatinib and nilotinib as first line options for newly diagnosed patients.

Given the recent data showing superiority of nilotinib and dasatinib in newly diagnosed patients, high dose imatinib (600 or 800 mg daily) is not recommended as initial therapy for patients newly diagnosed with CML. rIFNα and HSCT are also no longer used as first line therapy but can be considered for patients who cannot tolerate TKI therapy. In addition, rIFN-α is still an option in case of pregnancy, for which imatinib should not be administered either at conception or during gestation.

Management of advanced stage chronic myeloid leukemia:

All five currently available TKIs are approved in the USA and Europe for treatment of AP CML, and all except nilotinib are also approved for treatment of BC CML [43,63,66,102]. Although TKI therapy is moderately effective in patients with AP/BC CML, the overall effectiveness of TKI therapy in advanced CML is less robust than that observed in early-stage disease. Due to this TKI therapy can be used as bridge for other treatment alternatives mainly for patients who are eligible to allo-HSCT and for other treatment options such as chemotherapy, omecetaxine and rIFNα [24,43,97].

Management of accelerated phase chronic myeloid leukemia:

After bone marrow, cytogenetic and mutational analysis; treatment for AP CML can be initiated. The 2014 NCCN guideline recommends either dasatinib 140 mg once daily or nilotinib 400 mg twice daily or bosutinib 500 mg once daily as appropriate choices to AP CML following standard dose TKI therapy [24]. In addition to this, European leukemia Net guideline also recommends to use imatinib 400 mg twice

daily for AP CML [12]. The selection of TKI therapy is based on prior therapy and/or mutational analysis. Allo-HSCT can be considered based on response to TKI therapy or alternatively omacetaxine can be used for patients with AP CML due to resistance or intolerance to two or more TKIs. Especially patients demonstrating a confirmed fivefold increase in BCR-ABL transcript levels and/or loss of MMR should be referred for allo-HSCT [24,25,97].

Management of blast crisis chronic myeloid leukemia: Treatment of patients with BC CML is based on type of acute presentation of blasts. Approximately 50% of all the BC phase cases are of myeloid subtype, 25% are of lymphoid subtype and the rest are undifferentiated. So, the management is based on its presentation. If it is ALL/lymphoid type BC CML, 2014 NCCN guideline recommends TKI therapy alone or in combination with ALL type chemotherapy. If it is AML/myeloid type BC CML TKI alone or in combination with AML type chemotherapy is used [24].

Monitoring of treatment response: Monitoring response to TKI therapy is key management strategies of CML to allow an early assessment of efficacy or failure. Response to TKI therapy is the most important prognostic factor. Response to TKI therapy is determined by the measure of hematologic, cytogenetic and molecular responses. According to NCCN guideline, the goal of TKI therapy is to achieve a CCyR with in 12 or 18 months of initiation of therapy and to prevent disease progression to AP or BP [24,25].

Complete hematologic response, which is defined as normalization of peripheral blood counts with no immature blood cells, WBC less than 10,000 cells/mm³, platelet count less than 450,000 cells/mm³ and free of signs and symptoms with complete disappearance of splenomegaly [24].

The second treatment response monitoring marker is cytogenetic response, which is determined by the decrease in the number of Ph positive metaphases as determined by bone marrow aspirate and cytogenetics and is divided into groups according to the percentage of Ph positive bone marrow metaphases [24,43]:

Complete cytogenetic response (CCgR): 0% Ph chromosome

Partial cytogenetic response (PCgR): between 1 and 34% of Ph chromosome,

Minor cytogenetic response (MCgR): between 35 and 65% of Ph chromosome.

Minimal cytogenetic response(mCgR): between 66 and 95% Ph chromosome

The last marker is molecular response, which is determined by the decrease in the amount of BCR-ABL chimeric mRNA defined by RT-PCR using the International scale standardized baseline which is the most sensitive assay available for quantification of BCR-ABL chimeric mRNA [24,43].

Major molecular response (MMR): transcript level of 0.1% or less (≥ 3 log reduction in BCR-ABL transcripts),

Complete molecular response (CMR): No BCR-ABL transcript is detectable by real-time PCR.

Criteria for treatment response and failure with imatinib therapy are judged relative to the duration of therapy. According to the European Leukemia Net, optimal response to imatinib requires a CHR within three months; a PCyR within six months and CCyR at 12 months and a MMR at 18 months. Failure of imatinib treatment results in no CHR

at 3 months, less than PCyR at 12 months and no MMR at 18 months [25]. In conclusion the treatment response and failure is summarized in Table 5 [103].

Discussion

In 2013, CML experts and patients with CML have multiple treatment options in the CML therapeutic armamentarium, including five TKIs (imatinib, nilotinib, dasatinib, bosutinib, and ponatinib), omacetaxine (protein synthesis inhibition), and older agents (hydroxurea, and interferon alpha). Most patients with CML would be expected to live their normal functional life though not molecularly, cured as long as they continue therapy and compliant with TKI based regimens. Close monitoring for signs of resistance to change therapy in a timely manner and/or consider alloHSCT before CML progression is important to achieve the desired treatment outcomes [24,25].

Future Perspectives and Conclusion

Future directions will focus on the potential molecular cure of CML (i.e., achievement of a durable CMR and its persistence after discontinuation of TKI therapy) [42]. Even if effective TKI therapy and full treatment penetration worldwide is established; still the incidence of CML is increasing annually which is estimated to be close to 160,000 patients with CML in the US and about 3 million patients worldwide by 2030 to 2040 [11]. This may represent a considerable burden on patients and the healthcare systems in relation to drug availability, compliance, potential development of long-term side effects, and costs. Therefore, it is critical to continue research into therapies that increase the rates of durable CMRs. This may be achievable with the current more potent new generation TKIs alone, or in combination with other available (peg-interferon α and omacetaxine) or investigational therapies (JAK2 inhibitors, hedgehog inhibitors, stem cell poisons, and vaccines). Such strategies may improve the eradication of minimal residual disease, potentially obviating the need for indefinite therapy with TKIs [15,42]. Further understanding of the pathophysiologic events downstream of BCR-ABL may also help in the development of new strategies to target them [32].

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Authors' Contribution

This work was carried out in collaboration with the following authors. 'Author AMF' designed the study, searched the information, and wrote the first draft of the manuscript. 'Author BAW' reviewed the manuscript and managed the literature searches. 'Author MAW' reviewed the manuscript, managed the literature searches and organized and managed the final manuscript. All authors read and approved the final manuscript.

Conflict of Interest

Authors declare that there is no conflict of interest regarding publication of this manuscript.

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