Review Article

CHRONIC MYELOGENOUS LEUKEMIA: A REVIEW AND UPDATE OF CURRENT AND FUTURE THERAPY

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ABSTRACT

Leukemia is a cancer of marrow and blood, which is a clonal myeloproliferative disease, characterized by the presence of oncogenic Philadelphia chromosome, formed by a reciprocal translocation between chromosomes 9 and 22, resulting in the novel chimeric oncoprotein BCR/ABL. Chronic leukemia typically progresses slowly and permits the growth of greater numbers of more developed cells. If the cell change takes place in a type of marrow cell that normally goes on to form red blood cells, some kinds of white blood cells and platelets, the leukemia is called "myeloid. Therapy for chronic myeloid leukemia depends on the stage of CML patient. After diagnosis and confirmation of CML positive patient, treatment available for patients includes imatinib that is an early diagnosed treatment for CML but after some duration of time, it may lead to resistance to imatinib treatment. Dasatinib, nilotinib, bosutinib & ponatinib can be used for the treatment of CML as secondary treatments. Ponatinib is also found effective against T315i mutation patients. Omacetaxine mepesuccinate can be given with a mechanism of action independent of tyrosine kinase inhibition. Clinical trial for development of advanced therapy, which includes combination therapy and newer developed a treatment against CML are going on. It is required to develop better drug therapy, which will not cause genetical mutation and drug resistant. It is also required to find out thecause of resistance and what are the possible ways by which better therapy for CML is possible.

Keywords: Philadelphia (Ph) chromosome, chronic myeloid leukemia, Imatinib, Tyrosine Kinase Inhibitor (TKI), Haematological Response (HR), Cytogenetic Response (CR), Molecular Responses (MR), Reverse Transcriptase Polymerase Chain Reaction (RTPCR), BCR-ABL gene, T315I mutation, Imatinib-Resistance

INTRODUCTION

Leukemia is a cancer of the marrow and blood. The four major types of leukemia are acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia and chronic lymphocytic leukemia.

Acute leukemia is rapidly progressing disease that affects mostly cells that are partly or completely undeveloped. These immature cells cannot perform their normal functions. Chronic leukemia typically progresses slowly and permits the growth of greater numbers of more developed cells. In general, these more mature cells can carry out some of their normal functions.

Chronic myeloid leukemia (CML) is called by several other names, including "chronic myelogenous leukemia," "chronic granulocytic leukemia" and "chronic myelocytic leukemia" [1].

Extracellular vesicle (EV) is a way of intercellular communication. It communicates besides soluble factor and tunneling nanotubule. EVs transfer signals within or at their limiting membrane. It is providing a mechanism by which cells can exchange more complex information than previously thought [2–5]. It has been proven that in addition to proteins, mRNAs and microRNAs, there are DNA fragments within EVs [6–10]. By endocytosis or by fusion, the existence of DNA in EVs that could be transferred from one cell to another. The transferred EV DNAs have pathophysiological significance, not only to increase the DNA-coding mRNA and protein levels, but also influence the function of the recipient cells [6].

Tumor-derived EVs are fully equipped to facilitate the escape of tumor cells from immune surveillance. While escaping tumor EVs also are involved in the establishment of an optimal environment for newly formed and metastatic tumor cells. It is interesting to find that the tumor-derived EVs could prod normal cells towards a tumor phenotype [11].

CML is a clonal myeloproliferative disorder of a pluripotent stem cell first described by John Hughes Bennett in 1845 at The Royal Infirmary of Edinburgh [12].

As a special tumor, CML is a clonal myeloproliferative disease which is characterized by the oncogenic Philadelphia chromosome formed by a reciprocal translocation between chromosomes 9 and 22 that result in the novel chimeric protein BCR/ABL (breakpoint cluster region, BCR; Abelson murine leukemia viral oncogene, ABL), that dictates the pathophysiology of CML [2,14-16,17].

CML is an acquired stem cell disorder which is characterized by expression of the BCR-ABL oncoprotein. Animal models, as well as theoretical considerations on the age-specific incidence of CML in human populations, suggest that aberrant BCR-ABL expression alone may be enough to explain the chronic phase of the disease [18-24].

Approximately 50 % of CML patients are 66 y and older. In the earlier studies age appeared a poor prognostic factor for survival and was included as such in all staging models. It is not clear whether this age effect was due to poorer disease biology, or to other age-related factors, including competitive causes of death, increased risk of treatment-related complications, or contra-indications to the curative bone marrow transplant [25-28].

A systematic literature search was conducted on the electronic databases PubMed Central®, National Cancer Institute, American Society of Hematology (ASH), American Cancer Society®, National Comprehensive Cancer Network (NCCN) Guidelines®. The literature search covered the time period of 1960 to 2016. The search terms were keywords from MeSH with efficacy, resistance, and related concepts combined with the drug terms including synonyms within the approved indications.

History

In 1845, it was reported a "Case of hypertrophy of the spleen and liver in which death took place from suppuration of the blood". Only a few weeks later, it was published a very similar case. Although one cannot know for sure, these two patients probably represent the first descriptions of the disease that later became known as CML. While it was thought that the patient had an infection. It was also suspected a neoplastic disorder that was soon called white blood disease or leukemia. In 1872, it was observed by one scientist that

leukemia cells originated in the bone marrow. The next decades saw the differentiation into myeloid versus lymphoid and acute versus chronic leukemia.

A real quantum leap, however, was the discovery by Philadelphia cytogeneticists Peter Nowel and David Hungerford of an abnormally small G-group chromosome that we now call the Ph chromosome.

In the 1980s, the translocation partners were identified as BCR and ABL, followed by the discovery that unregulated tyrosine kinase activity is critical to BCR-ABL's ability to transform cells. A faithful murine disease model established in 1990.

Therapy for CML was developed slowly. In 1865, it was described that use of arsenic is nothing too novel because the use of arsenic for cancer therapy had been described in the Indian Ramayana more than 2000 y earlier. Splenic irradiation was introduced in the 1920s for symptomatic relief. Effective control of blood counts became feasible with busulfan (1959), followed 10 y later when the better-tolerated hydroxyurea became available, probably the first intervention with a (modest) prolongation of survival. In the mid-1970s, a breakthrough was achieved when the Seattle group reported the disappearance of the Ph chromosome in CML patients who underwent allotransplant, the first cure of CML. Soon later, interferon-α was found to induce durable complete cytogenetic responses and long-term survival, although in only a small fraction of patients. In 1992, Alexander Levitzki proposed the use of ABL inhibitors to treat leukemia driven by ABL oncogenes. At about the same time, scientists at Ciba-Geigy had synthesized a potent inhibitor of ABL that was termed GCP57148B and is now known as imatinib.

In 2008, the majority of patients diagnosed with chronic phase myeloid leukemia can expect to have durable responses with good quality of life. From 20% to 30% patients who fail for imatinib treatment, second-line treatments are an effective salvage strategy. However, once the disease has progressed beyond the chronic phase, allotransplant is still the recommended treatment for all eligible patients. Unfortunately, residual leukemia may persist even in the best responders and that therapies directed at the BCR-ABL tyrosine kinase are not curative since they fail to eradicate the CML stem cells. Thus, the CML saga continues and much work remains to be done [29].

CML is a rare hematologic cancer that originates in the bone marrow. It represents about 20% of all leukemia, and an estimated 5,000 new patients were diagnosed with the disease in the United States in 2010. The disease is slightly more common in men than it is in women and it primarily affects older individuals. Although the median age at diagnosis is 65 y, it can occur across the lifespan: in the years 2004 to 2008, 20% of patients were diagnosed at age 44 y or younger, 30% between ages 45 to 64 and 50% at age 65 or older [30, 31].

Significant advances in the treatment of CML have increased the survival rate significantly. In 1975, the 5-year survival rate for a newly diagnosed patient was 19%; in 2002, it was 53%. With tyrosine kinase inhibitor (TKI) therapy, the most recent overall survival (OS) rate with 8 y of treatment was 85% [30, 32]. With prolonged survival, CML can be managed in a manner similar to that used for a serious illness [30, 33] with an emphasis on ongoing patient education, support and symptom management [30].

Mechanism of chronic myeloid leukemia

Approximately 90% of patients with CML have an acquired genetic abnormality, the Ph chromosome [34]. The Ph is a shortened chromosome 22 resulting from a reciprocal translocation between the long arms of chromosomes 9 and 22t (9;22q34;q11) [35, 36]. In this translocation, the c-ABL proto-oncogene is transposed from its normal position on chromosome 9 to a 5.8 kb major breakpoint cluster region M-BCR on chromosome 22, forming a BCR-ABL fusion gene [36, 37]. The new gene encodes p210BCR/ABL, an oncoprotein that has increased tyrosine kinase (TK) activity [38, 39] and increased binding to the actin cytoskeleton [40] compared with the p145 Abelson protein, both of which contribute to transformation. The presence of p210BCR/ABL causes growth factor independence

and leukemic cell growth in hematopoietic cell lines [41-43]. Transplantation of BCR-ABL-transduced hematopoietic stem cells or transgenic expression of p210BCR/ABL induces leukemia, lymphomas and CML-like syndromes [44-52] proving the direct causal relationship to CML.

The p145ABL protein, the product of the Abelson gene, is a TK whose function is not totally known. There is evidence that p145ABL is important for cell growth [53-55], induction of apoptosis [56-58] and is involved in DNA repair [59-61]. Although p145ABL is found mainly in the cell nucleus, there is mounting evidence that it plays a role in cell signalling from integrin's [62] as well as other cell surface receptors such as the B cell receptor and CD19 [34, 63].

Risk factors for chronic myeloid leukemia

• High dose radiation, such as an atomic bomb blast or nuclear reactor accident

• Age (the risk of getting CML goes up with age)

• Gender (this disease is slightly more common in males than females, but it's not known why)

Sign and symptoms of chronic myeloid leukemia

General symptoms of CML can include weakness, feeling very tired most of the time (fatigue), night sweats (that drench the sheets), weight loss (without trying), fever, bone pain, enlarged spleen (felt as a mass under the left side of the ribs), pain or sense of "fullness" in the belly, feeling full after eating even a small amount of food, bone or joint pain.

Many of the symptoms of CML happen because the leukemia cells crowd out the cells that make blood in the bone marrow. As a result, the person does not have enough blood cells and platelets that are working the way they should.

• Anemia is a result of a shortage of red blood cells. It can make a person feel short of breath, tired, cold, lightheaded and weak.

• Not having enough normal white blood cells (*leukopenia*) increases the risk of infections.

• Not having enough blood platelets can lead to easy bruising, bleeding, frequent or severe nosebleeds, and bleeding gums [64].

Diagnosis of chronic myeloid leukemia

Routine blood tests

Blood cell counts and blood cell exam

The complete blood count (CBC) is a test which measures the levels of different blood cells, such as red blood cells (RBC), white blood cells (WBC), and platelets. This is the first test require if it has been suspected leukemia or other blood problem. In CML patients have increased the level of WBC and decreased the level of RBC or blood platelets. These findings may suggest leukemia, but it usually needs to be confirmed with another blood test or a test of the bone marrow.

Blood chemistry tests

These tests are not required to confirm if a person has leukemia or not. But for patients already known to have CML, these tests require deciding that patient doest not has liver or kidney problems caused by the spread of leukemia cells or by the side effects of certain drugs used for treatment. These tests decide that the patients require any treatment to correct low or high blood levels of certain minerals.

Examine under a microscope

Blood and bone marrow samples need to observe under a microscope by a pathologist. The pathologist will observe the size and shape of the cells as well as other features to divide the cells into specific types. This process is to see whether or not the cells look mature. The most immature cells are called *blasts*. The blasts do not work the way they should, and they can keep on forming new cells, crowding out normal, mature cells.

Genetic tests

Chromosomes are long chains of DNA found in every cell. Chromosome mutation which leads to CML is called the *Philadelphia chromosome*. Ph chromosome found in the leukemia cells of almost all patients with CML, which can be by cytogenetic, FISH and PCR methods in samples of blood and/or bone marrow.

Imaging tests

Imaging tests are used to take images of the inside of the body. They are not used to find CML, but they may be done to help fig. out if it involves certain organs (like the spleen).

CT (Computed tomography) scans

CT scan is a special kind of x-ray in which a beam of light moves around the body, taking images from many angles. CT scans are not required to find CML, but may be done if leukemia is growing in other parts of a boy like in spleen.

MRI (Magnetic resonance imaging)

MRI scans are very helpful for imaging of the brain and spinal cord. Powerful magnets and radio waves have been used in this test to make images of the inside of the body. It takes longer time than CT scans up to an hour.

Ultrasound

Ultrasound test uses sound waves to make images of internal organs. Ultrasound can look for enlarged organs in the belly (abdomen). This test is a very easy to perform on patients compared to other machinery tests. For most scans, you lie on a table and a technician moves a kind of wand (transducer) over the part of the body being looked at, which is first smeared with a gel.

Chest x-ray

A chest x-ray is only a plain x-ray of the chest. It is only used to find if someone has CMLwith lung problems.

Staging of chronic myeloid leukemia

Staging is the process of finding out how far cancer has spread. Most types of cancer are staged based on the size of the tumor and how far it has spread from where it started. This system does not work for leukemias because they do not often form a solid mass or tumor. Also, leukemia starts in the bone marrow and, in many people; it has already spread to other organs when it is found.

Phases of chronic myeloid leukemia

CML is divided into 3 phases that help predict the patient's outlook. Doctors call these *phases* rather than stages. The phases are based on the number of immature white blood cells, called *blasts*, that are seen in the blood or bone marrow. From less to more serious, they are:

- Chronic phase
- Accelerated phase
- Blast phase (also called *acute phase* or *blast crisis*) [64]

Chronic phase

People with chronic phase CML may have no symptoms during this phase, or CML symptoms may be present prior to treatment due to changes in blood cell counts or spleen enlargement. If present, chronic phase symptoms resolve promptly when people are treated. Effective therapy initially lowers the total white cell count to near-normal levels. The improved white cell count is accompanied by a reduction in spleen enlargement, improvement in the haemoglobin concentration and return to general well-being. Bleeding and infectious complications are uncommon in the chronic phase. Once treated, people with chronic phase CML are typically able to participate fully in their usual activities.

Accelerated phase

Anemia may develop or progress and cause fatigue, the white cell count may either fall to very low levels or rise because of the accumulation of blast cells, and platelet counts generally decrease.

The blast count often increases in the blood and bone marrow in the accelerated phase (and is further elevated in blast crisis). The spleen may become enlarged; the patient may lose his or her sense of well-being (in this phase, individuals more commonly feel ill) and other complications may follow.

Blast crisis

In this phase, the number of blast cells increases in both bone marrow and blood; the red cell, platelet and neutrophil counts can be very low, and patients may experience episodes of infection and bleeding as a result. Other symptoms commonly encountered include fatigue, shortness of breath, abdominal pain, bone pain and/or spleen enlargement. Unfortunately, blast crisis is similar to acute leukemia in its effects on the patient. In about 25 percent of people, the transformation in the blast crisis takes on the appearance of acute lymphoblastic leukemia, while in the majority it takes on the appearance of acute myeloid leukemia [1].

Clinical evidence indicates that all CML patients undergoing imatinib treatment should be monitored closely in order to assess their response to therapy and to detect early relapse. There are three different types of responses in CML: (1) Haematological Response (HR), (2) Cytogenetic Response (CR) and (3) Molecular Responses (MR). A complete hematologic response (CHR) is defined as the normalization of blood counts and spleen size. Blood counts can be assessed using biweekly testing until a CHR is attained and then testing can be performed every 3 mo. Cytogenetic monitoring is the most widely used technique to monitor response to patients with CML [65]. Typically, it is quantitated by determining the decrease in the number of Ph+metaphase cells using both bone marrow aspiration and cytogenetic evaluation techniques.

A major cytogenetic response (MCR) is said to be achieved when Ph+metaphase is present in 0–35% of cells. In contrast, the absence of Ph+metaphase cells leads to complete CR (CCR). Fluorescent in situ hybridization (FISH), which analyzes a higher number of cells (up to 200), can be used instead of conventional cytogenetic assessment for quantifying cells that are Ph+. However, a significant background level of false-positive results limits the use of FISH and prevents full correlation with the conventional assessment.

The recent European Leukemia Net (ELN) recommendations[66] suggests cytogenetic testing first at 3 and 6 mo, then every 6 mo until a CCR is achieved and confirmed and subsequently every 12 mo if regular molecular monitoring cannot be assured. An MR is determined by a decrease in the amount of BCR-ABL chimeric mRNA. A complete molecular response (CMR) is achieved when there is no detectable BCR-ABL chimeric mRNA as assessed by reverse transcriptase-polymerase chain reaction (RT-PCR).

The methodology of RT-PCR is probably the most sensitive assay to detect BCR-ABL chimeric mRNA; in fact, it can detect even one CML cell with a background of more than 100,000 normal cells. Quantitative RT-PCR (Q-PCR) measures the actual percentage of BCR-ABL mRNA transcripts and shows a significant correlation between the results obtained from peripheral blood and the bone marrow.

The cytogenetic and molecular monitoring of the response to TKIs treatment provides important prognostic information. A 5-year follow-up in the IRIS study showed that no patients progressed to the accelerated blast phase after 12 mo if a CCR and an MMR were obtained [69]. The estimated progression-free survival (PFS) at 24 mo was 100% for patients who received CCR and MMR at 12 mo [69]. Monitoring the response to second-generation TKIs requires the same tests, but earlier and more frequent testing may be appropriate because responses are more rapid. On the basis of the magnitude of HR, CR and MR, and on the time when these responses are achieved, the overall response to imatinib can be defined as optimal, suboptimal or failed (table 2).

An optimal response is defined as no indication that a change of therapy may improve a patient's survival. A suboptimal response is where the patient may still have a substantial long-term benefit from continuing the ongoing specific treatment, but the chances of an optimal outcome are considerably reduced, and thus, suboptimal responders may be eligible for alternative approaches. A failed

response indicated that a favorable outcome is unlikely and that the patient should receive a different treatment whenever available and applicable. The definition of the response to the second-generation TKIs dasatinib and nilotinib as second-line therapy of patients with imatinib-resistant CML-CP was also provided by the new ELN recommendation (table 3) [66].

Table 1: Criteria for haematological, cytological and molecular response [66]

Response	Criteria	Monitoring
Haematological		
Complete (CHR)	Complete normalization of peripheral blood count: white blood cell count<$10*10^9$ L^{-1}, platelet count<$450*10^9$ L^{-1}; no immature cells; no splenomegaly	Check every 2 w until CHR achieved, then monitor every 3 mo
Partial	Same as complete haematological except for; persistent of immature cells; platelet count<50% of pretreatment count, but>$450*10^9$L^{-1}; splenomegaly<50% of pre-treatment extent but persist	
Cytogenic		
Complete (CCR)	0 Ph+metaphases	Check every 6 mo until CCR achieved then every 12-18 mo
Major(MCR)	0-35% Ph+metaphases (complete+partial)	
Partial	1-34% Ph+metaphases	
Minot	36-90% Ph+metaphases	
Molecular		
Complete (CMR)	BCR-ABL mRNA undetectable by RT-PCR;	Check every 3 mo
Major (MMR)	>=3 log reduction of BCR-ABL mRNA	

Ph+: Ph-positive chromosome

Table 2: Definitions of response to first-line Imatinib therapy in chronic phase CML patients [69]

Evaluation time	Response		
	Optimal	Suboptimal	Failure
3 mo	CHR and at least minor CR (Ph+=<65%R)	No CR (Ph+>95%)	Less than CHR
6 mo	At least MCR (Ph+=<35%)	Less than MCR (Ph+>35%)	No CR (Ph+>95%)
12 mo	CCR	Less than CCR	Less than MCR (Ph+>35%)
18 mo	MMR	Less than MMR	Less than CCR
Any	Stable or improving MMR	Lose of MMR ABL kinase domain mutation predicted to confer low-level resistant	Lose of CHR loss of CCr ABL kinase domain mutation predicted to confer high-level resistant

CML: Chronic Myeloid Leukemia, HR: Haematological Response, CR: Cytogenetic Response, CHR: Complete Haematological Response, MCR: Major Cytogenetic Response, CCR: Complete Cytogenetic Response, MMR: Major Molecular Response

Table 3: Definitions of the response to second-generation TKI (a second-line therapy) in Imatinib-resistant or intolerant chronic phase CML patients [66]

Evaluation time	Response	
	Suboptimal	Failure
3 mo	Minor CR (Ph+36-65%)	No CR(Ph+95%); new mutations
6 mo	PCR (Ph+1-35%)	Minimal CR(Ph+66-95%); new mutations
12 mo	Less than MMR	Less than PCR(Ph+35%); new mutations

TKI: Tyrosine Kinase Inhibitors; Ph+: Philadelphia Chromosome Positive; CR: Cytogenetic Response; PCR: Partial Cytogenetic Response; MMR: Major Molecular Response

However, the presence of a small number of point mutations and amplification of BCR-ABL kinase level lead to the emergence of resistance, resulting in relapse episodes in patients who were in a CCR on imatinib therapy [70]. Point mutations in BCR-ABL kinase domain are frequently involved in imatinib resistance and may be an important determinant in clinical decisions (discussed later). However, current evidence does not support mutation screening on a routine basis unless there is an indication of a loss of response. Several recent reports suggested that routine mutation screening could provide valuable information, such as predicting response to specific TKIs and identifying patients at high risk of disease progression [71, 72]. In addition, BCR-ABL Q-PCR monitoring results can be used to select patients with an increased risk of mutation, since some studies showed that elevations in BCR-ABL transcript levels might indicate a potential for BCR-ABL gene mutations and the emergence of imatinib resistance [73-75]. However, the optimal cut-off of increased BCR-ABL mRNA to predict mutation is still controversial. The National Comprehensive Cancer Network (NCCN) guidelines provisionally recommended mutation screening in cases with a 10-fold or greater increase of BCR-ABL mRNA is detected [65]. However, a study by Press *et al.* showed that a 10-fold threshold to trigger mutation screening was insensitive and not universally applicable, and a 2.6-fold increase in BCR-ABL mRNA was the optimal cut-off for predicting a concomitant mutation [76].

Comorbidities of the patient, the side effect profile, and the cost of the TKI of interest should be an important consideration in decision making. Whatever TKI is chosen as frontline, noncompliance or treatment failure should be recognized early as a prompt intervention increases the chance of achieving best possible response [77].

Therapeutic monitoring

The first generation of TKI

Imatinib was the first FDA (Food and Drug Administration) approved TKI for the treatment of advanced stage Ph+CML patients. This was information from two successful phase II studies in CML-AP and CML-BC patients [78, 79] using 600 mg/day of imatinib. Previous phase I and phase II clinical studies in CML patients resistant or intolerant to rIFN-α confirmed its clinical efficacy and safety [80, 81]. Imatinib is also approved by the FDA as a first-line treatment for patients with CML-CP based on data from a randomized phase III trial known as IRIS [82] that compared Imatinib 400 mg daily with IFN-α plus cytosine arabinoside (Ara-C) in 1106 previously untreated CML-CP patients. The crossover was allowed in patients that experienced treatment failure or intolerance. The most recent 6-year update data reported that 63% of all patients randomized to receive imatinib were still on study treatment and showed a CCR at the last assessment. The best cumulative CCR rate was 82%; the estimated event-free survival at 6 y was 83%. In 95% of patients, imatinib was well tolerated, as only 5% of patients discontinued treatment due to adverse effects. Moreover, no new adverse events were reported following long-term use of imatinib [83]. However, due to the relatively high rate of crossovers (~90%) from rIFN-α plus Ara-C group to imatinib group within a year of the study, perplexes the true determination of the survival benefit with Imatinib versus IFN-α plus Ara-C in the IRIS study. Until now, the maximum tolerated dose of imatinib had not been established, and an initial dose of 400 mg daily for adult CML-CP patients was recommended. Several prospective, non-randomized studies reported that responses to imatinib were more rapid and superior in the patients who were treated with doses of 600 or 800 mg daily [84, 85].

Although first-line imatinib treatment achieved an extremely high response rate and a low relapse rate in CML patients, some patients do experience imatinib resistance or intolerance. In 31% of patients who did not achieve a CCR during 12 mo of treatment and 13% still had not achieved CCR after 5 y of treatment. In addition, 3–7% of patients in that trial, experienced treatment failure during the first 3 y and 5% of patients discontinued imatinib because of intolerable adverse effects [69]. Therefore, many patients require alternative treatment in the case of imatinib failure or intolerance.

Imatinib has characterized a revolution in the treatment of CML drastic modification in overall survival. However, with 400 mg dosage of imatinib, one-third of the treated patients does not reach the criteria associated with an optimal outcome and could potentially benefit from a different treatment strategy. Several trials for modified imatinib-based treatments and second-generation tyrosine kinase as front-line therapy have been performed. In some studies, high-dose (800 mg per day) or dose-adapted imatinib or imatinib plus interferon was reported to be better cytogenetic and molecular responses compared with standard-dose imatinib, although no improvements in progression-free survival (PFS) or overall survival (OS) have been so far reported [86].

Efficacy data are comparable for first and second generation TKIs, and so physicians should consider the BCR-ABL1 mutation profile while prescribing drug therapy to patients who are resistance to first generation TKIs. Few BCR-ABL1 mutations seem to be less responsive to any of the three second-line TKIs, and therefore, it is recommended to choose the second-line TKI which has shown clinical activity against the specific mutation in these cases. For patients with all other mutations and for patients with no mutations, it is recommended to choose the second-generation TKI based on the patient's disease history. If dasatinib or nilotinib get fail, a third-generation TKI ponatinib is available for patients with T315I mutations. However, the optimal dose of ponatinib is still under investigation. Overall, it is recommended to select a drug that minimizes the likelihood of worsening the patient's past side effects or comorbid conditions [87].

The second-generation of TKIs

Dasatinib

As mentioned above, dasatinib inhibits a number of kinases, including BCR-ABL and Src and is more potent than imatinib against BCR-ABL TKs [88, 89]. Dasatinib has been clinically evaluated in phases I, II, and III trials in adult's Ph+CML patients, who are intolerant or resistant to imatinib therapy. A phase I study [90] reported the effects of dasatinib (15–240 mg/day) once or twice daily in 4 w treatment cycles in the patients with various phases of CML or with Ph+ALL that could not tolerate or were unresponsive to imatinib treatment.

The results indicated that a CHR was achieved in 37 out of 40 CML-CP patients, an MHR in 31 of 44 CML-AP and MCR in 45% CML-BC or 25% Ph+ALL patients. A response was maintained in 95% of patients with chronic phase disease and in 82% of patients with accelerated phase disease after median follow-up periods of more than 12 and 5 mo, respectively. In addition, the highest dose of dasatinib (240 mg) was well tolerated, with significant clinical responses occurring among all BCR-ABL genotypes, except for those with the T315I mutation.

Several phase II studies, known as the SRC/ABL Tyrosine Kinase Inhibition Activity Research Trials (START) that examined the effect of dasatinib in Ph+CML patients resistant to imatinib or intolerant of its adverse effects. Dasatinib also induced aMR, and significantly decreased the BCR-ABL/ABL transcript ratios from 66% at baseline to 2.6% after 9 mo [91].

Grade 3/4 thrombocytopenia and neutropenia were reported in 48% and 49% of the patients, respectively. Non-hematologic toxicity (any grade) consisted primarily of diarrhea (37%), headache (32%), fatigue (31%), dyspnea (30%) and pleural effusion (27%). Pleural effusions were classified as grade 3 in 6% of reported events, with no reports of grade 4 (table 5) [92].

The randomized phase II trial (Src-ABL Tyrosine kinase Inhibition Activity Research Trial (START)-R) [93] compared 400–600 mg/day of imatinib to a high dose (800 mg/day) of Imatinib in CML-CP patients resistant to imatinib. A total of 150 patients were randomized (2:1) to receive treatment with dasatinib 70 mg twice daily (n = 101) or imatinib 800 mg daily (n = 49). After a median follow-up of 15 mo, dasatinib produced a significantly greater CHR (93% vs. 82%, p = 0.034) and MCR (52% vs. 33%, p = 0.038) rate compared to 800 mg of imatinib. An MMR was also more frequent with dasatinib than imatinib treatment (16% vs. 4%; p = 0.038). The probability of treatment failure was lower [hazard ratio (HR) = 0.16] but the PFS was significantly greater (HR = 0.14) in dasatinib-treated patients. Furthermore, the most recent 2-year follow-up results confirmed the significant PFS and OS benefit with dasatinib versus high-dose imatinib for these patients (table 4) [94].

The START-A trial evaluated the safety and efficacy of dasatinib in CML-AP patients with resistance or intolerance to imatinib [95]. An 8-month follow-up of the first 107 patients enrolled in the study indicated an overall, major or complete HR was obtained in 81%, 64% and 39% of patients, respectively. In addition, 33% and 24% of these patients attained a major or complete CR, respectively. In 69 patients who achieved an MHR, only 7 relapsed and progressed to the disease, however, 76% of patients were estimated to be alive and were progression-free after 10 mo.

The response rates in 60% of patients with baseline BCR-ABL mutations did not differ from the total population. Dasatinib was well tolerated, and no imatinib-intolerant patients discontinued dasatinib because of AEs. The follow-up data from all 174 patients have confirmed the safety and efficacy of dasatinib for CMP-AP patients with resistance or intolerance to imatinib. After a median follow-up of 14.1 mo, an MHR and CHR were attained in 64% and 45% of patients respectively, and an MCR and CCR were achieved in 39% and 32% of patients, respectively (table 4). These responses were achieved irrespective of the imatinib status (resistance or intolerance), prior stem-cell transplantation or the presence of a prior BCR-ABL mutation. The 12-month PFS and OS in these patients were 66% and 82%, respectively [96].

The efficacy of dasatinib for CML-BC patients with Imatinib resistance or intolerance was evaluated in the START-B (myeloid blast crisis, MBC-CML patients) and START-L (lymphoid blast crisis, LBC-CML patients) trials [97, 98].

Table 4: Initial phase II data for second-line therapy with dasatinib or nilotinib after Imatinib failure in Philadelphia chromosome-positive CML patients [94]

Drug	Phase II study design	No. of patients	Follow-up (months)	CHR (%)	MCR (%)	CCR (%)
Dasatinib	Single arm trail in imatinib resistant or intolerant CML-CP patients (START-C)	387	15.2	91	59	49
	Randomized 2-arm trail in Imatinib resistant CML-CP patients (START-R)	101	24	93	53	44
	Single arm trail in imatinib resistant or intolerant CML-AP patients (START-A)	174	14.1	45	39	32
	Single arm trail in imatinib resistant or intolerant MBC-CML patients (START-B)	109	12	25	33	26
	Single arm trail in imatinib resistant or intolerant LBC-CML patients (START-L)	48	12	29	52	46
Nilotinib	Single arm trail in imatinib resistant or intolerant CML-CP patients	321	19	94	59	41
	Single arm trail in imatinib resistant or intolerant CML-AP patients	137	11	31	32	20

CML: Chronic Myeloid Leukemia, CP: Chronic Phase, AP: Accelerated Phase, MBC: Myeloid Blast Crisis, LBC: Lymphoid Blast Crisis, CHR: Complete Hematological Response, MCR: Major Cytogenic Response, CCR: Complete Cytogenic Response, START: Src-ABL Tyrosine kinase Inhibition Activity Research Trial

In the LBC-CML patients, the 8-month and 12-month follow-up results indicated that the MHR rates were 31% and 35%, respectively, and the MCR rates were 50% and 52%, respectively. The median PFS and OS were 3.0 and 5.3 mo, respectively. The initially approved dose of dasatinib for CML patients resistant or intolerant to imatinib was 70 mg twice daily. However, a longer follow-up of the data from the phase I trial of dasatinib indicated that the once-a-day treatment group experienced significantly fewer adverse effects compared to those treated twice daily [90]. In addition, the median daily doses for patients with CML-CP during the START-C and START-R trials were 101 mg and 103 mg, respectively [91, 93]. In the CA180-035 trial, the efficacy and safety of 140 mg dasatinib once daily were compared to the 70 mg twice-daily regimen in CML-AP patients with imatinib resistance or intolerance. After a median follow-up of 15 mo, 140 mg dasatinib daily doses demonstrated equivalent efficacy but improved safety compared to the 70 mg twice-daily regimen [101]. Therefore, based on data from this phase III studies, the FDA has approved dasatinib 100 mg daily for CML-CP patients and 140 mg daily for CML-AP and CML-BC patients [65].

Currently, the efficacy of dasatinib is being evaluated as a first-line treatment in previously untreated CML-CP patients in an ongoing phase II trial by Borthakur and Kantarjian [102]. The results indicated a rapid CCR and a favorable toxicity profile with dasatinib treatment.

Nilotinib

The FDA approved nilotinib, another second-generation BCRABL tyrosine kinase inhibitor, in 2007 for the treatment of Imatinib resistance or intolerance in CML patients. In a phase I dose escalation study, nilotinib was found to be significantly more effective than imatinib-resistant CML patients, with a relatively favorable safety profile compared to imatinib [103]. Subsequently, a phase II trial was conducted [104] where 280 imatinib-resistant or intolerant patients were enrolled and treated with 400 mg b. i. d. of nilotinib. The MCR and CCR rates after a 6 mo follow-up were 48%, and 31%, respectively. Survival past 12 mo was estimated to be 95% in the nilotinib-treated patients. Nilotinib was effective in patients harboring BCR-ABL mutations associated with imatinib resistance (except T315I) and also in patients with a resistance mechanism independent of BCR-ABL mutations. The reported AEs were mostly mild to moderate, and there was minimal cross-intolerance to imatinib. A minimum 19-month follow-up result of all 321 patients enrolled in the study showed that nilotinib produced a rapid and sustained CHR and MCR rates. A CHR and MCR were observed in 94% and 59% of patients, respectively, and 78% of patients maintained an MCR after 24 mo. The estimated OS rate was 88% at 24 mo. The safety profile of dasatinib did not change with longer follow-up intervals [105]. Le Coutre *et al.* [106] conducted a phase II trial evaluating the efficacy and safety of nilotinib in CML-AP

patients with resistance or intolerance to imatinib. Initially, 119 patients were enrolled with median treatment duration of 202 d. The HR and MCR rates were 47% and 29%, respectively, and the 12 mo OS rate was 79%. Non-hematologic AEs reported were mostly mild to moderate in severity. The most common grade 3 or higher hematologic AEs were thrombocytopenia (35%) and neutropenia (21%). Grade 3 or higher bilirubin and lipase elevations occurred in 9% and 18% of patients, respectively, resulting in treatment discontinuation in 1 patient. Long-term follow-up results of the total 137 patients confirmed that nilotinib induces a rapid and sustained response in CML-AP patients who do not respond to prior imatinib treatment, and there was a significantly favorable risk/benefit ratio. The HR, CHR, MCR and CCR rates were 56%, 31%, 32% and 20%, respectively, and the median time to HR was 1month. After 24 mo, 54% and 70% of patients maintained HR and MCR, respectively, and the estimated OS at 24 mo were 67%. Only 9% of patients discontinued therapy due to drug-related AEs [106]. Thus, based on the results from the above studies, the food and drug administration (FDA), in 2007, approved nilotinib for the treatment of Ph+CML-CP or CML-AP patients with resistance or intolerance to imatinib.

Nilotinib has also been shown to have efficacy in CML-BC patients. A phase II study reported the safety and efficacy data in 136 CML-BC patients treated with nilotinib. The results showed that the HR, MCR, CCR rates were 21%, 40% and 29%, respectively and the OS was 42% at 12 mo [104]. However, more than half of the patients discontinued treatment due to disease progression and therefore, the FDA has not approved nilotinib for the treatment of CML-BC patients at this time. The efficacy of nilotinib was evaluated in another phase II trial (GIMEMA CML Working Party) as a first-line treatment in previously untreated CML-CP patients [108]. A total of 73 patients were enrolled and followed up for 210 d. In the intent to treatment (ITT) analysis, the CHR rates at 3 and 6months were 100% and 98%, respectively, and the CCR rates were 78% and 96%, respectively. The cytogenetic and molecular responses to nilotinib were significantly faster than that of imatinib. Only 1 patient with the T315I mutation progressed to the accelerated or blast phases at 6 mo. All AEs (grade 3/4) were manageable by appropriate dose adjustments [109, 110].

Bosutinib

Bosutinib is an orally administered Src/ABL inhibitor, estimated to be 45 to 50 times more potent than imatinib, with the minimal inhibitory activity of PDGFR and c-KIT [111]. This increased specificity is expected to produce less myelosuppression and fluid retention than other TKIs. The phase I study identified a treatment dose of 500 mg daily and showed evidence of clinical efficacy. Phase II studies in patients with CML-CP, who have failed imatinib and second-generation TKIs therapy are ongoing [112, 113]. Preliminary data for response to bosutinib among patients in chronic, accelerated, and blast phase (myeloid and lymphoid) after imatinib

failure are summarized in table 5. The most common AE with bosutinib were gastrointestinal (nausea, vomiting, diarrhea); these were usually grade 1-2, manageable and transient, diminishing in frequency and severity after the first 3-4 w of treatment. Bosutinib is being assessed in the front-line setting for treatment of patients who have CML-CP.

Table 5: Response to second-generation TKIs (Dasatinib, Nilotinib, and Bosutinib) in patients who are Imatinib-resistant or intolerant to chronic phase, accelerated phase and blast phase [113]

Response	Percent response										
	Dasatinib				Nilotinib				Bosutinib		
	CP N= 387	AP N= 174	MyBP N= 48	LyBP N= 48	CP N= 321	AP N= 137	MyBP N= 105	LyBP N= 31	CP N= 146	AP N= 51	BP N= 38
Median Follow-up (mo)	15	14	12+	12+	24	9	3	3	7	6	3
% Resistant to Imatinib	74	93	91	88	70	80	82	82	69	NR[a]	NR[a]
% Hematologic Response	-	79	50	40	94	56	22	19	85	54	36
CHR	91	45	27	29	76	31	11	13	81	54	36
NEL	-	19	7	6	-	12	1	0	-	0	0
% Cytogenetic Response	NR	44	36	52	NR	NR	NR	NR	-	NR	NR
Complete	49	32	26	46	46	20	29	32	34	27	35
Partial	11	7	7	6	15	12	10	16	13	20	18
% Survival (at 12 mo)	96(15)	82(12)	50(12)	50(5)	87(24)	67(24)	42(12)	42(12)	98(12)	60(12)	50(10)

AP: Accelerated Phase, CHR: Complete Hematological Response, CP: Chronic Phase, LyBP: Lymphoid Blast Phase, MyBP: Myeloid Blast Phase, MEL: No Evidence of Leukemia, NR: Not reported

Investigational Agents for use after failures with two TKIs or in the presence of T315I mutations

Ponatinib

Ponatinib is a multikinase inhibitor that has shown the inhibitory activity of BCR-ABL wild-type, BCR-ABL-T315I, and all other tested variants. Initial dose escalation data showed efficacy at 30 mg daily with no dose-limiting toxicities. Preliminary data are available in 32 patients with CML, Ph (+) ALL, and other hematologic malignancies. Twelve of the 32 patients exhibited T315I mutations. Of the twelve patients, 7 (58%) with CML-CP attained a CHR; 2 (17%) attained a CCyR (1 with CML-CP and 1 CML-AP), and 1 (8%) with CML-CP attained a PCyR. One patient with CML-CP with the nilotinib-resistant F359C mutation attained a CCyR and MMR on AP24534 [114].

Omacetaxine mepesuccinate

The development of resistance to TKIs has led to the development of omacetaxine, a taxine with a mechanism of action independent of tyrosine kinase inhibition. Phase II/III studies in patients with CML status after failed therapy with multiple TKIs, and a significant proportion with baseline mutations, are ongoing. Preliminary data in patients without T315I mutations demonstrate 80% CHR rates, 20% MCyR rates and 10% MMR rates in CML-CP patients; 75% hematologic response rates including return to chronic phase and CHR, and 5% CCyR rates in CML-AP; and 8% hematologic response rate including return to chronic phase and CHR in CMLBP [115]. In those with CML-CP with T315I mutations, results show achievement of an 85% CHR rate, 28% CyR rate, 15% MCyR rate, 15%MMRrate, and 57% reduction in the T315I clone. OS was not met in this group of patients. In CML-AP, 37.5% showed hematologic response with an OS of 18.8 mo. In CML-BP, the hematologic response was demonstrated in 30% with an OS of 1.8 mo [116].

An update combining both of the above study populations was presented at the American Society of Hematology (ASH) annual meeting of 2010. Thirty-six of the 93 chronic-phase patients had been treated previously with three or more TKIs. Over a median follow-up period of 7.5 mo, 27 of 36 patients (75%) achieved or maintained a CHR and 7 (19%) achieved a major CyR (4 complete and 3 partial) with omacetaxine, with a median duration of at least 4 mo. These findings support the further investigation of this agent in patients failing other TKI therapy [117]. Grade 3 to 4 hematologic AE included thrombocytopenia (65%), neutropenia (48%), anemia (40%), febrile neutropenia (12%), bone marrow failure (12%), pancytopenia (7%), and febrile bone marrow aplasia (6%). Grade 3 to 4 nonhematologic AE included fatigue (6%). Grade 1-2 AE included diarrhea, fatigue, nausea, vomiting, fever, headache and asthenia [115-117].

Advanced drug therapy for CML

Aurora kinase inhibitors

The Aurora kinase family consists of serine-threonine kinases which are very important for different stages of the mitosis. Two family members of Aurora A and B found to be overexpressed in some neoplasias.

Few of the following Aurora kinase inhibitors are in pre-clinical and clinical evaluation: PHA-739358 (danusertib), AT9283, MLN8237XL-228, KW-2449 and MK-0457. Danusetib has been proven for safety and efficacy in patients having T315I mutation in phase I clinical study.

AT9238 is a multi-kinase inhibitor which also inhibited cells with the T315I mutation. It has been observed that AT9238 is well-tolerated during phase I clinical trial and having anti-leukemic activity [118-122].

Hsp90

A molecular chaperone which interacts with various proteins like Raf, Akt, FLT-3 and Bcr-Abl, Hsp90 maintains these proteins in a stable and functional conformation. Geldanamycin and its derivative, 17-allylamino-17-demethoxygeldanamycin (17-AAG) bind to the ATP-binding pocket of Hsp90 and inhibit its chaperone activity which leads to down-regulation of Bcr-Abl and also induction of apoptosis in CML cell lines. It has also been found that Geldanamycin and 17-AAG inhibited the cell growth of some mutant lines (E255K and T315I). Hsp90 has its limits, and there are some cross-resistant types. It has been observed that combination therapy of imatinib and 17-AAG leads to synergistic inhibition of growth and induction of apoptosis in cross-resistant cell lines but not in the imatinib-sensitive counterparts. 17-AAG may also block the imatinib efflux [122, 123].

Arsenic trioxide (As2O3)

Arsenic trioxide (As2O3) induces apoptosis in Bcr-Abl-positive cell lines and reduces proliferation of CML blasts without affecting the

CD34+progenitors. The combination of As2O3 with imatinib exerted additive to synergistic effect. This combination induced cell death in imatinib-resistant cell lines with overexpressed Bcr-Abl or bearing M351Tor Y253F mutations, but it does not affect the T315I mutants [123, 124].

Homoharringtonine (HHT)

HHT is a by-product of a plant alkaloid which inhibits protein synthesis and induces apoptosis. The combination of HHT with imatinib is synergistic or additive on CML-derived cell lines. Omacetaxine and chemgenex are semisynthetic HHT derivatives that if combined with imatinib showed promising activities. Omacetaxine is now in phase II trials with TKIs-resistant patients with or without the T315I mutation [122, 123].

Histone deacetylases (HDAC)

HDAC are the catalysts in deacetylation of lysine residues at the amino termini of nucleosomal core histones. Histone deacetylase inhibitors (HDI) such as suberoylanilide hydroxamic acid (SAHA, vorinostat) generates hyperacetylated histones which cause transcriptional upregulation of the cyclin-dependent kinase inhibitor, p21, cell-cycle arrest and apoptosis in tumor cells. It has also been found that SAHA induces expression of a key cell-cycle regulator p27, and its application is associated with downregulation of the p210 Bcr-Abl protein. The synergetic effect of inducing apoptosis in imatinib-resistant CML cell lines has been observed between SAHA and imatinib. The co-treatment with nilotinib and the HDI LBH589 (panobinostat) was very effective in inducing apoptosis in K-562 and LAMA-84 CML cell lines. LBH589 showed efficacy in imatinib-resistant cell lines bearing the T315I and E255K mutations, and this was associated with depletion of Bcr-Abl. A published study showed that when HDI valproate combined with imatinib, increase in antileukemic efficacy and sensitivity for imatinib-resistant CML cells occurs [123, 125].

Proteasomes

Proteasomes cause degradation of different cellular proteins. Bortezomib, a proteasome inhibitor was shown to inhibit proliferation, to stop the cell cycle in the G2/M phase and to promote apoptosis in imatinib-sensitive and imatinib-resistant CML cell lines. Because of antagonistic drug-drug interactions, Co-treatment of bortezomib and imatinib isn't recommended. However, if a low dose bortezomib exposure of CML cell lines is followed by imatinib, there are some additive effects. Synergistic interactions between bortezomib and the HDI SAHA has also been reported and bortezomib with flavopiridol in *in vitro* as well [123].

Farnesyl transferase inhibitor (FTIs)

Current FTIs as antileukemic agents like tipifarnib and lonafarnib are under investigation. Ras-MAPK signal pathway which is responsible for the formation of Bcr-Abl through protein-protein interactions are inhibited by FTIs and plays a central role in leukemogenic transformation. The combination imatinib and tipifarnib were well tolerated and active in patients with imatinib-resistant CML which T315I mutant. Lonafarnib is a selective inhibitor of primary progenitor cells derived from CML patients which reduced colony formation of progenitor cells and showed activity in imatinib-resistant CML cell lines.

Sorafenib (BAY 43-9006)

Sorafenib (BAY 43-9006) is a multi-kinase inhibitor of the RAS/Raf pathway which is involved in leukemogenesis downstream from Bcr-Abl. Drug concentrations of 5-10 µM were found to induce apoptosis via the mitochondrial pathway in imatinib-resistant cell lines. The combination of sorafenib and vorinostat (HDAC inhibitor) triggers cell dysfunction through Mcl-1 downregulation and p21 inhibition. Sorafenib is approved for the treatment of hepatocellular and renal cancers. Phase I and Phase II trials are also carried out in CML patients [122].

CI-1040

CI-1040 was the first MEK inhibitor which entered a clinical trial in for the treatment of CML. CI-1040 in combinations with imatinib, dasatinib, HDAC inhibitors, arsenic trioxide and HSP 90 inhibitors has also been studied. CI-1040 with arsenic trioxide and HSP 90 combinations were tested with a positive effect in patients with T315I mutation. Because of the challenging pharmacokinetic properties, clinical advancement is unlikely, but a derivate (PD0325901) is under development [122].

mTOR (mammalian target of rapamycin)

The protein kinase, mTOR is a downstream mediator of the PI3K/Akt pathway which controls cell growth and survival. Rapamycin (sirolimus) is the prototype compound of this group, but clinical usefulness has been limited because it has poor aqueous solubility and chemical stability. However, in a small clinical trial, four out of six patients with imatinib-resistant disease responded to oral rapamycin. Rapamycin also significantly inhibited the cell growth in Ph+cell lines with or without the T315I mutation. The combination of imatinib and another mTOR inhibitor, everolimus, was associated with an increased expression of c-Abl and inhibition of Bcr-Abl. In the presence of inhibited Bcr-Abl, c-Abl enters the nucleus and modulates apoptosis. A Phase I trial with imatinib and everolimus has been completed while a study with temsirolimus is currently in accrual [122].

Investigational agents

There are several new targeted tyrosine kinase inhibitors under development and targeted to the underlying causes of Imatinib resistance and disease progression (table).

Drug target	Drug target
IMATINIB	BCR-ABL, c-kit, and PDGFR *
DASATINIB	BVCR-ABL, SRC FAMILY KINASES, c-kit EPHRIN RECEPTOR KINASES and PDGFR
NILOTINIB	BCR-ABL, c-kit T, and PDGFR
SKI-606	BCR-ABL and Src FAMILY KINASES
VX-680	BCR-ABL, AURORA KINASES and FLT3 KINASE
BIRB-796	BCR-ABL, P38 MAP+KINASE
ONO 12380	BCR-ABL and LYN KINASE

* PDGFR= Platelet Derived Growth Factor Receptor, +MAP= Mitogen-Activated Protein

Most of these new molecules have shown promising *in vitro* activity against a subset of BCR-ABL mutants and also might suppress the proliferation of Imatinib-resistant cells in which the cause of the resistance is overexpression of BCR-ABL [126, 127].

Future concern

Imatinib has transformed CML from an immediately life-threatening disease to one that is treatable with daily oral medication that makes it possible to improve both overall survival and maintain the quality of life. However, increasing the incidence of imatinib resistance and intolerance necessitates the development of alternative therapies. There is a substantial amount of data supporting the improvement in outcome in long-term follow-up of the second-generation TKIs, nilotinib and dasatinib. Improving outcome in the front-line setting should be the direction of further scientific research, including the implementation of second-generation TKIs as front-line therapy.

Despite extraordinary progress, a true cure for CML is not generally achieved by Abl kinase inhibitors. TKIs are potent inhibitors of BCRABL kinases (among others), resulting in rapid reduction of the majority of cells carrying the Ph chromosomal marker. However, suppression of ABL-driven hematopoiesis may be insufficient to eradicate quiescent stem cells. Studies assessing the combination of TKIs with promising agents are ongoing. These combinations include TKI and hedgehog inhibitors, omacetaxine, vaccines and hypomethylating agents. If successful, this strategy could lead to a safe and permanent discontinuation of therapy in patients with a good response. The impact of using more potent agents in the front-line setting on the potential to discontinue TKI therapy remains to be determined. The future of CML therapy may include early use of these potent agents, perhaps in combination with new molecules, to help more patients achieve CMR, which could lead to therapy discontinuation and cure [128].

The use of vaccines directed against proteins associated with malignant cells might also be used to target T315I-carrying cells. In a small study in 16 patients with CP CML, and who were treated with imatinib or IFN-α, the addition of a vaccine targeting the BCR-ABL–derived p210 fusion protein to therapy deepened cytogenetic responses in all patients [128, 129].

CONCLUSION

The introduction of the BCR-ABL TKIs has revolutionized the management of Ph+CML patients. Patients diagnosed with CML today, as opposed to 10–20 y ago, are expected to have a substantially longer survival rate. However, further improvements in prognosis and complete disease eradication are goals that have yet to be reached in CML treatment. The use of first-generation BCR-ABL TKI imatinib has yielded some degree of successes as a first-line therapy. However, there are some patients who are resistant or intolerant to imatinib therapy. The currently approved second-generation TKIs, dasatinib and nilotinib, are effective in most patients who experience treatment failure with imatinib. However, these agents are not efficacious in a small group of resistant patients as a consequence of the interaction of multiple factors including T315I mutation. Indeed, advanced therapy and investigational new drugs in understanding chemotherapeutic failure have provided us with novel strategies to overcome CML disease. It seems pertinent to further explore and determine the resistance mechanisms and to ascertain the resistance profiles of these known BCR-ABL TKIs in order to provide the optimal treatment regimens.

CONFLICT OF INTERESTS

Declare none

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