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IMATINIB RESISTANCE IN PHILADELPHIA CHROMOSOME-POSITIVE CHRONIC MYELOID LEUKEMIA

Rivky Kops

Chronic myeloid leukemia (CML) is a disorder of blood stem cells in bone marrow, which leads to a rapid production of white blood cells. Of the patients diagnosed with CML, 95% have the Philadelphia (Ph) chromosome, which means that chromosome 22 is smaller than regular (22q-). Historically, the median survival time for chronic phase CML patients was four to five years, while the accelerated and blast (profusion of immature red blood cells in circulation) phases had a much shorter survival time. Recently, due to the revolutionary new drug imatinib, CML patients diagnosed early have a higher survival rate. Nevertheless, some patients may show resistance to imatinib, and alternative treatments must be considered (Hochhaus and La Rosée 2004).

CHRONIC MYELOID LEUKEMIA

Chronic myeloid leukemia originates in a single pluripotent bone marrow stem cell. It accounts for approximately 15% of all leukemia cases (Liesveld and Lichtman 2011). As shown in Figure 1 below, the long ("q") arms of chromosome 9 and 22 swap DNA, resulting in a longer chromosome 9 (9q+) and shorter chromosome 22 (22q-).

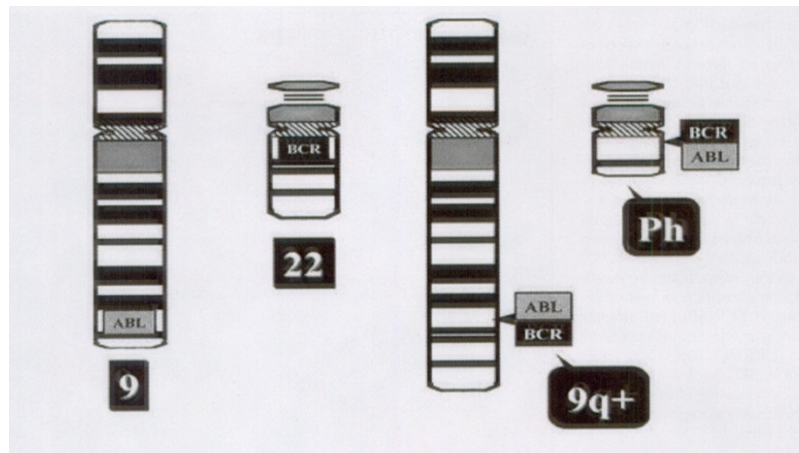


Figure 1: Normal chromosomes 9 and 22, and 9q+ and 22q- resulting from the reciprocal BCR-ABL translocation. Source: Litzow 2006

Chromosome 22q- is known as the Philadelphia chromosome and is the identifying characteristic of CML in over 90% of cases. It occurs when the Abelson oncogene (ABL) of chromosome 9 at 9q34 fuses with the breakpoint cluster region (BCR) of chromosome 22 at 22q11. BCR is a multiplier gene, and ABL codes for a tyrosine kinase which is heavily suppressed in healthy cells (Encyclopedia of the Human Genome). The resulting BCR-ABL gene codes for a constitutively active tyrosine kinase which induces rapid stem cell differentiation by inducing cell growth and bypassing signals that block cell mitosis. These new BCR-ABL+ stem cells have

lower proliferation capacities compared to normal stem cells, but the tremendous increase in stem cells results in a net increase in leukocytes. Granulocytes, and often megakaryocytes, are the main cells arising from the malignant stem cells. However, studies have also found erythroblasts and macrophages with the Philadelphia chromosome, leading to the belief that CML arises in a pluripotent stem cell (Liesveld and Lichtman 2011).

Early stage chronic myeloid leukemia is asymptomatic; the abnormally high percentage of white blood cells compared to red blood cells is frequently only detected as part of a routine complete blood count. Common CML symptoms are anemia; extreme blood granulocytosis; splenomegaly; early satiety and unintentional weight loss; and, seldom, thrombocytosis. A chronic phase is usually followed by an accelerated phase, which is characterized by blasts making up 15% of the red blood cells circulating in the bloodstream. Historically, median survival rate in the accelerated phase has been one to two years, with many dying before reaching blast crisis. Blast phase, characterized by 30% immature cells, had a median survival of three to six months. Ninety percent of patients are diagnosed in the chronic stage. In the chronic stage, survival rates and remission rates are more optimistic compared to the accelerated and blast phases (Pemmaraju et al. 2011).

There are three markers of remission: hematological, cytogenetic, and molecular response. Complete hematological remission is marked by white blood cell counts returning to normal levels of less than $10 \times 10^9/L$ and the disappearance of CML symptoms. However, while quality of life is much improved with the normalization of white blood cell counts, hematological remission is a poor indicator of long-term survival. Cytogenetic response means that cells bearing the Ph chromosome are not being produced. Partial cytogenetic response is defined as 1 to 35% of metaphases remaining Ph positive, while complete cytogenetic response means that no mature cells bear the Ph chromosome. Complete molecular response means that there are no detectable BCR-ABL transcripts (Pemmaraju et al. 2011). In an IRIS (International Randomized Study of Interferon and STI-571) trial, which compared the efficacy of drugs targeting CML, achieving a complete cytogenetic response was determined to be the most important factor in long-term survival. Of the patients achieving complete cytogenetic response but incomplete molecular response, the five-year survival rate was 98% (Wetzler et al. 2012). Therefore, achieving a complete cytogenetic response was established as the goal of treatment (Pemmaraju et al. 2011). Progression-free survival, which means that patients have not progressed from the chronic phase to a more advanced state, is also used as a benchmark of successful therapy, since patients in the chronic phase usually experience few side effects and have a higher quality of life.

Because the vast majority of CML patients display the Ph chromosome, the BCR-ABL fusion is the best target for therapy to treat CML. Imatinib is the first truly targeted drug to inhibit a tyrosine kinase (Marx 2001), and it has granted CML patients a hopeful prognosis.

IMATINIB

Imatinib, a highly targeted tyrosine kinase inhibitor, uses hydrogen bonding to bind to the contact site in the inactive configuration of the BCR-ABL kinase. This

hinders the ATP binding site so that the affected cell has no source of energy for proliferation and survival. This process is shown in Figure 2.

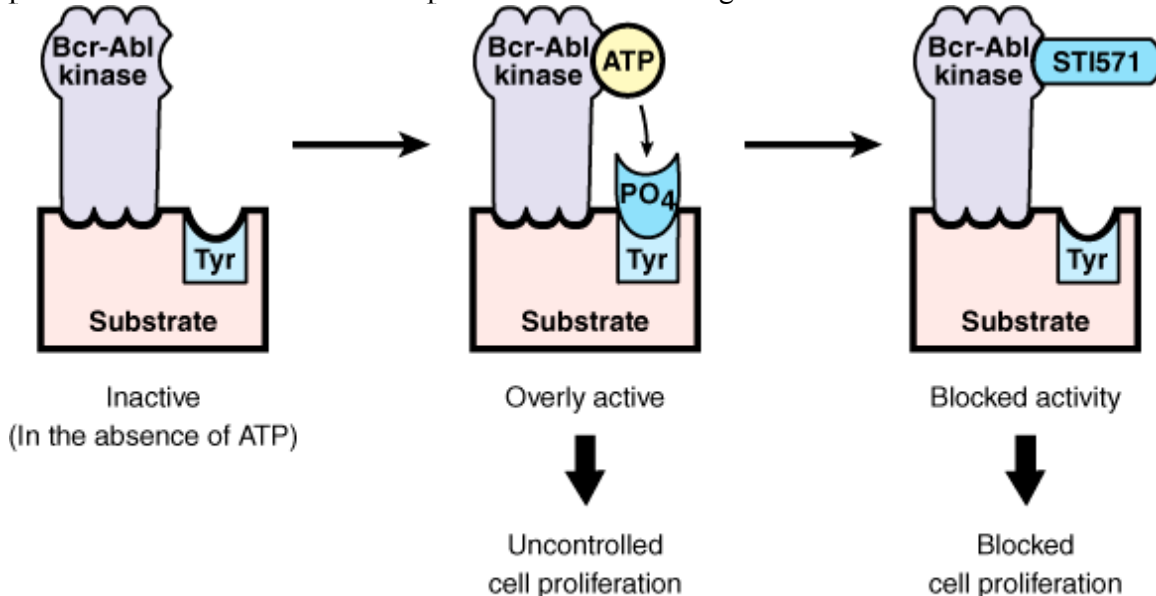


Figure 2: Imatinib (STI571) filling ATP binding site of BCR-ABL tyrosine kinase. Source: Feng et al. 2010

Imatinib also induces apoptosis in Philadelphia-chromosome-positive cells without affecting Ph negative cells (Moen et al. 2007). It has a very high success rate, and patients diagnosed in the early chronic phase now have an estimated survival of 20 to 30 years. The rate of complete cytogenetic response for early chronic phase is about 80%, and five-year progression-free survival is 96.7%. Imatinib is well tolerated, with less than 3% of patients showing resistance to it (Pemmaraju et al. 2011). The structure of imatinib is shown in Figure 3.

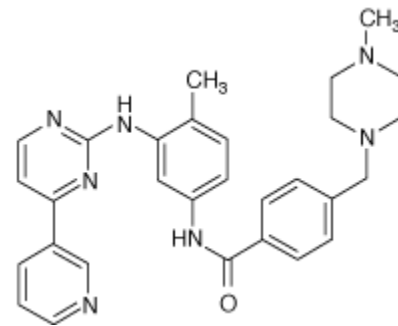


Figure 3: Structure of imatinib. Source: Chabner et al. 2011.

Prior to the introduction of imatinib, patients were treated with interferon ($\text{IFN-}\alpha$), which treated CML more effectively than standard chemotherapy. $\text{IFN-}\alpha$ was successful in achieving a complete cytogenetic response in 5 to 25% of patients. Combining $\text{IFN-}\alpha$ with cytarabine yielded better results and a greater probability of survival. In an IRIS trial, patients were randomly chosen for either $\text{IFN-}\alpha$ with cytarabine or imatinib. Imatinib showed significantly higher rates of complete cytogenetic response and lower toxicity levels than $\text{IFN-}\alpha$ with cytarabine. At 19 months, the percent of imatinib-treated patients achieving complete cytogenetic remission was 79%, compared to 11% achieved in patients treated with $\text{IFN-}\alpha$ with cytarabine. At the five-year follow-up, the percent of complete cytogenetic remission from imatinib had increased to 82%. There are no five-year follow-up data for the group taking $\text{IFN-}\alpha$ because most of that group switched to imatinib treatment. Additionally, health-related quality of life was maintained among the patients on imatinib, while those receiving $\text{IFN-}\alpha$ with cytarabine experienced a deterioration in

quality of life. Imatinib was therefore established as the primary therapy for chronic myeloid leukemia (Moen et al. 2007).

The standard dose for imatinib is 400 mg/day, with doses under 300 mg/day yielding unsatisfactory results. The TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) trial investigated the possible benefit of doubling imatinib dose to 800 mg/day. While patients taking 800 mg/day initially fared better, the percentages of complete cytogenetic responses over a longer period were nearly equal: 64% for 800 mg/day and 58% for 400 mg/day. Since long-term toxicity levels have not been assessed for the higher dose, the standard dose is currently 400 mg/day (Pemmaraju et al. 2011).

Imatinib, unlike previous treatments for CML, is unique in that it can effect a hematological remission for patients in the accelerated and blast phases (Marx 2001). However, 4-5% of patients on imatinib, particularly those who have progressed past the chronic stage, become resistant to the drug and relapse (Biotech Business Week 2006), including 80% of patients in blast crisis (Marx 2001). Others may never achieve remission with imatinib.

IMATINIB RESISTANCE

Imatinib resistance results from BCR-ABL gene amplification and point mutations. Some causes of resistance can be countered by dose escalation, while others render imatinib useless.

Some patients relapse due to gene amplification, which leads to increased kinase activity. The BCR-ABL gene produces more tyrosine kinase than standard dose imatinib (400 mg/day) can counter. The tyrosine kinase produced by BCR-ABL overexpression causes too many leukemia cells to be produced. While imatinib still functions properly, the leukemia cells proliferate at an even faster rate than usual. If the patient has not become imatinib resistant, an increased dosage of 600 or 800 mg/day may overcome the rapid proliferation of cells and bring about a remission. In particular, patients who achieved a complete cytogenetic remission and then lost the remission benefit from increased dosage (Pemmaraju et al. 2011).

Some patients are completely resistant to imatinib. Imatinib resistance is categorized as either primary or acquired. Primary resistance means that the patient never responds to the medication. Acquired resistance means a loss of imatinib-benefit after previously benefiting from it, which can be on a hematological, cytogenetic, or molecular level (Hochhaus and La Rosée 2004).

Point mutations, individual changes in gene sequencing, often confer drug resistance. They are thought to occur due to the inherent genetic instability of cancerous cells (Marx 2001). The dominant mechanism of imatinib resistance is genetic mutation in the kinase domain (ABL portion) of BCR-ABL. The mutated Ph chromosome contains an amino acid residue different than the regular BCR-ABL oncogene, coding for a slightly different tyrosine kinase. Since imatinib competitively inhibits the BCR-ABL tyrosine kinase by snugly fitting into the contact site, any change in the binding site can prevent it from binding effectively. Additionally, mutations often lock the protein in its active configuration, and imatinib binds only to the inactive configuration. Imatinib's pronounced specificity in binding makes resistance common (Liesveld and Lichtman 2011).

There are four main regions of the protein that are prone to resistance-conferring mutations: the ATP binding loop, or P-loop; the imatinib contact site; the catalytic domain; and the activation loop, which controls catalytic activity and changes conformation depending on protein activation (Litzow 2006). Although over 40 point mutations have been identified, 85% of mutations occur at seven amino acid residues: M244V, G250E, Y253F/H, and E255K/V in the P-loop; T315I at the contact site; M351T and F359V in the catalytic domain (Cang and Liu 2008). Usually only a single point mutation is detected in an imatinib-resistant patient, but occasionally patients have multiple mutations (Hochhaus and La Rosée 2004).

P-loop mutations account for 36-48% of all mutations (Cang and Liu 2008). The tyrosine kinase is composed of two flexible loops: the P-loop and the activation loop (An et al. 2010). When a mutation occurs in the P-loop, the configuration changes, causing the activation loop to fold outward into the active configuration and remain that way. Imatinib binds only to the inactive form of BCR-ABL and is, therefore, ineffective against most forms of P-loop mutations (Litzow 2006).

Contact site mutations confer high levels of resistance as well. The 315th amino acid of the tyrosine kinase serves as a contact point for imatinib. The threonine present at 315 forms a hydrogen bond with imatinib, a step that is crucial in order for imatinib to fill the ATP binding pocket (Hochhaus and La Rosée 2004). The switch of threonine to an isoleucine residue confers resistance in two ways. First, isoleucine does not form a hydrogen bond with imatinib like threonine does, so imatinib cannot form the bond critical for the drug's inhibitory effect on tyrosine kinase. Second, isoleucine is bulkier than threonine, so it acts as a "gatekeeper" by adding residue to the contact site, sterically hindering imatinib (Tanaka et al. 2010). In fact, the T315I mutation confers resistance to all second-generation tyrosine kinase inhibitors as well, as will be expounded upon later.

According to the MD Anderson algorithm for treating CML, if a patient has not achieved a complete hematological response within three months from the start of treatment, the patient is deemed imatinib resistant and switched to a different treatment method. Likewise, a patient who has not achieved a complete cytogenetic remission at 18 months is switched to a different therapy. If at any point in imatinib treatment, a patient relapses and loses a level of remission, it indicates a need for alternative treatment (Pemmaraju et al. 2011). The MD Anderson algorithm for CML treatment is shown in Figure 4.

ALTERNATIVES

Several alternative forms of treatment have been suggested for patients not responding satisfactorily to imatinib. They include allogeneic stem cell transplantation, novel tyrosine kinase inhibitors, aurora kinase inhibitors, and reactive oxygen species generators.

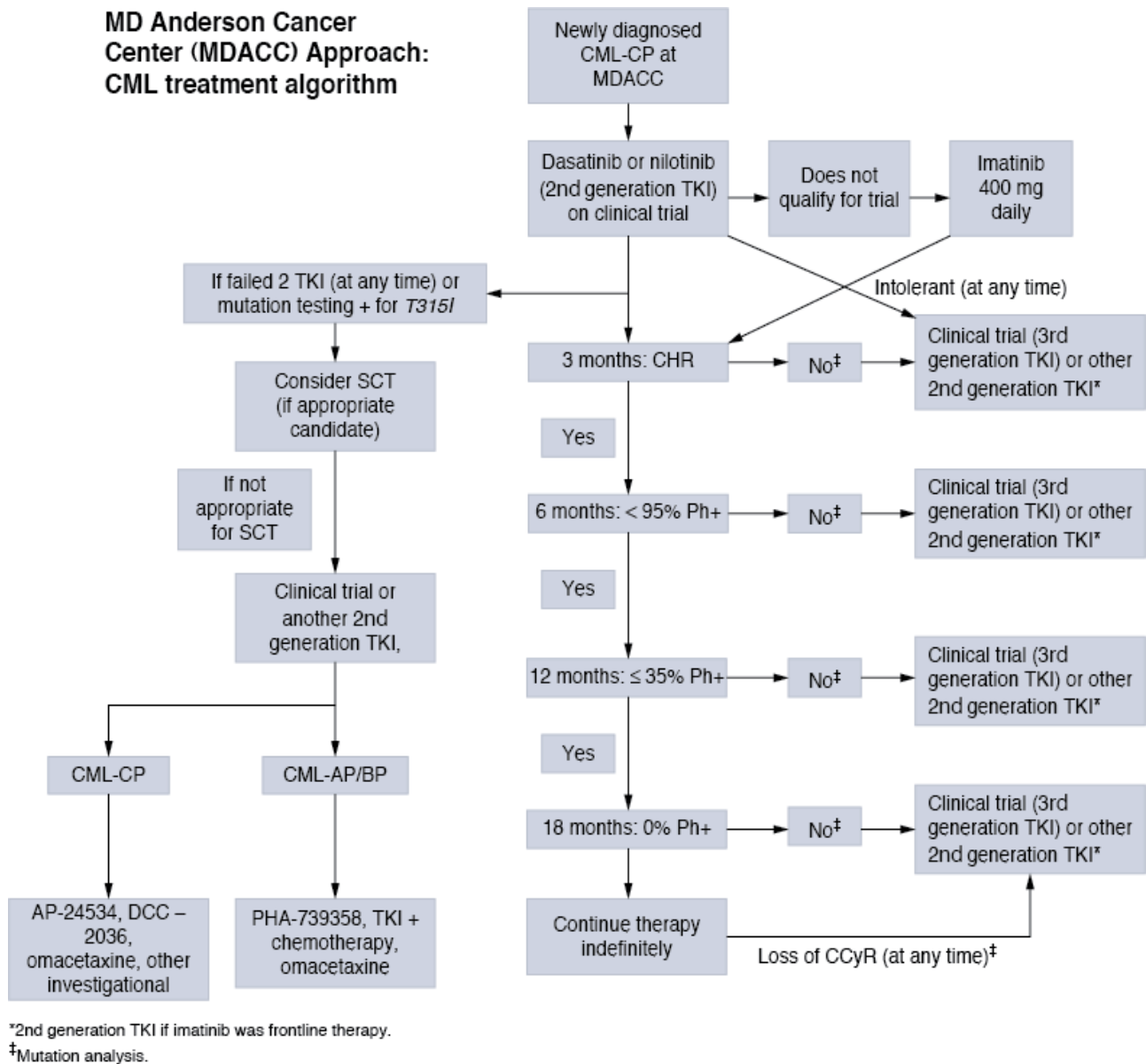


Figure 4: The MD Anderson algorithm for treatment of CML. Patients who fail to achieve the desired remission level within the specified timeframe or relapse are switched to a different therapy. Source: Pemmaraju et al. 2011

Allogeneic stem cell transplantation (SCT) is currently the only potentially curative treatment for CML (Linker and Damon 2011). All other therapies control the BCR-ABL oncogene expression; allogeneic SCT destroys the stem cells bearing the gene (Pemmaraju et al. 2011). SCT involves heavy chemotherapy and/or radiation regimens to destroy the diseased cells, ridding the body of the disease, and the transplant of healthy stem cells to the patient's bone marrow to replenish the cells destroyed by chemotherapy. Autologous SCT, in which healthy stem cells are extracted from the patient prior to chemotherapy and reintroduced afterwards, is sometimes used (Liesveld and Lichtman 2011). However, autologous SCT is associated with high morbidity levels due to the high-dose chemotherapy preparatory regimen. Allogeneic SCT uses stem cells from a well-matched donor which are infused

with mature donor leukocytes. This is more effective than autologous SCT because the grafted leukocytes recognize any remaining cancerous stem cells as foreign and attack them. This graft-versus-malignancy effect successfully eradicates malignant stem cells not destroyed by the preparatory regimen. Therefore, the pre-transplant regimen does not need to be as rigorous, making allogeneic SCT therapy an option for older patients (ages 60-75) who cannot tolerate standard high-dose chemotherapy (Linker and Damon 2011). Prior to the introduction of imatinib, allogeneic SCT was the treatment of choice for younger patients with a well-matched donor. However, allogeneic SCT has high morbidity levels due to incidence of graft-versus-host, in which the donor's cells attack the host. Therefore, with the introduction of imatinib, allogeneic SCT is no longer first-line therapy for chronic phase CML. However, it still remains useful for treating patients with poor response to imatinib and in patients with the T315I mutation (Liesveld and Lichtman 2011).

Following the success, and mindful of the flaws, of imatinib, several second-generation tyrosine kinase inhibitors (TKI) were created. These TKIs counter different imatinib resistance-conferring mutations. The three second-generation TKIs that are currently available are dasatinib, nilotinib, and bosutinib. Each has a distinct advantage over imatinib.

Dasatinib is a powerful TKI that inhibits many tyrosine kinases. It exhibits 300 times greater potency against the unmutated form of BCR-ABL than imatinib. Unlike imatinib, it binds to both the active and inactive forms of BCR-ABL and is, thus, unaffected by P-loop mutations (Cang and Liu 2008). Although effective against most mutations, it is ineffective against T315I, V299L, F317L, and a few others. Dasatinib has impressive results; over 50% of patients in chronic phase who failed imatinib therapy achieved a complete cytogenetic response with dasatinib. The standard dose for dasatinib is 100 mg daily, based on minimal toxicity levels and maximum performance. Dasatinib has few side effects and is overall well tolerated (Pemmaraju et al. 2011).

Based on dasatinib's effectiveness against imatinib-resistant CML, a study was conducted using dasatinib as front-line therapy in newly diagnosed chronic phase CML. Results were impressive and swift. Within six months, 90% of patients achieved complete cytogenetic remission (compared to historical records of \approx 80% with imatinib); within 12 months, 45% of patients had further improved to major molecular remission; and within 24 months, 71% achieved major molecular remission (Pemmaraju et al. 2011). The structure of dasatinib is shown in Figure 5.

Nilotinib is structurally similar to imatinib but modified to increase drug potency and selectivity. Like imatinib, it binds to the inactive configuration of BCR-ABL, locking the activation loop in the closed form to block the ATP binding site. Unlike imatinib, however, nilotinib forms hydrogen bonds with the amino acids at 286 and 381, two residues not prone to mutation (Chabner et. al. 2011). In a study of 321 chronic phase CML patients who failed imatinib treatment, 46% achieved a complete cytogenetic response with nilotinib. Nilotinib has an advantage over imatinib because

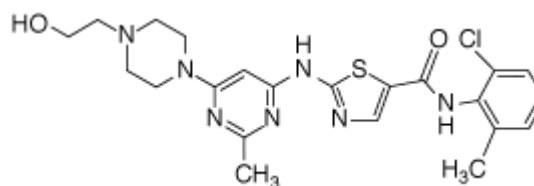


Figure 5: Molecular formula for dasatinib. Dasatinib binds both the active and inactive configurations of ABL-BCR tyrosine kinase. Source: Chabner et al. 2011

it is effective against nearly all mutations, with the exception of T315I (Pemmaraju et al. 2011). Some P-loop mutations have shown in-vitro resistance to nilotinib, so patients with P-loop mutations might benefit more from dasatinib (Cang and Liu 2008). Nilotinib is approved at 400 mg twice daily and is well tolerated (Pemmaraju et al. 2011).

Due to nilotinib's high success rate in imatinib-resistant patients, studies were conducted using nilotinib as the initial therapy for early chronic phase CML. Over 90% of patients achieved a complete cytogenetic response within six months, and an astounding near 80% of patients achieved a major molecular remission by 12 months. More significantly, one study showed that by 12 months, less than 1% of patients had progressed to the accelerated or blast phases, compared to 4% in patients receiving imatinib (Pemmaraju et al. 2011). The structure of nilotinib is shown in Figure 6.

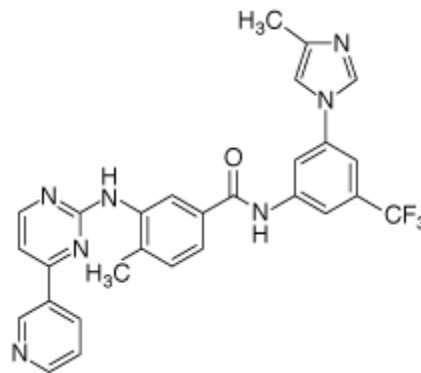


Figure 6: Molecular structure of nilotinib. Like imatinib, nilotinib binds only the inactive conformation of the BCR-ABL protein. Source: Chabner et al. 2011

Bosutinib is another potent TKI currently in development. It is 30-50 times stronger than imatinib against unmutated CML and is active against almost all BCR-ABL mutations. Bosutinib has success rates similar to the other second-generation TKIs; over 40% of chronic phase CML patients who switch to bosutinib because of imatinib resistance achieve a complete cytogenetic response. Bosutinib has an advantage over other TKIs due to its greater selectivity. Unlike the other TKIs, bosutinib has less off-target outcomes, which is theorized to reduce toxicity associated with other TKIs. Unfortunately, though, as with the other TKIs, bosutinib is ineffective against the T315I mutation (Cang and Liu 2008).

The efficacies of the three second-generation TKI's, dasatinib, nilotinib, and bosutinib, are summarized in Table 1.

Despite the efficacy of second-generation TKIs, none are successful in combating the T315I, and alternate therapies are necessary.

Aurora kinase inhibitors are a new class of CML therapy. Aurora kinases have been implicated in intensifying certain cancers, so combatting aurora kinases with aurora kinase inhibitors holds promise for controlling CML (Tanaka et al. 2010). MK-0457 was the first aurora kinase inhibitor to show activity against T315I. It binds to the amino acid at 381, and not at 315, thereby avoiding the steric clash with isoleucine (Quintas-Cardama and Cortes 2008). However, despite the promising results of MK-0457, trials were stopped due to concerns of cardiotoxicity (Cang and Liu 2008). Other aurora kinase inhibitors, like XL228, PHA-739358, KW-2449, and AT9238, are in various stages of clinical trials (Quintas-Cardama and Cortes 2008). Though the introduction of aurora kinase inhibitors in T315I+ CML is recent, results of early trials look promising since aurora kinase inhibitors do not bind to T315 and, therefore, are unhindered by isoleucine.

Another alternative for imatinib- and TKI-resistant CML is the use of reactive oxygen species (ROS). ROS are the main catalysts of redox dysregulation and oxidative stress within cells, especially cancerous cells (Wondrak 2009). The BCR-

Table 1: Response to Second-Generation TKI's											
PERCENT RESPONSE											
	<i>Dasatinib</i>				<i>Nilotinib</i>				<i>Bosutinib</i>		
	P	P	yBP	yBP	P	P	yBP	yBP	P	P	P
	=387	=174	=109	=48	=321	=137	=105	=31	=146	=51	=38
Median follow-up (mo)	5	4	2	2	4						
% Resistant to imatinib	4	3	1	8	0	0	2	2	9	R	R
% Hematologic Response		9	0	0	4	6	2	9	5	4	6
CHR	1	5	7	9	6	1	1	3	1	4	6
% Cytogenetic Response	R	4	6	2	R	R	R	R	R	R	R
Complete	9	2	6	6	6	0	9	2	4	7	5
Partial	1				5	2	0	6	3	0	8
% Survival (at 12 months)	6 (15)	2 (12)	0 (12)	0 (5)	7 (24)	7 (24)	2 (12)	2 (12)	8 (12)	0 (12)	0 (10)

CP, chronic phase; AP, accelerated phase; BP, blast phase; MyBP, myeloid blast phase; LyBP, lymphoid blast phase; NR, not reported.
Source: Pemmaraju et al. 2011

ABL oncogene promotes ROS-generated redox imbalances, and this dysregulation can be manipulated to induce cell death. The introduction of exogenous ROS-generating species increases oxidative stress in cancerous cells, leading to rapid protein degradation and cell death (Zhang et al. 2008). Redox imbalances operate under synthetic lethality, which means that only cancerous cells are killed, not normal cells (Wondrak 2009). PEITC (β -phenylethylisothiocyanate) is a naturally-occurring ROS-generating agent. In one experiment, when introduced in cells bearing normal BCR-ABL and cells with the T315I mutation, PEITC completely inhibited cell growth, raised oxidative levels twofold, and caused over 60% cell death (Zhang et al. 2008). The viability of ROS-generating agents like PEITC in vivo has not yet been established, but early research shows promise (Wondrak 2009).

SUMMARY

Chronic myeloid leukemia is no longer as frightening a diagnosis as cancer can be. The historic median survival of 4-5 years is a thing of the past. Novel targeted drugs can restrain BCR-ABL+ stem cells to the point that the disease is virtually undetectable. Imatinib, the first molecularly targeted anticancer therapy, is so effective that over 95% of patients maintain progression-free survival at five years. Even the few patients who are resistant to imatinib are not left without hope. Allogeneic stem cell transplants can cure the disease in healthy patients with a well-matched donor. Second-generation tyrosine kinase inhibitors can effect remission in most patients bearing imatinib-resistant BCR-ABL mutations. Dasatinib, nilotinib, and bosutinib are second-generation TKIs with differing potentials against the different mutations. Though none of these TKIs can counter the T315I contact site mutation, other therapies can. Aurora kinase inhibitors and ROS-generating agents are in various stages of clinical trials and show tremendous potential for treatment of T315I+ CML. Aurora kinase inhibitors do not bind to the threonine at 315, so they are not rendered ineffective in blocking the tyrosine kinase activity. ROS-generating agents prevent proliferation and induce cell death by critically raising intracellular oxidative levels in cancerous cells. With the wealth of scientific research and experimentation that has abounded regarding CML in the past 15 years, chronic myeloid leukemia has become a truly treatable disease.

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