REVIEW ON CHRONIC MYELOID LEUKEMIA

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ABSTRACT

In the past decade clinical and laboratory studies have led to important new insights into the biology of chronic myeloid leukemia (CML). Basic science has defined the molecular pathogenesis of CML as unregulated signal transduction by a tyrosine kinase. Clinical science has demonstrated that it is curable through immune-mediated elimination of leukemia cells by allogeneic T lymphocytes. Clinical Features CML is a malignant clonal disorder of hematopoietic stem cells that results in increases in not only myeloid cells but also erythroid cells and platelets in peripheral blood and marked myeloid hyperplasia in the bone marrow.[1]

Chronic myeloid leukemia (CML) is probably the most extensively studied human malignancy. CML was first described in 1844/5 when Virchow coined the term leukemia (Leukämie). This is the commonest myeloproliferative neoplasm and possibly the commonest adult leukemia. chronic myeloid leukemia is also known as Chronic myelogenous leukemia. It is charachterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate. Consequently, the peripheral blood cell profile shows an increased number of granulocytes and their immature precursors, including occasional blast cells. CML accounts for 20% of all leukemias affecting adults.[1]

Key words:*Blood cancer, CML,Tcells, B cells etc*

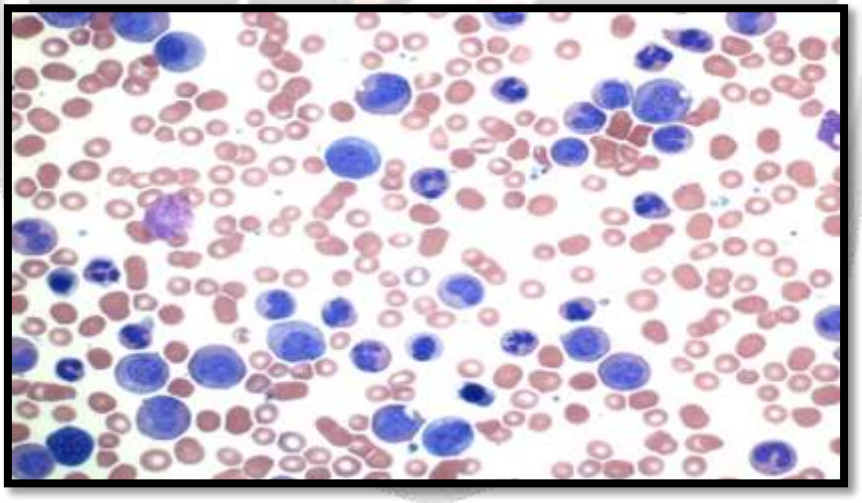

Fig 1 : Chronic Myeloid Leukemia

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 aecting myeloid, monocytic, erythroid, megakaryocytic, B-cell and sometimes T-cell lineages .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 . 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 suffcient for malignant transformation of CML. [2]

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 . 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. 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)

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 . 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 last 1970sThere 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 [2]

PATHOPHYSIOLOGY AND CLINICAL STUDY

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 . 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 . 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 . 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.[6,7]

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 . 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.[8]

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 AB. Thee 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. thee 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 .

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Depending on the breakpoint in the BCR gene, three main types of BCR-ABL genes can be formed because of alternative splicing. 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 suficient for the malignant transformation of CML, and responsible for the phenotypic abnormalities of CP CML.[9]

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 . Generally, a graphical view of the most common transcripts and a summary of their frequencies are given in Figure 2 and Table 1, respectively.[2,3]

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

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]. 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 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)

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.[2,3]

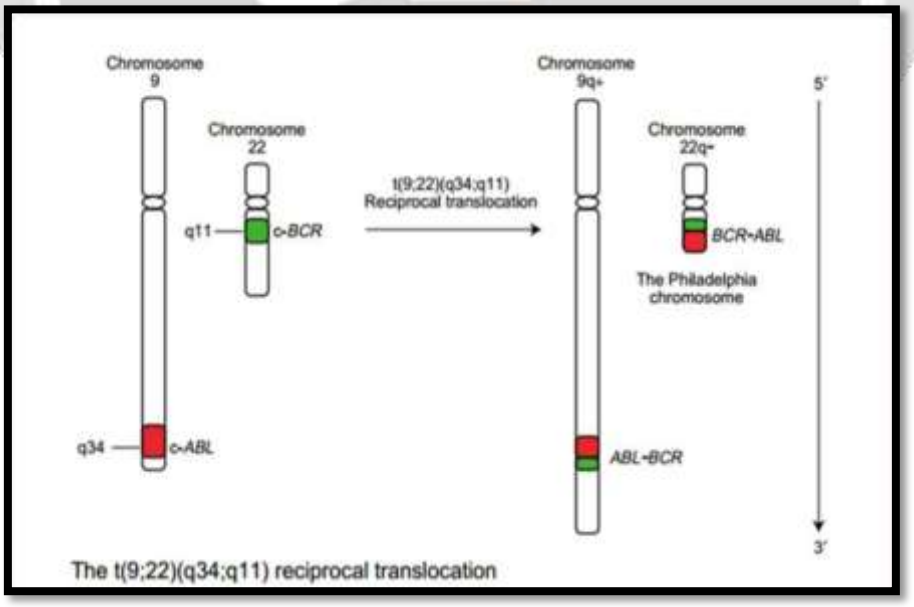

Fig 2: Reciprocal Translocation

DIAGNOSIS AND MANAGEMENT

The diagnosis of CML is based on anamnesis, physical examination, and laboratory data, including cytogenetic and molecular tests. Through the association of these information, it is possible to identify the disease stage and to direct the most appropriate monitoring and treatment.[10,11]

The diagnosis of CML usually occurs during routine medical appointments or blood tests in asymptomatic individuals. About 30% to 50% of patients diagnosed with CML in the United States are asymptomatic. The absence of symptoms is more common in the first of the three phases of the disease, the CP. Most CML diagnoses occur during this period, approximately 85%, with 40% being asymptomatic. Right after the CP, most patients can progress to an accelerated phase (AP), and then the so-called BC can occur. However, approximately 20% of individuals progress directly from the CP to a BC, without any typical manifestation of the AP[12,13]

During the CP, the individual's immune system, if competent, maintains an asymptomatic status over a long period. However, the CP can also manifest with symptoms such as anemia, splenomegaly, fatigue, weight loss, malaise, easy satiety and fullness, or pain in the upper left quadrant can occur. The less common manifestations during a CP are priapism, bleeding, thrombosis, retinal hemorrhage, and hepatomegaly. Splenomegaly is the most common physical condition associated with CML, found in 50%-60% of the cases, whereas hepatomegaly develops in only 10%-20% of the patients.[14]

During AP, the patients present with more severe symptoms that can include bone pain, skin infiltrate, lymphadenopathy, and worsening of the anemia. Moreover, fever, arthralgia, and abdominal pain may also occur as results of splenic infarction. The BC manifests as an acute leukemia with worsening of the symptoms present in the previous stages with bleeding, fever.

Atypical CML (a CML) affects about 5% of patients with CML, and includes absence of Ph chromosome and negative BCR-ABL1 rearrangement, leukocytosis with left shift, splenomegaly, and marked myeloid dysplasia. These patients usually have a more unfavorable prognosis with poor response to treatment. Considering that most patients are asymptomatic and the need for differential diagnosis with other hematological and systemic conditions, some tests are essential for the diagnosis of CML, such as blood count, bone marrow (BM) aspirate, cytogenetics, karyotyping, and qualitative and quantitative PCR. The diagnostic workup, according to the latest European Leukemia Net (ELN) recommendations, should include physical examination with emphasis on the presence of hepatomegaly or splenomegaly, electrocardiogram, biochemical profile, complete blood cell count and differential count, BM aspirate for morphology, and cytogenetics performed by chromosome banding analysis of Giemsa-stained metaphases as well as molecular study, preferably through reverse transcriptase polymerase chain reaction (RT-PCR) to detect, typify, and quantify the BCR-ABL1 transcripts. The molecular testing is becoming widely available, replacing the cytogenetic monitoring.[15,3

TREATMENT OF CML

The CML treatment has changed over time, as new medications are developed, especially those that are able to provide a balanced risk vs benefit ratio. Some of the theories that support the use of immunotherapy in the treatment of CML are related to the fact that this leukemia has a slow development as well because the leukemic cells are accessible since they are found in the blood and in the lymphatic system. Moreover, these cells have a very specific tumor antigen — the aforementioned BCR-ABL oncoprotein. CML is considered one of the most sensitive neoplasms to immune manipulation, in addition to having well-established therapies that allow an important reduction in tumor mass. Given this, the last 20 years deserve to be highlighted for an important progress in the understanding of tumor immunology, whether in the area of passive or active immunotherapy. With regard to passive immunotherapy, hematopoietic stem cell transplantation (HSCT) and the donor leukocyte infusion can be mentioned, while vaccines are part of active immunotherapy[16,3]

FIRST LINE TREATMENT

TKIs

TKIs are the current standard treatment for patients with CML. After all, they have been able to effectively prolong patient survival, along with their rates of cytogenetic and molecular responses.

"Imatinib" is considered a first-generation TKI as it is a pioneer in the activity of inhibiting platelet-derived growth factor (PDGFR), KIT, and ABL, with successful clinical development, being approved for the treatment of CML in 2001. This is the gold-standard treatment, as it results in more expressive cytogenetic and molecular responses and has fewer adverse effects than interferon-alpha (IFN-a). The half-life of imatinib is approximately 14 h in the human body Recent reports suggest that almost half of CML patients treated with imatinib who obtained a lasting complete MR are able to discontinue treatment without relapse The number of natural killer (NK) cells appears to be an interesting parameter to be used as a prognostic factor for treatment with imatinib. After all, some studies have shown an increase in NK cell count along with the successful interruption of this immunotherapeutic. In addition, some studies report that imatinib induces a complete hematological and cytogenetic response in approximately 83% of patients with CML for 10 years. Some common adverse effects include edema (due to changes in the permeability of small vessels), weight gain, conjunctival irritation, bleeding from mucous membranes, diarrhea, and even skin rash. Less frequently, it can cause changes in liver enzymes, anemia, thrombocytopenia, and neutropenia. Despite the increasing number of patients who obtain cytogenetic responses with this drug, about 30% of patients experience resistance to therapy, half of them showing the development of a point mutation in the ATP binding domain of the oncoprotein.[17,27]

"Dasatinib" is a second-generation TKI and has become a central issue for research in the treatment of CML. So far, the number of CML patients who have benefited from treatment with this TKI remains unknown. Moreover, it has a shorter time on the market compared to imatinib[17]. Dasatinib is known as a "double inhibitor" because it inhibits, in addition to PDGFR and KIT, several members of the Scr family of tyrosine kinase. In addition, it has a half-life of 3-6 h and has a potency around 325 times greater than that of imatinib. This medication is recommended for use when there is resistance to imatinib as well as other second- and third-generation TKIs. The DASISION study demonstrated that the CCyR and Major MR (MMR) rates for the use of dasatinib at the dose of 100 mg, once daily, were higher and resulted in a faster and more effective response than that observed with the use of imatinib at a dose of 400 mg, once daily. However, an important factor that can become an obstacle in the treatment of CML with this medication is the presence of pleural effusion as the main adverse effect in 30% to 40% of patients, which can lead to a discontinuation rate of 29%[18]. Other adverse reactions may include thrombocytopenia in higher rates when compared with imatinib, which can lead to gastrointestinal bleeding. Joint pain may be present and, rarely, pulmonary hypertension, which appears to be reversible with discontinuation of medication[19]. With regard to the follow-up of patients using this medication, the dose of dasatinib can be reduced to 50 mg per day, or even be administered every other day, if the disease is optimally controlled.[20]

"Nilotinib" is a highly specific derivative and inhibits BCR-ABL with a potency approximately 25 times greater than that observed with imatinib, whether administered at a dose of 150 mg twice daily or 200 mg twice daily. In addition, its use is approved for the treatment of patients with newly diagnosed CML in CP and patients with CML in CP or AP who are resistant or intolerant to prior therapies. This medication has a peak serum concentration about 3 h after administration, that its bioavailability is increased by about 82% when ingested with a high-fat meal compared to the fasting state, and that its metabolism is mainly via cytochrome P450 3A4. With regard to adverse effects related to this medication, studies have reported elevations in total bilirubin, acute pancreatitis, and, mainly, development of a kind of "metabolic syndrome"[21]. Valent et al demonstrated in their study that, over a period of 5 years, nilotinib was associated with a prevalence of diabetes and cardiovascular events of 15% and 20%, respectively. These effects are of extreme concern, especially when this medication is used as a first line therapy, because of its potential lethality. However, another publication by Hochhaus et al reported that even with these possible effects, the use of nilotinib 300 mg twice daily has a positive risk-benefit ratio. Therefore, continuous monitoring and evaluation of cardiovascular risk factors is required for patients selected for treatment.

"Bosutinib" is an oral SRC/ABL TKI licensed since 2012, which has shown to be effective in the treatment of resistant CML that does not harbor mutations in the T315l or V299L ABL KD, in all disease phases. The main factor that distinguishes it from the inhibitory potential from other TKIs is that it does not block PDGFR or KIT. Unlike previous TKIs, it has a relatively lower toxicity and its side effects are usually gastrointestinal disorders, such as diarrhea, which usually resolves spontaneously after 1 wk to 2 wk, cutaneous manifestations such as rash, in up to 20% of patients, and joint pain. In addition, bosutinib has been shown to have a safe cardiovascular profile, similar to imatinib, with a dose of 300 to 500 mg per day being recommended. In addition, Tiribelli et all provided data that demonstrate that bosutinib is a good therapeutic choice in patients who develop pleural effusion when using dasatinib.[22,27]

Table 1 : Drug Responses

TKI Choice	Early Molecular Response	Complete Cytogenetic Response at 12 months	Major Molecular Reasponse at 12 months	Accelerated /Blast Phase Transformation	Overall survival at 5 Years
Dasatinib vs Imatinib	84 % vs 64%	83% vs 72%	46% vs 28%	4.6% vs 7.3%	91% vs 90%
Nilotinib vs Imatinib	91% vs 67%	80% vs 65%	44% vs 22%	0.7% vs 4.2%	93.7% vs 91.7%
Bosutinib vs Imatinib	75% vs 57%	77% vs 66%	47% vs 37%	2.2% vs 2.6%	94.5% vs 94.6%

New drug generations

Given the growing prevalence of TKI resistance in CML, various clinical trials have been conducted in order to make new drug options available for the patients affected by this disease.

Asciminib

Asciminib is one of the most promising drugs among those aiming to be alternatives in the TKI resistance scenario. This medicine is an allosteric inhibitor that binds to the myristoylation site and alters the conformation of the KD to keep it inactive, and has the negative and muted BCR-ABL1 as its target; that is, ABL1 mutations such as gatekeeper T315I are not able to promote resistance to this drug. Considering asciminib as a promising drug to deal with the resistance and side effects of TKIs and aiming to increase the speed of response and the rates of deep molecular remission, there are currently phase 1 and phase 2 studies evaluating therapy with asciminib alone or combined with nilotinib, imatinib, and dasatinib. These studies aim to validate its safety, tolerability, and potential as first-line therapy. The preliminary results of the phase 1 study published showed that asciminib achieved response in patients heavily pretreated, with unacceptable TKIs' side effects, failure in ponatinib treatment or T315I mutation, presenting as a promising alternative in these cases [23,27]

Radotinib

Radotinib is a BCR-ABL oral inhibitor indicated for newly diagnosed CML patients and for those with resistance to at least one TKI. Besides inhibiting the salvage-type BCR-ABL kinase, radotinib also inhibits other kinases, such as PDGFRα, PDGFRβ, c-kit, and SRC, when used in higher concentrations. However, this drug presents no consistent effectiveness against T215I. A phase 3 study carried out in various Asian countries compared radotinib vs imatinib in newly-diagnosed CML. The results showed significantly higher and faster MMR rates in the radotinib group after 12 mo and 48 mo of follow-up.[24,27]

"Danusertib"

Aurora kinases are serine/threonine kinases that are crucial for coordinated cell division. They participate in the maturation of centrosomes, in the formation of mitotic fuse, in chromosomal segregation, and in cytokinesis. In that context, danusertib promotes the inhibition of the catalytic domain of aurora kinases as well as inhibits ABL and its mutated variations, including T315I. This drug takes advantage of the crystal structure of the T315I KD and binds to the ATP-binding pocket of the enzyme active conformation, neutralizing the steric hindrance resultant from the substitution of threonine for isoleucine. A phase 1 study about danusertib, that included 37 patients, showed subtle positive responses in patients with TKI-resistant CML in accelerated and blastic phases who carry T315I as well as in Ph chromosome-positive ALL. Among CML patients, 20% achieved a complete hematologic response and a CCR was observed in one individual.[25,27]

Immunotherapy:

Vaccines are important immunotherapy components, being considered active immunotherapies. The advance in the knowledge on the BCR-ABL protein and its biological aspects has led to the development of a considerable diversity of studies based on the evaluation of vaccines based on peptides such as Pr-3, WT-1, and HSP70

IFN-α was widely used in the treatment of CML in the 1980s, due to its disrupting role in the expression of the BCR-ABL1 gene, in the activation of cell apoptosis factors, and in the recognition and elimination of CML-characteristic cells, in addition to promoting normal quiescent hematopoietic stem cell cycling. The average rate of CCyR with IFN is 13%, ranging from 5% to 33%. This component targets highly quiescent leukemic stem cells, which have a high self-renewal capacity. Essers et al demonstrated that INF-α was able to sensitize these stem cells. However, some adverse effects, such as flu symptoms, arthralgia, myalgia, neutropenia, and depression, contributed to the discontinuation of its use. Currently, the discussion about the use of INF-α has returned, but in a combined use with TKIs.[26,27]

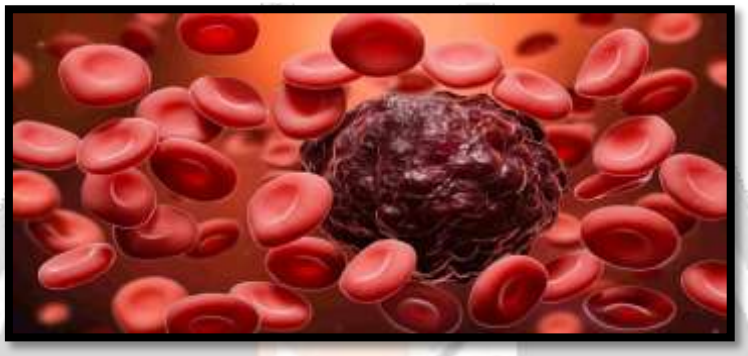

Fig 3: Normal blood cells vs CML blood cells

MARKETED PREPARATION

Table 2: Marketed Prpration

SR NO	Drug	Strength	Brand Name	Manufacturing Company
1.	IMATINIB	400 MG	IMAT 400 IMATIB 400	ZYDUS (CELEXA) CIPLA
2.	DSATINIB	50 MG	SPRYCEL SPINIB	BMS INDIA PVT LTD. ZYDUS (ONCOSCIENCES)
3.	NILOTINIB	200 MG	TASIGNA NILOTIB	NOVASRTIS CAPRANE PHARMACEUTICAL PVT. LTD
4.	BOSUTINIB	400 MG 500 MG	BONITAR BOSUTRIS	SUN PHARMA. MYLAN
5.	ASCINIB	40 MG	SCEMBLIX	NOVARTIS

CASE STUDY

We reported one case of chronic myeloid leukemia. The patient was 85 years old man. He was presented to his primary care physician with 2 months of decreased in urination , problem in passing the stool , fatigue , weight loss, shortness in breath.

On investigation of blood (Bone Marrow test) all metaphases are analysed are abnormal and show t (9,22) which is consistant with chronic myeloid lukemia. This test detects mutations in the ABL Kinase domain of the BCR-ABL transcript and Predicts resitance to Dasatinib based on the mutation.

So the patient started with first line treatment "Dasatinib 50 mg." twise a day. After the duration of 4 years at the age of 89 years old, patient achieved complete haematological response . The patient responded to treatment with tyrosine kinase inhibitor drug dasatinib. When patient was detected with CML the ratio of mutation was 46.232, after the duration of 4 years the ratio of mutation is 0.006. Patient shows the complete responce to dasatinib treatment.

CONCLUSION

CML experts and patients with CML have multiple treatment options in the CML therapeutic armamentarium,including TKIs like " Dasatinb, Imatinib, Nilotinib ,Bosutinib, Asciminib and several agents. Most patient with CML would be expected to have normal life span and be potentially, functionally through not molecularly cured. That is as long as they contineou therapy with TKIs based regimens, in order to change therapy in a timely manner before CML progression.

Although the knowledge about CML cytogenetics has been well elucidated, the role of innate and adaptive immunity in the prevention as well as in the development of this disease and the role of additional mutations should be understood to a broader extent, allowing the advancement of new therapies, aiming to improve the quality of life and survival of these patients. New drugs and the advancement of immunotherapy are essential to tackling TKI resistance and maintaining low residual levels of cancer cells.

REFERENCE

1. Molecular Biology Of Chronic Myeloid Leukemia ; Michael W. N. Deiniger, John M. Goldman, Junia V. Melo
2. Current Management Approaches of Chronic Myeloid Leukemia January 2017 Journal of Cancer Science and Therapy
3. **https://www.researchgate.net/publication/319648942_Current_Management_Approaches_of_Chronic_Myeloid_Leukemia**
4. Lugo TG, Pendergast AM, Muller AJ, Witte ON (1990) Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. Science 247: 1079-1083
5. Campbell ML, Li W, Arlinghaus RB (1990) P210 BCR-ABL is complexed to P160 BCR and ph-P53 proteins in K562 cells. Oncogene 5: 773-776.
6. Brian R, Smith MD (1990) Regulation of hematopoiesis. Yale J Biol Med 63: 371-380.29.
7. Lento W, Congdon K, Voermans C, Kritzik M (2013) Wnt signaling in normal and malignant hematopoiesis. Cold Spring Harb Perspect Biol 5.
8. Frank DA, Varticovski L (1996) BCR/abl leads to the constitutive activation of stat proteins, and shares an epitope with tyrosine phosphorylated stats leukemia 10: 1724-1730
9. Daley GQ, Baltimore D (1988) Transformation of an interleukin 3-dependent hematopoietic cell line by the chronic myelogenous leukemia-speci□c P210bcr/abl protein. Proc Natl Acad Sci USA 85: 9312-9316
10. Associação Brasileira de Hematologia E Hemoterapia, Sociedade Brasileira de Patologia, Sociedade Brasileira de Pediatria. [Chronic myeloid leukemia]. Rev Assoc Med Bras (1992). 2013;59:220-232. [PubMed] [DOI] [Cited in This Article: 2] [Cited by in Crossref: 3] [Cited by in F6Publishing: 3] [Article Influence: 0.3] [Reference Citation Analysis (0)]

11. Sawyers CL. Chronic myeloid leukemia. N Engl J Med. 1999;340:1330-1340. [PubMed] [DOI] [Cited in This Article: 1] [Cited by in Crossref: 1066] [Cited by in F6Publishing: 1104] [Article Influence: 44.4] [Reference Citation Analysis (0)]
12. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2012 update on diagnosis, monitoring, and management. Am J Hematol. 2012;87:1037-1045. [PubMed] [DOI] [Cited in This Article: 1] [Cited by in Crossref: 85] [Cited by in F6Publishing: 96] [Article Influence: 7.7] [Reference Citation Analysis (0)]
13. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2014 update on diagnosis, monitoring, and management. Am J Hematol. 2014;89:547-556. [PubMed] [DOI] [Cited in This Article: 6] [Cited by in Crossref: 135] [Cited by in F6Publishing: 148] [Article Influence: 15.0]
14. Flis S, Chojnacki T. Chronic myelogenous leukemia, a still unsolved problem: pitfalls and new therapeutic possibilities. Drug Des Devel Ther. 2019;13:825-843. [PubMed] [DOI] [Cited in This Article: 4] [Cited by in Crossref: 36] [Cited by in F6Publishing: 43] [Article Influence: 9.0] [Reference Citation Analysis (0)]
15. Quintás-Cardama A, Cortes JE. Chronic myeloid leukemia: diagnosis and treatment. Mayo Clin Proc. 2006;81:973-988. [PubMed] [DOI] [Cited in This Article: 3] [Cited by in Crossref: 136] [Cited by in F6Publishing: 145] [Article Influence: 8.0] [Reference Citation Analysis (0)]
16. Berke Z, Andersen MH, Pedersen M, Fugger L, Zeuthen J, Haurum JS. Peptides spanning the junctional region of both the abl/bcr and the bcr/abl fusion proteins bind common HLA class I molecules. Leukemia. 2000;14:419-426. [PubMed] [DOI] [Cited in This Article: 2] [Cited by in Crossref: 36] [Cited by in F6Publishing: 36] [Article Influence: 1.6] [Reference Citation Analysis (0)]
17. Branford S, Rudzki Z, Harper A, Grigg A, Taylor K, Durrant S, Arthur C, Browett P, Schwarer AP, Ma D, Seymour JF, Bradstock K, Joske D, Lynch K, Gathmann I, Hughes TP. Imatinib produces significantly superior molecular responses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Leukemia. 2003;17:2401-2409. [PubMed] [DOI] [Cited in This Article: 2] [Cited by in Crossref: 119] [Cited by in F6Publishing: 124] [Article Influence: 6.3] [Reference Citation Analysis
18. Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boqué C, Chuah C, Pavlovsky C, Mayer J, Cortes J, Baccarani M, Kim DW, Bradley-Garelik MB, Mohamed H, Wildgust M, Hochhaus A. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood. 2014;123:494-500. [PubMed] [DOI] [Cited in This Article: 1] [Cited by in Crossref: 302] [Cited by in F6Publishing: 323] [Article Influence: 30.2] [Reference Citation Analysis (0)]
19. Weatherald J, Chaumais MC, Savale L, Jaïs X, Seferian A, Canuet M, Bouvaist H, Magro P, Bergeron A, Guignabert C, Sitbon O, Simonneau G, Humbert M, Montani D. Long-term outcomes of dasatinib-induced pulmonary arterial hypertension: a population-based study. Eur Respir J. 2017;50. [PubMed] [DOI] [Cited in This Article: 1] [Cited by in Crossref: 71] [Cited by in F6Publishing: 73] [Article Influence: 11.8] [Reference Citation Analysis (0)]
20. Iriyama N, Ohashi K, Hashino S, Kimura S, Nakaseko C, Takano H, Hino M, Uchiyama M, Morita S, Sakamoto J, Sakamaki H, Inokuchi K. The Efficacy of Reduced-dose Dasatinib as a Subsequent Therapy in Patients with Chronic Myeloid Leukemia in the Chronic Phase: The LD-CML Study of the Kanto CML Study Group. Intern Med. 2018;57:17-23.
21. Tian X, Zhang H, Heimbach T, He H, Buchbinder A, Aghoghovbia M, Hourcade-Potelleret F. Clinical Pharmacokinetic and Pharmacodynamic Overview of Nilotinib, a Selective Tyrosine Kinase Inhibitor. J Clin Pharmacol. 2018;58:1533-1540.
22. Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, le Coutre PD, Etienne G, Dorlhiac-Llacer PE, Clark RE, Flinn IW, Nakamae H, Donohue B, Deng W, Dalal D, Menssen HD, Kantarjian HM. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30:1044-1054.
23. G Lindström HJ, Friedman R. The effects of combination treatments on drug resistance in chronic myeloid leukaemia: an evaluation of the tyrosine kinase inhibitors axitinib and asciminib. BMC Cancer. 2020;20:397.
24. Zabriskie MS, Vellore NA, Gantz KC, Deininger MW, O'Hare T. Radotinib is an effective inhibitor of native and kinase domain-mutant BCR-ABL1. Leukemia.
25. Borthakur G, Dombret H, Schafhausen P, Brummendorf TH, Boissel N, Jabbour E, Mariani M, Capolongo L, Carpinelli P, Davite C, Kantarjian H, Cortes JE. A phase I study of danusertib (PHA-739358) in adult patients with accelerated or blastic phase chronic myeloid leukemia and Philadelphia

chromosome-positive acute lymphoblastic leukemia resistant or intolerant to imatinib and/or other second generation c-ABL therapy. Haematologica. 2015;100:898-904.

26. Lin C, Li Y. The role of peptide and DNA vaccines in myeloid leukemia immunotherapy. Cancer Cell Int. 2013;13:13.
27. https://www.wjgnet.com/2218-4333/full/v12/i2/69.htm#refB136217