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Review Article

Approaches to Managing Philadelphia Chromosome Positive Chronic Myeloid Leukaemia Patients: A Short Review

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ABSTRACT

Chronic Myeloid Leukaemia (CML) is a neoplastic disease which offshoot from alterations in the Deoxyribonucleic Acid (DNA) of a specific bone marrow cell. It's a well-known hematopoietic stem cell cancer that accounts for 15%-20% of all adult leukaemia cases.

The review article aimed to provide an overview of approaches for managing the development of CML, along with the treatment concerns for special populations like paediatrics, geriatrics, pregnant and lactating women.

The literature search for the review was conducted in Pub Med, Scopus indexed journals.

Chronic Myeloid Leukaemia is the most enormously studied cancers and the effective therapy with the drugs starts from 1953 with alkylating agent, but the use was reduced due to adverse effects. The Interferon alpha treatment had a primary importance on the outcome of patients with CML before the emergence of Imatinib. Imatinib is a tyrosine kinase inhibitor that was named the "Magical Bullet" because of its ability to treat CML with miraculous results. CML has become a manageable disease due to the clever nature of BCR-ABL targeting drug treatments, which have an average survival rate of more than 90%. With the number of patients achieving molecular full remission, HSCT remains the most successful anti leukemic therapy for CML.

Keywords: Chronic Myeloid Leukaemia (CML), Deoxyribonucleic acid, Tyrosine kinase inhibitor, Hematopoietic Stem Cell Transplantation (HSCT), Imatinib

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INTRODUCTION

Chronic Myeloid Leukaemia (CML) is a neoplastic disease which offshoot from alterations in the Deoxyribonucleic Acid (DNA) of a specific bone marrow cell (Khan N and Abbas A, 2014). It's a well-known malignant condition that affects hematopoietic stem cells and accounts for 15%-20% of all adult leukemia cases (Flis S and Chojnacki T, 2019). CML is a clonal bone marrow stem cell disorder which is distinguished by hyper proliferation of the granulocytes(neutrophils, eosinophil's, basophils) so it is also called as myeloproliferative disorder. Blast cells are the progenitor of CML cells which propagate and endure better than the ordinary cells (Khan N and Abbas A, 2014).

Philadelphia chromosome (Ph) is an abnormal shortened chromosome and is the hallmark of CML. This is developed due to the mutation between chromosome 9 and chromosome 22 which results in the shortening of chromosome and lead to the evolution of a new chimergic oncogene called BCR-ABL gene (Khan N and Abbas A, 2014). The mechanism by which the Ph chromosome is formed and the time required for progression of the disease is unknown. CML develops when a single, pluripotent, hematopoietic stem cells earn a Ph chromosome carrying the BCR-ABL gene (Goldman JM and Melo JV, 2003). CML becomes pathogenic when the Abelson Murine Leukaemia (ABL) gene on chromosome 9 fuses with the Break-point Cluster Region (BCR) gene on chromosome 22, resulting in the expression of an oncoprotein (Jabbour E and Kantarjian H, 2012).

Anaemia, splenomegaly, nausea, weight loss, malaise, left upper quadrant fullness or discomfort, increased sweating are the most common symptoms (Flis S and Chojnacki T, 2019). Bleeding due to platelet deficiency, thrombocytosis, gouty arthritis (due to elevated uric acid levels), priapism, retinal haemorrhage, upper gastrointestinal ulceration, and bleeding are also rare forms. Splenomegaly is the most prevalent clinical symptom of CML, occurring in 50%-70% of patients, whereas hepatomegaly is less common and lymphadenopathy, skin penetration, and other tissue penetration are uncommon. Headache, bone pain, arthralgia, splenic infarction pain, and fever are the most common symptoms associated with the CML transformation (Jabbour E and Kantarjian H, 2012). The amount of premature white blood cells or blasts in the blood or bone marrow determines the disorder's progression through three stages: Chronic phase, accelerated phase, and blast crisis *(Table 1)* (O'Dwyer ME, *et al*., 2003). This review aimed to combine all the treatment modalities for the CML patients and highlight the therapy concerns for special populations like paediatrics, geriatrics, pregnant and lactating women for reducing the risks and management of the disease.

Table 1: Phases of Chronic Myeloid Leukemia (CML)

Parameters	Chronic Phase (CP)	Accelerated phase	Blast crisis
Percentage blast cells	10%-15%	>15%<30%	>30%
Symptoms	Asymptomatic and if symptoms exist it might be mild and vague which includes fatigue, weight loss, abdominal fullness	Persistent unexplained fever bone pain, hepatomegaly	Fever, fatigue, weight loss, anaemia, thrombocytopenia, Increased infections, lymphadenopathy, Central Nervous System (CNS) disease
Blood or bone marrow	Myeloid hyperplasia	Myeloid hyperplasia	Myeloid hyperplasia

Median disease duration	3-5 years	6-9 months	3-6 months
White Blood Cell (WBC) count	>50 × 109 L	Over 50,000	-
Haemoglobin	Normal/slightly low	Low	Very low
Platelets	Normal/high/low	High/low	Low
Cytogenetics	Ph+ (Positive)	Ph+	Ph+
Splenomegaly (enlarged spleen)	Present	Present	Present

LITERATURE REVIEW

Chemotherapy

The invention of oral Busulphan, an alkylating agent, in 1953 marked the beginning of effective drug therapy. Due to side effects such as myelosuppression, marrow fibrosis, and prolonged aplasia, the use of Busulphan has been limited. Despite the fact that it was the preferred therapy for almost two decades and is still used in allogenic stem cell transplantation conditioning regimens, it is no longer the preferred therapy.

Hydroxy urea: Since hydroxy urea, a ribonucleotide reductase inhibitor, was introduced into CML care in 1972, it increased median survival rates from 44 to 58 months when compared to Busulphan; however, no therapy stopped progression to Blast Crisis-Chronic Myeloid Leukaemia (BC-CML) (Woessner DW, *et al.*, 2011). It is an excellent chemotherapeutic agent that was used to limit leukocyte proliferation before the advent of Tyrosine Kinase Inhibitors (TKIs) and Interferon, and is now used as a short-term monotherapy to reduce leukocytosis in *de novo* CML prior to TKIs (Westerweel PE, *et al.*, 2019). The usual adult dose of hydroxy urea for CML is 15 mg/day orally as a single dose. Since its oral administration, hydroxy urea has been well absorbed, converted to nitroxide free radical, and diffused into cells, where it quenches the tyrosyl free radical at the active site of ribonucleotide reductase, inactivating the enzyme. The entire complex is inactivated, and DNA synthesis is selectively inhibited, resulting in S phase cell death and synchronization of the remaining cells (Yarbro JW, 1992).

Cytarabine: Combining an intermediate dose of cytarabine with Imatinib for the first-line treatment of chronic phase CML has been shown to be effective in clinical practice, and it is also the hallmark of induction chemotherapy. Cytarabine works by interrupting DNA synthesis. It works by rapidly converting cytosine arabinoside triphosphates into cytosine arabinoside triphosphates, which damage DNA while the cell cycle is in the S step of DNA synthesis. They also prevent DNA synthesis by inhibiting DNA and RNA polymerases, as well as nucleotide reductase enzymes. However, later it was observed that there was no beneficial effect in adding cytarabine with Imatinib, while it did increase adverse events.

Homoharringtonine and omacetaxin: Homoharringtonine (HHT), a plant alkaloid derived from the Cephalotaxus genus, and omacetaxine, a synthetic formulation of HHT, both inhibit ribosomal protein translocation and hence have anti-CML activity. The drug is approved for the treatment of patients with persistent and accelerated CML who have failed two or more TKIs in the United States (Westerweel PE, *et al.*, 2019).

Targeted therapy

Tyrosine Kinase Inhibitors (TKIs) are drugs that target and exploit the aberrantly expressed BCR-ABL enzyme. They have less severe side effects when compared with other treatments (Jabbour E and Kantarjian H, 2012). TKIs used for the treatment of CML include: Imatinib (Gleevec), Dasatinib (Sprycel), Nilotinib (Tasigna), Bosutinib (Bosulif), Ponatinib (Iclusig). Patients with a history of cardiac disease or peripheral artery disease should be closely watched and monitored regularly when taking TKIs because certain patients experience severe cardiac side effects such as congestive heart failure and QT interval prolongation (Melge AR, *et al.*, 2019).

Imatinib: Imatinib (Gleevec or Glivec), is a tyrosine kinase inhibitor which was discovered by a biochemist Nicholas Lyndon in the late 1990s. And the drug was initially called as "Magical bullet" because it showcased the ability to produce miracle effect in the treatment of CML and certain other types of cancer. O'Brien conducted the landmark IRIS (International Randomized trial of Interferon and STI571) study in CML. In a randomized trial, they compared Imatinib to a combination of Interferon alpha and Cytarabine in 36 Chronic phase-Chronic Myeloid Leukaemia (CP-CML) patients. Imatinib produces full hematological and cytogenic responses in 95.3 percent of patients and 73.8 percent of patients, respectively. It is also used for other types of cancers like GI stromal tumors, dermatofibro sarcoma protuberans, anaplastic thyroid cancer, malignant melanoma, recurrent epithelial ovarian cancer, chordoma, aggressive fibromatoses, systemic mastocytosis, hypereosinophilic syndrome, Ph positive acute lymphoblastic leukemia etc (Kumar NM, *et al.*, 2018).

Imatinib is a 2-phenyl amino pyrimidine derivative that prevents protein tyrosine phosphorylation by binding to the ATP binding site and locking it in a closed or self-inhibited conformation, thereby preventing the enzyme action of the protein. The drug is mainly administered by oral route and has a bioavailability greater than 90% and principally metabolized by Cytochrome P450, CYP3A4, CYP3A5 (Iqbal N, 2014). Interactions between Imatinib and inhibitors or inducers of these enzymes can occur, resulting in differences in Imatinib and co-administered drug plasma concentrations (Hochhaus A, *et al.*, 2017).

Imatinib drug side effects include fluid retention, fever, diarrhea, nausea, fatigue, lack of appetite, stomach distention, edema, skin rashes, dizziness, and muscle cramps, as well as several other serious side effects including myelosuppression, cardiac failure, and liver function disorders in some rare cases (Mughal TI and Schrieber A, 2010; Hemakumar A and Pavithran K, 2020).

A prospective randomized trial conducted by Immune Reconstitution Inflammatory Syndrome (IRIS) suggested that a dose of 400 mg/day Imatinib was found superior than cytarabine with Interferon alpha, even though a dose of 300 mg/day was sufficient to treat majority of patients who are in chronic phase of CML. The daily dose of 400 mg is considered to be well explored and tolerated (Joske DJ, 2008).

Dasatinib: Dasatinib is at the prominence of the second generation TKIs. This drug inhibits both BCR-ABL following Proto-oncogene Nonreceptor Tyrosine Kinase (SRC) family kinase and thereby demonstrate its benefit against Imatinib-resistance leukemia's (Joseph D, *et al.*, 2017). Dasatinib showed greater affinity towards the BCR-ABL kinase Adenosine triphosphate (ATP) packets which helps them to interrelate with the protein in multiple conformation states. This compound has a 325-fold higher kinase inhibitory activity than Imatinib since it can obstruct the phosphorylation of ABL catalyzed peptide substrate. Hence Dasatinib is considered as a better efficacious choice for the controlling CML at chronic phase (Sullivan C, *et al.*, 2010).

Nilotinib: Nilotinib is designed to use in CML chronic phase and also in the accelerated phase in case of the Imatinib resistance. It has the mechanism of action similar to that of Imatinib. This drug was developed in such a manner that it should bind to the BCR-ABL better than Imatinib. So that it can achieve greater potency and has fewer mutations (Jabbour E and Kantarjian H, 2012).

Interferon therapy or immunotherapy

Certain *in vitro* studies revealed that Interferon alpha (IFN-α) generates an immunomodulatory response by restoring the bone marrow microenvironment in different ways like modulating gene expression, directly inhibiting cell growth and cell proliferation by encouraging apoptosis. The drug demonstrates its ability to induce cell differentiation and apoptosis by specifically targeting key cell cycle regulators such as cyclins (cyclin D, cyclin E, and cyclin A), cyclin dependent kinases, and retinoblastoma protein, and thereby obstructing or expanding cell cycle phases. By activating the immune cells of the host, such as B and T lymphocytes, natural killer cells, and antigen-presenting dendritic cells, IFN-α has the ability to reduce CML (Talpaz M, *et al.*, 2013). Since after the first discovery of Interferon, it has been classified as type I IFN (a, b), type II and type III etc. But in the case of CML the type I IFN is seemed to be more prominent. IFN gets bind to the type I IFN receptor subunits where Interferon-Alpha/beta Receptor 1 (IFNAR1) and IFNAR2 are present. The later possess the ability to activate the Janus Tyrosine Kinase 1 (JAK 1) and tyrosine kinase 2. After ligand binding happens which there by mediate the process of phosphorylation of JAK1 and tyrosine kinase 2 and hence induces the transcription of signal Transducer and Activator of Transcription (STAT) proteins mainly STAT1, STAT2, STAT3 and STAT5 by activating signal transduction and activators of the STAT proteins. After that an Interferon Stimulated Gene Factor 3 (ISGF 3) complex is built since the phosphorylated STAT1 and STAT2 form a complex with a phosphorylated Interferon Regulatory Factor 9 (IRF9). This ISGF3 complex promotes the transcription process of Interferon Sensitive Genes (ISG). Upon the activation of these ISG results in mediating apoptosis cell cycle control, immune modulatory effects, target gene transcription etc (Burchert A, 2014). Before the emergence of Imatinib, IFN-α had been widely used in the treatment of patients where the drug helped in the achievement of hematologic as well as molecular remission in CML patients when given at high doses.

Challenges associated with IFN-α therapy: It is crystal clear that Interferon alpha has brought a revolutionary change in saving the lives of many patients with CML. But still the positive effect of this drug is weakened due to pious complications associated with its use. The patient's quality of life is mostly influenced by the drug's side effects. IFN-α has been associated with several adverse effects in nearly every organ system. The onset of flu-like signs, hematological toxicity, elevated transaminase, nausea, vomiting, and psychological sequelae are all dose-dependent side effects (Sleijfer S, *et al.*, 2005). IFN-α has been linked to a number of neuropsychiatric side effects as used in conjunction with the antiviral ribavirin for chronic Hepatitis C Virus (HCV) infection or the treatment of various malignancies such as malignant melanoma and renal cell carcinoma. Excluding the fact that depression is the most well-known of these side effects, IFN-α may cause a variety of syndromes, including acute confusional state, which progresses quickly after the start of high dose IFN-α, depressive syndrome, which develops over weeks to months of therapy, and psychotic states, which are characterized by excessive irritability and anxiety, but can also include euphoria. Another challenge which limits its use is the bioavailability. This drug is injected on a daily basis due to its short half-life (Raison CL, *et al.*, 2005).

Radiation therapy

Radiation therapy, in combination with chemotherapy, has long been used to cure cancer (Miyoshi I, *et al.*, 2020). In the first half of the twentieth century, splenic irradiation was the most common treatment, which offered pain relief but little benefit in terms of quality of life (Woessner DW, *et al.*, 2011).

High-energy particles or waves, such as x-rays, gamma rays, electron beams, or protons, have the ability to destroy cancer cells by causing tiny breaks in their DNA, preventing them from developing. Major side effects associated with this therapy are fatigue, skin changes occur at the area ranges from mild rashes to blistering and peeling. Furthermore, if the radiation is concentrated on the neck or back, the internal lining of the mouth and throat can turn red and irritated; vomiting and nausea are also common side effects when the radiation is focused on the pelvis or abdomen.

Surgery

Chronic myeloid leukemia may display varying tendency for enlargement of spleen which can result in hyper catabolic symptoms, thrombocytopenia, portal hypertension and mechanical discomfort. Splenectomy is the surgery to remove the spleen (Sullivan C, *et al.*, 2010). In advanced cases, the benefits of splenectomy are limited to symptomatic relief and the treatment of delayed engraftment following allogenic bone marrow transplantation (Mesa RA, *et al.*, 2000).

If splenomegaly is caused by leukemia or another illness, the spleen becomes active in extracting blood cells, resulting in a lack of red blood cells and platelets. As a result, splenectomy raises blood cell numbers, platelet counts, and reduces the need for blood transfusions. The surgery is linked to a 9% mortality rate, as well as the development of severe thrombocytosis, hepatomegaly, and leukemic transformations after splenectomy (Sreekar H, *et al.*, 2011).

Allogenic Hematopoietic Stem Cell Transplantation (HSCT)

Allogenic Hematopoietic Stem Cell Transplantation (HSCT) is a widely successful therapy for CML and has long been considered the treatment of choice, with multiple patients experiencing long-term molecular full remissions. Allogenic stem cell transplantation is the most effective antileukemic treatment for CML, with the majority of patients experiencing molecular full recovery with undetectable BCR-ABL rearrangement through polymerase chain reaction analysis. Due to opioid overdose, Graft Versus Host Disease (GVHD), and infectious complications, allogenic stem cell transplantation carries a high risk of treatment-related morbidity and mortality (Champlin R, *et al.*, 2011; Barrett AJ and Ito S, 2015). Through stem cell transplantation, heavy doses of chemotherapy are used to destroy leukemia cells while in other circumstances, a reduced dose of radiation is used to kill leukemia cells while not harming normal bone marrow cells. After that, the recipient gets a blood-forming stem cell transplant to help rebuild his or her bone marrow.

Allogenic and autologous stem cell transplants are the two major forms of stem cell transplants. To minimize the risk of complications, allogenic transplants use stem cells from a donor. The tissue type of the patient must be "matched" by the donor. A close partner, such as a brother or sister, is a strong match, but paired unrelated donors are only included in exceptional cases. The only proven cure for CML is allogenic transplantation, which is the most common form of transplant. However, this type of transplant will result in serious life-threatening complications, making it an unsuitable choice for the elderly or those with other health issues. In an autologous transplant, the patient's own stem cells are removed from the blood or bone marrow and then replaced. The greatest drawback is that leukemic cells and stem cells can be combined together. Patients that fail to respond to Imatinib have two main options: Allogenic Hematopoietic Stem Cell Transplantation and 2nd generation TKIs (Champlin R, *et al.*, 2011). Effective TKI's displaced stem cell transplantation because it represented no immediate drug related mortality. But still Stem Cell Transplantation (SCT) is preferred for patients in more advanced phase and selected cases of CP (Barrett AJ and Ito S, 2015). Complications that may occur suddenly after the transplant is due to the bone marrow wipe out by medicines or radiation before the transplant includes mucositis, throat pain, nausea, vomiting, bacterial infections, fungal infections, bleeding, interstitial pneumonitis, Graft Versus Host Disease(GVHD), Hepatic Veno-Occlusive Disease (VOD, Graft failure. Long term risks of transplant includes organ damage, relapse, secondary cancers, abnormal growth of lymph tissues infertility, cataracts, and hormonal changes.

Treatment for special population

Managing CML in pregnancy: CML accounts for 10% of all pregnancy-related leukaemia's, with a yearly average of one per 100,000 births (Palani R, *et al.*, 2016). Women with CML in the rapid or blast stages can require urgent treatment with TKIs and/or induction chemotherapy, but there is no need for elective termination in the case of CML-CP (Ault P, *et al.*, 2006).

In general, patients in blast crisis are urged to wait until their pregnancy is close to term and there is no imminent danger to the baby until beginning chemotherapy. After delivery, induction chemotherapy may be initiated (Zhou L, *et al.*, 2013). Leukapheresis is a treatment choice for patients who have chronic leucocytosis and thrombocytosis, particularly in the first and second trimesters, since it normalizes blood levels without harming the foetus (Thauvin-Robinet C, *et al.*, 2001).

Regular leukapheresis is a laboratory technique used to normalize blood levels such that white blood cells are $<100 \times 10^9$/L and platelets are $<500 \times 10^9$/L. If the white cell count is $>100 \times 10^9$/L, it should be done on alternating days or at regular weekly or fortnightly intervals, depending on the stability of blood counts (Cortes J, *et al.*, 2008; Abruzzese E, *et al.*, 2014). There is yet lack of information concerning the safety of second and third generation TKIs like Nilotinib, Bosutinib and Ponatinib in pregnancy *(Table 2)*. However in regard to the incidence of spontaneous abortion, teratogenic effects and all other foetal deformities caused by Imatinib and Dasatinib, the advice to consider taking TKIs before getting pregnant and to keep off them during the pregnancy (Kumar AR, *et al.*, 2000).

Likewise Hydroxycarbamide is also not recommended during pregnancy as it causes intrauterine foetal deaths during first trimester (Mubarak AA, *et al.*, 2002; Fadilah SA, *et al.*, 2002). In the second and third trimesters, the use of hydroxycarbamide was implicated in the development of pre-eclampsia (Abruzzese E, *et al.*, 2016).

Managing CML in pediatrics: Chronic myeloid leukemia accounts for 3% of all childhood leukemia. Children with CML have more offensive characteristics, such as a higher White Blood Cells (WBC) count, an expanded spleen in comparison to body height, and a higher prevalence of advanced phases at diagnosis, among other things.

Both adults and children have the same expectations when it comes to CML care i.e. reduced probability of disease progression and mortality in the event of disease remission (Andolina JR, *et al.*, 2012).

Children were shown to have a significantly higher chance of either rapid process or blast crisis transfer. Imatinib, Dasatinib, and Nilotinib are three TKI medicines that have been approved for use in children. The duration of TKI therapy might be longer in children when compared to adults and they require strict follow up care (Suttorp M, *et al.*, 2011).

Patients are started on allopurinol, oral hydration and hydroxyurea before the diagnosis. Imatinib is started after the establishment of diagnosis. It is the standard of the care in first line treatment and it is available in the strength of 100 mg and 400 mg. Imatinib is well tolerated in CML pediatric population (Thijsen SF, *et al.*, 1999). Dasatinib has been approved for the treatment of chronic phase CML patients who are older than one year. Dose of Dasatinib tablet was 60 mg/m^2 and oral suspension powder is 72 mg/m^2. Dasatinib related side effects such as pleural effusion, pulmonary artery hypertension and pericardial effusion which are commonly seen in adults are absent in pediatric population. Nilotinib is an approved treatment in pediatrics CML patients older than one year of age and are prescribed at a dose of 230 mg/ml twice daily. Nilotinib related adverse effects such as thrombocytopenia, hyperbilirubinaemia, neutropenia, elevation of liver enzymes, rash, QT prolongation, nausea and vomiting are observed in children (Pushpam D and Bakhshi S, 2019).

AHSCT (Allogenic Hematopoietic Stem Cell Transplantation) is another treatment choice for children with CML. Hematocrit (HCT) is generally preferred for patients who have an insufficient reaction or intolerance to TKIs, and TKIs can be continued indefinitely without HCT. Advancement of illness, occurrence of a resistant mutation, or inability to achieve full cytological recovery after one year of TKI therapy are all signs for HCT in infants (Chaudhury S, *et al.*, 2016).

Managing CML in geriatric patients: Around half of CML patients are above the age of 60. In the United States, the Surveillance, Epidemiology, and End Results (SEER) Program records a median age of diagnosis of 67 years, while other European registries record a median age of diagnosis of about 60 years (Balducci L and Dolan D, 2014). TKIs increased the overall life span of CML patients, bringing it closer to that of the general population and extending the survival rate of the majority of patients indefinitely, according to population estimates *(Table 3)* (Cortes J, *et al.*, 2003).

Table 2: Therapies recommended based on pregnancy stage

Stage	Therapies
First trimester	Leukapheresis If platelets are greater than 500×10^9/L, take aspirin +/−Low molecular weight heparins (LMWH) During organogenesis, avoid IFN-, hydroxycarbamide, and TKIs. Pegylated IFN-α is contraindicated
Second trimester and Third trimester	Leukapheresis If platelets are greater than 500 × 10^9/L, take aspirin +/−LMWH IFN-may be used. Pegylated IFN-α is contraindicated Consider combination of both Leukapheresis and IFN-alpha if needed
Breastfeeding	Because of the possibility of secretion into breast milk, TKIs and hydroxycarbamide are contraindicated. IFN-α is not advised.

Table 3: Therapies recommended for geriatric patients

S.no	Drugs	Adverse Drug Reactions (ADRs)	Recommendations
1	Bosutinib	Gastrointestinal toxicity especially diarrhoea (at a dose of 200 mg or 300 mg daily)	Titrate the dosage upward as gastrointestinal toxicity subsides, as suggested by the Food and Drug Administration (FDA) (400 mg to 500 mg initial starting dose)
2	Nilotinib and Ponatinib	Early and accelerated PAOD (Peripheral Arterial Occlusive Disease)	For those with proven heart disease, aggressive examination for and treatment of detected cardiovascular risk factors, as well as clinical assessment for Peripheral Arterial Occlusive Disease (PAOD) activity with Ankle-Brachial Index (ABI) tests or avoidance of these medications was recommended for those with extreme cardiovascular risk factors (peripheral, coronary, or cerebral).

3	Dasatinib	The most frequent pulmonary complication is pleural effusion, which causes nausea, shortness of breath, chest pain, and/or fatigue. Another pulmonary condition is pulmonary arterial hypertension, which normally appears several months after starting treatment but is exceptionally rare.	Dasatinib should be closely monitored in older patients because they may be less likely to handle a compromised respiratory condition. Minor symptoms of this complication can necessitate chest x-ray screening and, if possible, immediate treatment (treatment suspension, antibiotics, diuretics, thoracentesis). If other treatment alternatives are available, serious or chronic cases should cause dose restriction or discontinuation of dasatinib. Patients with a prior cardiovascular history, including heart disease, should avoid dasatinib.

Challenges faced during management of TKI therapy in elderly patients

Managing the complications involved with polypharmacy is a special feature of successfully handling older people with TKIs. Drug-drug interactions can reduce the effectiveness of TKI therapy or increase the toxicity. Proton pump inhibitors, H2-antagonists, anti-emetics, anti-diabetic medicines, anti-platelet drugs, anticoagulants, anti-hypertensive, antibiotics, and medications that greatly affect the Cytochrome P450 pathway have been found to have pharmacologic associations with Imatinib, Dasatinib, and Nilotinib, according to reports (Extermann M and Wedding U, 2012; Varadhan R, et al., 2014). TKI metabolism is slowed by P450 inhibitors, which can lead to further complications (Deotare U, *et al*., 2016).

When deciding on an initial treatment plan, patients' co-morbidities should be taken into account, particularly for the elderly, according to treatment recommendations. Findings suggest that TKI therapy can be effective in patients with chronic health problems who are on multiple medications, despite the fact that they have a greater risk of polypharmacy and a higher degree of co-morbidity, including very elderly patients (over 75) (Luskin MR and de Angelo DJ, 2018; Smith A, *et al.*, 2011). Since allogeneic stem cell transplantation for older CML patients is uncommon, it's important to improve TKI effectiveness by addressing adherence problems and closely tracking response (Cortes JE, *et al*., 2018; Rohrbacher M, *et al.*, 2009).

The rapid and blast phases of CML are challenging to control in the elderly population, not only because of a greater risk of acquired mutations than in younger people, but also because of increased co-morbidities (Pallera A, *et al*., 2016; Haouala A, *et al.*, 2011).

CONCLUSION

In this review paper we summarized that even though targeted drug therapy had made a breakthrough in the treatment of CML during the last decade resulting in prolonged survival but TKI's are not curative. In some cases TKI resistance resulting in progression to advanced phases, chronic side effects with long exposure, financial burden and ultimately death. Allogeneic stem cell transplantation remains an important, potentially curative treatment choice for CML patients who do not respond to Imatinib. However, this type of transplant will result in serious life-threatening complications, making it an unsuitable choice for the elderly or those with other health issues. Resistance to Imatinib has led to the production of second-generation tyrosine kinase drugs such as Nilotinib, Dasatinib, and Ponatinib etc.

In the case of special populations, TKI therapy can be effective for geriatric patients with chronic health problems and handling the complications involved with polypharmacy is a particular feature of successfully treating elderly people with TKIs. The treatment of children with CML is not systematized. It often follows the guidelines developed for adult patients even though the disease presentation and progression of CML is different in children and adults. The duration of TKI therapy might be longer in children when compared to adults and they require strict follow up care and in case of pregnant women, leukapheresis is a treatment choice for patients who have chronic leucocytosis and thrombocytosis, particularly in the first and second trimesters. Imatinib and Dasatinib are contraindicated and there is lack of information concerning the safety of second and third generation TKIs like Nilotinib, Bosutinib and Ponatinib in pregnancy. Because of the possibility of secretion into breast milk, TKIs and hydroxycarbamide are not recommended for lactating women.

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