Pharmacology of tyrosine kinase inhibitors in chronic myeloid leukemia; a clinician's perspective

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Abstract

Objective In this review, we have summarized the pharmacokinetics, pharmacodynamics and adverse effects of imatinib, dasatinib, nilotinib, bosutinib, ponatinib and radotinib with focus on pharmacogenomic studies with clinical end points. We have discussed the key phase 3 trials of tyrosine kinase inhibitors (TKI) comparing with each other, treatment free remission (TFR) and selection of TKI. Upcoming concepts and related trials in the management of chronic myeloid leukemia (CML) along with future directions have been touched upon.

Evidence acquisition PubMed, Embase, Google, Cochrane library and Medline were searched to identify relevant literature for the review. [Clinicaltrial.gov](https://clinicaltrials.gov) was searched for upcoming data and trials.

Results There are lot of gap in pharmacokinetics and pharmacodynamics of TKI. Imatinib appears to be the safest TKI. Newer TKI's achieve better achievement of therapeutic milestones, deeper molecular response and less chances of progression of CML compared to imatinib. Newer TKI appears to be better choice for achieving TFR. When the objective is survival, imatinib is still the TKI of choice. Primary prophylaxis with antiplatelet drugs for TKI having cardiovascular and thromboembolic side effects should be considered.

Conclusion Pharmacogenetic data of TKI is still immature to guide in therapeutic decision making in clinical practice. There is need for further research in pharmacology and pharmacogenomics of newer TKI's. Randomized controlled trials are required to decide the optimum TKI for TFR. Safe and effective TKI for targeting T315I mutation, CML accelerated phase and blast crisis are an active area of research.

Keywords Gene polymorphism and imatinib · Pharmacology of tyrosine kinase inhibitors · Selection of tyrosine kinase inhibitors · Tyrosine kinase inhibitors in chronic myeloid leukemia

Introduction

The landscape of chronic myeloid leukemia (CML) has transformed in the last few years due to the advent of novel tyrosine kinase inhibitors (TKI) and trials demonstrating the feasibility of treatment free remission (TFR). At present, we have imatinib as first generation TKI; nilotinib, dasatinib, bosutinib, radotinib as second generation TKI and ponatinib as third generation TKI. The pharmacokinetics, pharmacodynamics and pharmacogenetics of imatinib has been well studied

followed by dasatinib and nilotinib, whereas there is lacunae in existing literature regarding ponatinib, bosutinib and radotinib. Here, we aim to review the existing literature regarding pharmacology of each TKI, key phase 3 trials comparing them, TFR, choice of TKI in different clinical settings and upcoming studies on TKI.

Chronic myeloid leukemia

World Health Organization classifies haematological malignancies into myeloid neoplasm, lymphoid neoplasm and, histiocytic/dendritic neoplasm. Myeloid neoplasms are further classified into major groups of myeloproliferative neoplasm, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasm and acute myeloid leukemia. CML belongs to the group of myeloproliferative neoplasm [1]. CML is characterized by abnormal fusion due to

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reciprocal translocation between chromosome 9 and 22, t(9;22)(q34;q11), which gives rise to an abnormal chromosome 22 called Philadelphia chromosome. This chromosome codes for BCR-ABL1 fusion gene which codes for tyrosine kinase (TK). This constitutionally active TK activates downstream signalling pathways resulting in uncontrolled proliferation. Gradually, additional mutations are acquired and CML-chronic phase (CML-CP) evolves into accelerated phase (AP) and blast phase (BP) [2]. TKI are the cornerstone of treatment of CML and allogeneic hematopoietic stem cell transplant has a role to play in CML-AP and CML-BC.

Methods

PubMed, Embase, Google, Cochrane library and Medline were searched to identify relevant literature in English language for the review. [Clinicaltrial.gov](https://clinicaltrials.gov) was searched for upcoming data and trials. The following search terms were used: “pharmacokinetics” or “pharmacodynamics” and “imatinib”; “nilotinib”, “dasatinib”, “bosutinib”, “ponatinib” and “radotinib”. Relevant published guidelines and citations of references were studied. We selected only those pharmacokinetic and pharmacogenomic studies where end points were clinical outcomes. For topics where there were a large number of studies, we preferred important studies and published meta-analysis to summarize the data. We did not include in vitro studies unless clinical, effect of TKI’s on other drugs, TKI’s currently in trial and omacetaxine mepesuccinate. For the section “choice of TKI”, we selected only phase 3 trials.

Results and discussion

Imatinib

Pharmacology

Imatinib is the first targeted therapy developed for CML. Imatinib competitively inhibits BCR-ABL TK by binding at the ATP-binding site [3]. It is highly specific for BCR-ABL and inhibits growth and apoptosis in hematopoietic cells expressing BCR-ABL but spares the normal cells [3].

The metabolism of imatinib is summarized in Fig. 1. Imatinib is administered orally and is rapidly (t_{max} 1–2 h) and completely absorbed through the gastrointestinal tract. It is not affected by food intake [4]. Absolute bioavailability of imatinib is more than 97% [5]. Elimination half life of imatinib is 18–20 h enabling once daily dosing [6]. Imatinib is actively transported in intestine and thought to be mediated by proteins, namely solute carrier organic anion transporter family member 1A2

(OATP1A2 (SLCO1A2)) and organic cation/carnitine transporter 2 (OCTN2(SLC22A5)) [7]. Imatinib is bound to α -1 acid glycoprotein (AGP) (95%) whereas the remaining is bound to albumin and erythrocytes. Organic anion-transporting polypeptide 1B3(OATP1B3),OCTN2, and organic cation-transporter 1(OCT1) are carriers which are speculated to transport imatinib from systemic circulation to hepatocytes [7]. In liver, ATP-binding cassette sub-family C member 4 (ABCC4) expressed on the basolateral membrane of hepatocytes could be a possible efflux transporter pumping imatinib from hepatocyte into systemic circulation [7]. The cellular efflux from hepatocyte to bile canaliculus is mediated by P-gp (ABCB) and ATP-binding cassette super-family G member 2 (ABCG2) [8]. Liver is the primary site of metabolism of imatinib by the cytochrome P450 complex. Majority of imatinib is metabolized in liver and a small fraction is excreted in bile and urine. Imatinib does not penetrate blood-brain barrier [7]. Imatinib influx into CML blast cells is mediated by OCT1(SLC22A1) [9].

Impact of OCT1 on clinical outcomes

Gene expression analysis in leukemia cell lines has shown that *OCT1* expression is a composite surrogate for expression of transporters involved in intracellular uptake and retention of imatinib [10]. Patients with high pretreatment OCT1 had a significantly superior complete cytogenetic response (CCyR), progression free survival (PFS) and overall survival (OS); pretreatment OCT1 emerged as the most important predictor of CCyR achievement at 6 months [11]. Data from patients enrolled in Trial of Imatinib with Dose Escalation in chronic myeloid Leukemia (TIDEL) and Tyrosine kinase inhibitor Optimization and Selectivity (TOPS) trial have shown that patients with high OCT1 activity achieved higher percentage of major molecular response (MMR) at 24 months, when compared with low OCT1 activity (85% vs 45%) [12, 13]. Patients with high OCT1 achieved MMR irrespective of the dose of imatinib used. Patients in low OCT1 group who received a higher dose of imatinib had significantly higher log reduction in MMR when compared with a patient who received lower dose of imatinib. This study demonstrated that low expression of OCT1 can be overcome by using higher dose of imatinib [14]. Updated data from TIDEL 1 showed that patients with high OCT-1 activity achieved significantly higher MMR at 60 months when compared to patients with low OCT-1 activity (89% vs 55%), higher OS (96% vs 87%) and higher event free survival (EFS) (74% vs 48%) and lower kinase domain mutation rate (4% vs 21%) [12]. Analysis of data from TOPS study showed that imatinib when administered at 400 mg/day, MMR was higher in patient with high OCT-1 activity, whereas at dose of 800 mg/day MMR was independent of OCT-1 activity and patients with low trough

Fig. 1 Metabolism of imatinib. ABCB1: P-glycoprotein; ABCG2: ATP-binding cassette sub-family C member 4; ABCG2:ATP-binding cassette super-family G member 2; Cyp: Cytochrome; OATP: Solute carrier

organic anion transporter family member; OCT1:Organic cation-transporter 1; OCTN2:Organic cation/carnitine transporter 2

imatinib levels and low OCT-1 activity had lowest MMR and highest rate of imatinib failure [13]. Thus, OCT-1 activity appears to be a key determining factor for imatinib response, amenable to dose modification of imatinib and can be used to personalize imatinib dosing.

Polymorphism of *OCT1* gene can influence intracellular uptake of imatinib in CML cells and can impact the outcome in CML. *OCTN1* C allele (rs1050152) was significantly associated with deeper MMR [15]. The GG genotype at *SLC22A1* (rs683369) was significantly associated with high rate of loss of response and treatment failure with Imatinib in Canadian population [16]. In a study of Malaysian patients G allele carriers of *SLC22A1* C480G and A allele carriers of *G1222A*, were significantly associated with imatinib resistance [17]. Polymorphism of OATP1B3, which is encoded by *SLCO1B3*, can also influence therapeutic outcome of imatinib. In Indian patients *SLCO1B3* 334TT genotype was found to be significantly related with a higher risk of failure of cytogenetic response at 12 months though there was no significant difference in molecular response (MR) at 18 months [18]. In a study conducted in Brazil, *SLCO1B3* 699GG and 344TT genotypes were significantly associated with good imatinib response and carriers of 699GA/AA and 334TG/GG

genotypes had significantly low chance of responding to standard dose of imatinib [19]. As these studies were done in limited ethnic subgroups and different polymorphisms were studied, further studies are required to understand the impact of *OCT1* gene polymorphism with clinical outcomes.

Effect of plasma protein binding of imatinib on clinical outcome

AGP is encoded by the *ORM1* gene. As AGP is the key molecule which binds to imatinib, polymorphism of *ORM1* gene may affect the free drug availability and influence resistance to imatinib. In a study from France, patients with higher level of AGP resulted in lower clearance of plasma imatinib and its main metabolite (CGP74588) [20]. Single nucleotide polymorphism (SNP) in *AGP* gene did not correlate with treatment failure of imatinib [16]. Unpublished data by Ankathil et al. [21] did not find any association of *ORM1* 520 G > A polymorphism with imatinib resistance, due to rarity of the genotype in Asian population. In populations, where the *ORM1* 520 G > A polymorphism is present at higher frequencies, its impact on imatinib resistance may be worth exploring.

Impact on clinical outcome of imatinib due to transport gene polymorphism

Genetic polymorphism of transporter genes can affect drug delivery and efficacy of imatinib. *ABCB1* gene which encodes Pgp has been studied with respect to imatinib pharmacogenetics in CML. Most frequent SNP polymorphism of *ABCB1* gene are c.1236C > T, c.2677G > T/A and c.3435C > T [22]. A meta-analysis of 1826 patients analyzed the effect of these three SNP on imatinib response in CML patients [23]. On analysis, of *ABCB1* c.1236C > T polymorphism, the 1236CC genotype was significantly associated with increased response to imatinib in Asian population. *ABCB1* c.3435C > T polymorphism was significantly associated with better imatinib response and 3435 T allele was associated with worse response to imatinib [23]. Another meta-analysis of Asian patients found that *ABCB1* C1236T polymorphism was associated with increased risk of imatinib resistance while, no association was found with *ABCB1* G2677T or C3435T polymorphism with imatinib resistance [24]. In contrast to the aforementioned meta-analysis, meta-analysis by Wang et al. [25] did not find any association of *ABCB1* gene polymorphism with imatinib response. Another recent meta-analysis suggested that *ABCB1* polymorphisms were not associated with MMR and complete molecular response (CMR) with use of imatinib [26]. These different results arise due to heterogeneous studies in terms of study population, dose of drug, different inclusion and exclusion criteria and heterogeneous endpoints of outcome.

In a meta-analysis of 771 patients, *ABCG2* C421A polymorphism was significantly associated with higher MMR in patients receiving imatinib, specifically in those with Asian descent [26]. At present, data is heterogeneous and conflicting and requires further validation before being implemented in clinical practice.

Impact of cytochrome P450 on clinical outcomes

Imatinib is metabolized in the liver by CYP3A5, CYP3A4 and CYP2A8 to its predominant metabolite N-desmethyl-imatinib [27]. In Malaysian patients, heterozygous (AG) and homozygous variant (GG) genotype of *CYP3A5**3 were significantly associated with low risk of imatinib resistance [28]. Similarly, in a study from Egypt *CYP3A5**3 polymorphism was associated with inferior outcome [29]. In a study from India, *CYP1A1**2C wild type genotype (AA) was associated with poor cytogenetic response [30]. Apart from these, genetic polymorphism of glutathione-S-transferase, nuclear receptors and *BIM* gene have been studied in relation to therapeutic outcome of imatinib with variable results [21]. Though, polymorphism in imatinib metabolising genes have been identified, further studies are warranted for development of strategies which can modulate clinical outcome.

In contrast to above studies, a study of 112 CML patients, did not find any association of *CYP3A5**3 (rs776746), *CYP3A4**1 (rs2740574), *CYP2C9**3 (rs1057910), *SLC22A1* (rs683369), *ABCB1* (rs1045642, rs1128503), *ABCG2* (rs2231142) and *ABCC2* (rs717620) polymorphisms with imatinib plasma level and achieving an optimal clinical response was studied, did not find any association of the studied polymorphism with imatinib level and an optimal clinical response [31]. Unless well designed clinical trials explore the effects of transport molecules, gene polymorphism on clinical outcome and the appropriate dose of imatinib for such patients, it is not possible to tailor imatinib based on these variations.

Impact of therapeutic drug monitoring on clinical outcome

Imatinib plasma concentration has high interindividual variability with a coefficient of variation reported 50% and 45% for dose of 400 mg and 600 mg of imatinib respectively [32]. Imatinib trough plasma concentrations (C_{min}) at day 29 were notably higher in patients who achieved CCyR and imatinib C_{min} was predictive of higher CCyR independent of Sokal score [33]. In another study, C_{min} in patients who achieved MMR was significantly higher than in subjects who didn't achieve CMR and best sensitivity (77%) and best specificity (71%) for discriminating MMR was C_{min} at 1002 ng/ml [34]. In a cohort of 254 Japanese patients with CML, C_{min} > 1002 ng/ml had significantly higher probability of achieving MMR [35]. A review article has recommended C_{min} of 1000 ng/ml as the pharmacokinetic target for CML and suggests increasing imatinib dose by 200 mg once daily stepwise [36]. Practically measuring imatinib trough concentration is difficult as the sample needs to be taken immediately before the administration of next dose and complex equipments are required, hence it is not performed routinely [37]. With the advent of newer TKI's therapeutic drug monitoring of imatinib will have a limited role in future.

Adverse effects

Myelosuppression is a common in first 4–6 weeks after initiating imatinib. It is due to suppression of the leukemic clone and inhibition of normal haematopoiesis [38]. Myelosuppression is thought to be an expression of efficacy instead of drug toxicity [39]. In randomized trials grade 3/4 anemia has ranged from 5 to 7%, neutropenia 20–24% and thrombocytopenia 9–14% [40–42]. European LeukemiaNet (ELN) guidelines recommends to withhold drug at the first episode of grade 3/4 cytopenia till toxicity is less than grade 2 [39]. In case of recurrent episode imatinib can be restarted at lower dose and can be gradually escalated. Switching to alternate TKI is suggested in case of recurrent grade 3/4 cytopenia. G-CSF and erythropoietic agents can be administered to expedite recovery [39]. Grade 1 and 2 gastrointestinal side effects,

nausea, diarrhoea, abdominal pain and vomiting are common whereas grade 3/4 toxicity is uncommon [39]. Skin side effects are also common ranging from 9.5%–69% [43]. They appear within the first 3–4 weeks of treatment [44]. They may occur in form of edema, maculopapular erythematous rash, papulosquamous eruptions and pigmentary change. Musculoskeletal adverse effects such as myalgia and arthralgia are common, but serious events are rare [39]. Hepatotoxicity can occur with imatinib, grade 3/4 ranging from 3 to 6% which usually occur in first 2–8 weeks [45]. Imatinib causes hypophosphatemia in 25–49% of patients and decreased bone mineral density in approximately 50% of patients [40, 46, 47]. Thyroid abnormality was detected in 25% of patient treated with imatinib though majority were clinically asymptomatic [48]. Imatinib has does not male fertility. Females of reproductive age group are advised contraception as imatinib is teratogenic, though it is to be noted that normal pregnancies have also occurred when patients were on imatinib [49]. Effect of commonly prescribed drugs on imatinib have been summarized in Table 1.

Adverse effects specific to pediatric population

Growth deceleration occurs in prepubertal children. In a cohort of 108 patients 47.2% had growth impairment out of which 16.6% had grade 3 growth impairment [50]. In puberty catch-up growth occurs but its adequacy to attain the expected adult height is not known at present [51]. Imatinib dysregulates vitamin D, calcium and phosphate metabolism and has been reported to decrease bone mineral density in children [52, 53].

Dasatinib

Pharmacology

Dasatinib is a second generation TKI which inhibits c-KIT, BCR-ABL and SRC-family kinases, PDGFR- α and β and ephrin receptor kinase. Dasatinib binds to both active and inactive domain of BCR-ABL1 kinase protein [54]. Dasatinib is 325 times more potent than imatinib [55]. Dasatinib is administered orally, has rapid absorption with peak plasma concentration 0.5–3 h after administration. It is metabolized in liver by CYP3A4 and eliminated by fecal route. Dasatinib absorption is not influenced by food [54].

Imatinib uptake is predominantly mediated by OCT1 whereas dasatinib uptake is independent of OCT1 [56]. Dasatinib passively enters the cells [57]. In vivo studies suggest that ABCC4 (ATP Binding Cassette Subfamily C Member 4) mediates oral absorption of dasatinib from stomach [58]. Dasatinib efflux from the cell is mediated by ABCB1, ABCG2 and ABCC6 (ATP-binding cassette subfamily C member 6) [56, 57]. In vitro study on HEK293 and

K562 cell lines have shown that *ABCB1* variant (Asn400) is associated with lower intracellular dasatinib concentration due to increased efflux activity [59, 60]. In a retrospective study in Japanese population, natural killer group 2D receptor (NKG2D) HNK1/HNK1 (high-cytotoxic activity-related allele on NKG2D hb-1) haplotype was associated with quicker MMR [61, 62]. NKG2D gene polymorphisms need to be explored further biomarker for predictor of TFR. Data evaluating clinical outcomes of cytochrome polymorphism, efflux transporter protein encoding gene variants and therapeutic drug monitoring is limited.

Adverse effects

Dasatinib causes pleural effusions in 14–39% of patients. Median time of appearance is 5–11 months. It recurs in 70% of cases. They are managed by dose reduction or interruption, steroids and diuretics. Dasatinib can cause pulmonary hypertension in 0.45% of patients. Dasatinib has hypoglycaemic effect as it reduces fasting glucose [39]. Thyroid abnormalities were detected in 70% of patients though majority of them were subclinical and did not require therapy [48]. Dasatinib in frontline use caused grade 3/4 anemia, neutropenia and thrombocytopenia in 7%, 10% and 20% patients respectively [46]. In second and third line therapy dasatinib was associated with grade 3/4 anemia, neutropenia and thrombocytopenia in 19.2%, 45.8% and 47.2% patients respectively [39]. Management principles are same as imatinib. Dasatinib is associated with abortion and congenital abnormalities though uneventful pregnancies have also been documented. It has no clinically significant effect of male fertility [49]. In pediatric patients with CML, myalgia, arthralgia, bone growth impairment were reported, however pulmonary artery hypertension and effusions were not noted in children [63]. Drug interactions of dasatinib have been summarized in Table 1.

Nilotinib

Pharmacology

Nilotinib is 2nd generation TKI which competitively binds to the ATP binding site of the inactive conformation of BCR-ABL tyrosine kinase and it is 10–60 times more potent than imatinib. Nilotinib is administered orally and maximum mean concentration is achieved in median of 1.47 h with half life of 17 h therefore enabling daily dosing. Bioavailability of nilotinib is 30% [60]. Food affects nilotinib absorption, hence nilotinib is advised to take 2 h before food or 1 h after food [64]. In vitro studies in cell line HEK293 and K562, suggests that *ABCB1* variant (Asn 400) transports nilotinib from the cell, when compared to the wild variant [59, 60].

Nilotinib is 98% protein bound in in vitro studies. Nilotinib is predominantly metabolized by CYP3A4 [65, 66]. Patients

Table 1 Summary of tyrosine kinase inhibitors

Characteristics	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Radotinib
Tab strength	100 mg, 400 mg	20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg	50 mg, 150 mg, 200 mg	100 mg, 500 mg	15 mg, 45 mg	100 mg, 200 mg
Adult dose						
CML-CP	400 mg OD	100 mg OD	300 mg BD	500 mg OD	45 mg OD	300 mg BD
CML-AP	400 mg BD	140 mg OD	400 mg BD	500 mg OD	Approved for T315I mutation	400 mg BD
CML-BC	400 mg BD	140 mg OD	400 mg BD	500 mg OD		400 mg BD
Pediatric Dose						
CML-CP	340 mg/sqm OD	60 mg/sqm OD	230 mg/sqm BD	Not approved	Not approved	Not approved
CML-AP	400 mg/sqm OD	80 mg/sqm OD	230 mg/sqm BD			
CML-BC	500 mg/sqm OD	80 mg/sqm OD	230 mg/sqm BD			
Interaction with food	Taken with food	No interaction	Two hour before or one hour after food	Taken with food	No interaction	Not known
Common adverse effect	Fluid retention, Myalgia, arthralgia, GI-related, cytopenia	Pleural effusion, Pulmonary artery hypertension, cytopenia Bleeding/platelet dysfunction	Hyperlipidemia, hyperglycemia, myocardial infarction, stroke, peripheral artery occlusion, pancreatitis, QT prolongation	Diarrhea, elevated liver enzymes	Hypertension, Abdominal pain, Arterial thrombosis, hepatotoxicity	Myelosuppression, hepatotoxicity, hyperglycemia
Contraindication	None	None	Hypokalemia, hypomagnesemia, prolonged QT interval	Hypersensitivity	None	None
Drug interaction	Increased exposure: PPI, quinolones, azoles, CSA, valproic acid	Increased exposure: PPI, Beta blocker, ACE inhibitor, macrolide, azole, CSA	Increased exposure: Macrolides, valproic acid, cyclosporine, azoles	Increased exposure: Azoles	Increased exposure: Azole, protease inhibitor, macrolide, SRI	Data not available
	Decreased exposure: Dexamethasone, rifampicin, protease inhibitor, phenytoin, carbamazepine, lamivudine, metformin	Decreased exposure: Dexamethasone, phenytoin, carbamazepine	Decreased exposure: Dexamethasone, phenytoin, rifampicin	Decreased exposure: PPI, rifampicin	Decreased exposure: Rifampicin, carbamazepine, phenytoin	
Female of childbearing age	Contraception advised	Contraception advised	Contraception advised	Contraception advised	Contraception advised	Data not available
Breast feeding	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contra-indicated	Data not available

ACE angiotensin converting enzyme, AP accelerated phase, BC blast crisis, BD twice daily, CML chronic myeloid leukemia, CSA cyclosporine, GI gastrointestinal, OD once daily, PPI proton pump inhibitor, SRI serotonin reuptake inhibitor

with uridine diphosphate glucuronosyltransferase gene (*UGT1A1*) *TA(7)* polymorphism are susceptible to nilotinib induced hyperbilirubinemia [67, 68]. Clinical efficacy and toxicity of Nilotinib is not affected by *OCT1* and *ABCB1* polymorphism in contrast to imatinib [64].

In newly diagnosed CML-CP, Cmin of nilotinib was not associated with MMR [66]. In patients with imatinib resistant or intolerant CML, low Cmin of nilotinib was associated with longer time to achieve cytogenetic response and MMR [67, 68]. The potential role of therapeutic drug monitoring of nilotinib in optimizing nilotinib dose in imatinib resistant CML patients warrants further study.

Adverse effects

Nilotinib is associated with peripheral arterial occlusive disease, ischemic heart disease and cerebrovascular disease. Nilotinib is contraindicated in prolonged QT syndrome or if patients are on drugs causing prolonged QT syndrome. Hyperbilirubinemia is most frequent hepatic adverse effect [39]. In ENESTnd trial incidence of hyperglycemia was 6% and hypercholesterolemia 22% [40]. Hyperglycemia usually occurs in the first 2–3 week on initiation of nilotinib, and thus monitoring of blood glucose and lipid profile during treatment is advised [39]. Hypophosphatemia has been observed in 33% and thyroid abnormalities were seen in 55% patients, though they were rarely clinically significant [40, 48]. Grade 3/4 anemia, neutropenia and thrombocytopenia were observed in 3%, 10% and 12% patients respectively [40]. Common gastrointestinal adverse effects are nausea, diarrhea, abdominal pain and vomiting. Pancreatitis is rare ranging from 0.9 to 2% though lipase elevations have ranged from 29 to 47%. Nilotinib can cause fluid retention, skin rashes and myalgia [39]. Data on pregnancy outcome of nilotinib is limited. Though congenital anomalies have been reported with nilotinib, yet it appears that nilotinib is the safest TKI in pregnancy [49]. Effect of commonly prescribed drugs on nilotinib have been summarized in Table 1.

Bosutinib

Pharmacology

Bosutinib is a 2nd generation TKI which competitively inhibits Src and ABL tyrosine kinases [68]. Bosutinib is orally administered and attains peak plasma concentration in 3 to 6 h with bioavailability of 33.85% [69]. Half life ranges from 32.4 to 41.2 h enabling daily dose [69]. Bosutinib should be taken with food as food increases bosutinib solubility leading to enhanced absorption. Due to enhanced absorption, less bosutinib remains in the intestine leading to decrease gastrointestinal side effects [70]. Bosutinib is metabolized in liver by CYP3A4 [70]. In vitro and in vivo studies suggest that

bosutinib efflux from the cell is mediated by P-gp, and its expression determines the intracellular concentration of bosutinib [71]. Drug transport molecules ABCG2 and SLC22A1 doesn't appear to play role in bosutinib efflux [71, 72]. In Japanese patients, polymorphisms of ABCB1, ABCG2 and CYP3A4 did not influence bosutinib Cmin, however polymorphism of NR1I2 (Nuclear Receptor Subfamily 1 Group I member 2) influenced Cmin (notably, those with NR1I2 7635G/G and 8055 T/T genotype had lower Cmin) [73]. The recommended dose of bosutinib is 400 mg once a day for CML-CP and 500 mg once daily for imatinib resistant and intolerant patients.

Adverse events

Diarrhea grade 3/4 is seen in 9–10% of patients. Hepatotoxicity with elevated aspartate transaminase/alanine transaminase is observed in 25–30% and 15–22% whereas grade 3/4 toxicity is seen in 11–9% and 6–9% patients respectively [46, 74, 75]. Grade 3/4 cardiac toxicity in the form of congestive cardiac failure and atrial fibrillation was seen 4% and 1% patients respectively [46]. Fatigue, rash, headache, edema and myalgia occur but grade 3/4 toxicity is rare [44, ,]. Grade 3/4 anemia, neutropenia and thrombocytopenia was seen in 3.5–11%, 6.7–16% and 16.4%–26% patients respectively [44, ,]. Effect of commonly prescribed drugs on bosutinib have been summarized in Table 1.

Ponatinib

Pharmacology

Ponatinib is 3rd generation TKI structurally designed to overcome the resistance of T315I mutation. Ponatinib is administered orally and peak concentration is achieved within 6 h [76]. It is metabolized in the liver by CYP3A4, CYP3A5, CYP2C8 and CYP2D6 to active metabolites [77]. Ponatinib is transported by P-gp and MRP1/2 whereas ABCB1, ABCG2 and OCT-1 are not involved in transport which are key in transport of imatinib [78, 79]. Ponatinib absorption is not affected by food intake [80]. Ponatinib Cmax correlates with the dose administered. A dose of 30 mg daily also appears to be sufficient to prevent resistance to ponatinib [81]. Ponatinib is administered at a dose of 45 mg once daily.

Adverse events

Rash, abdominal pain, headache, myalgia, arthralgia, fever, diarrhea and dry skin are common adverse effects but they are rarely grade 3/4 [82, 83]. Grade 3/4 neutropenia and thrombocytopenia is seen in 4% and 12% respectively in newly diagnosed CML-CP patients. Lipase elevation grade 3/4 was seen in 14%. Hypertension of any grade

was seen in 18% out of which 5% was grade 3/4 [82]. Serious adverse events cardiovascular(3%), cerebrovascular(2%) and peripheral vascular events (2%) were seen in newly diagnosed CML-CP patients [82]. In heavily pretreated patients grade 3/4 anemia(10%–32%), neutropenia (17%–37%) and thrombocytopenia (35%–44%) were seen [84]. Grade 3/4 hypertension was present in (8%–14%) and serious adverse effect cardiovascular (12%), cerebrovascular (10%), peripheral vascular(11%) and venous thromboembolism (5%) were seen in this heavily treated population [84]. Effect of commonly prescribed drugs on ponatinib have been summarized in Table 1.

Ponatinib is effective against patients who have received multiple TKI and achieves durable responses, with the drawback of serious thromboembolic events. Cardiovascular assessment and risk stratification should be done in patients who are considered to be candidates for ponatinib. Dose reduction of ponatinib is suggested as a strategy to reduce cardiovascular events in those at risk patient based on efficacy shown in trials and case series [81, 83, 85]. Patients at moderate risk of cardiovascular disease can be started at dose of 30 mg and reduced to 15 mg once patient achieves cytogenetic and molecular response. Patients who are already in molecular remission can be initiated at a dose of 15 mg [86]. Aspirin or clopidogrel as primary prophylaxis should be considered in all patients on ponatinib irrespective of dose because of very high risk of thromboembolic events, though at present data is lacking for the same [87].

Radotinib

Radotinib is second generation TKI with structure and resistance pattern similar to nilotinib [88]. Data for radotinib pharmacokinetics and pharmacodynamics is lacking. It is administered orally. Radotinib has been used in 300 mg twice daily and 400 mg twice daily; 300 mg twice daily was more effective and tolerable and is the approved dose [89].

Common toxicities were rash, pruritus, constipation, diarrhea, fatigue, myalgia and headache [89]. Grade 3/4 anemia (6%–10%), neutropenia (19%–24%) and thrombocytopenia (14%–16%) were seen in newly diagnosed CML-CP patients. Radotinib causes hepatotoxicity, grade 3/4 ALT elevation (20%–26%), AST elevation (5%–6%) and hyperbilirubinemia (27%–42%) were seen. Hyperglycemia was seen in 11% [89].

Which TKI to use?

With the advent of second generation and third generation TKI, each new TKI has been compared to imatinib in newly diagnosed CML-CP patients. Data from key phase 3 trials are summarized below.

Nilotinib vs Imatinib

Long term outcome of ENESTnd trial have been reported where imatinib has been compared to nilotinib 300 mg twice daily and nilotinib 400 mg twice daily in newly diagnosed CML-CP patients [90]. At the end of 5 years nilotinib significantly achieved higher MMR than imatinib. Number of progression to CML-AP/BC and deaths were significantly lower in nilotinib arm. Five year EFS, PFS and OS of nilotinib 400 mg twice daily was significantly higher than imatinib. Cardiovascular events were more with nilotinib 400 mg twice daily (all grade 13.4%, grade 3/4 8.7%), nilotinib 300 mg twice daily (all grade 7.5%, grade 3/4 4.7%) when compared to imatinib (all grade 2.1%, grade 3/4 1.8%). Hyperglycemia, increased lipase, liver enzymes and hyperbilirubinemia were also higher in nilotinib arms whereas hematological adverse events were higher in imatinib. On comparing the risk benefit ratio nilotinib 300 mg twice daily appears to be the appropriate dose [90]. In ENESTchina study patients on nilotinib 300 mg twice daily had significantly higher MMR at 12 and 24 months than patients on imatinib. Rates of CCyR at 24 months and the estimated rate of freedom from progression to CML-AP/BC were similar in both the arms [91].

Nilotinib is superior to imatinib in terms of depth of response and prevention of progression of CML-CP with a different toxicity profile. However, there was no notable difference in OS, EFS and PFS between the two drugs.

Dasatinib vs Imatinib

Dasatinib versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients (DASISION) a phase 3 randomized trial compared safety and efficacy of dasatinib with imatinib [46]. Cumulative 5 year MMR was significantly higher with dasatinib. Dasatinib achieved faster and deeper molecular responses, though OS and PFS were similar. Pleural effusion was seen in 28% vs 0.8%, pulmonary hypertension was seen in 5% vs 0.45% respectively with dasatinib and imatinib [46].

Dasatinib was similar to nilotinib and yielded better responses without benefit in OS. As OS rates are high, large sample size with longer follow up will be required to prove if nilotinib and dasatinib have survival benefit over imatinib.

Bosutinib vs Imatinib

Bosutinib was compared with imatinib in, phase 3 Bosutinib Safety and Efficacy in Newly Diagnosed CML (BELA) randomized trial with primary end point of CCyR at 12 months [92]. MMR at 12 month and 24 month was significantly higher in bosutinib but there was no statistically significant difference in CCyR at 12 month and 24 month when compared with imatinib. There was no difference in EFS and OS at

2 years, though 2 years is a very short duration of follow up. Bosutinib had higher grade 3/4 diarrhea, increased ALT and vomiting. Imatinib had higher incidence of myalgia, muscle spasms, bone pain and peripheral edema though grade 3/4 toxicities were occasional. Bosutinib was not superior to imatinib in terms of primary end point CCyR but attained faster CCyR, superior MMR, and higher response rates at 3, 6 and 9 months with a different toxicity profile [92]. In phase 3 randomized trial, Bosutinib Versus Imatinib for Newly Diagnosed CML (BFORE) trial MMR and CCyR at 12 months was significantly higher with bosutinib. Similar to BELA trial grade 3/4 gastrointestinal and hepatic toxicities were higher in bosutinib arm compared to imatinib arm [74].

Bosutinib appears to be a promising alternative of imatinib, but follow up duration of trial is short at present. Another phase 3 trial comparing with imatinib is undergoing (NCT02130557). There is a need to compare bosutinib with dasatinib or nilotinib in randomized controlled trials.

Ponatinib vs Imatinib

Ponatinib 45 mg once daily was compared with imatinib 400 mg once daily in phase 3 randomized trial to assess safety and efficacy wherein primary end point was MMR at 12 months [82]. The trial was terminated earlier due to vascular events with ponatinib reported in other trials. At 12 months only 13 patients on imatinib and 10 patients were available for evaluation of MMR out of which 5 and 8 patients respectively achieved MMR. At 3, 6 and 9 months percentage of patients achieving MMR and CCyR with ponatinib was significantly higher than imatinib. Out of 154 patients in the ponatinib arm five patients had cardiovascular, three cerebrovascular and three had peripheral vascular side effect. Grade 3/4 rash, abdominal pain hypertension, elevation in amylase and ALT were higher in ponatinib arm [82].

Multivariate analysis from pooled patients from trials of ponatinib has established that pancreatitis, cardiac failure, cardiovascular, cerebrovascular and atheroembolic events are significantly related to the dose of ponatinib [93]. The possibility of harnessing the unique activity of ponatinib and simultaneously by curtailing the serious adverse event with a dose of ponatinib is being explored in the OPTIC trial (NCT02467270) for upfront CML patients and OPUS trial (NCT02398825) in imatinib resistant CML-CP.

Radotinib vs Imatinib

Radotinib 300 mg twice daily and 400 mg twice daily was compared to imatinib 400 mg once daily in phase 3 randomized, Results of Safety and Efficacy of Radotinib Compared with Imatinib in Newly Diagnosed Chronic Phase CML (RERISE) trial [89]. At 12 months MMR rates were significantly higher in patients receiving radotinib 300 mg twice a

day and radotinib 400 mg twice daily compared with imatinib 400 mg twice a day. The CCyR rate at 12 months with radotinib 300 mg twice daily was significantly higher when compared with imatinib. CCyR at 12 months with radotinib at a dose of 400 mg twice daily was not significantly different from imatinib. Radotinib had higher grade 3/4 elevated AST, elevated ALT, hyperbilirubinemia and elevated lipase compared to imatinib. Hematologic toxicities were less in radotinib 300 mg twice daily compared to radotinib 400 mg twice daily. Other toxicities were similar in all the three arms [89].

The follow up of RERISE trial is of short duration and done in Asian ethnicity with smaller body size. Tolerability of radotinib 300 mg twice daily was better than 400 mg twice daily, which can be attributed to small body size. There is evidence to suggest that radotinib 400 mg twice daily might be an appropriate dose for patients weighing more than 65 kg [94]. Further studies are required to determine the appropriate dose of radotinib, specially in other ethnicities.

Treatment free remission: Our current goal

Treatment free remission (TFR) is defined as a sustained deep molecular response after cessation of TKI in selected patients with predefined criteria [95]. Clinical trials have studied the stopping of imatinib and second generation TKI in CML. Discontinuation of imatinib has resulted in TFR outcome ranging from 39 to 61% [96–100]. All trials recruited patients with MR⁴ (log reduction in BCR-ABL 4) for a year and with a median duration of therapy for more than 3 years [95–99]. Nilotinib when used in first line yielded a TFR of 48.9% [101]. Second generation TKI when used in second line resulted in TFR ranging from 48 to 63.3% [102, 103]. At present, patients older than 18 years, diagnosed in CML-CP with TKI treatment duration more than 5 years, MR^{4.5}, deep molecular response duration of more than 2 years, and those who had an optimal response to TKI are recommended for TFR [104].

In EURO-SKI trial on the last day of TKI intake expression of ABCB1, OCT1 and ABCG2 were analyzed. Only high ABCG2 expression correlated with TFR, suggesting the role of ABCG2 as a predictive marker for TFR [105].

How and what to choose?

ELN guidelines recommend imatinib, nilotinib and dasatinib as first line options in CML-CP whereas NCCN guidelines recommend bosutinib in addition to these three [106, 107]. Ponatinib is currently approved only in patients with T315I-positive CML-CP/AP/BP or in situations where no other TKI can be used, hence it is the only TKI not used in first line [108]. Due to multiple TKI options and life of CML patients approaching that of normal population, choice of TKI depends

on risk category, treatment goals, age, comorbidities, cost, ease of administration and availability of TKI [109, 110]. Sokal, Euro and European Treatment and Outcome Study (EUTOS) scores are used to predict outcome in CML-CP patients [107]. Nilotinib and dasatinib attained higher MMR and MR^{4.5} irrespective of risk category [46, 90] Nilotinib showed OS and PFS benefit for intermediate and high risk patients based on Sokal score, though they were not the primary objective [90]. High risk Sokal patients on bosutinib attained higher MMR compared to imatinib, though follow up was only 1 year [74]. Thus, second generation TKI should be preferred in intermediate and high risk category of CML patients [106].

Second and third generation TKI attain earlier, deeper response and fewer chances of progression to CML-AP/BC as compared to imatinib in newly diagnosed CML-CP patients. In all phase 3 trials primary end points of second and third generation have been met except with ponatinib which was terminated earlier. However, survival has not been the primary end point of these trials and there is no significant difference in survival when compared with imatinib [109]. In younger patients TFR is a desirable goal. For TFR a TKI with early, deep and sustained response is required, hence second generation TKI is the drug of choice. Elderly patients where survival is the goal imatinib will still be the preferred drug due to its safety profile [109].

Comorbidities play a further role in refining the choice of TKI. In patients with cardiovascular risk factors and diabetes mellitus, dasatinib or bosutinib is preferred over nilotinib. Nilotinib or bosutinib is preferred in patients with lung diseases, pulmonary hypertension and patients who are at risk of bleeding [106]. For other patients considering molecular response as end point nilotinib appears to be the best drug [111]. The drawback of nilotinib is twice daily administration and timing in relation to food. Bosutinib is not preferred in patient with pancreatitis, liver disease, inflammatory bowel disease and peptic ulcer disease. In patients with a history of pancreatitis dasatinib is the preferred drug [112]. Imatinib had the most favourable safety profile when it was compared with other TKI in a meta-analysis [111]. Imatinib can be used irrespective of any comorbidities. Generic imatinib is available and is comparatively cheaper. In many countries due to lower cost of imatinib and maximum clinical experience, it is still the first-line drug in CML-CP. Radotinib is currently approved only in Korea in the upfront setting for CML-CP [88].

Newer strategies in CML treatment: Upcoming trials

There is a need to explore the pharmacokinetics and pharmacogenetics of second and third generation TKI and how they impact clinical outcomes. At present, association of dasatinib, nilotinib, imatinib and bosutinib pharmacokinetic parameters with clinical outcome, toxicities and germline genetic variant

are being studied (NCT03885830). Studies on the effect of genetic polymorphism of imatinib metabolizing enzymes and membrane transporter on molecular response of imatinib are going on (NCT03262974). The results of these studies will help in deciding the choice of TKI based on pharmacogenetic profile of the patient.

TKI tolerability and toxicity depend on dose. Dose reduction is a potential strategy to mitigate the adverse effects. Ponatinib dose reduction studies are under going (NCT02467270, NCT02398825) as mentioned above. Similarly, efficacy and safety of dasatinib 50 mg vs 100 mg daily is being evaluated in phase II trial (NCT03625388).

Newer TKI yield better responses than imatinib at the expense of cost and different toxicity profile. So switching TKI during maintenance is another possible option. A study where nilotinib is used to achieve cytogenetic response and subsequently imatinib will be used as maintenance is ongoing (NCT01316250).

ABL001(asciminib) is first allosteric inhibitor of BCR-ABL1 and is currently undergoing phase 3 trial (NCT03106779) with bosutinib as comparator arm in previously treated CML-CP with two or more TKI [113, 114]. In a three-arm trial, asciminib and imatinib combination is being compared with imatinib and nilotinib NCT03578367. K0706 a novel TKI, is currently under phase I/2 trial (NCT02629692) [115]. HQP1351 a multikinase inhibitor is undergoing phase 2 trial (NCT03883087) in CML-CP and in CML-AP (NCT03883100) with T315I mutations [116, 117]. PF-114 is a third generation TKI which is active against T315I and has completed phase I clinical trial [118]. Apart from ponatinib, T315I can be targeted in future, with these new molecules.

Drugs are being identified to administer in combination with TKI or sequentially after TKI administration to increase molecular response (NCT02767063). Ruxolitinib in combination with TKI (dasatinib or nilotinib) is being compared with single TKI (nilotinib or dasatinib) in randomized phase two trial (NCT03654768) [119].

Combination of TKI's is another novel approach to enhance efficacy of TKI's in CML. Nilotinib is being combined with interferon to attain deeper molecular response in phase III TIGER trial (NCT01657604) and another study (NCT02201459). Similarly, bosutinib is being combined with ropeginterferon (NCT03831776).

Attaining TFR is the new goal in CML, yet a major proportion of patient do not attain CMR. Patients who fail to achieve CMR on TKI are being investigated for the role of ruxolitinib (NCT01751425) and pembrolizumab (NCT03516279) to attain CMR.

CML-AP/BC has poor outcomes. DNA methylation of genes is a key event during progression of CML-AP/BC. Hence, a combination of hypomethylating agents with TKI are being investigated. Dastinib is being combined with

decitabine in phase I/II trials for CML-AP/BC (NCT01498445). Ponatinib and 5-azacytidine combination are being studied in CML-AP/BC (NCT03895671). Combination of axitinib with bosutinib is also being evaluated in phase I/II trial (NCT02782403).

Future direction of TKI in CML

In this review we have summarized the key pharmacogenetic studies of imatinib and other TKI's. However, the interpretation of these studies is limited due to lack of adequate statistical power and heterogeneous nature of the studies. There is an unmet need for multicentric, multiethnic well designed clinical trials with uniform and relevant end points to establish the role of pharmacogenetics in predicting TKI response and outcome. As CML progression on TKI still has poor outcomes, it is imperative to identify pharmacogenetic predictors of CML progression in patients treated with TKI.

There is a lack of studies delineating the detailed pharmacokinetics and pharmacodynamics of the newer TKI, specially bosutinib, ponatinib and radotinib. Clinical trials studying newer TKI's should also explore the molecules and their gene polymorphisms which are involved in transport and metabolism of these TKI.

TFR has emerged as new goal of CML treatment. Second generation TKI appears to be better than imatinib in attaining TFR than TKI, but it needs to be established in randomized control trial with TFR as an endpoint. Simultaneously, pharmacogenomics needs to be integrated in these trial so that pharmacogenetic predictor of TFR can also be identified. Sequential use of TKI's needs to be explored to attain a deeper TFR than the conventional single agent TKI.

Nilotinib has cardiovascular side effects and ponatinib has life threatening thromboembolic events. We need data to define the optimal strategy for reduction of cardiovascular risk in patients on nilotinib and thromboembolic prophylaxis in patients on ponatinib. At present ponatinib is the only TKI effective against T315I. There is need for TKI which do not have life threatening side effect and are yet active against T315I mutation.

Pediatric CML is an understudied area. Optimal choice of TKI in pediatric patient and feasibility of TFR in pediatric population needs to be studied. Pharmacokinetics and pharmacodynamics of TKI may not be the same in pediatric population as adult population and these need to be delineated.

Conclusion

We present here a comparative review of the pharmacokinetics, pharmacogenomics, clinical usage, efficacy and toxicity data of TKIs used for CML. Pharmacogenetic data for TKI at present are not mature enough to be implemented in clinical

practice. Though, phase 3 trials, have been conducted for newer TKI's there are lacunae in the pharmacology of newer TKI's. Imatinib is still the most commonly used TKI worldwide. Where survival is the goal, imatinib appears to be a safe, cheap and reasonable option. When the goal is TFR second generation TKI appears to have greater potential, though trials are required to address this.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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