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The Role of JAK2 Gene in Imatinib-Resistant Chronic Myeloid Leukemia: A Review

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ABSTRACT

Chronic myeloid leukemia (CML) is still an incurable disease. Despite the effective treatment with commercially available tyrosine kinase inhibitors (TKIs), CML is still of interest to many researchers worldwide. Imatinib was the first available TKI and is still the gold standard for CML therapy worldwide. Recently, there is growing evidence of imatinib-resistant CML. Researchers have hypothesized various extrinsic factors that could contribute to imatinib-resistant CML. Among such suspected factors, the dysregulation of the Janus-kinase-2 (JAK2) gene has been the subject of research by several groups to reveal its role in CML. Trials of treatment with JAK2 inhibitors in patients with CML, who have JAK2 gene mutations, show a relatively good therapeutic response, but to date, the role of the JAK2 gene in CML is still being debated due to different studies results. In this review, controversies about the JAK2 gene in the imatinib-resistant CML and the recent clinical trials with JAK2 inhibitor are discussed.

Keywords: Chronic myeloid leukemia, tyrosine kinase inhibitors, philadelphia chromosome, imatinib resistant, JAK2 inhibitor.

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INTRODUCTION

Despite effective treatment with commercially available tyrosine kinase inhibitors (TKIs), chronic myeloid leukemia (CML) is still an incurable disease and becomes of interest to many researchers around the world. It is predicted that up to 25% of CML patients will switch TKIs at least once during their life due to TKI resistance. (1) Even in patients achieving a complete response, including those with undetectable breakpoint cluster leukemia (BCR) - Abelson murine leukemia (ABL) transcript levels, there is evidence of the existence of BCR-ABL cells at the stem cell level, (2, 3) and positivity of BCR-ABL genomic deoxyribonucleic acid (DNA) by a polymerase chain reaction (PCR). (4, 5) The persistence of CML leukemia stem cells (LSC) is suspected secondary to their insensitivity to TKI despite effective tyrosine kinase inhibition, suggesting that other extrinsic pathways (out of BCR-ABL gene) contribute to their survival. (6, 7) Amongst such suspected pathways, the dysregulation of Janus-kinase 2 (JAK2) gene has been the subject of research by several groups in an attempt to reveal its role in CML. (8-14). The purpose of the present article is to provide a comprehensive overview of current, available literature regarding the role of JAK2 gene in CML.

Chronic myeloid leukemia overview

Chronic myeloid leukemia is a myeloproliferative disease, arising from a reciprocal translocation of the ABL gene on chromosome-9 with BCR gene on chromosome-22 [t (9;22) (q34; q11)], with the foreshortened long arm chromosome 22 known as Philadelphia (Ph) chromosome. The mutation results in a BCR-ABL fusion gene that expresses BCR-ABL oncoprotein with high tyrosine kinase activity.(15) BCR-ABL is an active tyrosine kinase responsible for cells growth and replication through many signalling pathways such as rat sarcoma (RAS), rapidly accelerated fibrosarcoma (RAF), JUN kinase, MYC, and STAT.(16-22) The fusion of the BCR-ABL gene is found in almost 90% of cases of CML and is consistently related to cell morphology, clinical features, and laboratory studies.(23) The molecular pathogenesis of CML is well understood, chronic phase (CP) CML is driven by the continuously active tyrosine kinase protein, leading to malignancy of myeloid cells with the stimulation of mitosis, disruption of cytoadherence and stromal cells regulatory function, and the inhibition of apoptosis. BCL-ABR fusion protein, which is also thought to promote genomic instability, causing secondary mutations and to the blast phase. (24)

Imatinib-resistant chronic myeloid leukemia

Imatinib mesylate or 2-phenylalaminopyrimidine (ST1571) was the first available tyrosine kinase inhibitor (TKI) and is still the gold standard for CML therapy worldwide. (15, 25-27) Food and Drug Administration approved imatinib for the treatment of refractory CML cases in February 2002. Imatinib interferes with the phosphorylation of proteins involved in BCR-ABL signal transduction, through competitive inhibition at the adenosine triphosphate (ATP) binding site of BCL-ABR oncoprotein.(24) The BCR-ABL oncoprotein inhibition results in apoptosis of the hematopoietic stem cells that express BCR-ABL with sparing the normal cells.(28) According to The International Randomized Study of Interferon and ST1571 (IRIS), as shown in an 8-year follow up, imatinib has proven to be effective for CML patients with estimated event-free survival (EFS) rate and overall survival (OS) rate of 81% and 93%, respectively.(29) Besides the impressive results reported by previous studies, a subset of patients treated with imatinib develop resistance, approximately 33% of patients with CML treated with imatinib do not achieve a complete cytogenetic response (CCyR).(30-32) In addition to intrinsic tyrosine kinase activity, there is growing

evidence of extrinsic factors that could contribute to imatinib-resistant CML. Amongst such suspected factors, the dysregulation of the JAK2 gene has been the subject of research by several groups in an attempt to reveal its role in CML.(8, 10-14, 33).

Mechanism of tyrosine kinase inhibitor resistance

There are two types of TKIs resistance; primary resistance designates a failure to achieve time-dependent endpoints of complete hematologic response (CHR), CCyR and major molecular response (MMR) in the initiation of TKI therapy, while secondary or acquired resistance is characterised as the loss of treatment response. (34) From the initial level, TKI resistance can be classified as either BCR-ABL-dependent or BCR-ABL independent pathways. The distinction does have a great degree of clinical relevance, as it describes the strategy required to fight drug resistance. BCR-ABL-dependent resistance is the mechanisms that suppress significant BCR-ABL kinase inhibition, such as point mutations in the kinase domain (KD) that diminish drug binding or cellular processes that impede with TKI bioavailability and result in suboptimal drug concentrations at the tissue target. Mutations in the KD of BCR-ABL are the most extensively studied mechanism of TKI resistance in CML but fail to explain anywhere from 20–40% of resistant cases. Contrary, BCR-ABL-independent resistance is mediated through other alternative survival pathways acting in the context of significant TKI inhibition of BCR-ABL. BCR-ABL-independent resistance is mediated through multiple alternative survival pathways. These pathways have a significant role in BCR-ABL-independent primary or secondary resistance. These BCR-ABL-independent resistance mechanisms are an essential contributor to minimal residual disease, likely due to leukemia stem cell persistence despite deep molecular response to TKI therapy. (35, 36)

BCR-ABL-Dependent TKI Resistance

BCR-ABL KD Mutations

Two principles define the leading cause of resistance by KD mutations. Mutations might exist de novo or mutations may be induced by TKIs during therapy. (37-39) Hotspot mutations in several kinase domains are the principal mechanism of TKIs resistance. Point substitutions in only twelve residues (M244, G250, Q252, Y253, E255, V299, F311, T315, F317, M351, F359 and H396) account for most resistance-related KD mutations.(40) The main parts of TKI- resistant ABL1 point mutations reduce the flexibility of the enzyme decreasing accessibility of the drug binding site.(41-44) T315I was the first mutation shown in relapsed CML patients,(37, 45) and causes the highest level of resistance to the first and second generations of TKIs by replacing the threonine at 315 for isoleucine disabling formation of a hydrogen bond at this position for the TKI binding targets.(46)

There are three structural motifs of tyrosine kinase active sites, including activation loop (A-loop), ATP-binding loop (P-loop) and aspartate-phenylalanine-glycine (DFG) motif. These three motifs exist in two principal form. In the inactive state, the activation loop (A-loop) is in a closed position, and the DFG motif in an outward position. Contrary, in the active state the A-loop is in an open form, and the DFG motif is aligned toward the catalytic site. (47) There are two type of TKIs, type-1 TKI (dasatinib and bosutinib) compete directly with ATP for binding in ATP-binding loop, whereas type-2 TKI (imatinib, nilotinib, ponatinib and bosutinib) more known as stabilizers of an inactive enzyme conformation. These structural differentiations have essential consequences as they inform the number and types of mutations that show resistance to a given TKI. (48-52)

Point mutations in the ABL kinase domain resulting in decreased drug binding is the main mechanism of acquired resistance to imatinib in CML. (38) Imatinib binds to and stabilizes an inactive kinase conformation with A-loop in a closed position, P-loop in an extensive downward displacement, DFG-out conformation, and a hydrogen bond with threonine 315(52) (53) This binding site is reflected in several estimated mutations associated with imatinib resistance. T315 hotspot mutation confers resistance by impeding inhibitor access or eliminating critical hydrogen bonds. The second group of mutations, including those within the ATP binding loop (P-loop mutations thought to prevent the structural arrangements required for optimal imatinib binding), confer resistance by limiting ABL from adopting the specific conformation required for high-affinity imatinib binding. Last, mutations in regulatory motifs such as the activation loop (A-loop) stabilize an active conformation motif that is inaccessible by imatinib. (49, 52-54)

Second-generation TKIs such as nilotinib and dasatinib have been demonstrated to show a smaller spectrum of resistant mutations. Nilotinib exhibits a similar binding form to imatinib. It was developed from the imatinib blueprints, but has a much-enhanced molecular fit, significantly increasing binding affinity. It had increased approximately 30-fold potency because of an improved molecular fit to the enzyme.(49, 54) Dasatinib is a dual SRC/ABL inhibitor with more than 300-fold improved potency compared with imatinib.(55) Nilotinib and dasatinib overwhelm some of the imatinib-resistant mutants, and they have been demonstrated to show a modest spectrum of resistant mutations.(49, 56) Nilotinib tightly binds to inactive ABL conformation and dasatinib binds to ABL with more compliant conformational compared with imatinib. Unfortunately, both of them make a hydrogen bond with T315, therefore they cannot overwhelm the resistance inferred by it. Further, both have different resistance mutation spectrum, nilotinib commonly associated with F359V/C/I, E255K/V, Y253H, or T315I mutations, whereas dasatinib mutation spectrum is T315A, V299L, F317L/V/I/C, or T315I mutations as hotspots. Resistance mutations observed in patients treated with bosutinib have a spectrum related to dasatinib. (48, 57-61) Ponatinib, binds ABL in the same conformation to that observed with imatinib, but opposite with imatinib, no hydrogen bond is made with T315I. (62)

Another BCR-ABL-Dependent TKI Resistance

Besides the KD mutations, overexpression of BCR-ABL oncoprotein, drug influx/efflux mechanism, and TKIs bioavailability can contribute to TKI resistance. The correlation between increased BCR-ABL expression via BCR-ABL gene amplification, Ph duplication, and differential regulation of oncogene transcription is less specific than in cases of KD mutations. Recent studies show high levels of the BCR-ABL oncoprotein are associated with more advanced stage disease, allowing adequate kinase activity to persist despite the presence of TKIs, allowing leukemia cell survival until a KD mutation is acquired and confers overt resistance. (53, 63-65)

Several transporters disruptions such as reduced drug-influx transporter Organic-cation transporter-1 (OCT-1) (66-68), or increased drug-efflux transporter ATP-binding cassette transporters (ABCB1 and ABCG2) could explain the suboptimal response to TKI therapy. (66, 69-73) Organic-cation transporter-1 and is a cellular influx pump

for imatinib demonstrated to influence intracellular drug availability. Low OCT-1 activity reduced intracellular imatinib concentration and imparted BCR-ABL dependent imatinib resistance. High OCT-1 activity is predictive of improved MMR rates, EFS, and OS in patients treated with imatinib. (67, 68, 74, 75) ABCB1 and ABCG2 are a family of the intestinal ABC transport protein. Chronic exposure to imatinib has been associated with the induction of ABCG2 and ABCB1 drug transport pumps. Several studies have reported these drug-efflux pumps can function as an active outward transport mechanism for imatinib and play an important role in drug-drug interaction and cellular resistance to imatinib. (70, 76, 77)

All of the TKIs used in CML are subject to extensive hepatic first-pass metabolism by CYP3A4. Therefore, patients on TKIs should undergo thorough medication reconciliation to avoid potential drug-drug interactions. Low bioavailability can negatively impact TKIs efficacy. General CYP3A4-inducing medications and supplements include dexamethasone, rifampicin, phenobarbital, phenytoin, carbamazepine, and St. John's wort. (78) Dasatinib bioavailability is affected by gastric pH-modifying medications such as H2-antagonists and proton pump inhibitors due to the drug's low solubility in solutions with a pH >4.0. Patients must be instructed to take antacids 2 hours before or 2 hours after dasatinib administration to avoid dasatinib absorption reductions. (79, 80)

BCR-ABL-Independent TKI Resistance

Mutations in the BCR-ABL gene are an important mechanism of TKI resistance in CML, but nearly 40% of clinical TKI failure cases occur in the setting of continued BCR-ABL inhibition. (81) However, in 50% or more of imatinib-resistant CML patients, there is no mutation in BCR-ABL and the data of such BCR-ABL-independent imatinib resistance is not well understood. (82, 83) It is proposed that activation of alternative survival pathways must be responsible for primary or secondary resistance. (35) Activation of several genes such as STAT-3, PI3K/AKT, RAF/MEK/ERK, XPO1, RAN, and EZH2 are reported to be associates with BCR-ABL-independent TKIs resistance. (84-88) In this review, we will focus on discussing the JAK2-STAT5 pathway on its role in imatinib-resistant CML.

Overview of JAK2-STAT signalling pathway in the CML pathogenesis

JAK2 gene is a gene in the family Janus kinase, which was initially composed of 4 genes (JAK1, JAK2, JAK3 and Tyk2). Under normal circumstances the JAK2 gene has an essential role in the regulation of the hematopoiesis process by encoding the cytoplasmic kinase protein enzyme, activating several cell transductions signals such as the STAT, ras-mitogen-activated protein kinase (MAPK), and phosphoinositide-3-kinase (PI3K) pathway. JAK2 functions as a regulation of maturation, proliferation, apoptosis, and myeloid cell differentiation. (89-92) The role of disruption of JAK2 gene expression has been demonstrated in polycythemia vera, essential thrombocytosis, and primary myelofibrosis.

The role of JAK2 in the pathogenesis of CML can be explained by activation of the JAK-STAT pathway due to active protein kinase from the BCR-ABL gene (Figure 1). The active tyrosine kinase protein from the BCR-ABL gene in CML or hematopoietic growth factors (HGFs) bind to specific cell surface receptors in the JAK2-STAT5 signalling pathway causing phosphorylation of the STAT5 by JAK2 protein, which then activates the JAK-STAT pathway. Although the BCR-ABL gene regulates JAK2 gene expression, there is no linear relationship between the two, (8, 9, 93) and JAK2 gene expression can increase without the influence of the signal from the BCR-ABL gene. The factors causing the mechanism of JAK2 activation without stimulation of the BCR-ABL gene are not completely clear. (94) Several theories are suspected to be the cause of this event, particularly the role of cytokines (especially interleukin-3 (IL-3) and interferon (IFN)).(10, 92) This theory is demonstrated by studies that show a significant relationship between various cytokines on the progression of CML. (95, 96) Another factor thought to play a role in increasing JAK2 expression includes mutation of the JAK2 gene itself. Double mutations in the BCR-ABL gene and the JAK2 gene are rarely reported. Several case reports have found various evidence in the incidence of JAK2 mutations in CML patients, reported between 2.5 - 44%. (97-101)

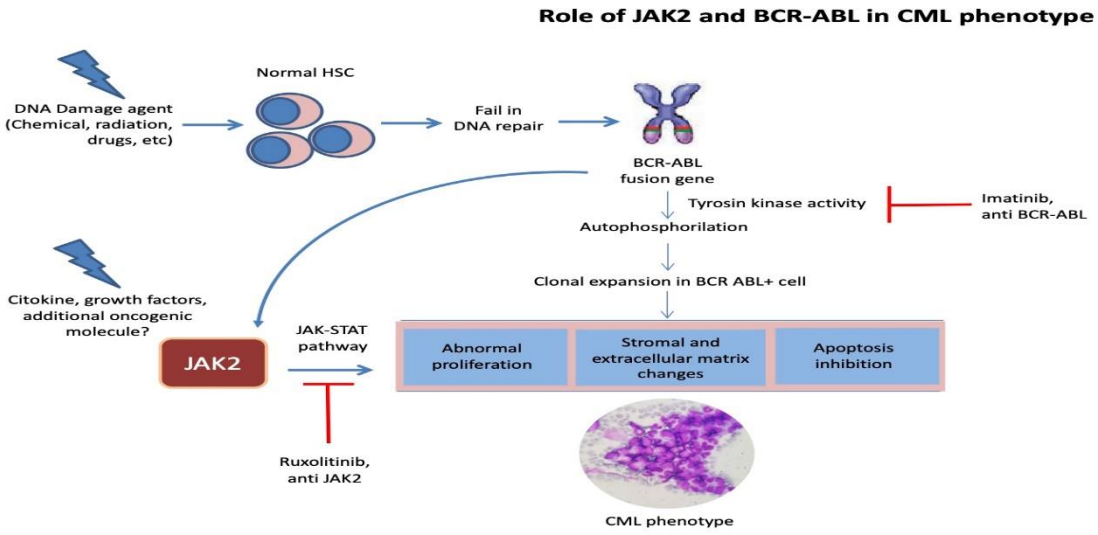

Figure 1. The role of JAK2 and BCR-ABL in CML phenotype.

Controversies of JAK2 gene in the CML pathogenesis

In CML patients who have JAK2 gene mutations, trials of treatment with JAK2 inhibitors show a fairly good therapeutic response, but to date, the role of the JAK2 gene in CML is still being debated by experts due to different research results. (8, 14, 91)

Early evidence in the discovery of the role of JAK2 in the pathogenesis of CML begins with several in vitro and animal studies. Xie et al. found that the correlation between JAK2 and ABL triggers JAK2 phosphorylation that is not affected by BCR-ABL tyrosine kinase inhibitors such as imatinib. (102) The study also reported that JAK2 could increase Myc expression, thereby contributing to the anti-apoptotic ability of CML cells. (103) Another study by Gallipoli et al. observed that JAK2 inhibitors in vitro have a positive effect on decreasing the activity of the JAK-STAT pathway. This effect correlates with increased apoptosis of CML progenitor cells better than tyrosine kinase inhibitors alone. (8) Similar studies conducted by Okabe et al. and Lin et al. report the same results. (104, 105) Furthermore, a study conducted by Zhang et al in 2016 reported there is an increased number of thrombopoietin receptor MPL in CML, and the human CML with high MPL expression had reduced sensitivity to TKI treatment but increased sensitivity to JAK inhibitor. (106)

Some studies opposed the role of the JAK2 gene in CML; one animal study conducted by Grundschober et al. with BCR-ABL p210 lacking JAK2 showed a drastic increase in disease progression and severe splenomegaly. (107) Warsch et al. reported the same results in an in-vitro study. They reported that there were no significant differences between CML cells with and without the JAK2 gene. The elimination of JAK2 had no impact on proliferation, cell cycle progression, and induction of apoptosis. The result of the study was favoured by the in-vivo study showing the same result. (14, 91, 94)

Current update of JAK2 inhibitor therapy in CML and ongoing phase II study of ruxolitinib

To provide the latest update on JAK2 inhibitor therapy in CML, we searched PubMed/MEDLINE (https://www.ncbi.nlm.nih.gov/pubmed/) in September 2020. Full-text articles were identified using the Mesh terms "Leukemia, Myelogenous, Chronic, BCR-ABL Positive," AND "INCB018424" [Supplementary Concept] - Mesh term for ruxolitinib, AND "Clinical Trial [Publication type]. There were a completed phase I clinical trials (NCT01702064), which investigated the tolerability and safety of treating chronic phase CML patients with ruxolitinib combined with nilotinib. The result was satisfying; the combination was safe and well-tolerated, warranting further research with a larger sample in a phase 2 trial. (108)

There are also two ongoing clinical trials in SWOG Cancer Research Network. The Rando PhII Ruxolitinib + BCR-ABL TKIs in CML w/Molecular Disease is a phase II, randomized, ongoing clinical trial (SWOG clinical trial number S1712) which add ruxolitinib to patient receiving dasatinib/nilotinib/bosutinib as first or second line therapy for a minimum of 6 months prior to enrollment. Eligible patients are have a diagnosis of chronic CML (no history of progression to accelerated or blast phase), have detectable BCR-ABL transcripts (International Scale value of >0.0032% and </= 1.0% within 21 days prior to randomization), be receiving treatment with: dasatinib (40-140 mg daily) or nilotinib (150-400 mg BID) or bosutinib (200 - 500 mg daily) as first or second line therapy for a minimum 6 months prior randomization, not have any history of resistance to any prior TKI drug, 18 years old or older, have complete history and physical examination within 28 days prior randomization, when applicable have QTc interval < 500 ms (by Fridericia calculation) on ECG within 7 days prior randomization, have platelet value >/= 100,000/mm^3, ANC > 1000/mm^3, hemoglobin >/= 8g/dL, AST and ALT </= 2.5x IULN, total bilirubin </= 1.5x IULN and serum creatinine </= 1.5 x IULN within 7 days prior to randomization, and not be pregnant or nursing.(109)

The HJKC3-0002 trial (Treatment free remision after combination therapy with ruxolitinib plus tyrosine kinase inhibitors) is an open label, ongoing phase II clinical trial with a target of 14 participants. The eligible patients will have a confirmed chronic phase CML and must have previously attempted to discontinue TKI therapy under physician supervision. Eligible patients will begin ruxolitinib in combination with their TKI on cycle 1 day 1 of the combination phases. They will continue combination therapy for a total of 12 cycles (each cyles will be 28 days). At the end of 12 cycles ruxolitinib will be discontinued and any patient who has met the criteria for the treatment free remission (TFR) screening phase will enter into the TFR phase. Once in the TFR phase, participants will discontinue their BCR-ABL TKI and be monitored off treatment. The purpose of this study is to determine if adding ruxolitinib to a TKI, prior to a second attempt at stopping a TKI will lead to prolonged treatment free remission. (110) The summary of current ruxolitinib clinical trials in CML patients was provided in Table 1.

Table 1. Several ruxolitinib clinical trials in CML cases.

Author, Year	NCT Number/ Phase	Outcome Measures	Status	Conclusion	References
Sweet K, 2018	NCT01702064/ Phase I	• Phase I: Maximum Tolerated Dose (MTD)	Complete	Ruxolitinib in combination with nilotinib in chronic myeloid leukemia patients was safe and well tolerated.	(108)
Sweet K, 2019	NCT03610971/ Phase II	• 12 Month Treatment Free Remission (TFR) • Adverse Events Possibly Related to Study Treatment	Recruiting	-	(110)

Sweet K, 2018	NCT03654768/ Phase II	• Rate of molecular response 4.5 (MR 4.5) after 12 months • Drug toxicity • Overall survival • Progression-free survival	Recruiting	-	(111)
Kantarjian, 2013	NCT01751425/ Phase I	• Residual disease as measured by polymerase chain reaction (PCR) (Phase II)	Terminated	Terminated because no additional benefit was noted with the addition of ruxolitinib.	(112)
Hochhaus A, 2018	NCT02253277/ Phase I	• Occurrence of dose limiting toxicities (DLTs) • Safety and tolerability profile of nilotinib and ruxolitinib administered in combination • Trough levels of nilotinib and ruxolitinib administered in combination • Clinical activity of nilotinib and ruxolitinib administered in combination	Complete	No Study Results Posted	(113)
Kim D, 2013	NCT01914484/ Phase I/II	• Phase I: Maximum Tolerated Dose (MTD) (Time Frame: Average of 6 months) • Phase II: Major cytogenetic response	Complete	No Study Results Posted	(114)
Burke P, 2018	NCT02973711/ Phase I/II	• Maximum Tolerated Dose (MTD) of ruxolitinib when combined with nilotinib (Time Frame: 2 Years) • The number of patients that achieve a Complete Molecular Response (CMR) (Time Frame: 2 Years)	Suspended (Temporarily on hold)	-	(115)
Eghtedar A, 2012	NCT00674479/	Response Rate (Time Frame: Patients will be evaluated after each full cycle of therapy-28 days for response)	Completed	Ruxolitinib has modest antileukemic activity as a single agent and very well tolerated treatment.	(116)

CONCLUSION

There is a possible role of JAK2 gene and its pathway in imatinib-resistant CML patients. Despite a relatively good therapeutic response in trials of treatment with JAK2 inhibitors, several studies oppose the role of JAK2 gene in CML. The current version of the review states that further research is required to provide evidence of the role of JAK2 gene in imatinib-resistant CML.

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