



After Imatinib Treatment Failure in Chronic Phase CML: What Can We Do?

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ABSTRACT

Chronic myeloid leukemia (CML) is characterized by reciprocal translocation between chromosome 9 and 22. This translocation will activate the tyrosin kinase, leads to underlying pathogenesis of CML. Imatinib is the first line of tyrosine kinase inhibitor (TKI) to treat chronic phase of CML, but resistance has been a significant problem. NCCN has announced recommendation to treat imatinib resistance, including high-dose imatinib, the use of nilotinib or dasatinib.

Keywords: CML, Imatinib, NCCN

ABSTRAK

Leukemia mielositik kronik (LMK) terjadi karena translokasi resiprokal antara kromosom 9 dan 22. Translokasi ini akan mengaktifkan enzim *tyrosin kinase* yang mencetuskan LMK. Imatinib adalah terapi lini pertama dari golongan *Tyrosin Kinase Inhibitor* (TKI) untuk LMK fase kronik. Namun, resistensi terhadap imatinib menjadi masalah yang cukup signifikan. NCCN telah mengeluarkan rekomendasi untuk menangani resistensi imatinib, yaitu pemberian imatinib dosis tinggi, nilotinib atau dasatinib. **Nicholas Wijayanto, Wulyo Rajabto. Jika Imatinib Gagal pada Terapi LMK Khronik: Apa Pilihannya ?**

Kata kunci: LMK, Imatinib, NCCN

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder of stem cell. CML is about 20% from all leukemia in adult. CML characterized by the Philadelphia (Ph) chromosome, it formed because a reciprocal translocation between chromosomes 9 and 22. Translocation of chromosomes 9 and 22 results in fusion of BCR and ABL gens to forms BCR-ABL. This fusion genes is activating the tyrosin kinase (TK). This tyrosin kinase, known as a causative agent underlying CML pathogenesis which is being a target for treatment of CML.^{1,2}

Imatinib was the first line of tyrosin kinase inhibitor (TKI), an agent for the treatment of CML patient in chronic phase. However, Imatinib resistance due to fail of the treatment has been a significant problem that limits the long-term benefits of the drug in CML patient. Imatinib resistance can be a primary and secondary resistance. Primary resistance is characterized by suboptimal response or

treatment failure while secondary resistance develops after an initial response to imatinib therapy and loss of achieved response.^{1,3}

Causes of imatinib resistance can be multifactorial; mostly, it is associated with mutation of BCR-ABL that inhibit imatinib to bind ABL. This mutation can arise spontaneously or the result of imatinib therapy. Mutation of ATP-binding-loop (P-loop) of the ABL kinase domain is the most frequently occur during imatinib treatment. Another mechanisms include overexpression and amplification of BCR-ABL, increased activity of drug transporter protein and activation of BCR-ABL-Independent signaling pathways.³⁻⁵

Since the detection of primary or acquired imatinib resistance, hematopoietic stem cell transplantation (SCT) is still a valid treatment option but associated with morbidity and mortality. The NCCN recommendation for second-line treatment includes high-dose

imatinib, dasatinib and nilotinib or another TKI. Patients with primary imatinib resistance must be switched to dasatinib or nilotinib. High dose imatinib can be considered for patient with secondary resistance.⁶

Second line treatment with high-dose imatinib

Imatinib high-dose therapy (600-800 mg per day) is used in patient with imatinib resistance after standard-dose imatinib. This higher dose is based on findings that BCR-ABL mutations will result to intermediate resistance to imatinib and suggesting that higher dose will be able to overcome the resistance. In other way, overproduction of BCR-ABL, another mechanism of resistance, will respond to increased dose. The important thing is that increased of imatinib dose do not benefit most patient who doesn't achieve Cytogenetic response (CyR) to first-line imatinib therapy.⁷

On the other side, patients with suboptimal response of CyR to initial standard-dose

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imatinib, appear to respond well to increased imatinib dose. A study has evaluated the efficacy of imatinib dose escalation in patients with secondary resistance to standard dose imatinib. Jabbour et al., reported on 84 patients with secondary imatinib resistance in chronic phase CML, who have increased dose from 400 to 800 mg (n=72) or 300 to 600 mg (n=12) of imatinib. Complete CyR were seen in 40% of all patients and 30% maintained a Complete CyR while still receiving imatinib after 5 years and only 5% with hematological resistance to imatinib with higher dose therapy.^{8,9}

This treatment need to be monitored for severe adverse effect including congestive heart failure, hematology toxicity, hepatotoxicity and fluid retention.¹⁰

Second line treatment with Dasatinib

After the clinical introduction of imatinib, incidence of primary and secondary resistance were described. The first second-generation of tyrosin kinase inhibitor was dasatinib with demonstrated potent Src/Abl kinase inhibition and antiproliferative activity in CML cell lines. Even there is a significant sequence homology between Abl and Src kinase, imatinib is unable to bind and inhibit the enzyme. It was identified that dasatinib was able to bind Bcr-Abl.¹¹

SRC/ABL tyrosine kinase inhibition activity research trial (START) showed that dasatinib 70 mg twice daily induced high response rates in patients with CML-CP (n= 101). In START-R, CML-CP patient with failed imatinib 400-600 mg treatment, received either dasatinib 70 mg twice daily or imatinib 800 mg once daily. Comparisons performed after a minimum of 2 years and suggested that dasatinib induced higher rates of Complete CyR (44 % vs 18 %) than imatinib. This trial showed that dasatinib has superior efficacy over imatinib in second-line treatment for CP-CML.¹²

Second line treatment with Nilotinib

Nilotinib is a highly selective Bcr-Abl inhibitor approved for imatinib resistant CML. Nilotinib can increase potency to imatinib, thus may override some forms of imatinib resistance. It also binds to the inactive conformation of the ABL protein, is active against all imatinib-resistant BCR-ABL mutations. Nilotinib was given 800 mg per day as NCCN recommendation.^{13,14}

Giles FJ (2010) et al, gave nilotinib 600 mg twice daily to 39 patients with imatinib treatment failure. After 18 months, patients with complete CyR were 24%. The observation from this study that some patients achieved response with nilotinib, tyrosine kinase inhibitor with increased selectivity for bcr-sbl. While nilotinib is similarly active in CML patients who have a imatinib failure, these agents have a distinct adverse event profiles, which reflect their different kinase inhibition profiles.^{15,16}

Another study from Giles FJ (2013), included 321 patients; 59% patients achieved major cytogenetic response and 45% achieved

complete CyR while on study. The estimated rate of overall survival and progression-free survival at 48 months was 78% and 57%, respectively.¹⁷

Third-line treatment with Bosutinib

Bosutinib, a second-generation dual inhibitor of SRC/ABL kinases, is currently approved in Europe and USA for treatment of adult patients with CML chronic phase, accelerated phase and blast phase. Bosutinib has very potent inhibition against activity of SRC and ABL kinase. Golas documented potent and antiproliferative and pro-apoptotic activity of bosutinib against CML culture (K562, KU812 and Meg-01).¹⁸ Cortes et al (2010)

Test results	Treatment options
Complete cytogenetic response or <i>BCR-ABL</i> ≤1% but >0.1% by QPCR using the International Scale	Stay on same dose of current TKI
Partial cytogenetic response or <i>BCR-ABL</i> <10% but >1% by QPCR using the International Scale	Maybe <i>BCR-ABL</i> gene mutation test, and discuss taking your TKI the right way and all medicines you take <ul style="list-style-type: none"> Switch to different TKI other than imatinib (preferred) Stay on same dose of current TKI Increase imatinib dose up to 800 mg as tolerated (if other TKI or omacetaxine isn't a good option)
Less than a partial cytogenetic response or <i>BCR-ABL</i> >10% by QPCR using the International Scale	Need <i>BCR-ABL</i> gene mutation test, and discuss taking your TKI the right way and all medicines you take <ul style="list-style-type: none"> Switch to a different TKI other than imatinib Clinical trial And, discuss HCT
Cytogenetic relapse	Need <i>BCR-ABL</i> gene mutation test, and discuss taking your TKI the right way and all medicines you take <ul style="list-style-type: none"> Switch to different TKI other than imatinib (preferred) Increase imatinib dose up to 800 mg as tolerated (if other TKI or omacetaxine isn't a good option) Clinical trial And, discuss HCT

Figure 1. Recommendation CML treatment follow-up from NCCN 2016.²²

Primary treatment	Second-line treatment options	Next treatment options	
Imatinib	Dasatinib	Nilotinib or Bosutinib or Ponatinib	
	Nilotinib		Dasatinib or Bosutinib or Ponatinib
	Bosutinib		Dasatinib or Nilotinib or Ponatinib
Dasatinib	Nilotinib	Bosutinib or Ponatinib	
	Bosutinib	Nilotinib or Ponatinib	
Nilotinib	Dasatinib	Bosutinib or Ponatinib	
	Bosutinib	Dasatinib or Ponatinib	

- Clinical trial
- Discuss HCT based on response
- Omacetaxine

Figure 2. NCCN recommendation for second-line treatment in TKI's resistance.²²



gave bosutinib 500 mg/day for 288 CP-CML patients previously treated and were intolerant or resistant to Imatinib. After 24 months follow-up, 86% patients achieved complete hematologic remission and 53 % had major cytogenetic response (MCyR), 41% has a complete CyR. This study showed that bosutinib was effective against all phases of intolerant or resistant CML with gene mutation. Bosutinib was active as a third-line agent in patient who failed imatinib followed by dasatinib or nilotinib.¹⁹

Recommendation of second-line treatment

The detection of primary or secondary imatinib resistance should promptly change the treatment. NCCN has published recommendation for secondary treatment for imatinib failure. Patient with primary resistance or patients who lost a hematological or cytogenetic response or who progress to advanced disease during imatinib therapy, must be switched to dasatinib, nilotinib or bosutinib. Secondary resistance may be

considered after high-dose imatinib (600-800 mg per day).²⁰⁻²²

Mutations of BCR-ABL must be used as a guide to select second-line therapy. Dasatinib, nilotinib, and bosutinib have a different activity against specific mutations. Result from mutation screening may be used to choose between treatment. Dasatinib is most appropriate for patient with F359C/V mutation, nilotinib is for patient with F317L mutations, whereas bosutinib is effective against another BCR-ABL mutations.^{22,23}

Another recommendation also published from ESMO. In case of imatinib intolerance, switch to another TKI, taking into consideration the side effects of the first TKI, and comorbidities. In case of failure of imatinib, switch to nilotinib, or dasatinib, taking into consideration the presence and the type of BCR-ABL KD mutation. In case of failure of nilotinib or dasatinib, taking into consideration the presence and the type of

BCR-ABL KD mutation, consider alloHSCT.²⁴

Alberta Health Service also give a recommendation on treatment options following inadequate response to standard imatinib dose. Imatinib dose escalation, switch to second-generation TKI (nilotinib, bosutinib, ponatinib) are still being a choice for imatinib inadequate response.²⁵

Conclusion

Imatinib resistance has been a problem in CP CML treatment, either primary or secondary resistance. There is no guideline for standard second-line treatment due to imatinib resistance. The best action is check for compliance, adherence of patients and also BCR-ABL gene mutation, and then choose the second-line treatment recommendation from NCCN, ESMO or Alberta Health Service, which are high-dose imatinib therapy, change to dasatinib, nilotinib or bosutinib.

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