

Combating Drug Resistant Chronic Myelogenous Leukemia with Jak2 Kinase Inhibition

Development of drug resistance is a major reason for treatment failure in cancer therapy. Imatinib resistance in chronic myelogenous leukemia (CML) is a good example of acquired drug resistance. CML is characterized by unregulated proliferation of myeloid cells and by the Philadelphia (Ph) chromosome,¹ which contains the translocated Bcr-Abl fusion gene.² Imatinib (GleevecTM) has become the standard therapy for CML treatment³ because imatinib can inhibit the kinase domain of Bcr-Abl, and inhibit the unregulated proliferation of CML cells;⁴ however, evidence of imatinib resistance in CML cells has been reported.⁵

In addition to mutations within the imatinib binding site, mutations on Bcr-Abl outside of the binding site can cause imatinib resistance, because these mutations alter the conformation of Bcr-Abl protein and stabilize its active conformation. Alternatively, Bcr-Abl gene amplification can contribute to imatinib resistance.⁶ Moreover, it has been postulated that there are off-target resistance mechanisms in drug resistant CML. The expression of the multidrug resistance protein-1 and the overexpression and activation of certain proteins such as Lyn kinase are good examples of off-target resistance mechanisms.⁷ Thus far, alternative Bcr-Abl kinase inhibitors have been considered the most promising strategy for combating imatinib resistance.⁸

Dasatinib is a drug for the treatment of on-target imatinib-resistant and off-target imatinib-resistant CML, such as Lyn kinase overexpression.⁹ Because unlike imatinib, dasatinib can bind to the active conformation of Bcr-Abl⁹ and Lyn kinase. Although dasatinib has activity against most kinase domain mutants, it cannot inhibit the T315I mutation of Bcr-Abl. Dasatinib also has its own specific mode of binding; it is possible that there are many undiscovered sites other than T315I.⁸ Also, CML still has a potential to generate off-target dasatinib resistance. Therefore, other strategies are clearly required to address resistance caused by the T315I mutant and possible off-target dasatinib resistant CML.¹⁰

Current research of the Bcr-Abl kinase signaling pathway leads to the hypothesis that Jak2 kinase can be utilized as an alternative target for drug resistant CML. Lim *et al.* discovered SHP1 has inhibitory activity against Bcr-Abl through a recombinant tyrosine phosphatase ABD/SHP1c. By fusing the catalytic domain of SHP1 (SHP1c) to the Abl binding domain (ABD), they inhibited the Bcr-Abl activity.¹¹ The Bcr-Abl inhibitory effect of SHP1 was further validated by immunoprecipitation.¹² Also, SET inhibition of PP2A has been demonstrated by Li and coworkers.¹³ Neviani *et al.* discovered the relationship among SET, PP2A, and SHP1 via shRNA and immunoprecipitation experiments.¹⁴ Additionally, Samanta *et al.* discovered that Jak2 siRNA decreases the expression level of SET kinase.¹⁵ From these results, we can construct Jak2-SET-PP2A-SHP1-Bcr-Abl signaling pathway, and this signaling pathway can be further validated with Jak2 inhibitors.¹⁵

Because Jak2 kinase has a key role in the Bcr-Abl/Lyn/Akt signaling pathway, we may be able to address on-target and off-target drug resistance problems with Jak2 kinase inhibitors. Further validation of Jak2 kinase inhibition as an alternative or complementary approach may lead to novel chemotherapeutic strategy for drug resistant CML.

Reference

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