"Development of a Fast, Sensitive, and Cost-Effective Detection Method for T315I Mutation in Tyrosine Kinase Inhibitor Resistance for Chronic Myeloid leukemia Patients"

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ABSTRACT

The detection of the BCR-ABL fusion gene and the identification of tyrosine kinase inhibitor (TKI) mutations are essential for the treatment of chronic myeloid leukemia (CML). The constitutively active tyrosine kinase encoded by BCR-ABL fusion gene is responsible for the uncontrolled growth of myeloid cells. The management of CML is severely restricted by the development of TKI resistance brought on by mutations in the ABL kinase domain. To enhance patient outcomes, early detection of resistance mutations allows for beneficial changes, such as switching to different TKIs or combination therapies. For this reason, our research aimed to develop a new technique for the early and more sensitive detection of TKI mutations using RT-PCR instead of Sanger Sequencing. As a proof of concept, we developed ARMS based RT-PCR to detect the most common BCR-ABL mutation T315I. The sensitivity of our method is 0,1 mutant copies in 70000 wild type copies which is far higher than Sanger sequencing. Twenty patients that had persistently detected BCR-ABL fusion transcripts were tested by our new method. Four of our patients (20%) were positive for T315I mutation. These patients were tested for BCR-ABL mutations using Sanger sequencing and only one showed a positive result. When we tested samples from this positive case retrospectively, our

method gave a positive result two years earlier than Sanger sequencing could detect. In conclusion, our method is a very sensitive and specific method that can detect BCR-ABL T315I mutation earlier than can Sanger sequencing, which can lead to better disease treatment and management.