Biomarker Assay for Residual Chronic Myeloid Leukemia Stem/Progenitor Cells during Treatment with ABL-Tyrosine Kinase Inhibitors

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Abstract

The use of tyrosine kinase inhibitors (TKI) such as imatinib mesylate (IM) targeted against BCR-ABL has proven successful in chronic myeloid leukemia (CML) and long-term survival has become a reality. However, several mathematical models and ex-vivo examinations suggested that IM-therapy does not eradicate CML stem cells. We recently reported the investigation of residual CML diseases during TKI treatment using FACS-sorting and quantitative RT-PCR of BCR-ABL among each population; total mononuclear cells, hematopoietic stem cells, and myeloid progenitors. Moreover, we need to develop the evaluation method of the residual CML stem cells to establish rational TKI-cessation strategies in CML.

Keywords: BCR-ABL; Chronic myeloid leukemia; Leukemia stem cells; Tyrosine kinase inhibitors

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder that is characterized by the presence of a fusion oncogene, BCR-ABL, which encodes a protein with constitutive tyrosine kinase activity [1]. The mechanisms for TKI insensitivity of CML stem remains unclear; factors such as quiescence, high level of BCR-ABL expression, acquired mutations in the oncogene, and overexpression of membrane transporter proteins in these cells may play a role [2-4].

In a more recent study, the nonrandomized Stop Imatinib (STIM) study, IM treatment was discontinued in patients with CML who had achieved complete molecular remission (CMR) of more than 2-year duration [17]. Of the 69% of patients with complete follow-up, 61% relapsed from CMR states (nevertheless, all patients who relapsed responded safely to the reintroduction of IM). The remaining patients maintained CMR states, suggesting that TKI treatment may cure some proportion of patients with CML [18,19] Ross et al. proposed the sensitive measurement of minimal residual disease using genomic PCR method with patient-specific primers [20]. Moreover, we need to develop the evaluation method of the residual CML stem cells to establish rational TKI-cessation strategies in CML.

Acknowledgements

The preparation of this review was partially supported by Grants-in-Aid from the National Institute of Biomedical Innovation and from the Ministry of Education, Culture, Sports, Science and Technology on Scientific Research, Japan.

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Received April 22, 2012; Accepted May 05, 2012; Published May 12, 2012

Citation: Minami Y, Naoe T (2012) Biomarker Assay for Residual Chronic Myeloid Leukemia Stem/Progenitor Cells during Treatment with ABL-Tyrosine Kinase Inhibitors. J Mol Biomarkers Diagn 5/8:001. doi:10.4172/2155-9929.5/8-001

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Conflict of Interest Disclosure

T Naoe received research grants from Janssen, Novartis, Kyowa-Hakko Kirin, Bristol-Myers Squibb and Chugai. They did not in any way influence the content of the paper. Y Minami declares no conflict of interest.

References


Figure 1: CML-CP stem cells and leukemic myelopoesis.

- Schematic representation showing myelopoiesis in normal adults. Surface markers, such as CD34 and CD38 are differentially expressed upon differentiation.
- Schematic representation showing how leukemic myelopoiesis is differently deregulated at different stages of hematopoiesis in patients with CML-CP. (Adapted from ref. 6.)
Figure 2: Representative analysis of HSC/Progenitors in CML-CP bone marrow cells. Using FACSaria, in CML-chronic phase (CP) bone marrow cells, we examined CD34+38- and CD34+38+ populations, and analyzed BCR-ABL transcripts among each sorted population: total mononuclear cells, HSC/Thy-1+, HSC/Thy-1−, common myeloid progenitors (CMP), granulocyte macrophage progenitors (GMP) and megakaryocyte erythroid progenitors (MEP).