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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 normal, myelopoiesis is sustained through the life by the regulated proliferative and differentiation activity of a large pool of hematopoietic stem cells (HSCs) (Figure 1A). Cells within hematopoietic hierarchy can be distinguished by their proliferative and differentiation activity which they display under conditions designed to optimally elicit these, either *in vivo* (where the most primitive cells are called long-term repopulating cells, LTRCs) or *in vitro* (as long-term culture-initiating cells, LTC-ICs and CFCs) [5,6]. Surface markers, such as CD34 and CD38 are differentially expresses upon differentiation, progenitors being mostly $CD34^{+}CD38^{+}$ and HSCs exclusively $CD34^{+}CD38^{-}$ [7]. In patients with CML-chronic phase (CP), normal and leukemic cell population co-exist (Figure 1B) [1,4,8,9]. In the stem cell compartment, normal HSCs often outnumber the small numbers of their leukemic counterparts. However, current evidence suggests that the normal HSCs are outcompeted by the CML stem cells when these begin to proliferate and differentiate which the CML stem cells also attempt more frequently due to their higher turnover and increased probability of differentiation. The autocrine secretion of IL-3 and Granulocyte colony stimulating factor (G-CSF) by primitive leukemic progenitors likely contributes to growth advantage of leukemic myeloid progenitors and mature cells in patients resulting in their dominance of peripheral blood and bone marrow of newly diagnosed CML patients with mature CML cells [6].

The use of tyrosine kinase inhibitors (TKI) such as imatinib mesylate (IM) targeted against BCR-ABL has proven successful in CML and long-term survival has become a reality [10,11]. However, several mathematical models and *ex-vivo* examinations suggested that imatinib (IM) therapy does not eradicate CML stem cells [3,8,12-14]. We recently reported a method for investigation of CML-CP cases during TKI treatment using FACS-sorting and quantitative RT-PCR of *BCR-ABL* among each population; total mononuclear cells, HSC, and myeloid progenitors (Figure 2) [9,15,16]. From each population, we collected at least 5,000 cells (most samples were over 20,000 cells), and the limited number of sorting cells was one critical reason for the methodological limitation regarding subtle quantitative evaluation. In the HSC population by this method, more than 30% cells are supposed to have stem cell potential, likely as LTC-ICs (Figure 1B). In optimal responders to IM therapy, *BCR-ABL* transcripts in the HSC populations tended to be more retentive than other populations. Treatment with the second-generation of ABL-tyrosine kinase inhibitors (2nd TKIs), dasatinib or nilotinib induced more rapid reduction of *BCR-ABL* transcripts even in the HSC population, which implied that second TKI therapy can be a more promising approach than IM treatment for early reduction of CML stem cells [16].

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.

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Conflict of Interest Disclosure

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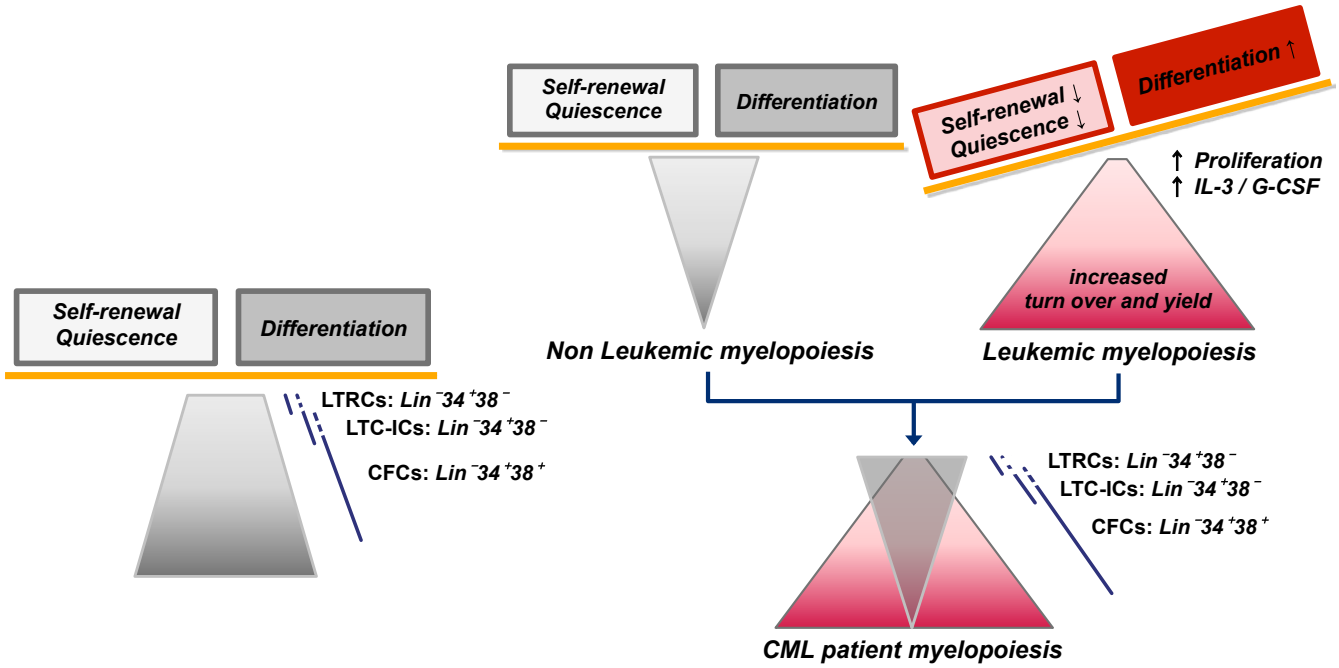

Figure 1: ***CML-CP stem cells and leukemic myelopoiesis.***
(A) Schematic representation showing myelopoiesis in normal adults. Surface markers, such as CD34 and CD38 are differentially expressed upon differentiation.
(B) Schematic representation showing how leukemic myelopoiesis is differently deregulated at different stages of hematopoiesis in patients with CML-CP. (Adapted from ref. 6).

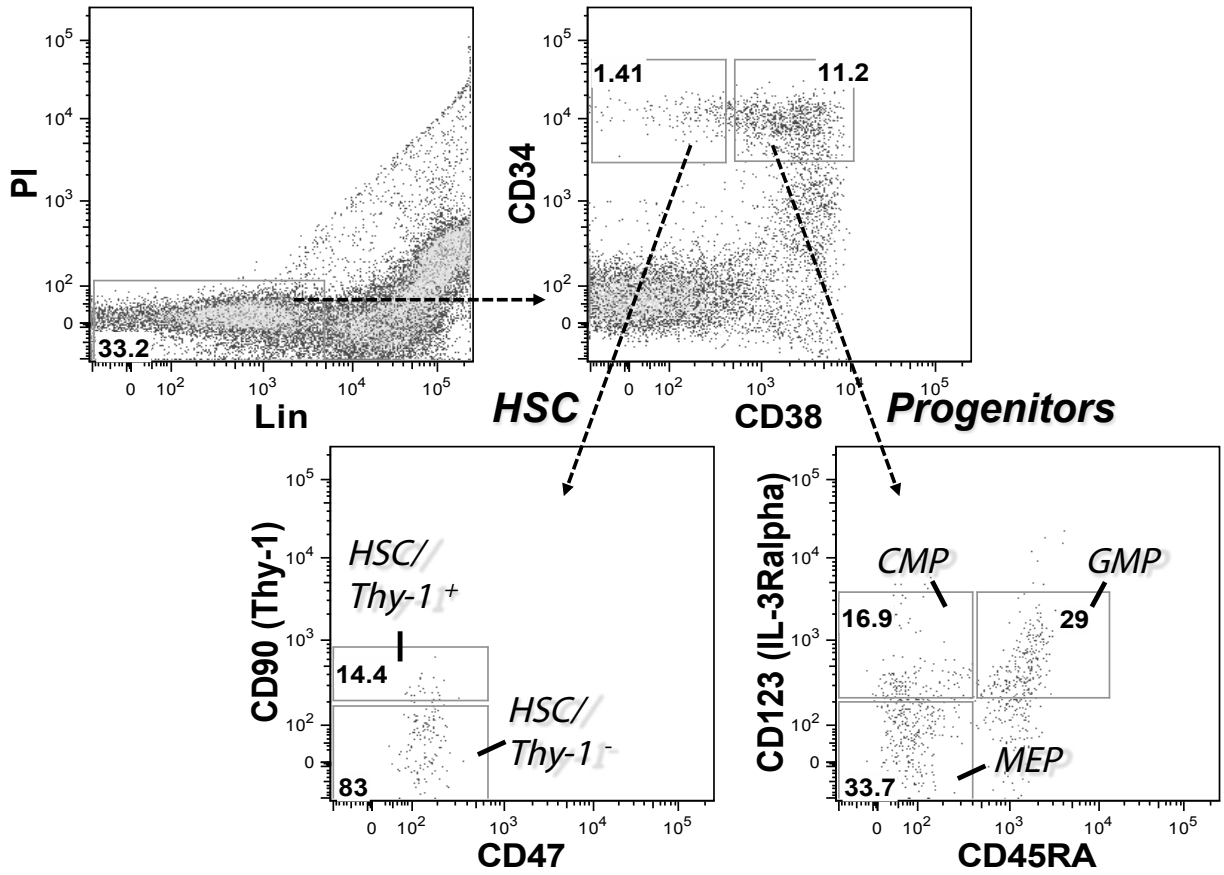

Figure 2: ***Representative analysis of HSC/Progenitors in CML-CP bone marrow cells.*** Using FACSAria, in CML-chronic phase (CP) bone marrow cells, we examined $CD34^{+}38^{-}$ and $CD34^{+}38^{+}$ populations, and analyzed *BCR-ABL* transcripts among each sorted population; total mononuclear cells, HSC/Thy-1^{+}, HSC/Thy-1^{-}, common myeloid progenitors (CMP), granulocyte macrophage progenitors (GMP) and megakaryocyte erythroid progenitors (MEP).

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