Chronic myelogenous leukemia (CML) is a clonal myeloproliferative neoplasm that is caused by generation of a BCR-ABL1 fusion gene encoding a constitutively active tyrosine kinase (1). The discovery of small molecule tyrosine kinase inhibitors (TKIs) targeting ABL1 tyrosine kinase, such as the first-generation TKI imatinib mesylate (IM) and the second-generation TKIs dasatinib, nilotinib and bosutinib, has dramatically improved the prognoses of CML patients (1,2). However, long-term treatment with TKIs does not appear to completely cure most CML patients (3-9), and the majority continues on these therapies for fear of suffering a relapse if they stop their treatment. Thus, it has become important to provide CML patients with solid information and some hope that they can eventually safely discontinue or finish their TKI therapy regimens, which have side-effects and are expensive.

The “Stop IM” (STIM) trial conducted by Mahon et al. investigated if and how treated CML patients could maintain a cure after stopping TKI therapy. Importantly, the results of this ground-breaking effort indicated that 39% of CML patients who underwent IM treatment and had achieved deep molecular response (DMR) for at least 2 years did not show any signs of disease relapse. Thus, even after it is stopped, dasatinib treatment may decrease the chance of disease relapse and provide a curative benefit to CML patients. This work by Imagawa et al. strongly supports the clinical utility of the second-generation TKI dasatinib for CML treatment.

Keywords: Chronic myelogenous leukemia (CML); tyrosine kinase inhibitor (TKI) therapy; dasatinib discontinuation (DADI); deep molecular response (DMR)

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Dasatinib interacts with both the active and inactive conformations of the ABL1 tyrosine kinase, whereas IM binds only to the catalytically inactive form (15). Indeed, dasatinib inhibits not only ABL1 kinase, but also cKIT, PDGF, ephrin receptor kinase, SRC, and the Src family kinases FGR, FYN, HCK, LCK and YES (15). Importantly, dasatinib may also be implicated in suppressing signal transduction in cells on the immune system.

Previous studies have indicated that the CML patients who have the most favorable prognoses following dasatinib therapy are those bearing a relatively high number of large granular lymphocytes (16-18). In the STIM trial, the CML patients with the best prognoses after cessation of IM therapy had an increased number of natural killer (NK) cells (10). In same vein, Imagawa et al. found that a high frequency of NK cells was associated with improved treatment-free survival of CML patients after DADI (14). The molecular mechanism by which dasatinib might regulate NK cell survival, and how high numbers of these NK cells contribute to the suppression of CML disease relapse, are mysteries. Nevertheless, these results suggest that NK cell-based immune surveillance may play an important role (Figure 1).

Dasatinib to exert inhibitory activity on a broad spectrum of kinases (15). Indeed, dasatinib inhibits not only ABL1 kinase, but also cKIT, PDGF, ephrin receptor kinase, SRC, and the Src family kinases FGR, FYN, HCK, LCK and YES (15). Importantly, dasatinib may also be implicated in suppressing signal transduction in cells on the immune system.

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It is now widely accepted that CML is a stem cell disorder whose cell-of-origin is the normal hematopoietic stem cells (HSCs) (1). It has recently been shown that quiescent CML stem cells are insensitive to TKI therapy, and that reprotole of these residual CML stem cells is responsible for CML recurrence following TKI therapy (19). Interestingly, administration of dasatinib alone can eliminate the CML stem cell population in a murine CML model (20). It remains unclear whether dasatinib directly eradicates CML stem cells through an off-target effect, or whether dasatinib's enhancement of the NK cell population supports an innate immune response that contributes to CML stem cell eradication; indeed, both mechanisms may be involved.

In addition, IM treatment has been shown to deplete the highly suppressive FoxP3+ regulatory T (Treg) cells in CML patients, thereby allowing anti-cancer immune responses to proceed fully and deliver a therapeutic effect (21). Dasatinib can also suppress Treg cells (22), although the molecular mechanism by which TKIs might inhibit a kinase activity responsible for controlling Treg functions is elusive. Thus, further investigations of the effects of dasatinib on immune suppression/tolerance and/or the self-renewal capacity of CML stem cells may yield tangible contributions to the early diagnosis of disease recurrence in CML patients. Moreover, a combination of dasatinib plus a novel agent supporting CML immunotherapy or CML stem cell therapy may constitute.
a new approach to preventing CML relapses in the future. Of note, a new version of a DADI trial (UMIN000011099) is under way for CML patients who have received at least 3 years of first-line dasatinib therapy and have maintained DMR for at least the last 12 months. Based on the work of Imagawa et al., a large proportion of patients in this trial can expect a significant curative benefit even after they stop their TKI therapy. The future looks bright for advances in CML TKI-based treatments.

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Footnote

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