Original Study

Final 3-year Results of the Dasatinib Discontinuation Trial in Patients With Chronic Myeloid Leukemia Who Received Dasatinib as a Second-line Treatment

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Final Results of Dasatinib Discontinuation in CML Patients

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Abstract

We describe the results of a prospective trial of the discontinuation of second-line dasatinib treatment in chronic myeloid leukemia patients who maintained a deep molecular response for > 1 year. The treatment-free remission rate at 36 months was 44.4%. High natural killer cell counts before discontinuation correlated significantly with successful therapy discontinuation.

Introduction: We previously reported an interim analysis of the DADI (dasatinib discontinuation) trial. The results showed that 48% of patients with chronic myeloid leukemia in the chronic phase who maintained a deep molecular response (DMR) for ≥ 1 year could discontinue second- or subsequent-line dasatinib treatment safely at a median follow-up of 20 months. However, the results from longer follow-up periods would be much more useful from a clinical perspective. **Patients and Methods:** The DADI trial was a prospective, multicenter trial conducted in Japan. After confirming a stable DMR for ≥ 1 year, dasatinib treatment subsequent to imatinib or nilotinib was discontinued. After discontinuation, the loss of DMR (even of 1 point) was defined as stringent molecular relapse, thereby triggering therapy resumption. The predictive factors of treatment-free remission (TFR) were analyzed. **Results:** The median follow-up period was 44.0 months (interquartile range, 40.5-48.0 months). The estimated overall TFR rate at 36 months was 44.4% (95% confidence interval, 32.0%-56.2%). Only 2 patients developed a molecular relapse after the 1-year cutoff point. The presence of imatinib resistance was a significant risk factor for molecular relapse. Moreover, high natural killer cell and low $\gamma\delta^+$ T-cell and $CD4^+$ regulatory T-cell ($CD25^+CD127^{low}$) counts before discontinuation correlated significantly with successful therapy discontinuation. **Conclusion:** These findings suggest that discontinuation of second- or subsequent-line dasatinib after a sustained DMR of ≥ 1 year is feasible, especially for patients with no history of imatinib resistance. In addition, the natural killer cell count was associated with the TFR.

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Keywords: CML, DADI, Natural killer cell, Stop trial, Treatment-free remission

Introduction

Second-generation tyrosine kinase inhibitors (TKIs), including dasatinib and nilotinib, are better at inhibiting BCR-ABL kinase activity than the first-generation TKI imatinib mesylate. Second-generation TKIs were introduced initially as a second-line treatment for the patients with disease resistant or who were intolerant to imatinib and resulted in a remarkable response rate.[1] Because subsequent studies demonstrated that second-generation TKIs show superior efficacy to imatinib for newly diagnosed chronic myeloid leukemia (CML),[2,3] their use as a first-line treatment has increased.

TKIs have dramatically improved the life expectancy of patients with CML, with a recent study showing that the survival of CML patients will be determined more by comorbidities than by the CML itself.[4] This situation has highlighted the adverse events associated with the long-term administration of TKIs, which include cardiovascular disease.[5] To date, a number of clinical trials have been conducted to investigate the feasibility of discontinuing imatinib for patients who have achieved a durable deep molecular response (DMR). The pioneering STIM (stop imatinib)[6] and TWISTER[7] trials, in which CML patients discontinued imatinib after ≥ 2 years of molecular remission at the level of MR4.5 (*BCR-ABL1* transcript levels of ≤ 0.0032% standardized to the International Scale [IS]) or deeper, showed that ~40% of the patients maintained molecular remission (ie, entered a period of treatment-free remission [TFR]).

Although accumulating evidence has shown that discontinuing imatinib is feasible, trials of patients receiving second-generation TKIs are lacking. Therefore, we conducted a phase II trial to investigate whether long-term TFR was achievable after discontinuing second- or subsequent-line dasatinib treatment after imatinib resistance or intolerance (the DADI trial [dasatinib discontinuation]). Dasatinib was discontinued in patients who had achieved DMR (*BCR-ABL1* 0.0069% IS) for ≥ 1 year. We previously reported the results of an interim analysis of a study with a median follow-up period of 20 months after dasatinib discontinuation.[8] Recently, the long-term follow-up results of an imatinib stop trial (STIM1) were reported, in which no molecular recurrence was observed after 22 months.[9] However, the long-term follow-up results of second-line TKI stop trials have scarcely been reported. Thus, it is important to examine whether long-term remission can be maintained in second-line treatment settings. We report the final, planned 3-year analysis of the DADI trial (Japan Primary Registries Network no. UMIN000005130).

Patients and Methods

Study Patients

Patients with CML in the chronic phase who were undergoing second- or subsequent-line dasatinib therapy after receiving imatinib were eligible if they had achieved a DMR (before registration). Patients were also required to be aged ≥ 15 years, with adequate