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Research paper

Regulatory T cell inhibition by dasatinib is associated with natural killer cell differentiation and a favorable molecular response—The final results of the D-first study

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ABSTRACT

We evaluated the effects of regulatory T cell (Treg) inhibition during dasatinib treatment on the anticancer immune response, particularly on natural killer (NK) cells and cytotoxic T lymphocytes (CTLs). Fifty-two newly diagnosed Japanese patients with chronic myeloid leukemia (CML) in the chronic phase were enrolled in the D-first study; all received 100 mg of dasatinib once daily and were followed for at least 36 months. The cumulative deep molecular response (DMR, MR4) rate was 65% by 36 months; the 3-year overall survival was 96%. $CD4^+$ T cell counts were stable, whereas the proportion of $CD4^+CD25^+CD127^{low}$ (Treg) cells decreased in a time-dependent manner. The DMR rate by18 months was significantly better in low Treg patients (< 5.7% at 12 months) compared to the remaining patients (odds ratio 4.07). NK cell and CTL counts at several time points were inversely correlated with Treg counts. Furthermore, the degree of NK cell differentiation ($CD3^-CD57^+$/$CD3^-CD56^+$) was closely and inversely correlated with the proportion of Treg cells throughout the observation period, and showed a gradually increasing trend. In conclusion, our results demonstrate that Treg inhibition by dasatinib contributes to better treatment response through enhancement of the immune system, particularly via NK cell differentiation.

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1. Introduction

Dysregulation of the immune system plays a critical role in malignant disease progression [1]. Regulatory T cells (Tregs) have a pivotal role in cancer immunology [2]; several studies revealed that Treg infiltration into the tumor microenvironment is strongly associated with poor clinical outcomes [3–9]. Therefore, several cancer immunotherapeutic approaches based on the inhibition of Tregs are being clinically tested. Successful clinical trials that evaluated the benefit of immune-checkpoint inhibitors, including an anti-CTLA-4 monoclonal antibody, support a new strategy of targeting regulatory immune cells, which can achieve drastic anti-tumor results in selected patients with advanced tumors [10,11]. However, the impact of peripheral blood Tregs on long-term outcomes of patients with leukemic diseases, including chronic myeloid leukemia (CML), has not been fully evaluated.

The development of tyrosine kinase inhibitors (TKIs) has dramatically improved the outcomes of patients with CML in the chronic phase (CP-CML), which is caused by a *BCR-ABL1* chromosomal translocation (the Philadelphia chromosome) [12–14]. Dasatinib, a second generation BCR-ABL1 kinase inhibitor, is more effective against CP-CML than the first generation inhibitor imatinib [15]. In addition to direct antitumor effects by blocking tyrosine kinase, dasatinib also possesses an immunomodulating effect that may enhance its anti-tumor activity [16,17]. Importantly, it has been shown that the proportion of Tregs is reduced during dasatinib therapy, particularly in patients with lymphocytosis; this is evidence of an immune response against Philadelphia chromosome-positive leukemias [16].

Achievement of a deep molecular response (DMR) is an important CP-CML treatment goal, as it enables the achievement of long-term treatment-free remission in some patients who are receiving TKIs such as imatinib [18–21], dasatinib [22], and/or nilotinib [23]. However, the prognostic markers for predicting DMR have not been established. We previously reported that a shorter halving time of *BCR-ABL1* transcripts and early cytotoxic lymphocyte expansion were associated with the achievement of DMR in newly diagnosed CP-CML patients treated with dasatinib [24,25]. Herein, the long-term results of the D-first study were analyzed after a minimum follow-up period of 36 months. We prospectively investigated the impact of the proportions of lymphocyte subsets on the response to dasatinib treatment, as well as the association between Tregs, cytotoxic lymphocyte proliferation, and natural killer (NK) cell differentiation.

2. Patients and methods

2.1. Study design

This open-label, multicenter, prospective phase II clinical trial, the 'D-first study' (ClinicalTrials.gov identifier: NCT01464411), was conducted by the Kanto CML study group. Detailed information regarding the study design and patient characteristics were described previously [24]. Briefly, 52 patients with newly diagnosed CP-CML were enrolled between June 2011 and June 2012, and were treated with dasatinib 100 mg once daily. All patients were followed for a minimum of 36 months. This study was approved by the research ethics boards of all participating institutions, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients prior to enrollment.

2.2. Evaluation of treatment response and molecular analysis

Patients were assessed for molecular response before and 1, 3, 6, 9, 12, 15, 18, 24, and 36 months after commencing dasatinib treatment by real-time quantitative polymerase chain reaction (PCR) analysis of *BCR-ABL1* transcripts standardized on an International Scale (BCR-ABL1 IS). The primary endpoint of the study was the rate of DMR achievement by 18 months; DMR was defined as less than 50 copies of *BCR-ABL1* transcript per microgram of RNA, normalized to *GAPDH*, which ensured a BCR-ABL1 IS of < 0.01% (MR4). Immunophenotyping of lymphocyte fractions in the peripheral blood samples was performed by flow cytometry before and 1, 2, 3, 6, 9, 12, 15, 18, 24, and 36 months after commencing dasatinib treatment at a centralized laboratory (Bio Medical Laboratories (BML), Tokyo, Japan).

2.3. Flow cytometric analysis of lymphocytes

Isotype controls were used to set gating boundaries. The $CD4^+$ lymphocyte count was calculated by multiplying the total lymphocyte count by the percentage of the $CD4^+$ lymphocyte subset. Immunophenotyping of lymphocyte fractions in the fresh peripheral blood samples was performed before and 1, 2, 3, 6, 9, 12, 15, 18, 24, 36 months after commencing dasatinib treatment at BML. Lymphocytes were classified according to their immunophenotypes as determined by flow cytometry (FACSCalibur, Becton–Dickinson, NJ), as described previously [26]. Cytotoxic T lymphocyte (CTL) lineages were defined according to the expression of $CD3^+CD8^+$; NK cells were identified as $CD3^-CD56^+$, and differentiated NK cells were $CD3^-CD57^+$. Tregs were defined as lymphocytes with $CD4^+CD25^+CD127^{low}$ expression.

2.4. Statistical analysis

The results are shown as mean values ± standard errors of the mean. The correlation between 2 factors was evaluated with the Pearson product-moment correlation coefficient. The 2-tailed Fisher's exact test was used to determine statistical significance; a p-value less than 0.05 was considered a statistically significant result. Receiver operating characteristic (ROC) curves were generated, and area under the curve (AUC) values were used to evaluate the correlations between the expression of Tregs and prognosis. The optimal thresholds along the ROC curves were determined using the Youden index. The statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing) [27].

3. Results

3.1. Efficacy and safety profile of first-line dasatinib treatment in Japanese CP-CML patients

The findings following the first 18 months of dasatinib treatment in our patients have been reported previously [24]. In this study, we analyzed the final outcomes after at least 36 months of follow-up, at which time 40 of the 52 patients (77%) were still undergoing dasatinib treatment. The reasons for drug discontinuation in the remaining patients are listed in Table 1; 9 patients (18%) had discontinued dasatinib by 36 months due to drug-related non-hematologic adverse events, while another 3 (6%) requested switching from dasatinib to another

Table 1
Treatment status and reasons for dasatinib discontinuation at 36 months.

Status at 36 months	Patients, n (%)
Received treatment	52 (100)
Still on treatment.	40 (77)
Discontinued treatment	12 (23)
Drug-related adverse event	
Pleural effusion	3 (6)
Pericardial effusion	1 (2)
Proteinuria & systemic edema	1 (2)
Pulmonary hypertension	1 (2)
Malaise	1 (2)
Elevation of intraocular pressure	1 (2)
Interstitial pneumonia	1 (2)
Requested to change medication	3 (6)

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