Characteristics of Patients With Development of Large Granular Lymphocyte Expansion Among Dasatinib-Treated Patients With Relapsed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia After Allogeneic Stem Cell Transplantation

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Abstract

The current study assessed the efficacy and safety of dasatinib monotherapy for the 9 patients with relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia after allogeneic stem cell transplantation. Six of 9 patients manifested large granular lymphocytes (LGLs) expansion accompanied by adverse events, but 3 of them have been alive with molecular complete remission and a persistent increase of LGLs.

Introduction: Widespread use of tyrosine kinase inhibitors (TKIs) in combination with chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-SCT) has totally changed the existing treatment strategies for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ALL). However, the prognosis after relapse after allo-SCT is still dismal. **Patients and Methods:** We analyzed the clinical outcome of therapy using dasatinib, a second-generation TKI, in 9 patients with relapsed Ph^+ALL after allo-SCT. Dasatinib was initiated at a median time of 168 days after allo-SCT at dosages ranging from 20 mg to 100 mg daily. **Results:** Six of 9 patients manifested a marked increase in large granular lymphocytes (LGLs), but all 6 patients discontinued dasatinib because of adverse events (AEs) such as pleural effusion. Four of 6 patients resumed dasatinib, and 3 of them have been alive with molecular complete remission and a persistent increase of LGLs. **Conclusion:** Our results demonstrated that dasatinib therapy can induce LGL expansion accompanied by AEs, but this phenomenon can be associated with long-term survival benefit in a proportion of relapsed Ph^+ALL patients after allo-SCT.

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Introduction

The Philadelphia chromosome is found in 20% to 30% of adults with acute lymphoblastic leukemia (ALL),[1-3] and the poor prognostic relevance of the Philadelphia chromosome-positive ALL (Ph+ALL) is well established. Therefore, it has long been concluded that the outcome with Ph+ALL chemotherapy alone is not sufficient to recommend allogeneic hematopoietic stem cell transplantation (allo-SCT) during first complete remission (CR).[4,5] Chemotherapy based on imatinib, a tyrosine kinase inhibitor (TKI) that targets BCR-ABL (protein with tyrosine kinase activity encoded by break point cluster region and proto-oncogene *ABL* hybrid genes), produces a very high CR rate in patients with Ph+ALL, although the treatment cannot provide a complete cure. Nonetheless, chemotherapy based on TKIs prepares a high proportion of patients with Ph+ALL for allo-SCT,[6-8] which results in improved outcomes.[6-10] Especially, Ravandi et al have reported that negative minimal residual disease (MRD) was closely associated with improved survival.[8] However, the prognosis after relapse after allo-SCT is dismal compared with that for other treatment modalities, including donor lymphocyte infusion and second allo-SCT.[11-13] Thus, novel approaches are needed to treat patients with relapsed Ph+ALL after allo-SCT.

Imatinib has also been used to treat recurrent leukemia after allo-SCT in Ph+ALL patients; however, the long-term disease-free survival (DFS) rate was only 5% if hematological relapse occurred after allo-SCT.[14] It was subsequently reported that MRD-guided imatinib therapy for early intervention Ph+ALL patients after allo-SCT might improve DFS, but approximately half of the treated patients still experienced a hematological relapse.[14] In addition, Kebriaei et al have reported that imatinib administration before or after allo-SCT had a significant effect on transplantation outcome.[15]

Dasatinib, the second-generation TKI, inhibits the BCR-ABL oncoprotein with much greater potency than imatinib. In addition, dasatinib demonstrates off-target kinase activity by also inhibiting SRC (protein encoded by proto-oncogene *SRC*) and LCK (lymphocyte-specific protein tyrosine kinase), for example, which have physiological functions in immune response.[16-18] Recent reports have indicated that dasatinib can induce large granular lymphocyte (LGL) lymphocytosis, whereas imatinib and nilotinib do not.[19-21] In addition, this phenomenon is closely correlated with favorable outcomes.[19,21] These results suggest that dasatinib monotherapy can be a more suitable candidate for treatment of imatinib-resistant Ph+ALL and relapse after allo-SCT.[16,22-25] Besides, other reports have also demonstrated the efficacy of dasatinib in combination with intensive chemotherapy for the patients with relapsed Ph+ALL and blastic crisis phase of chronic myelogenous leukemia (CML)[26,27]; however, the safety of dasatinib with intensive chemotherapy after allo-SCT still remains unknown. The aim of this study was to investigate the efficacy and safety of dasatinib monotherapy, including the immunological aspects, for the patients with molecular or hematological relapsed Ph+ALL after allo-SCT.

Patients and Methods

Patient Characteristics

We retrospectively analyzed the efficacy and safety of dasatinib therapy in 9 patients (median age, 55 years; range, 37-63 years; 6 male and 3 female) with relapsed Ph+ALL after allo-SCT between 2009 and 2012 at the Fukuoka Blood and Marrow Transplantation Group. This study was approved by the institutional review boards of the participating hospitals. Written informed consent was obtained from all patients. Patient characteristics are summarized in Table 1. The p190 (e1a2) and p210 (b2a2 or b3a2) *BCR-ABL* transcripts were expressed in 6 and 3 of the patients, respectively. Eight patients (Case 1, 2, 3, 5, 6, 7, 8, and 9) received induction therapy (daunorubicin, vincristine, cyclophosphamide, and prednisolone) with imatinib. After induction therapy, all of the patients received first consolidation therapy with high-dose cytarabine, mitoxantrone, and TKI. Subsequently, they received second consolidation with high-dose methotrexate, vincristine, and TKI; TKI included imatinib in 5 patients (Case 1, 5, 7, 8, and 9), and dasatinib in 3 patients (Case 2, 3, and 6). In addition, they received intrathecal administration of methotrexate. Case 4 was diagnosed as the relapsed Ph+ALL 23 years after the first allo-SCT. She received dasatinib at the dose of 140 mg orally daily and prednisolone as reinduction therapy.[28] She gained second CR and thereafter underwent the second allo-SCT. Patients with Ph+ALL were considered to be indicated for allo-SCT in CR as soon as possible. Conditioning before allo-SCT and prophylaxis for graft versus host disease (GVHD) was performed according to each institutional standard. The median duration from diagnosis to allo-SCT was 5 months (range, 4.5-160 months), and the median follow-up duration after allo-SCT was 21 months (range, 9-58 months). Before allo-SCT, 7 patients achieved a complete cytogenetic response (CCR; Case 1, 2, 4, 5, 7, 8, and 9), 1 patient relapsed (Case 3), and 1 patient did not achieve CR (Case 6). Three of the 7 patients who achieved CCR had undetectable MRD before allo-SCT (Case 4, 5, and 9), whereas the remaining 4 patients had detectable MRD (levels detected using polymerase chain reaction [PCR] analysis; Case 1, 2, 7, and 8). Related peripheral blood (PB) stem cell transplantation (PBSCT) was performed in 1 patient, unrelated bone marrow transplantation in four, unrelated PBSCT in 1, and unrelated umbilical cord blood transplantation in 3. Six patients developed acute Grade II to IV GVHD and 3 patients developed chronic GVHD (Table 1).

Clinical Laboratory Analyses and LGLs

Peripheral blood leukocyte morphology was analyzed from May–Grünwald–Giemsa-stained smears. During the dasatinib therapy, lymphocytes with typical LGL morphology were increased to 10% or more among PB leukocytes (normal range for LGL cells is 2%-6% among leukocytes[29]) in some cases. In other reports, LGL lymphocytosis was defined as an absolute increase in lymphocyte count (eg, $> 3.6 \times 10^9$/L, or institutional upper normal limit, with LGL morphology).[19] In our study, there were cases in which the recovery of white blood cell count was insufficient after allo-SCT; therefore, "increased LGL" was defined as an increase of LGL to more than 10% of the absolute PB leukocyte count. Immunophenotyping was done with flow cytometry using antibodies against the following antigens: CD3, CD4, CD8, CD16, CD45, CD56, CD57, human leukocyte antigen-DR, CD62L, CD45RA, CD45RO, T-cell receptor (TCR)-α/β and TCR-γ/δ with isotype controls. Examination of granzyme B and TCR gene rearrangement was not performed.

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