Successful treatment with ABL tyrosine kinase inhibitor for patients with acute myeloid leukemia with BCR-ABL1

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ABSTRACT

Acute myeloid leukemia (AML) with BCR-ABL1 is rare and has a poor prognosis with conventional chemotherapy or ABL tyrosine kinase inhibitors (TKIs) alone. We reported a case of AML with BCR-ABL1 patient who was successfully treated with dasatinib alone; additionally, we previously reported another case of long-term remission maintained with imatinib monotherapy. These results suggested that a treatment with a novel and significantly potent TKI may be effective in AML with BCR-ABL1 patients with low tumor burden and without additional chromosome aberrations and ABL kinase domain mutations.

1. Introduction

BCR-ABL1 (i.e., Philadelphia chromosome) is usually present in 90%–95%, 20%, and 5% of patients with chronic myeloid leukemia (CML), adult lymphoblastic leukemia/lymphoma (ALL), and pediatric ALL, respectively. However, it is also observed in less than 1% of de novo acute myeloid leukemia (AML). BCR-ABL1 observed during the course of hematopoietic malignancies is rare and is associated with poor prognosis [1-4]. Philadelphia chromosome-positive AML was a controversial entity, and it was not described as a distinct entity in the 2008 revision of the World Health Organization (WHO) classification [5]. During the past years, several case reports and reviews on Philadelphia chromosome-positive AML and myelodysplastic syndrome have been published, which is now included as a provisional entity, “AML with BCR-ABL1,” in the 2016 revised WHO classification of myeloid malignancies [6]. AML with BCR-ABL1 is considered an aggressive disease with poor response to traditional AML therapy or ABL tyrosine kinase inhibitor (TKI) therapy alone [6]. Recent reports suggest improved survival with TKI therapy followed by allogeneic hematopoietic stem cell transplantation (HSCT) [7]. On the contrary, molecularly targeted therapy including TKI is required in patients with organ complications or elderly patients who are not eligible for allogeneic HSCT. Previously, we had reported Philadelphia chromosome-positive AML patient who was treated with imatinib mesylate [8]. In that report, we concluded that the therapeutic effect of imatinib monotherapy on this disease was limited. However, more potent ABL inhibitors developed in recent years, including dasatinib, are expected to be more effective than the previous inhibitors for this disease.

Here, we reported a case of AML with BCR-ABL1 patient who was successfully treated with dasatinib alone. And we investigated the conditions of patients who could expect TKI treatment for AML with BCR-ABL1.

2. Case report

The patient was a 77-year-old female who was referred in September 2015 following the complaint of progressive pancytopenia. She had been followed up for 5 years in an outpatient clinic since she had undergone aortic prosthesis replacement, but evidence of a preceding CML was not observed in physical examination and blood examination 6 months before referral (Table 1). Physical examination revealed that hepatosplenomegaly and lymphadenopathy were not observed. Peripheral blood count showed pancytopenia without blast appearance (red blood cells, 2.54 × 10^{12}/L; hemoglobin, 8.1 g/dL; hematocrit value, 25.8%; white blood cells, 1.56 × 10^{9}/L; and platelet count, 82 × 10^{9}/L, in Table 1). Bone marrow aspiration was moderately hypocellular with myeloid hypoplasia. Blastic cells with vacuoles increased to 11.8%; these blasts were positive for myeloperoxidase and myeloid antigens cluster of differentiation (CD) 13, CD33, CD34, and human leukocyte antigen–DR isotype, but were negative for lymphoid antigens.

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of the reasons why dasatinib was effective in this patient is that it is a more potent ABL kinase inhibitor than imatinib [9]. Recently, ponatinib and bosutinib have been developed as significantly potent TKIs effective for leukemia with BCR-ABL1 [9]. These new generations of TKI will be a promising treatment agent against AML with BCR-ABL1 in the future.

Although the effect of TKI monotherapy on AML with BCR-ABL1 has been reported to be limited, long-term survival has been obtained with TKI treatment in our experienced cases [8]. A summary of the two cases of AML with BCR-ABL1 treated with TKI that we reported is shown in Table 2. In the case we reported previously, chemotherapy was required to achieve remission, but in both cases, maintenance therapy using TKI provided deep molecular remission and prevented the recurrence of the disease. Several reasons for the success of TKI treatment in AML with BCR-ABL1 are based from these two cases. The first reason is the low proportion of blasts in the bone marrow, which means that the tumor burden is low. AML with BCR-ABL1 is considered a heterogeneous disease entity, and bone marrow blast ratios have been reported from high to low cases. TKI monotherapy cannot be expected to achieve remission in patients with high tumor burden. The second reason is that there were no additional chromosomal abnormalities. Among AML with BCR-ABL1, cases with additional chromosomal abnormalities such as monosomy 7 or monosomy 5/del5q have been reported as having a poor prognosis [10]. The third reason is that there were no ABL kinase domain mutations conferring resistance to TKI treatment. Some ABL kinase domain mutations are effective in 2nd or 3rd generation TKIs such as dasatinib or ponatinib, but there are also mutations that are resistant to TKI treatment. In our case, not only additional chromosomal abnormalities but also ABL kinase domain mutations were not observed. It has been suggested that TKI monotherapy may be effective only in cases with such favorable conditions.

In conclusion, we reported a case of AML with BCR-ABL1 patient who was successfully treated with TKI monotherapy. AML with BCR-ABL1 is generally reported to have a poor prognosis with conventional chemotherapy and TKI treatment, but TKI treatment may be effective in elderly patients who have low tumor burden and without chromosomal abnormalities and ABL kinase domain mutations conferring resistance to TKI treatment. Additionally, the significantly potent ABL kinase inhibitor developed in recent years will be a beneficial agent in the future treatment for AML with BCR-ABL1 patients. To confirm this result, it is necessary to accumulate similar cases in the future.

Authors’ contributions

(1) The conception and design of the study, acquisition of data, or analysis and interpretation of data: A.T., T.K., T.T., E.K., and H.W.

(2) Drafting the article or revising it critically for important intellectual content: A.T., T.K., T.T., E.K., and H.W.

(3) Final approval of the version to be submitted: A.T. and T.K.

Declaration of Competing Interest

The authors reported no potential conflicts of interest.

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### Table 1

Progress of clinical laboratory data in present case.

|                   | Before 6 months | At diagnosis | After treatment 3 months | After treatment 16 months |
|-------------------|-----------------|-------------|--------------------------|--------------------------|
| White blood cells (x10^3/μL) | 3.8             | 1.56        | 3.54                     | 6.26                     |
| Hemoglobin (g/dL)     | 12.5            | 8.1         | 10.3                     | 12.3                     |
| Platelets (x10^3/μL)  | 103             | 82          | 140                      | 157                      |
| Bone marrow blasts (%) | 11.8            | 1.6         |                          |                          |
| WT-1 mRNA (copies/μgRNA) | -              | 5100        | 50±                      | 50±                      |
| BCR-ABL1/ABL1%       | -               | 75.1789     | 0.642                    | 0.0068                   |

**WT-1; Wilms’ tumor suppressor gene.**

Karyotyping of marrow blood cells revealed 46, XX, t(9;22)(q34;q11.2) [20/20], and fluorescence in situ hybridization (FISH) revealed the presence of the BCR-ABL1 fusion signal in 27% of bone marrow cells. Furthermore, peripheral blood major BCR-ABL1/ABL1 iso ribonuclease acid (RNA) and Wilms’ tumor 1 messenger RNA (WT-1 mRNA) levels were 75.1789% and 5.1 × 10^3 copies/μgRNA, respectively (Table 1). Based on these results, she was diagnosed with AML with BCR-ABL1. No mutation was observed in the ABL kinase domain before treatment. She was administered with dasatinib alone because she was unable to tolerate systemic chemotherapy due to age and complications such as renal and heart failure, thoracic aortic aneurysm, and replacement of vascular prosthesis. After 3 months of treatment with 20 mg/day of dasatinib, her peripheral blood count improved except for mild anemia (Table 1). The bone marrow aspiration was slightly hypocellular with a normal myeloid/erythroid ratio, and the myeloblast level decreased to 1.6%. Her peripheral blood WT-1 mRNA levels were undetectable. BCR-ABL1 fusion signal was not detected by FISH analysis in bone marrow cells, and karyotype analysis showed 46, XX [20/20], which indicated that she achieved complete cytogenetic response. At 16 months from the start of dasatinib treatment, the BCR-ABL1/ABL1 iso mRNA levels were un

### Table 2

Summary of AML with BCR-ABL1 cases who treated with tyrosine kinase inhibitors in our institution.

| Reference | Age / Gender | WBC (x10^3/L) | Hb (g/dL) | Plt (x10^9/L) | Bone marrow blasts (%) | Karyotype | ABL kinase domain mutation | Treatment | Chemotherapy | TKI | Latest IS value (%) | Outcome |
|-----------|--------------|---------------|-----------|--------------|------------------------|-----------|---------------------------|-----------|--------------|-----|--------------------|---------|
| [8]       | 67/M         | 1.3           | 8.6       | 48           | 20                     | No        | No                        | Yes       | Imatinib      | 0.0024 | alive, 149 months  |
| Present case | 77/F     | 1.56          | 8.1       | 82           | 11.8                   | No        | No                        | Dasatinib | 0.0015      | alive, 46 months |

M ; male, F ; female, WBC ; white blood cell counts, Hb ; hemoglobin, Plt ; platelet counts, TKI ; tyrosine kinase inhibitor, IS ; Major-BCR-ABL1/ABL1 iso RNA.
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