Leukemia Research Reports 15 (2021) 100233

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

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

Asako Takeuchi [a], Toshinori Kondo [a,*], Taizo Tasaka [b], Seiko Yamada [a], Tadashi Hirose [a], Hirofumi Fukuda [a], Risa Shimizu [a], Yoshiko Matsuhashi [a], Eisei Kondo [a], Hideho Wada [a]

[a] Department of Hematology, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama Prefecture 701-0192, Japan
[b] Department of Transfusion Medicine and Cell Therapy, Saitama Medical Center, Saitama Medical School, Kawagoe, Japan

ARTICLE INFO

Keywords:
Acute myeloid leukemia
BCR-ABL1
Philadelphia chromosome
Tyrosine kinase inhibitor

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, 2.54×10^9/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.

* Corresponding author.
E-mail address: kondot@med.kawasaki-m.ac.jp (T. Kondo).

https://doi.org/10.1016/j.lrr.2020.100233
Received 9 April 2020; Received in revised form 26 June 2020; Accepted 13 December 2020
Available online 14 December 2020
2213-0489/© 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 1
Progress of clinical laboratory data in present case.

	Before 6 months	At diagnosis	After treatment 3 months	16 months
White blood cells (x10^9/L)	3.8	1.56	3.54	6.26
Hemoglobin (g/dL)	12.5	8.1	10.3	12.3
Platelets (x10^9/L)	103	82	140	157
Bone marrow blasts (%)	-	11.8	1.6	-
WT-1 mRNA (copies/μgRNA)	-	5100	50>	50>
BCR-ABL1/ABL1^{IS} (%)	-	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*^{IS} ribonucleic acid (RNA) and *Wilms' tumor 1* messenger RNA (*WT-1* mRNA) levels were 75.1789% and 5.1 × 10^3 copies/microgram RNA, 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*^{IS} RNA test was less than 0.01% (Table 1). Five years after initiating treatment with dasatinib, the patient still maintains a deep molecular response.

3. Discussion

AML with *BCR-ABL1* is a rare disease and has a poor prognosis with conventional chemotherapy. According to a previous report, the prognosis for AML with *BCR-ABL1* has improved with TKIs in combination with allogeneic HSCT in young patients [7]. However, the optimal treatment to this disease is not established yet. In elderly patients who are not eligible for allogeneic HSCT, chemotherapy with imatinib has been performed so far, but the treatment's effectiveness has been limited [1,8]. In our previous case report, imatinib monotherapy did not result into complete remission [8]. However, imatinib as a maintenance therapy was a sufficient treatment to prevent patient relapse from minimal residual disease after remission. In fact, this patient has surprisingly been alive for over 12 years in deep molecular response with continued imatinib treatment. In contrast, it was shown that complete remission can be obtained with dasatinib monotherapy in this case. One 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., S.Y., T.H., H.F., Y. M., 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.

Table 2
Summary of AML with *BCR-ABL1* cases who treated with tyrosine kinase inhibitors in our institution.

Reference	Age / Gender	WBC (x10^9/L)	Hb (g/dL)	Plt (x10^9/L)	Bone marrow blats (%)	Karyotype	*ABL* kinase domain mutation	Treatment Chemotherapy	TKI	Latest IS value (%)	Outcome
[8]	67/M	1.3	8.6	48	20	46, XY, t(9;22)(q34;q11.2)	No	Yes	Imatinib	0.0024	alive, 149 months
Present case	77/F	1.56	8.1	82	11.8	46, XX, t(9;22)(q34;q11.2)	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* ^{IS} RNA.

References

[1] C.P. Soupir, J.A. Vergilio, P. Dal Cin, A. Muzikansky, H. Kantarjian, D. Jones, R. P. Hasserjian, Philadelphia chromosome-positive acute myeloid leukemia: a rare aggressive leukemia with clinicopathologic features distinct from chronic myeloid leukemia in myeloid blast crisis, Am. J. ClinPathol 127 (4) (2007) 642–650.

[2] H. Tsuchiya, M. Migita, S. Yamamori, Y. Kaneko, N. Adachi, T. Nakamura, Y. Nobukuni, S.S. el-Sonbaty, I. Matsuda, A late-appearing Philadelphia chromosome in acute lymphoblastic leukemia confirmed by expression of BCR-ABL mRNA, Leukemia 9 (1995) 1689–1693 [PubMed: 7564511].

[3] K. Matsue, T. Miyamoto, M. Ito, K. Tsukuda, Late appearance of the Philadelphia chromosome with monosomy 7 in a patient with de novo AML with trilineage myelodysplasia, Am. J. Hematol. 49 (1995) 341–346 [PubMed: 7639280].

[4] T. Shimamoto, K. Ohyashiki, J.H. Ohyashiki, T. Fujimura, A. Kodama, K. Miyazawa, S. Aizawa, K. Toyama, Late appearance of a Philadelphia translocation with minor-BCR/ABL transcript in a t(7;11)(p15;p15) acute myeloid leukemia, Leukemia 9 (1995) 640–642 [PubMed: 7723398].

[5] H.S. Steven, et al., WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th Edition, IARC Press, Lyon, 2008.

[6] H.S. Steven, et al., WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues Revised, 4th Edition, IARC Press, Lyon, 2017.

[7] V.L. Lazarevic, M. Labopin, W. Depei, I. Yakoub-Agha, A. Huynh, P. Ljungman, N. Schaap, J.J. Cornelissen, N. Maillard, P. Pioltelli, T. Gedde-Dahl, S. Lenhoff, M. Houhou, J. Esteve, M. Mohty, A. Nagler, Relatively favorable outcome after allogeneic stem cell transplantation for BCR-ABL1-positive AML: a survey from the acute leukemia working party of the European society for blood and marrow transplantation (EBMT), Am. J. Hematol. 93 (1) (2018) 31–39.

[8] T. Kondo, T. Tasaka, F. Sano, K. Matsuda, Y. Kubo, Y. Matsuhashi, H. Nakanishi, Y. Sadahira, H. Wada, T. Sugihara, K. Tohyama, Philadelphia chromosome-positive acute myeloid leukemia (Ph+ AML) treated with imatinib mesylate (IM) A report with IM plasma concentration and bcr-abl transcripts, Leuk. Res. 33 (9) (2009) e137–e138.

[9] S. Redaelli, L. Mologni, R. Rostagno, R. Piazza, V. Magistroni, M. Ceccon, M. Viltadi, D. Flynn, C. Gambacorti-Passerini, Three novel patient-derived BCR/ABL mutants show different sensitivity to second and third generation tyrosine kinase inhibitors, Am. J. Hematol. 87 (11) (2012) E125–E128.

[10] E. Paietta, J. Racevskis, J.M. Bennett, D. Neuberg, P.A. Cassileth, J.M. Rowe, P. H. Wiernik, Biologic heterogeneity in Philadelphia chromosome-positive acute leukemia with myeloid morphology: the Eastern Cooperative Oncology Group experience, Leukemia 12 (1998) 1881–1885.