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Cytogenetic Remission in Response to Dasatinib Monotherapy in Mixed-phenotype Acute Leukemia with t(9;22)(q34.1;q11.2) Translocation

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Abstract The case of a 44-year-old Japanese woman diagnosed with mixed-phenotype acute leukemia with t(9;22)(q34.1;q11.2); BCR-ABL1 (MPAL-BA) is reported. Her white blood cell count was 5,100/μL with 13.0% blasts; positive for CD34, HLA-DR, MPO, CD33, CD19, cytoplasmic (cy) CD79a, CD22, CD10, and TdT; and negative for cyCD3. G-band cytogenetic analysis detected a normal karyotype. Fluorescence in situ hybridization detected BCR-ABL1 (9.0%) and a minor BCR-ABL1 mRNA at 4.2×10^4 copies/μg RNA. The patient was treated with dasatinib monotherapy (140 mg daily). Bone marrow examination revealed cytogenetic remission (CyCR) with minor BCR-ABL1 mRNA detected at 1.1×10^3 copies /μg RNA on day 31. No adverse events of dasatinib therapy were observed. MPAL-BA is very rare and dasatinib monotherapy efficacy for this diagnosis was previously unknown. The patient achieved CyCR with dasatinib monotherapy as first-line treatment. The present case suggests that dasatinib monotherapy may be effective and safe for MPAL-BA induction therapy.

Keywords: *mixed phenotype acute leukemia with t(9;22)(q34.1;q11.2), BCR-ABL1 translocation, mixed phenotype acute leukemia, BCR-ABL1, dasatinib*

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1. Introduction

Acute leukemia of ambiguous lineage is a rare disease accounting for less than 4% of all acute leukemias. Acute leukemia of ambiguous lineage shows no clear evidence of differentiation along a single lineage and generally has a poor prognosis. In 2017, the World Health Organization (WHO) classification introduced a revised diagnostic algorithm to define acute leukemia of ambiguous lineage [1]. The diagnosis of ambiguous lineage acute leukemia relies on immunophenotyping and flow cytometry. Myeloperoxidase is the most reliable marker to identify myeloid lineage, in the same way that cytoplasmic (cy) CD3 and CD19 determine for T and B lineages, respectively. However, the WHO classification revised 4th edition (2017) provides no definite threshold for the population size. According to the WHO classification, acute leukemia of ambiguous lineage is classified into acute undifferentiated leukemia (no lineage-specific antigens) and mixed-phenotype acute leukemia (MPAL; with blasts that express >1 antigens). Furthermore, MPAL is classified into MPAL with t(9;22)(q34.1;q11.2); BCR/ABL1 (MPAL-BA), t(v; 11q23.3); KMT2A-rearranged, B/myeloid not other specified, T/myeloid not other specified, and not other specified rare types [1,2]. The features of 100 patients with MPAL who fulfilled the earlier WHO 2008 criteria have been reported. Flow cytometric immunophenotyping showed 59 cases (59%) of MPAL patients with B cell and myeloid lineage, 35 cases (35%) of T cell and myeloid lineage, 4 cases (4%) of B cell and T cell lineage, and 2 cases (2%) of trilineage combinations (myeloid, B, and T cell lineage). Fluorescence in situ hybridization (FISH) analysis revealed the incidence of cytogenetic abnormalities of t(9;22)(q34;q11); BCR/ABL1 (20%); and translocations involving the 11q23 breakpoint (8%), complex (32%), aberrant (27%), or normal (13%) karyotypes. Moreover, harboring BCR/ABL1 was views as a statistically significant predictor for shorter survival. Among MPAL patients with BCR/ABL1, the 2-year survival is less than 20% [3]. There is no approved chemotherapy protocol for newly diagnosed MPAL-BA, although 20% of MPAL cases harbor BCR/ABL1, which strongly impacts survival. The results of imatinib-containing therapy among MPAL-BA have been reported [4], as have case reports describing dasatinib-containing therapy [5,6], although dasatinib efficacy in MPAL-BA patients remains unclear. This report presents the case of an MPAL-BA patient who achieved cytogenetic remission (CyCR) with dasatinib monotherapy.

2. Case Presentation

A 44-year-old female with a history of ureteral calculus presented at a hospital complaining of a chest pain. Laboratory tests revealed pancytopenia, and she was referred to our hospital for further evaluation. Physical examination revealed Eastern Cooperative Oncology Group (ECOG) performance of 0, body temperature of 36.3°C, blood pressure of 118/95 mmHg, heart rate of 98 beats/min, and oxygen saturation of 98% in room air. No petechial hemorrhage in oral mucosa, no palpable superficial lymph node, no palpable hepatomegaly, one transverse finger-palpable splenomegaly, and no petechial hemorrhage in the peripheral extremities were noted. The results of blood tests on admission showed that blasts appeared in the peripheral blood (white blood cell count of 5,100 /μL with accounting blasts; 13.0%), and anemia (hemoglobin level, 11.1 g/dL), thrombocytopenia (platelet count, 17,000 /μL), and elevated serum lactate dehydrogenase level (1,272 IU/L; Table 1). A bone marrow (BM) smear revealed an increase of blasts (26.0% of all nucleated cells), which were negative for peroxidase stain. Two time flow cytometry analyses of BM and peripheral blood samples revealed that blasts were positive for CD34, HLA-DR, MPO, CD33, CD19, cyCD79a, CD22, CD10, and TdT, and negative for cyCD3 (Figure 1a, b). G-band cytogenetic analysis of BM samples revealed normal karyotype. A polymerase chain reaction (PCR) test of minor BCR-ABL1 mRNA on a BM sample detected 4.2×10^4 copies/μgRNA. The application of FISH to peripheral blood samples detected BCR-ABL1 in 9.0% of the blood cells. Computed tomography revealed no hepatomegaly but mild splenomegaly. The patient was consequently diagnosed with MPAL-BA. The patient was treated with dasatinib 140 mg daily. On the 31st day after starting dasatinib treatment, BM examination revealed a decrease in the blast (1% of all nucleated cells) and FISH BCR-ABL1 in 0% and the minor BCR-ABL1 mRNA at 1.1×10^3 copies /μgRNA. The patient achieved CyCR. No dasatinib adverse events were observed. The patient subsequently continued to receive dasatinib 100 mg daily plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper CVAD) as consolidation therapy [7]. The result of PCR tests of minor BCR/ABL quantitative assay turned negative but the qualitative assay remained positive after the second course of consolidation therapy. The patient was transferred to another hospital for hematopoietic stem cell transplantation from an unrelated donor.

Table 1. Laboratory data on admission

Complete blood count			Coagulation					
White cell count	5100	/μL	Activated partial thromboplastin time	44.7	sec	Blood urea nitrogen	8.6	mg/dL
Red cell count	370×10^4	/μL	Prothrombin time	105.8	sec	Creatinine	0.54	mg/dL
Hemoglobin	11.1	g/dL	Fibrinogen	629	mg/dL	Uric acid	3.8	mg/dL
Hematocrit	30.1	%	D-dimer	43.2	μg/mL	Natrium	139	mEq/L
Platelet count	1.7×10^4	/μL				Potassium	3.9	mEq/L
Reticulocyte	9.0	‰	Biochemistry			Chloride	100	mEq/L
			Total protein	7.4	g/dL	Calcium	9.1	mg/dL
Differential count			Albumin	4.6	g/dL	C-reactive protein	12.35	mg/dL
Band neutrophil	11.0	%	Total bilirubin	0.5	mg/dL			
Segmented neutrophil	24.0	%	Direct bilirubin	0.1	mg/dL			
Monocyte	10.0	%	Alkaline phosphatase	327	U/L			
Lymphocyte	40.0	%	Aspartate aminotransferase	41	U/L			
Eosinocyte	1.0	%	Alanine aminotransferase	38	U/L			
Basophil	0.4	%	γ-glutamyltransferase	35	U/L			
Myelocyte	3.0	%	Lactate dehydrogenase	1272	U/L			
Metamyelocyte	2.0	%	Leucine aminopeptidase	49	U/L			
Blast	13.0	%	Cholinesterase	337	U/L			

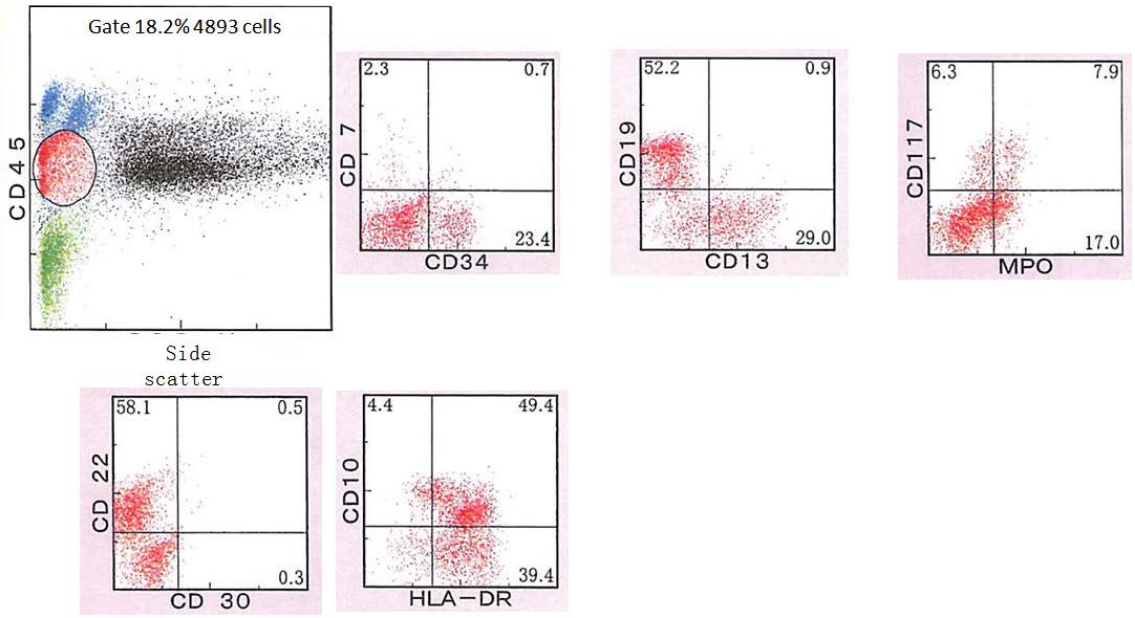

Figure 1.a. The results of flow cytometry analysis on bone marrow samples

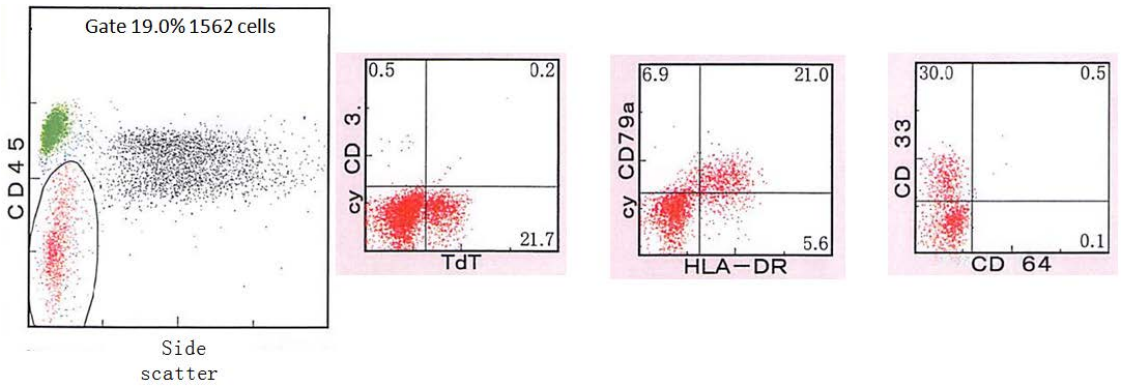

Figure 1.b. The results of flow cytometry analysis on peripheral blood samples

Table 2. Previous case reports of mixed-phenotype acute leukemia with t(9;22)(q34.1;q11.2); BCR/ABL1

	Age/Sex	Immunophenotype	Cytogenetics (Polymerase chain reaction)	BCR/ABL point mutation	Dasatinib dose (mg/day)	Combination therapy	Prior treatment	Treatment response	Reference
Case1	71/Female	B cell+Myeloid	45,XX,-7,t(9,22)(q34;q11.2)[19/20]	Y253H	50	vincristine prednisolone	chemotherapy, imatinib, nilotinib	cytogenetic CR	5
Case2	69/Female	B cell+Myeloid	46,XX (major BCR/ABL 41,000 copies/μgRNA)	not available	140	prednisolone	none	molecular CR	6
Case3	69/Female	B cell+Myeloid	45,XX,-7,t(9,22)(q34;q11.2)[14]/46,idem,-17,+mal[3]/46,XX[3]	not available	140	prednisolone	none	molecular CR	6
Our case	44/Female	B cell+Myeloid	46,XX (minor BCR/ABL: 4.2×10^4 /μgRNA)	not available	140	none	none	cytogenetic CR	

CR; Complete remission

3. Discussion

There is no accepted standard treatment for MPAL-BA. However, previous studies have reported tyrosine kinase inhibitor-containing chemotherapy, as well as specific imatinib-containing chemotherapy for MPAL-BA. Thirteen patients with MPAL-BA (positive for both myeloid and B-cell lineage) were analyzed. The complete remission rate after the initial induction therapy was 100%. The 5-year overall survival and disease-free survival rates were 55% and 46%, respectively [4]. Several case reports of dasatinib treatment of MPAL-BA also exist (Table 2). However, all patients were treated with dasatinib in combination with other agents, with all treatments proving successful.

The distinct feature of the current case is that the patient achieved CyCR after dasatinib monotherapy.

Dasatinib is a potent multikinase inhibitor targeting BCR-ABL and is 325-fold more potent than imatinib for inhibiting unmutated BCR-ABL. In addition, dasatinib inhibits the SRC family kinases (SRC, LCK, HCK, YES, FYN, FGR, BLK, LYN, and FRK), receptor tyrosine kinases (c-KIT, PDGFR, DDR1 and 2, c-FMS, and ephrin receptors), and TEC family kinases (TEC and BTK) [8]. Thus, dasatinib is known to inhibit not only BCR/ABL but also other genes. Moreover, MPAL is known to have heterogeneous gene mutations as well as chromosomal abnormalities. Therefore, the author hypothesized that induction therapy with dasatinib monotherapy is possible in MPAL-BA patients. The most frequent adverse events with dasatinib (e.g., myelosuppression, fluid retention, pleural effusion, gastrointestinal disorders, fatigue, headache, musculoskeletal disorders, rash, infection, bleeding, and pulmonary arterial hypertension). [8] No adverse events of dasatinib were observed in this case.

4. Conclusion

A patient achieved CyCR with dasatinib monotherapy as first-line treatment. The present case suggests that dasatinib monotherapy may be effective and safe for MPAL-BA induction therapy.

Conflict of Interest

The author has no competing interest to declare.

Informed Consent

The written informed consent for publication was obtained from the patient.

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