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Refractory acute promyelocytic leukemia successfully treated with combination therapy of arsenic trioxide and tamibarotene: A case report

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ABSTRACT

A 40-year-old male developed refractory acute promyelocytic leukemia (APL) after various treatments including all-trans retinoic acid, tamibarotene, arsenic trioxide (As_2O_3), conventional chemotherapy, and autologous peripheral blood stem cell transplantation. We attempted to use both tamibarotene and As_2O_3 as a combination therapy, and he achieved molecular complete remission. Grade 2 prolongation of the QTc interval *on the electrocardiogram* was observed during the therapy. The combination therapy of As_2O_3 and tamibarotene may be effective and tolerable for treating refractory APL cases who have no treatment options, even when they have previously been treated with tamibarotene and As_2O_3 *as a single agent.*

1. Introduction

Acute promyelocytic leukemia (APL) is driven by an oncogenic chromosomal translocation fusing the promyelocytic leukemia (*PML*) and retinoic acid receptor alpha (*RARA*) genes. The *PML/RARA* fusion protein causes a maturational block at the promyelocyte stage of myeloid differentiation. Differentiation therapy with all-trans retinoic acid (ATRA) alone or in combination with chemotherapy is a major advance in the treatment of APL and is regarded as the first paradigm of molecularly targeted therapy [1]. However, relapse/refractory APL patients demonstrating resistance to ATRA are recognized as a clinically critical problem.

Arsenic trioxide (As_2O_3) is also highly effective in the treatment of APL. Early studies conducted in China and the United States showed that this agent can induce sustained molecular remission when used as a single agent in patients who have a relapse after treatment with ATRA-containing regimens [2,3]. As_2O_3 acts through specific binding of the *PML* moiety of the disease-specific *RARA* oncoprotein, leading to its degradation and resulting in partial differentiation and induction of apoptosis of leukemic promyelocytes. Synergy of As_2O_3 and ATRA, which binds the *RARA* moiety of *PML/RARA*, has been shown at both the biological and the clinical levels.

On the other hand, tamibarotene is in the same family of drugs as ATRA, induces the differentiation of APL cells, and is applied to relapsed cases that have previously received ATRA treatment [4]. Tamibarotene has strong differentiation-inducing activity on human promyelocytic leukemia cells and is expected to be more effective and safe than ATRA [5].

While it has been reported that the combination therapy of As_2O_3 and ATRA is highly effective not only as the front-line treatment [6], but also in relapsed and treatment-refractory APL patients [7], showing fewer adverse events than the combination of ATRA and chemotherapeutic drugs, the efficacy and tolerability of the combination of As_2O_3 and tamibarotene are unknown. We herein report a patient with APL successfully treated with the combination therapy of As_2O_3 and tamibarotene, in whom both As_2O_3 and tamibarotene monotherapies had not been effective.

2. Case report

A 40-year-old Japanese male was admitted to our hospital because he presented with purpura on both legs in May 2011. Laboratory examinations revealed significantly abnormal findings,

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Table 1
Treatment history and outcome prior to combination of As_2O_3 and tamibarotene.

Phase of treatment	Drugs	Result of treatment
At initial diagnosis		
First induction therapy	ATRA, Ara-C, and IDA	hCR
Post-remission therapy 1	Ara-C and MIT	hCR
Post-remission therapy 2	Ara-C and DNR	hCR
Post-remission therapy 3	Ara-C and IDA	mCR
Maintenance therapy	ATRA	Molecular relapse
At first molecular relapse		
Re-induction therapy 1	Tamibarotene	hCR
Re-induction therapy 2	As_2O_3	hCR
Post-remission therapy 1	As_2O_3	hCR
Post-remission therapy 2	As_2O_3	hCR
Post-remission therapy 3	high-dose Ara-C	mCR
aPBSCT	Bu and MEL	mCR
At second molecular relapse		
Re-induction therapy	Tamibarotene	Hematological relapse

ATRA: all-trans retinoic acid, Ara-C: cytarabine, IDA: idarubicin, hCR: hematological complete remission, MIT: mitoxantrone, DNR: daunorubicin, mCR: molecular complete remission, aPBSCT: autologous peripheral blood stem cell transplantation, Bu: busulfan, MEL: melphalan.

including a white blood cell (WBC) count of 41,400/μL with 65.5% blasts and 22.5% promyelocytes, a hemoglobin level of 12.2 g/dL, and a platelet count of 20,000/μL. Blood coagulation parameters showed a fibrinogen level of 154 mg/dL, FDP level of 320.8 μg/mL, and D-dimer level of 70.9 μg/mL. A bone marrow aspiration study revealed the proliferation of blasts (65.5%) and promyelocytes (22.5%). A chromosome analysis based on a G-banding analysis showed the karyotype 46,XY,t(15;17)(q22;q21) [20/20]. On the basis of these findings, a diagnosis of acute promyelocytic leukemia was made. The patient received an induction therapy with JALSG APL 204 regimen-group C, which consisted of ATRA, cytarabine (Ara-C), and idarubicin, and achieved hematological complete remission (CR). Accordingly, he received three cycles of post-remission therapies and achieved molecular CR (Table 1).

However, although hematological relapse was not detected, the *PML/RARA* mRNA transcripts came to be recognized by an RT-PCR test during the period of maintenance therapy using ATRA. Thus, the patient was diagnosed as having molecular relapse and received tamibarotene (6 mg/m^2/day) for eight weeks, but the *PML/RARA* mRNA transcripts did not disappear. He then received a therapy with JALSG APL 205R regimen composed of As_2O_3 single treatment as a re-induction therapy and two cycles of As_2O_3 single treatment as post-remission therapy. However, the *PML/RARA* mRNA transcripts did not disappear during the following consolidation therapy.

He received high-dose cytarabine (2000 mg/m^2 twice a day) for five days and achieved second molecular CR. Accordingly, autologous peripheral blood stem cell transplantation (aPBSCT) was performed after the high-dose chemotherapy consisting of busulfan (1 mg/kg four times a day) for three days and melphalan (70 mg/m^2/day) for two days in August 2014. Engraftment was subsequently observed and he was discharged while remaining in molecular CR.

However, a second molecular relapse occurred nine months after the aPBSCT. Tamibarotene was used again, but resulted in a hematological relapse.

Then, we attempted to use both tamibarotene and As_2O_3 as a combination therapy. He achieved hematological and molecular CR on day 28 and on day 61, respectively (Fig. 1). Hematologic toxicities and hypertriglyceridemia were not detected, and grade 2 prolongation of the QTc interval *on the electrocardiogram* was observed during the therapy.

Subsequently, the patient underwent allogeneic bone marrow transplantation in January 2015, and the molecular CR has persisted so far for eleven months since the transplantation.

3. Discussion

Reports have included speculation on the molecular mechanisms of resistance to ATRA and As_2O_3. In terms of the mechanism of resistance to ATRA, genetic mutations (i.e. missense, nonsense, and deletions) have been identified on the *RARA* ligand binding domain (LBD) in *PML-RARA*. These mutations accumulate in the three subregions of the LBD domain [8]. In vitro analyses using ATRA-resistant NB4 cells and mutated-*PML-RARA* expressing Cos-1

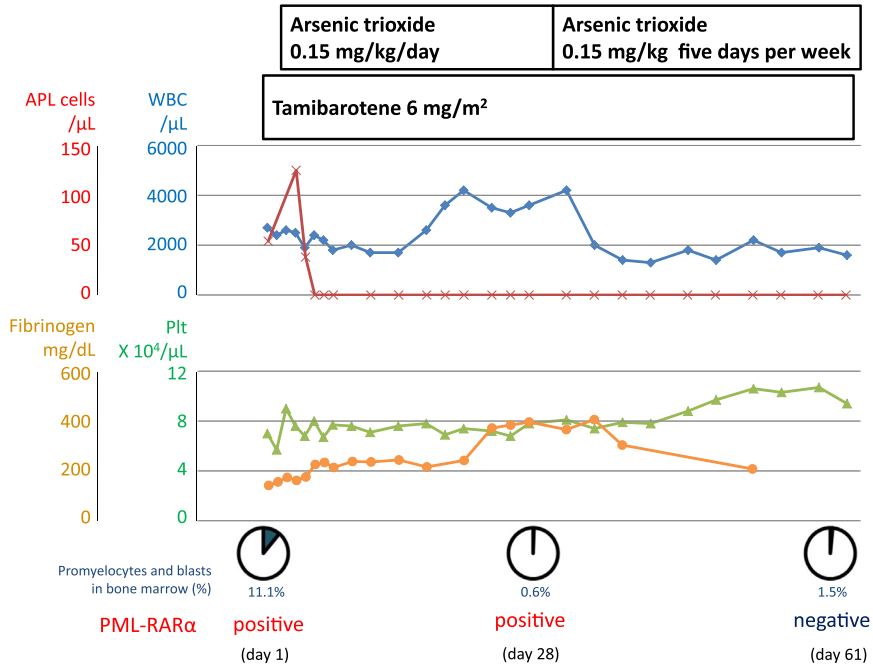

Fig. 1. Clinical course after second molecular relapse. The patient received the combination chemotherapy of tamibarotene and As_2O_3. He attained hematological CR and molecular CR on day 28 and on day 61, respectively. APL: acute promyelocytic leukemia, WBC: white blood cell, Plt: platelet.

cells [9] indicated that ATRA-binding affinity with mutated *PML-RARA* was lower than that with *PML-RARA* without mutations because of conformational changes in LBD. Furthermore, ligand-dependent N-CoR/SMRT co-repressor release and co-activator recruitment, which are critical for the transcriptional activation of genes with RARE sites and morphological cell differentiation, are impaired under the therapeutic dose of ATRA [9].

On the other hand, information on As_2O_3 resistance remains limited compared with that on ATRA resistance. Goto et al. reported the first molecular basis for clinical resistance to As_2O_3 in APL using two As_2O_3-resistant patients [10]. The authors concluded that *PML*-B2 domain mutations may play an important role in aberrant molecular responses to As_2O_3 and may be critical for As_2O_3 resistance in APL.

To overcome these resistance mechanisms in APL cells, a number of drugs have been tested. Tamibarotene is approximately 10 times more potent than ATRA as an in vitro inducer of differentiation, and is chemically more stable than ATRA [5]. Although the precise mechanism of the combination of tamibarotene and As_2O_3 in overcoming therapy resistance of APL cells is not known, we suppose a certain synergistic effect of the drugs, as is observed in the combination of ATRA and As_2O_3 [6,7]. Most importantly, our refractory patient, who had previously been treated with both tamibarotene and As_2O_3 monotherapies and could not enter hematological CR, achieved molecular CR by the combination therapy without severe adverse events, and has been in the molecular CR although the subsequent allogenic stem cell transplantation might significantly affect the clinical course. The combination of As_2O_3 and tamibarotene may be effective and tolerable for treating patients with refractory APL who have previously received various treatments including tamibarotene and As_2O_3, and have no treatment options.

Author's contributions

M.K. designed the experiments, performed the experiments and prepared the manuscript; D.A., F.I., R.H., J.A., Hid.K., H.N., A.S., M.M., R.S., S.M., and Y.O. designed the experiments and performed the experiments; H.M., Hir.K., and K.A. designed the experiments and prepared the manuscript.

Conflict of interest

The authors have no conflicts of interests or funding to disclose.

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