Successful eltrombopag treatment of severe refractory thrombocytopenia in chronic myelomonocytic leukemia

Two cases reports: A CARE-compliant article

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Abstract
Rationale: Thrombocytopenia in chronic myelomonocytic leukemia (CMML) is usually attributed to impaired marrow production resulting from cytotoxic drug use or CMML itself ("CMML-induced thrombocytopenia"). In very rare cases, immune thrombocytopenia (ITP) can be a complication of CMML ("CMML-associated ITP"). However, treatment of severe thrombocytopenia in patients with CMML is still a challenge.

Patient concerns: Case 1 was a 61-year-old female patient admitted to our hospital because of skin petechiae and purpura for 6 days. She had increased monocyte cell count (1.82 × 10^9/L), markedly decreased platelet count (2 × 10^9/L), hypercellularity of the megakaryocyte lineage with many immature megakaryocytes, and ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2) mutation. She failed to the treatment of corticosteroids, intravenous immunoglobulin (IVIg), TPO (thrombopoietin), and cyclosporin A (CsA). Case 2 was a 72-year-old female patient with thrombocytosis and monocytosis for 4 years, and thrombocytopenia for 6 months. After 10 courses of decitabine therapy, she had a persistent severe thrombocytopenia and decreased number of megakaryocytes, TET2 (tet methylcytosine dioxygenase 2) and SRSF2 (serine and arginine rich splicing factor 2) mutations were detected. She was dependent on platelet transfusion.

Diagnoses: Case 1 was diagnosed as CMML-associated ITP, and case 2 as CMML with decitabine therapy-induced thrombocytopenia.

Interventions: Both patients were treated with eltrombopag.

Outcomes: In both patients, the platelet counts returned to the normal within 1 week after eltrombopag therapy. The platelet count in case 1 patient remained stable at 141–200 × 10^9/L for 20 months with stopping therapy for 3 months. In case 2 patient, eltrombopag was stopped 1 month later. Her platelet count decreased to 41 × 10^9/L, but was stable at ∼30 × 10^9/L for 3 months with platelet transfusion independency for 12 months. Both patients had no adverse effects with eltrombopag.

Lessons: CMML-associated ITP is very rare and easily misdiagnosed. To the best of our knowledge, case 1 is the first reported case of the successful treatment of CMML-associated ITP with eltrombopag. Both CMML-associated ITP and decitabine therapy-induced thrombocytopenia in these 2 patients were highly sensitive and safe to eltrombopag therapy.

Abbreviations: BM = bone marrow, CMML = chronic myelomonocytic leukemia, CPSS = CMML-specific prognostic scoring system, CPSS-P = CMML-specific prognostic scoring system including platelet count, CsA = cyclosporin A, FAB = French-American-British, FISH = fluorescence in situ hybridization, ITP = immune thrombocytopenia, IVIg = intravenous immunoglobulin, MD-CMML = myelodysplastic CMML, MDS/MPN = myelodysplastic syndrome/myeloproliferative neoplasm, MP-CMML = myeloproliferative CMML, PB = peripheral blood, PCR = polymerase chain reaction, SRSF2 = serine and arginine rich splicing factor 2, TET2 = tet methylcytosine dioxygenase 2, TPO = thrombopoietin, TPO-RA = thrombopoietin receptor agonist, WBC = white blood cell, WHO = World Health Organization, ZRSR2 = zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2.

Keywords: chronic myelomonocytic leukemia, decitabine, eltrombopag, immune thrombocytopenia, thrombocytopenia, thrombopoietin receptor agonist
1. Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder with overlapping myelodysplastic and myeloproliferative features. Patients with CMML present with peripheral mononcytosis ($\geq 1 \times 10^9/L$) and monocytes accounting for $\geq 10\%$ of the white blood cell (WBC) count.\(^1,2\) In 1994, the French-American-British (FAB) Cooperative Leukemia Group proposed a method to classify patients into 2 subtypes based on WBC count: patients with WBC counts of $\geq 10^9/L$ were considered to have myelodysplastic CMML (MD-CMML), and those with WBC counts of $< 10^9/L$ had myeloproliferative CMML (MP-CMML).\(^3\)

In 2008 and 2016, the World Health Organization (WHO) classifications also recognized CMML as a subset of myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN). According to the 2008 WHO classification, CMML was categorized into CMML-1 ($< 5\%$ blasts plus promonocytes in the peripheral blood [PB] and $< 10\%$ blasts plus promonocytes in the bone marrow [BM]), and CMML-2 (5–19% blasts plus promonocytes in the PB or 10–19% blasts plus promonocytes in the BM). According to the 2016 WHO classification, CMMLs were recategorized as CMML-0 ($< 2\%$ blasts plus promonocytes in the PB and $< 5\%$ blasts plus promonocytes in the BM), CMML-1 (2–4% blasts plus promonocytes in the PB and 5–9% blasts plus promonocytes in the BM), and CMML-2 (5–19% blasts plus promonocytes in the PB and 10–19% blasts plus promonocytes in the BM and/or Auer rods present).\(^2,3\)

Thrombocytopenia is presented in $\sim 40\%$ of CMML patients.\(^4\) Thrombocytopenia in CMML is usually related to marrow defects resulting from cytotoxic drug use or CMML itself, which is termed “CMML-induced thrombocytopenia.” In very rare cases, immune thrombocytopenia (ITP) can be a complication of CMML.\(^4,5\) and is termed “CMML-associated ITP.” In general, CMML-associated ITP is routinely treated as the primary ITP using corticosteroids;\(^5\) whereas, for CMML-induced thrombocytopenia, CMML is treated with primary disease therapy (such as chemotherapy or decitabine) and supportive therapy (such as platelet transfusion). However, it is still challenging to treat CMML patients with severe refractory thrombocytopenia after failure to routine therapies.

Recently, our group successfully treated refractory thrombocytopenia in 2 CMML cases using the thrombopoietin receptor agonist (TPO-RA), eltrombopag. One case was CMML-associated severe refractory ITP, and the other was decitabine therapy-induced thrombocytopenia.

2. Case report

2.1. Case 1

A 61-year-old woman was admitted to the China-Japan Friendship Hospital (Beijing, China) in August 2015 due to the presence of skin petechiae and purpura for 6 days. The patient had a 10-year history of hypertension. Physical examination showed no lymphadenopathy, hepatomegaly, or splenomegaly. At admission, the WBC count was $10.7 \times 10^9/L$, the monocyte cell count was $1.82 \times 10^9/L$ (17% of the total count), the eosinophil cell count was $0.06 \times 10^9/L$, the basophil cell count was $0.16 \times 10^9/L$, the hemoglobin concentration was $127 g/L$, and the platelet count was $2 \times 10^9/L$. Bone marrow aspirate showing 1% myeloblasts, 0% monoblast, and 0% promonocyte. Megaloblastoid change of granulocytes or erythrocytes and micromegakaryocytes were $< 10\%$. Megakaryocytes were markedly hypercellular with $> 600$ megakaryocytes per smear, many immature megakaryocytes and no platelet produced megakaryocytes. The bone marrow biopsy showed hypercellularity and dysplasia of megakaryocytes with micromegakaryocytes and naked nucleus megakaryocytes (Fig. 1). Flow cytometric analysis of the bone marrow aspirates showed an abnormal phenotype in granulocytes and monocytes and CD34$^+$ immature myeloid cells were at 0.6% (Fig. 2). Several somatic mutations associated with myelodysplasias were detected in the present case. JAK2, CALR, MPL, TET2, DNMT3A, IDH1, ASXL1, EZH2, RUNX1, SF3B1, SRSF2, ZRSR2, SETBP1, U2AF2, CEL, SFI, NF1, and TP53 were analyzed by pyrosequencing, and only ZRSR2 (zinc finger CCCH-type, RNA binding motif, and serine/arginine rich 2) was identified to be mutated. No BCR/ABL1, TEL-PDGFR, TEL-PDGFR, NIN-PDGFR, GIT2-PDGFR, HIP1-PDGFR, BCR-PDGFR, and BCR-FGFR1 fusion genes were detected by polymerase chain reaction (PCR). PDGFR, PDGFR, and FGFR1 were negative as demonstrated by fluorescence in situ hybridization (FISH). The karyotype was 46, XX [20]. The patient was diagnosed as CMML with CPSS (CMML-specific prognostic scoring system) 0, CPSS-P (CMML-specific prognostic scoring system including platelet count) intermediate-1, FAB-M, 2016 WHO-CMML-0, and complicated with ITP.

After admission, the patient was given high-dose intravenous immunoglobulin (IVlg) (0.4 g/kg/d) for 5 days, dexethamsone 10 mg/d for 7 days and prednisone 1 mg/kg/d for 3 weeks. After receiving this regimen for 2 weeks, the platelet count did not increase. Therefore, 15,000U thrombopoietin (TPO; 3SBIO Inc., China) was administered by subcutaneous injection for 12 days. The platelet count remained low at 1–18 $\times 10^9/L$ even with frequent platelet infusions, but the WBC count increased to 30.56 $\times 10^9/L$ and the monocyte counts increased to a peak value 6.0 $\times 10^9/L$. After 1 week, the patient received 5 mg/kg/d cyclosporin A (CsA) divided into 2 doses, and prednisone administration was decreased gradually. Although the platelet count appeared to increase slightly to a range of 4–30 $\times 10^9/L$ (median 25 $\times 10^9/L$) with platelet infusion, the CsA serum trough concentration ranged from 2.39 to 790.3 ng/mL, and renal insufficiency was demonstrated by increasing serum creatinine (213.3 μmol/L). CsA administration was terminated after 2 months of therapy, and from October 11, 2015, oral treatment with 50 mg/d eltrombopag (GlaxoSmithKline, India) was initiated. After 2 days of this intervention, the platelet count was increased to 78 $\times 10^9/L$, and after 5 days it was increased further to 170 $\times 10^9/L$. The eltrombopag dose was decreased to 25 mg/d after 2 weeks of administration. And 2 months later, eltrombopag was decreased to 12.5 mg/d, 3 months later was further decreased to 8.3 mg/d (1/6 tablet) and then was stopped 18 months later (on May, 2017), the platelet counts remained at 141–200 $\times 10^9/L$ and monocyte count was 1.04–2.23 $\times 10^9/L$ for nearly 20 months (till July 2017, Fig. 3). No adverse effects such as liver damage, diarrhea, or nausea, were observed.

2.2. Case 2

A 72-year-old woman who had experienced thrombocytosis and monocytosis for 4 years, and decitabine therapy-induced thrombocytopenia for 6 months was admitted to China-Japan Friendship Hospital in June 2016. In June 2012, the platelet count of this patient was 500 $\times 10^9/L$, WBC count was 40 $\times 10^9/L$, monocyte cell count was 2.0 $\times 10^9/L$ (differential count, 14%), and hemoglobin concentration was 110 g/L. Bone marrow (BM)
aspirate showed hypercellularity of the granulocytic, erythroid and megakaryocytic lineages, 1% myeloblasts, 0% monoblast and 0% promonocytes, and 117 megakaryocytes per smear. BM biopsy showed hyperproliferation of the granulocytic and megakaryocytic lineages and dysplasia of megakaryocytes. The karyotype was 46, XX [20]. The patient was diagnosed as CMML associated ITP. A. Megakaryocytes were markedly hypercellular (Wrights × 10). B. Megakaryocytic hyperplasia (HE × 400). C. CD61 immunohistochemistry: hypercellularity and dysplasia of megakaryocytes with micromegakaryocytes, naked nucleus, and hypolobated megakaryocytes (IHC × 400). D. CD34 immunohistochemistry: a few myeloid blasts positive (IHC × 400). E. CD68 immunohistochemistry: monocytes and macrophages positive (IHC × 400). F. AgNOR stain: + (×200). CMML = chronic myelomonocytic leukemia, ITP = immune thrombocytopenia.

In September 2014, the patient’s WBC count increased to 36.49 × 10^9/L with the monocyte count 2.11 × 10^9/L, however, the platelet cell count decrease to 64 × 10^9/L. The BM aspirate showed hypercellularity with 2.5% myeloblasts, 0% monoblast, and 0.5% promonocytes. The BM biopsy showed hypercellularity and dysplasia of granulocytic and megakaryocytic lineages with micromegakaryocytes, hypolobated and monocytic megakaryocytes, and with aggregation of myeloblasts (Fig. 4). The flow cytometric analysis of bone marrow aspirates showed abnormal phenotype in granulocytes with 3.49% blasts (Fig. 5). DNA extracted from bone marrow aspirates was used to perform pyrosequencing for JAK2, CALR, TET2, DNMT3A,
Figure 2. Flow cytometric analysis of the bone marrow aspirates in case 1 patient. There were abnormal phenotype in granulocytes and monocytes; CD34+ immature myeloid cells were at 0.6%. A. Low expression of Human Leukocyte Antigen-DR in monocytes. B. Abnormally decreased CD33 expression on a part of CD34+ myeloid progenitors. C. Abnormally decreased CD38 expression on a part of CD34+ myeloid progenitors. D. Low expression of CD14 in monocytes.

Figure 3. Case 1: MD-CMML-associated ITP. The patient was initially treated with intravenous immunoglobulin (IVIg), dexamethasone (Dx), prednisone, thrombopoietin (TPO), cyclosporin A (CsA), and platelet transfusion which were not effective, however, the white blood cells (WBC), monocytes (MONO), and serum creatinine (CR) were increased. Then etrombopag was initiated. The platelet count was increased to $78 \times 10^9\text{L}^{-1}$ 2 days later, $170 \times 10^9\text{L}^{-1}$ 5 days later, and was remained stable at $\sim 200 \times 10^9\text{L}^{-1}$. The etrombopag dose was decreased to 25 mg/d 2 weeks later. And 2 months later, etrombopag was decreased to 12.5 mg/d, 3 months later was further decreased to 8.3 mg/d (1/6 tablet) and then was stopped 18 months later. The platelet count has been stable at 140–200 $\times 10^9\text{L}^{-1}$ and monocyte count has been 1.04–1.95 $\times 10^9\text{L}^{-1}$ for nearly 20 months. CR = serum creatinine, CsA = cyclosporin A, Dx = dexamethasone, ITP = immune thrombocytopenia, IVIg = intravenous immunoglobulin, MD-CMML = myelodysplastic-chronic myelomonocytic leukemia, MONO = monocytes, PLT = platelets, Pred = prednisone, TPO = thrombopoietin, WBC = white blood cells.
IDH1, ASXL1, SF3B1, and SRSF2 genes, but only TET2 (tet methylcytosine dioxygenase 2) and SRSF2 (serine and arginine rich splicing factor 2) mutations were detected. No BCR-ABL1, TEL-PDGFRA, TEL-PDGFRB, NIN-PDGFRB, GIT2-PDGFRB, HIP1-PDGFRB, BCR-PDGFRB, and BCR-FGFR1 fusion genes were detected by PCR. The karyotype was 46, XX [20]. The patient received 12 courses of decitabine from September 2014 to June 2016. During the first 9 courses of decitabine therapy, transient thrombocytopenia appeared, but restored to normal before the subsequent course. However, after 10 courses of decitabine, the patients exhibited persistent thrombocytopenia with a platelet count of 10–20 × 10^9/L. The BM aspirate showed hypoplasia of megakaryocytes with only 8 megakaryocytes per smear, and with micromegakaryocytes, hypolobated, and monolobar megakaryocytes. The BM biopsy also showed micromegakaryocytes, hypolobated, and monolobar megakaryocytes. The flow cytometric analysis of bone marrow aspirates showed 3.26% blasts. Physical examination

Figure 4. Morphology of bone marrow aspirate (A and B) and histopathology and immunohistochemistry of bone marrow biopsy (C–H) in case 2 patient (CMML with decitabine-induced thrombocytopenia). A. Megaloblastoid change of myelocyte, and increased monocytes (Wrights × 100). B. Micromegakaryocytes and monolobar megakaryocytes (Wrights × 100). C. Cluster of myeloid blasts (HE × 400). D. CD34 immunohistochemistry: cluster of myeloid blasts (IHC × 400). E. Hypolobated megakaryocytic (HE × 400). F. CD61 immunohistochemistry: megakaryocytes hyperplasia, micromegakaryocytes, hypolobated and monolobar megakaryocytes (HE × 400). G. CD68 immunohistochemistry: monocytes and macrophages positive (IHC × 400). H. AgNOR stain: + (×200). CMML = chronic myelomonocytic leukemia.
did not reveal any lymphadenopathy, hepatomegaly, or splenomegaly. The patient was diagnosed as decitabine therapy-induced thrombocytopenia.

After admission in June 2016, the patients received 50 mg/d eltrombopag. The platelet count was increased to $30 \times 10^9/L$ after 3 days, to $140 \times 10^9/L$ by 1 week later, and then to $200 \times 10^9/L$ after 9 days. Subsequently, the eltrombopag dose was gradually decreased. After 1 month, eltrombopag administration was stopped due to financial issues, the platelet count was decreased to $41 \times 10^9/L$, but was stable at $\sim 30 \times 10^9/L$ for 3 months (Fig. 6). Then the patient refused to detect the platelet counts, however, she did not need platelet transfusion for 12 months (till July 2017). No adverse effects such as liver damage, diarrhea, or nausea, were observed.

3. Discussion
According to the 2016 WHO classification, the diagnostic criteria of CMML were as follows: peripheral blood monocytosis $>1 \times 10^9/L$; no Philadelphia chromosome or BCR-ABL1 fusion gene; no rearrangement of PDGFRA or PDGFRB; $<20\%$ blasts in the peripheral blood and bone marrow; dysplasia present in one or more myeloid lineages; if myelodysplasia is minimal or absent, CMML can still be diagnosed and if an acquired, clonal cytogenetic or molecular cytogenetic abnormality is demonstrated in the hematopoietic stem cell or if the monocytosis has persisted for $>3$ months, and other causes of monocytosis have been excluded. Case 1 was diagnosed as CMML according to criteria 1 to 4 and 5b, that is, ZRSR2 mutation with no other cause of monocytosis, and as MD-CMML with WBC count $<13.0 \times 10^9/L$. Case 2 was diagnosed as CMML, meeting all 5 of the above criteria, and as MP-CMML with WBC count $>13.0 \times 10^9/L$.

CMML is associated with various autoimmune diseases. The incidence of autoimmune diseases with MDS is 10% to 30%, and autoantibodies are detected in $\sim 50\%$ of patients with MDS. The phenomenon of autoimmune diseases in CMML may be associated with monocyte dysfunction, leading to persistent immune reactions, and increased production of autoantibodies.

CMML-associated ITP is rare and is easily misdiagnosed. Only 13 cases of CMML-associated ITP have been reported in the literature between 1984 and 2013, and 8 cases of CMML were identified in a retrospective cohort study of 565 ITP patients in 2014. To date, $\sim 21$ cases of CMML-associated ITP have been reported. Case 1 in our study was diagnosed as ITP according to the markedly increased megakaryocyte number ($>600$ megakaryocytes/smear) and increased immature megakaryocytes in BM aspirate, and lack of splenomegaly. Case 2 was considered as drug-induced thrombocytopenia because of the...
decreased number of megakaryocytes and dysplasia following decitabine therapy. When we treat CMML-associated ITP, the thrombocytopenia could be treated following the guideline on the primary ITP. Three patients with CMML-associated ITP were treated by using another TPO-RA, romiplostim, in a retrospective cohort study in 2014,[16] with complete remission observed in 1 patient and partial remissions in the 2 other patients. In our study, case 1 was a patient with CMML-associated ITP who had treatment failures with prednisone, IVlg, TPO, and CsA, and case 2 was a patient with decitabine-induced thrombocytopenia, both 2 patients rapidly achieved complete remission after using eltrombopag. Notably in case 1 patient, the WBC and monocyte counts were markedly increased following corticosteroid treatment. The corticosteroid may stimulate interleukin-1 and granulocyte-macrophage colony stimulating factor to induce proliferation of colony forming unit-granulocytes-macrophages, which can increase monocyte production.[17] Therefore, the use of corticosteroids in patients with CMML-associated ITP is not appropriate.

One study of eltrombopag use in patients with primary chronic refractory ITP showed that the response rate in the eltrombopag group was 59% comparing with 10% in the placebo group.[16] The RAISE study showed that platelet counts were increased to > 50 x 10^9/L in 79% of patients in the eltrombopag treatment group compared with 28% of patients in the placebo group.[18] In vitro, eltrombopag stimulated normal megakaryocyte production in acute myelogenous leukemia and MDS bone marrow cultures and dose not influence proliferation of malignant cells, but decreased their numbers.[19,20] There are several clinical trials currently using eltrombopag in patients with low-risk, moderate-risk, and high-risk MDS, in which eltrombopag was effective in 37% to 57% patients.[21] In our study, both ITP and decitabine therapy-induced thrombocytopenia in CMML patients were very successful to eltrombopag therapy. To the best of our knowledge, this is the first reported case (case 1) of the successful treatment of CMML-associated ITP with eltrombopag.

Modi et al[22] successfully treated severe thrombocytopenia with the use of eltrombopag in a patient with CMML after 4 courses of decitabine therapy, but the cause of thrombocytopenia in this patient could be the drug-induced thrombocytopenia just like the case 2 patient, and CMML-induced thrombocytopenia cannot be ruled out because of no bone marrow biopsy analysis was performed. Another report was from Ramadan et al[23] that eltrombopag was used in 7 patients with CMML after hypomethylating agents failure. Only 1 patient had a hematological improvement and 2 patients became platelet transfusion-independent. Unfortunately, 5 patients developed leukocytosis, 4 patients showed peripheral myeloblasts after treatment, and 1 patient developed grade 3 fibrosis from grade 0 to 1 at baseline. The cause of thrombocytopenia in these patients could also be the CMML or drug-induced thrombocytopenia. We have not observed such adverse effect of eltrombopag in case 2 patient compared with CMML patients of Ramadan et al, because the CMML itself in case 2 was under the control. Therefore, eltrombopag should be used with caution in the treatment of uncontrolled CMML patients.

The common adverse effects of eltrombopag include hepatotoxicity, fatigue, nausea, diarrhea, vomiting, peripheral edema, epistaxis, anemia, constipation, dizziness, headache, abdominal pain, backache, infection, myelobrosis, thrombosis, and others. It has been recommended to use eltrombopag at an initial dose of 50 mg/d in Westerners and 25 mg/d in Asian patients. In a Japanese clinical trial, the initial dose of eltrombopag was 12.5, 25, or 50 mg/d, with a median application time of 27.5 months (range, 9.9–23.3 mo). In this previous study, there were no obvious differences in adverse effects among the 3 groups and no patients required treatment termination due to the adverse effects of eltrombopag.[24] In our study, 2 patients were treated with eltrombopag using an initial dose of 50 mg/d, with no any adverse effects observed.

4. Conclusion

The thrombocytopenia in CMML patients is usually attributed to impaired marrow production caused by CMML, or as an adverse effect to chemotherapy. Thrombocytopenia can be caused by ITP, however, this is very rare and easily misdiagnosed. Our results indicate that the routine approaches for treating ITP, such as the use of corticosteroids, are not appropriate for patients with CMML-associated ITP. Eltrombopag may be safe and effective in patients with CMML-associated ITP and in those with decitabine therapy-induced thrombocytopenia.

Acknowledgments

The authors would like to thank Wei Wang, Li Gao, and Yin Tang from the Hematologic Laboratory in China-Japan Friendship Hospital for their contribution in providing figures of flow cytometric analysis, providing gene detected, and cytogenetic analyzed. And thank Ying Cai from Department of Laboratory Medicine in China-Japan Friendship Hospital for her contribution in providing cytomorphology figures of bone marrow smear. Also, thank Jie Lin from Department of Pathology in China-Japan Friendship Hospital for their contribution in providing figures of bone marrow biopsy.

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