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by Ji-Mo Jian, Zi-Jing Ye, Hong-Yuan Hao, Cheng-Lu Yuan and Jun Du

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Avatrombopag as a novel salvage therapy for refractory thrombocytopenia in *THPO*-mutated congenital amegakaryocytic thrombocytopenia after allogeneic hematopoietic stem cell transplantation

Ji-Mo Jian[1], Zi-Jing Ye[2], Hong-Yuan Hao[1], Cheng-Lu Yuan[1], and Jun Du[3*]

1. Department of Hematology, Qilu Hospital of Shandong University, Qingdao, Shandong, 266035, China.
2. Department of Clinical Medicine, Shanghai Jiao Tong University School of Medicine, Shanghai, 200025, China.
3. Department of Hematology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200127, China.

***Corresponding author：**

Jun Du, Department of Hematology, Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai, 200127, China.

Email: dujun-pathfinder@outlook.com

Authors' contributions:

Ji-Mo Jian: Conceptualization, methodology, investigation, resources, data curation, funding acquisition; writing - original draft, writing - review & editing.

Zi-Jing Ye: Methodology, data curation, visualization, writing - original draft, writing - review & editing.

Hong-Yuan Hao: Resources, writing - review & editing.

Cheng-Lu Yuan: Resources, writing - review & editing.

Jun Du: Conceptualization, methodology, resources, supervision, project administration, writing - review & editing.

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Congenital Amegakaryocytic Thrombocytopenia; Avatrombopag; THPO Mutation; Thrombopoietin Receptor Agonist

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare inherited bone marrow failure syndrome characterized by severe thrombocytopenia and absent or markedly reduced megakaryocytes in the bone marrow, without congenital anomalies, often progressing to aplastic anemia or secondary hematologic malignancies [1]. Here, we report a case of CAMT caused by a homozygous THPO mutation successfully managed with avatrombopag, along with a literature review. The study was approved by the institutional ethics committee, and written informed consent for publication was obtained.

A 6-year-old boy was admitted due to diarrhea more than 1 month after birth on April 22, 2017. Blood tests showed: WBC 7.61 $\times 10^9$/L, NEU 0.92 $\times 10^9$/L, RBC 3.34 $\times 10^{12}$/L, HGB 113 g/L and PLT 38 $\times 10^9$/L; stool occult blood was positive. The patient received antidiarrheal treatment and subsequently improved. During follow-ups, persistent thrombocytopenia was observed. The patient presented with intermittent cutaneous petechiae, which resolved spontaneously within 2-3 days. Occasional epistaxis occurred but was controlled with local compression. Easy bruising was noted following minor trauma. No further laboratory evaluation or specific treatment was performed at that time.

On May 20, 2018, he was readmitted for epistaxis. Hematological evaluation revealed: WBC 6.25 $\times 10^9$/L, NEU 0.21 $\times 10^9$/L, RBC 2.39 $\times 10^{12}$/L, HGB 79g/L, PLT 11 $\times 10^9$/L. Bone marrow aspiration from the sternum revealed a preserved marrow cellularity with a decreased granulocyte proportion and without dysplasia. The erythroid and lymphoid lineages showed no abnormalities. At low-power magnification ($\times$100), 15 megakaryocytes were observed: 1 immature, 12 mature without platelet formation, and 2 naked nuclei. Platelets were rare and scattered. Peripheral blood smear showed a reduced granulocyte proportion, mild erythrocyte anisocytosis, and rare scattered platelets. Flow cytometry, bone marrow karyotyping, comet assay, and mitomycin C testing revealed no significant abnormalities. Genetic testing for congenital bone marrow failure syndromes showed no definite relevant mutations. The patient received

corticosteroids, methylprednisolone, platelet transfusion, and supportive therapy, followed by oral prednisone (1.5mg/kg/day). Follow-up blood tests showed platelet counts fluctuating between 17-21 $\times 10^9$/L.

On July 5, 2018, whole-exome sequencing (WES) identified a homozygous mutation in the THPO gene (c.355C>T, p.R119C). Pedigree validation confirmed the mutation was inherited from both heterozygous, non-consanguineous parents. This variant has been classified as pathogenic and reported in CAMT patients. After several febrile episodes, the patient's platelet count further decreased and received platelet transfusions. Oral cyclosporine had been initiated during the diagnostic work-up, when aplastic anemia had not yet been completely excluded, but was poorly tolerated and discontinued. Other potential etiologies were also considered but were not supported. Immune thrombocytopenia was considered unlikely given the early-onset persistent thrombocytopenia, progressive bone marrow failure, and identification of a homozygous THPO mutation. Aplastic anemia was excluded based on preserved marrow cellularity, and myelodysplastic syndromes were not supported due to the absence of dysplasia and normal cytogenetics.

Follow-up bone marrow examinations after diagnosis demonstrated hypocellularity and a progressive attrition of megakaryocytes, culminating in complete depletion by November 2019. This dynamic change was consistent with the natural course of CAMT, characterized by gradual depletion of megakaryocytes over time. Given the progressive bone marrow failure, allogeneic hematopoietic stem cell transplantation (allo-HSCT) was performed to restore hematopoiesis.

The patient underwent allo-HSCT on August 6, 2020 (day 0), receiving peripheral blood stem cells from a fully HLA-matched unrelated donor. Prior to transplantation, the patient received three courses of romiplostim, which resulted in a transient platelet increase after the first dose but no sustained response. Pre-transplant evaluation on July 23, 2020, showed WBC 5.02 $\times 10^9$/L, NEU 0.34 $\times 10^9$/L, RBC 2.64 $\times 10^{12}$/L, HGB

100g/L, PLT 9 ×10⁹/L. On July 27, 2020, conditioning was performed with a regimen consisting of fludarabine (30 mg/m²/day, days −7 to −4), busulfan (0.8 mg/kg every 6 hours, days −8 to −6), cyclophosphamide (30 mg/kg/day, days −10 to −9), antithymocyte globulin (2 mg/kg/day, days −4 to −3), and melphalan (100 mg/m², day −3). Granulocyte engraftment occurred on day +10. Bone marrow chimerism analysis by short tandem repeat on day +13 post-transplant demonstrated full donor chimerism, which was sustained in five assessments on bone marrow or peripheral blood samples within 5 months. A bone marrow smear performed in November 2020 showed the presence of 5 megakaryocytes, while platelets were rarely observed, indicating partial restoration of megakaryopoiesis following allo-HSCT but inadequate platelet production. WES on May 31, 2021 showed disappearance of the previously identified homozygous THPO mutation (c.355C>T, p.R119C), consistent with donor-derived hematopoiesis after allo-HSCT. Following allo-HSCT, platelet counts showed a gradual increase to approximately 30 ×10⁹/L.

To facilitate post-transplant thrombopoietic recovery, the patient received multiple thrombopoietin receptor agonists (TPO-RAs), including recombinant human thrombopoietin (300 U/kg/day for 14 days), herombopag (2.5 mg/day for 2 weeks followed by 5 mg/day for 4 weeks), and romiplostim (10 μg/kg/week for 4 weeks). None produced a significant platelet response. Subsequently, starting in September 2022, the patient took oral avatrombopag.

On October 11, 2022, blood tests showed WBC 4.15 ×10⁹/L, NEU 1.18 ×10⁹/L, RBC 3.54 ×10^{12}/L, HGB 109g/L, PLT 39 ×10⁹/L. Thereafter, blood count gradually increased. On February 21, 2023, blood tests showed WBC 5.58 ×10⁹/L, NEU 3.04 ×10⁹/L, RBC 3.27 ×10^{12}/L, HGB 106g/L, PLT 45 ×10⁹/L. To date, following 3.5 years of continuous oral avatrombopag monotherapy for maintenance, the patient has achieved a marked and sustained hematologic response, with platelet counts remaining stably above 100 × 10⁹/L. The therapeutic regimen was well-tolerated, with no adverse events **(Figure 1)**.

The thrombopoietin (THPO) gene encodes thrombopoietin (TPO), the primary regulator of megakaryopoiesis and platelet production. Mutations can influence translational efficiency and circulating TPO levels [2]. TPO is predominantly produced by hepatocytes [3], and circulating TPO levels are mainly regulated by THPO gene expression and c-MPL-mediated clearance on platelets and megakaryocytes [4]. Binding of TPO to c-MPL activates JAK2 and downstream STAT5, MAPK, and PI3K/AKT signaling, thereby promoting megakaryopoiesis, platelet activation, and hematopoietic stem cell maintenance [3, 5].

CAMT is a rare autosomal recessive disease [6]. Most cases result from MPL mutations, whereas a minority are caused by THPO mutations. MPL mutations impair TPO signaling, resulting in severe thrombocytopenia due to absent megakaryocytes and progressive bone marrow failure [6, 7]. Allo-HSCT remains the only curative treatment, with HLA-identical sibling donor transplantation being first-line [7]. Recent European Society for Blood and Marrow Transplantation registry data reported favorable outcomes following allo-HSCT, with 6-year overall and disease-free survival rates of 85.6% and 66.9%, respectively [8].

However, the role of allo-HSCT in THPO mutation-associated disease remains less well defined [9]. Cumulative evidence indicates that allo-HSCT may be inadequate to directly or fully rectify thrombocytopenia in these patients, possibly because THPO mutations confer a hematopoietic cell-extrinsic defect, as thrombopoietin is primarily produced by hepatocytes [9]. Nevertheless, once progressive bone marrow failure develops during the natural course of CAMT, allo-HSCT remains an important therapeutic option for restoring hematopoiesis. TPO-RAs have emerged as potential treatments for hereditary thrombocytopenias, including THPO mutation-associated CAMT [9]. These agents bind to the c-MPL receptor and activate downstream signaling pathways, effectively mimicking the physiological action of endogenous TPO.

Romiplostim is a representative peptide-based TPO-RA that binds the extracellular

domain of the c-MPL receptor and may competitively interact with endogenous thrombopoietin[10], thereby activating signaling pathways [11]. A previous report has described a family with homozygous THPO p.R119C mutation in which three affected siblings responded well to romiplostim, while their parents were asymptomatic heterozygous carriers. This mutation impairs TPO-MPL interaction and reduces downstream signaling by approximately 50% compared with wild-type TPO [12]. In our case, the patient with homozygous THPO c.355C>T (p.R119C) showed partial hematologic improvement following allo-HSCT, but did not respond to romiplostim.

Avatrombopag is a small-molecule oral TPO-RA binds to the transmembrane domain of the c-MPL receptor and activates downstream signaling pathways, thereby promoting megakaryocyte proliferation and platelet production [13]. Currently, avatrombopag is approved for the treatment of pediatric patients aged ⩾1 year with persistent or chronic immune thrombocytopenia. Although its use in CAMT has not been widely reported, in our patient, avatrombopag resulted in a rapid and sustained hematologic response, with achievement of transfusion independence.

In this case, the differential efficacy of the two TPO-RAs may be explained by differences in receptor interactions. Romiplostim binds the extracellular domain of the c-MPL receptor in a manner similar to endogenous TPO, whereas avatrombopag binds the transmembrane domain. Previous studies have shown that THPO variants may influence thrombopoietin signaling through altered ligand-receptor dynamics [12]. Consequently, romiplostim may fail to sustain robust receptor activation, whereas avatrombopag activity appears to be preserved **(Figure 2)**. However, whether mutant TPO affects ligand-receptor interactions involving TPO-RAs remains unproven.

In summary, this case describes sustained hematologic recovery in a patient with THPO mutation-associated CAMT who underwent allo-HSCT for progressive bone marrow failure and subsequently achieved durable platelet recovery with avatrombopag. Following allo-HSCT, partial restoration of hematopoiesis was observed, while

subsequent avatrombopag therapy was associated with transfusion independence with platelet counts maintained stable at a relatively normal range. These findings support further investigation of allo-HSCT and avatrombopag in patients with THPO mutation-associated CAMT. The differential response to romiplostim and avatrombopag also highlights the need for further studies to clarify the effects of THPO mutations on TPO receptor activation and responsiveness to TPO-RAs.

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Figure 1.

Test results and treatment timeline of the patient with THPO mutation-associated CAMT.

The 6-year-old male patient presented with progressive thrombocytopenia and was diagnosed with THPO-mutation CAMT based on bone marrow examination, complete blood count and genetic testing. The patient subsequently received sequential and combined therapy with allo-HSCT and avatrombopag, resulting in marked hematologic improvement. Platelet counts have since remained stably above 100 $\times 10^9$/L during long-term follow-up.

Red blocks indicate ineffective treatment responses, whereas green blocks indicate effective responses.

Abbreviations: CBC, complete blood count; HGB, hemoglobin; PLT, platelet count; BMF, bone marrow failure; allo-HSCT, hematopoietic stem cell transplantation; CAMT, congenital amegakaryocytic thrombocytopenia; IVIG, intravenous immunoglobulin; TD, therapeutic dose; sc, subcutaneous injection; qd, once daily.

Figure 2.

Proposed schematic model of sequential and combined allo-HSCT and avatrombopag therapy in THPO mutation-associated CAMT.

Allo-HSCT contributes to the restoration of the bone marrow microenvironment and hematopoietic capacity but may be insufficient to directly and fully correct thrombocytopenia. Avatrombopag activates the c-MPL receptor and stimulates downstream signaling pathways, thereby promoting megakaryocyte proliferation and platelet production. The sequential and combined use of allo-HSCT and avatrombopag may exert complementary effects, potentially leading to sustained platelet recovery, transfusion independence, and long-term stable platelet counts.

Sex: Male
Age: 6 years old
Diagnose: CAMT (THPO mutation)

Test Results

2017-04-22

CBC
HGB 113 g/L
PLT 38 ×10⁹/L

2018-05-20

CBC
HGB 79 g/L
PLT 11 ×10⁹/L

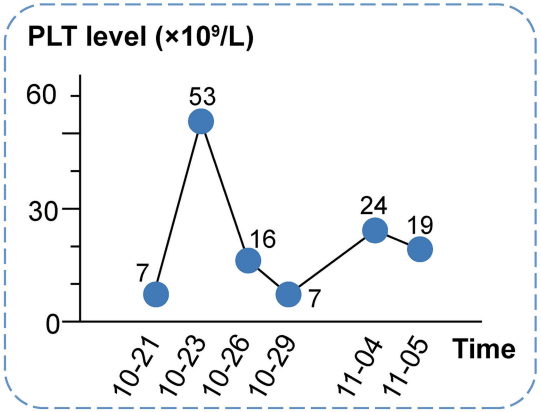
Bone Marrow
Megakaryocytes present without platelet production.

Additional tests
- flow cytometry (-)
- karyotyping: normal
- BMF gene panel (-)

2018-07-05

Whole-exome sequencing
THPO homozygous variant c.355C>T (p.R119C).

2019-10 ~ 2019-11



Treatment

- IVIG
- Methylprednisolone
- Platelet transfusion
- Prednisone 1.5 mg/kg/day

- Platelet transfusion
- Cyclosporine

romiplostim
- 2019-10-21 10ug/kg, sc
- 2019-10-28 20ug/kg, sc
- 2019-11-05 20ug/kg, sc

PLT transfusion
- 2019-10-21 x1TD
- 2019-10-29 x1TD

avatrombopag
Since 2023-03 20mg, qd

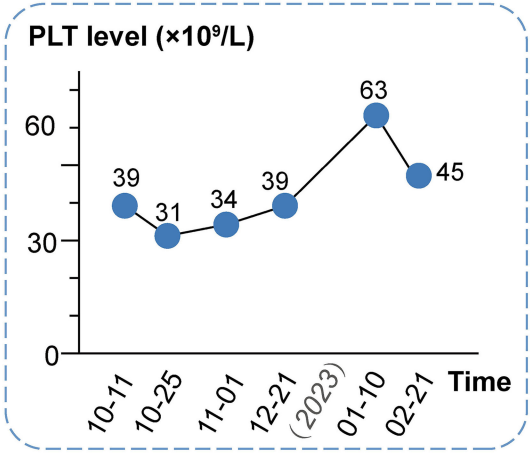
avatrombopag
2022-09 ~ 2023-03 10mg, qd

allo-HSCT
2020-08-06

2026-04

CBC
PLT maintained >100 ×10⁹/L.

2022-10 ~ 2023-02



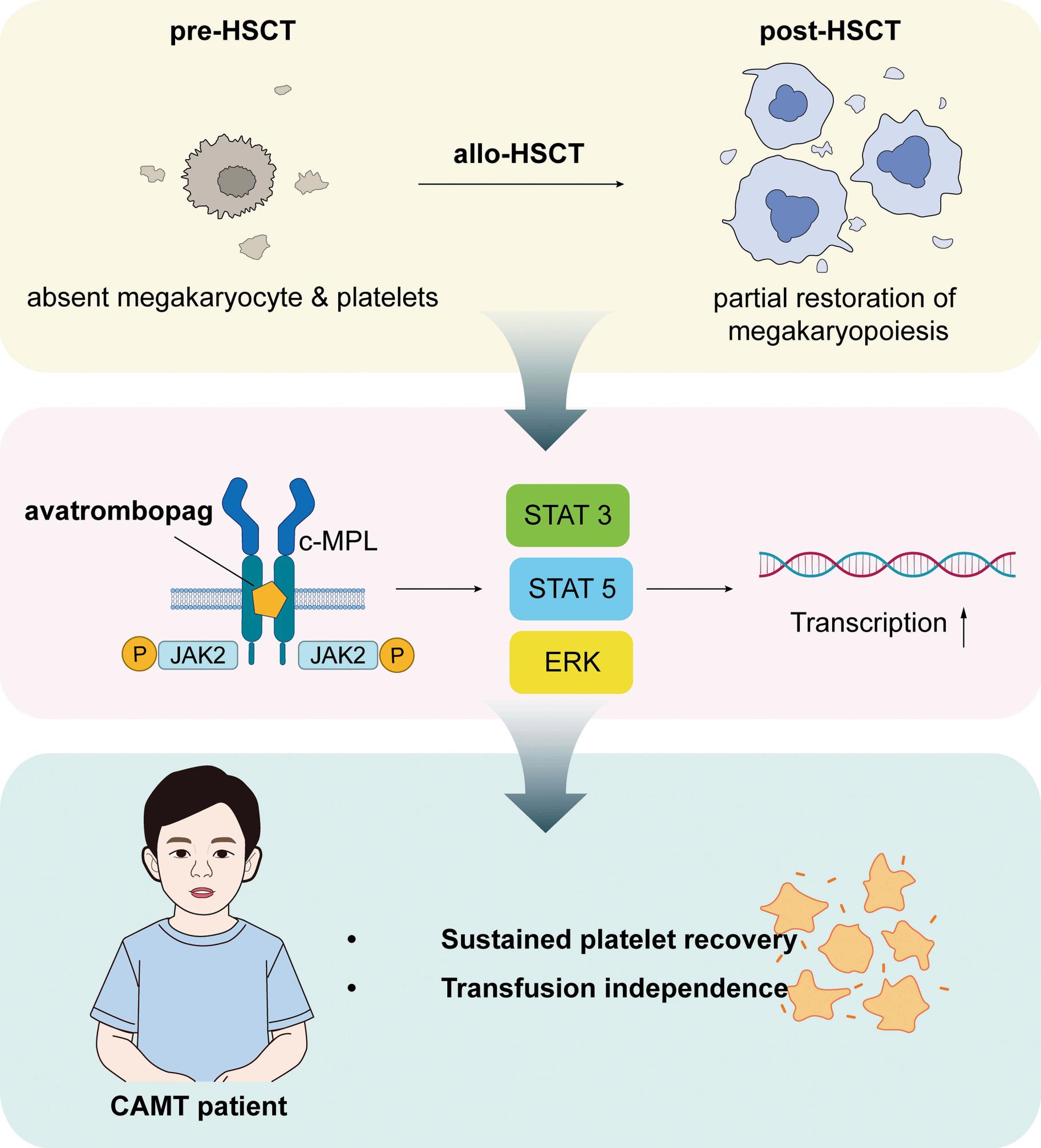
2020-09 ~ 2021-05

CBC
PLT uphill climbs to 30 ×10⁹/L.

Post-HSCT examinations
- Complete donor chimerism.
- THPO variant not detected.

2020-07-23

CBC
HGB 100 g/L
PLT 9 ×10⁹/L


pre-HSCT
post-HSCT
allo-HSCT
absent megakaryocyte & platelets
partial restoration of megakaryopoiesis
avatrombopag
c-MPL
P
JAK2
JAK2
P
STAT 3
STAT 5
ERK
Transcription
CAMT patient
Sustained platelet recovery
Transfusion independence