Treatment of Thrombocytopenia After Allogeneic Hematopoietic Stem Cell Transplantation with Eltrombopag

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History

• A 52 years old male patient

• Chief complain: Weight loss, fatigue

• Physical examination: Splenomegaly (16cm), hepatomegaly (20cm),

• Medical history: hypertension, chronic obstructive lung disease
Diagnosis

- Lab findings were as follows:
  - Wbc: 43x10^3 /µL
  - Hg: 6.7 g/dL
  - Plt: 143 x10^3 /µL

- Bone Marrow Bx: B lenfoblastic Leukemia with 80% blasts (CD34, PAX-5(+)).

- Diagnosed mature B-ALL on March, 2015
Risk Category

- Normal karyotype
- T(9,22) : Negative
- Age, 52y
- WBC > 30000 /µL
- Flowcytometry: Matur B-ALL

Evaluated as high risk
Treatment

- **Hoelzer I** (Prednisolon, Daunorubicin, Vincristine, L-Asparaginase)

- **Hoelzer II** (Cyclophosphamide, Ara-C, Methotraxate, 6-Mercaptopurine, prophylactic cranial radiotherapy)

- **Hoelzer III** (Ara-C, mitoxantrone)

- **Control biopsy: Complete Remission**
Treatment

- Patient was in complete remission and underwent Allo-HSCT

- Time from diagnosis to HSCT was: 5 months
Donor

- Female (his sister)
- Age, 65
- Full HLA matched (10/10)
- A Rh+ (Patient: B Rh-)
- She had no comorbidity
HSCT

- Conditioning regimen consisted of
  - Busulphan 4x0,8mg/kg, IV (on the day -6,-5,-4)  (total 9,6mg IV)
  - Fludarabine 30mg/m2/d (-8,-7,-6,-5,-4,-3)
  - ATG fresenius rabbit , 10mg/kg (-2,-1)
- CD34 : 7x10^6 /kg , 760ml
- GVHD prophylaxis : Mycophenolate mofetil+Methotrexate
  15mg/m2 (+1,+3,+6,+10),
- Stem cell source : peripheral blood
HSCT

- Neutrophil engraftment occurred on the day +18
- Platelet engraftment occurred on the day +15

Postransplantation on day +50

- Patient received donor leukocyte infusion (DLI)
Postransplantation on day +60

- Wbc: 870 (Neutrophil:20) /µL
- Hg: 8 g/dL
- Plt: 8 x10^3 /µL
- Bone marrow bx: Hypocellular
- Erythrocyte and platelet suspension required
• Evaluated as secondary engraftment failure

• Patient received G-CSF for a week without any recovery

• We planned second Allo-HSCT

(about 3 months, between two transplantations)
Second Transplantation

- Same donor

- Conditioning regimen consisted of;
  - ATG fresenius rabbit, 10mg/kg (-2,-1)
  - CD 34 : 8.8x10^6 cells /kg

GVHD prophylaxis: Mycophenolate mofetil + Methotrexate

15mg/m2 (+1,+3,+6,+10)
Second Transplantation

- Neutrophil engraftment was achieved on day +21
- However platelet counts remained below 10,000 / μL
- Platelet transfusions required (2-3 times in a week)
Postransplantation +40th day

- Wbc: $3 \times 10^3$ /µL (Neutrophil: 1470)
- Hg: 11 g/dL
- Plt: $9 \times 10^3$ /µL
- Intravenosus immunglobulin (two times) was administered without any recovery
Postransplantation +60th day

- **Wbc**: $3 \times 10^3 \, \mu L$
- **Hg**: 11 g/dL
- **Plt**: $7 \times 10^3 \, \mu L$
- Patient had mucosal hemorrhagies a few times
Postransplantation +60th day

- Bone Marrow Aspiration: megakaryocytes was decreased

- No GVHD, no viral infection or no disease relapse were observed.
Postransplantation +60th day

- Eltrombopag 50 mg daily was started

- After 10 days; Patient had hemoptysis (not massive) Control Plt: 23x10^3 µL

- Dose was increased to 100 mg/day
Postransplantation +90th day

- 30 days after Eltrombopag treatment,

  → Control Plt: \(32 \times 10^3/\mu l\)

- We continued to eltrombopag treatment for 3 months

- After 3 months plt count was >100000 / The treatment was stopped

- Thrombocyte counts are between: 250000-300000 /\(\mu l\)
• Now, 17 months after transplantation, patient is well

• Patient has full chimerism

• Not taking immunosuppressive treatment
PIT

- Prolonged isolated thrombocytopenia (PIT) was defined as the recovery of other cell counts with dependence of platelet transfusions more than 3 months (1)

- Reported between 2,6-37% in HSCT

- Associated with transplantation related mortality and over-all survival (2,3)

PIT

- PIT has several possible causes
  - Increased platelet destruction
    (associated with infection, immun-mediated processes, viral infection, adverse effects of medication)
  - Impaired platelet production
    (associated with poor graft function)
  - Or a combination of these mechanisms

Discussion

After HSCT, platelet recovery is influenced by many factors

- Donor type

- (Unrelated grafts lower plt counts)

- CMV infections

- Acute GvHD

- Infused stem cell dose

but not by stem cell source

Discussion-2

- Poor haematopoietic recovery treatment options*
  - DLI infusions
  - Immunosuppressive therapy (such as ATG)
- Corticosteroids, rituximab, intravenous immunoglobulin have been used to treat thrombocytopenia after HSCT **

Discussion-3

• Eltrombopag: Thrombopoietin receptor agonist*
  - Stimulating megakaryocyte growth and differentiation
  - It’s used orally

Discussion-4

- Has been used for years in treatment of immune thrombocytopenia (FDA)

- There are also studies reported the use of eltrombopag for thrombocytopenia after HSCT*

In our case

- The reason of secondary engraftment failure might be administration of profilactic DLI, in first HSCT
- Elderly donor might be the reason of prolonged isolated thrombocytopenia
- Any adverse affect was observed with eltrombopag treatment
- There was a gradual increase in platelet count
Conclusion

- Prolonged isolated thrombocytopenia is a major problem due to increased morbidity and mortality after Allo-HSCT

- No standard treatment approach has been available

- Use of Eltrombopag is getting widespread in PIT treatment

- Eltrombopag is a good therapeutic agent for thrombocytopenia caused by poor graft function with minimal toxic side effect