Rare post-transplant complications

The management of poor graft function

F. Patriarca
Azienda OUI- Università di Udine
POOR GRAFT FUNCTION (PGF)

DEFINITION

- cytopenia in at least 2 hematopoietic lines (neutrophil count $\leq 1.5 \times 10^9/L$, platelet count $\leq 30 \times 10^9/L$, Hb $\leq 8.5$ g/dL) for at least 2 consecutive weeks beyond day +14 post transplantation (primary PGF) or at any time point after achieving of engraftment (secondary PGF)

- transfusion requirement

- presence of full donor chimerism

- absence of severe GVHD, cytomegalovirus (CMV) reactivation, relapse, or drug-related myelosuppression.
RISK FACTORS FOR PGF

- Non HLA-id donor type
- HLA mismatch
- ABO incompatibility
- low cell dose
- uncontrolled GVHD
- viral infections
- myelotoxic agents

Case matched comparison between 26 pts with PGF and 104 pts from a selected control group, all transplanted from haploidentical donors

Sun YQ et al, Ann Hemat 2015
Bone marrow microenvironment in PGF

Kong Y, BMT 2016
<table>
<thead>
<tr>
<th>Clinical Case 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personal history:</strong></td>
</tr>
<tr>
<td>- Male, born 1962</td>
</tr>
<tr>
<td>- Job: mountaineer</td>
</tr>
<tr>
<td>- Married, no sons</td>
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<tr>
<td>- 2003: Left parotidectomy (pleomorfus adenoma)</td>
</tr>
<tr>
<td>- 2007: Lumbar slipped discs</td>
</tr>
<tr>
<td>- 2007: bronchial asma</td>
</tr>
<tr>
<td>- 2009: HBV contact</td>
</tr>
<tr>
<td><strong>Family history:</strong></td>
</tr>
<tr>
<td>- A sister born in 1961 with lung cancer</td>
</tr>
<tr>
<td><strong>Hematological history:</strong></td>
</tr>
<tr>
<td>- 6/2009: severe cytopenia</td>
</tr>
<tr>
<td>- marrow biopsy: severe aplastic anemia, 5% cellularity</td>
</tr>
<tr>
<td>- Karyotype: 46 xy</td>
</tr>
<tr>
<td>- Phenotype: non EPN clone</td>
</tr>
</tbody>
</table>
Treatment history:

- 6/2009: ATG Thymoglobulin course+Cya+PDN
- Darbopoietin between July and November 2009
- No response → unrelated donor search
- Testosterone (Andriol) between October 2009 and April 2010

Allogeneic transplant History

- date: April 30, 2010
- Donor unrelated 10/10 matched, ABO matched
- Conditioning: Flu-Cy-TBI 2 Gy-Thymo
- BM infusion: CD34+ 2,37 x 10^6/kg

Clinical post-transplant follow-up:

+ 10: E.coli and Enterococcus faecalis sepsis
+ 32: acute GVHD grade 2 (liver, high GI) responsive to 2 mg/kg 6 metil-PDN
+ 26: neutrophil count > 1 x 10^6/L
+ 100 no platelets recovery
+ 108: low GI GVHD
PRIMARY PGF DIAGNOSIS

+ 180: Hb 7.9 g/dL, PLT 15 x 10^9/L, WBC 0.9 x 10^6/L

+ 180: chimerism marrow: 97% donor; peripheral blood :100% donor

+180: bone marrow biopsy: cellularity 10%

•DNA-CMV,EBV, HHV6, adenovirus negative

•On treatment with CyA, PDN, filgrastim twice weekly, 1 platelets and 1 red cells transfusion weekly, deferasirox 1000 mg daily.

•Request second donation of the same unrelated donor
REINFUSION OF DONOR STEM CELLS

54 pts with primary or secondary PGF

**Figure 1.** Cumulative Incidence (CI) of trilineage recovery in the three groups. Recovery was significantly better in patients receiving CD34-selected boost donor cells.

**Figure 2.** Cumulative Incidence (CI) of non-relapse mortality (NRM) in the three groups. NRM was significantly lower in patients receiving CD34-selected boost donor cells.

Larocca A et al, Haematologica 2006
41 pts with primary or secondary PGF treated with CD34+ selected PB cells

### Table 1: Clinical Characteristics of 41 Patients Receiving Boost CD34+ Selected Cells

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>41</td>
</tr>
<tr>
<td>Conditioning before CD34+ PB</td>
<td>None</td>
</tr>
<tr>
<td>GVHD prophylaxis before CD34+ PB</td>
<td>None</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>37 (18-52)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>ALL n = 7, AML n = 8, CML n = 8, MFI n = 4, NHL n = 6, SAA n = 4</td>
</tr>
<tr>
<td>Donor type</td>
<td>HLA id n = 12, MUD n = 18, family mm n = 11</td>
</tr>
<tr>
<td>Source</td>
<td>BM n = 32, PB n = 9</td>
</tr>
<tr>
<td>Conditioning regimen at first HSCT</td>
<td>Myeloablative, n = 25 (58%)</td>
</tr>
<tr>
<td>CMV before CD34+ cell infusion</td>
<td>30 (73%)</td>
</tr>
<tr>
<td>TMA before CD34+ cell infusion</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>GVHD before CD34+ cell infusion</td>
<td>Grade I n = 36 (78%); grade II n = 5 (12%)</td>
</tr>
<tr>
<td>Conditioning regimen before CD34+ cells</td>
<td>None</td>
</tr>
<tr>
<td>GVHD prophylaxis after CD34+ cells</td>
<td>None</td>
</tr>
<tr>
<td>Median CD34+ infused (range)</td>
<td>3.45 x 10^5/kg (.05-22.5)</td>
</tr>
<tr>
<td>Median CD34+ cells infused (range)</td>
<td>5.6 x 10^5/kg (2.5-10)</td>
</tr>
<tr>
<td>Median days from first allogeneic HSCT (range)</td>
<td>140 d (48-574)</td>
</tr>
<tr>
<td>Median platelet count at CD34+ infusion (range)</td>
<td>2.1 x 10^9/L (5-193)</td>
</tr>
<tr>
<td>Median neutrophil count at CD34+ infusion (range)</td>
<td>1.44 x 10^9/L (0-3.2)</td>
</tr>
<tr>
<td>Median Hb level at CD34+ infusion (range)</td>
<td>8.9 g/dL (6.9-11)</td>
</tr>
<tr>
<td>Acute GVHD after infusion</td>
<td>Grade II-III n = 9, grade IV none</td>
</tr>
<tr>
<td>Median follow-up (range)</td>
<td>12.45 d (94-415)</td>
</tr>
</tbody>
</table>

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**Figure 1.**
(A) 1 of acute GvHD grade II; no patient had grades III to IV. (B) Clot lineages recovery. (C) Actuarial survival. (D) Actuarial survival in patients stratified for clonality response: a significant advantage for patients with clonality recovery.
32 patients (44% MFI) with PGF received a CD34+ selected PBSC (Miltenyi Biotec), from 2002 to 2011 at Hamburg and Marseille, without additional conditioning.

The median interval from HSCT to CD34+ SCB was 5 months (range, 2 to 228).

The median amount of CD34+ cells was $3.4 \times 10^6$/kg b.w. (range, .96 to 8.30). The median amount of CD3+ T cells was $9 \times 10^3$/kg b.w. (range, 2 to 70).

Klyuchnikov E et al, BBMT 2014
20 pts with PGF (7 with primary and 13 with secondary PGF) received MSCs ($1 \times 10^6$/kg) one to three times at 28-day intervals. 17/20 were responsive within 100 d. 11/20 were dead because of infections.

Liu X et al Cell Transpl 2014
POOR GRAFT FUNCTION TREATMENT

- On December 16, 2010 (+ 266 after the first HSCT)
- reinfusion of CD34+ selected cells $11,46 \times 10^6$/Kg and CD3+ cells $1,15 \times 10^4$/Kg from the same unrelated donor, without conditioning and without modification of GVHD prophylaxis
Ottobre 2011: stavamo avanzando verso il campo base del Mera Peak, cima Himalayana di 6476 m, situato nella regione Nepalese di Sagarmatha. Dalla sua cima si possono vedere l'Everest, il Lhotse e il Cho Oyu (tutti > 8000 m).

Dopo i due trapianti, la coppia di alpinisti prima ha riprovato a salire i 4000 europei (Gran paradiso nel giugno 2011), poi il 6000 Himlayano (ottobre 2011) in previsione dell'8000 che scalò successivamente nel 2012.
LAST FOLLOW-UP 13/12/2016 (+79 months)

- IS withdrawal in December 2011

- Bilateral femoral osteonecrosis needing left (June 2013) and right (March 2015) hip replacement

- Skin cancer (basalioma) September 2014 (only exeresis)

- Hb 15 g/dL, PLT 160 x 10^9/L, WBC 4.5 x 10^6/L
**Family history:**
- a 56-year old sister non HLA id

**Personal history:**
- Female, born 1967
- Job: cotton mill worker
- Divorced, a 18-year old daughter
- 1983: mononucleosis
- 1999: breast cysts

**Hematological history:**
- 8/2015: ALL B with hyperleukocitosis (> 200 x 10^6/L)
- Phenotype: B common
- Karyotype: Ph+
Treatment history:

- Sept to Dic 2015: dasatinib
- HAM x 2 cycles (Dic 2015 and Feb 2016)
- Feb 2016: p190 +, persistent cytopenia with transfusion dependency

Allogeneic transplant History

- date: April 28, 2016
- Donor unrelated 7/8 matched, ABO minor mismatched
- Conditioning: 12 Gy TBI+Cy
- GvHD prophylaxis: Cya-MTX-Thymo
- BM infusion: CD 34 + 1,42 x 10^6/kg

Clinical post-transplant follow-up:

- Grade IV mucositis
- + 17: neutrophil count > 1 x10^6/L
- + 41: PLT count >50 x10^9/L
- Grade II skin acute GVHD treated with MP2 mg/Kg
Since day +60 she developed anemia needing RC transfusion and reduction of platelet count to $20 \times 10^9/L$. She showed no signs of immune hemolysis or transplant-associated microangiopathy (TAM) except LDH 728 UI/L.

days + 30 and + 90 = p190 negative, marrow chimerism 99% donor
day+100 : bone marrow biopsy: cellularity 20%
no GVHD, no CMV, EBV, HV6, adenovirus
on Cya, acyclovir, fluco, pentamidina aerosol, darbopoietin
Admitted on day + 142 with worsening pancytopenia and new-onset hypertension. Mild oral chronic GVHD
Hb 8.3 g/dL, PLT 16 x 10⁹/L, WBC 1.9 x 10⁶/L
LDH 834 UI/L, total bilirubin 1.38 mg/dl, aptoglobine 129 mg/dl, 2% schistocytes, creatinine 1.5 mg/dL
Normal C3, C4, sC5b-9

Assumed diagnosis of secondary poor graft function

Interventions:
• tapered Cya
• stopped enalapril and administered amliodipine
• considered for eltrombopag protocol
• initiated deferasirox, when renal function was normalized
Eltrombopag 50 mg since October 24, 2016
Cya stopped November 11, 2016
Deferasirox 500 mg since December 7, 2016
Eltrombopag in patients with delayed post transplant thrombocytopenia

ITP0511

STUDY DRUG: Eltrombopag

Phase II

First version, Nov 2012

INVESTIGATOR SPONSOR
Gruppo Italiano Malattie Ematologiche (GIMEMA)

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## Late-onset thrombocytopenia: UDINE experience

<table>
<thead>
<tr>
<th>Patients</th>
<th>71</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>52 (17-69)</td>
</tr>
<tr>
<td>Diseases</td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>AML/ALL/MDS</td>
<td>34 (48%)</td>
</tr>
<tr>
<td>CLL/HL/NHL/MM</td>
<td>32 (45%)</td>
</tr>
<tr>
<td>Primary Myelofibrosis</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>PNH</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Type of transplant:</td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>25 (35%)</td>
</tr>
<tr>
<td>MUD</td>
<td>46 (65%)</td>
</tr>
<tr>
<td>CONV</td>
<td>27 (38%)</td>
</tr>
<tr>
<td>RIC/NM</td>
<td>44 (62%)</td>
</tr>
<tr>
<td>Median CD 34 x 10^6/kg (range)</td>
<td></td>
</tr>
<tr>
<td>all</td>
<td>5.6 (0.8-12.7)</td>
</tr>
<tr>
<td>bone marrow (14)</td>
<td>2.5 (0.8-4.6)</td>
</tr>
<tr>
<td>PB (57)</td>
<td>6.4 (1.6-12.7)</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>21 (3–44)</td>
</tr>
</tbody>
</table>

Zaja et al. Am J Hematology 2011
Late-onset thrombocytopenia

<table>
<thead>
<tr>
<th>Median PLT count</th>
<th>27/71 (38%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 &lt; 100 $\times 10^9$/L</td>
<td>28 $\times 10^9$/L (7-86)</td>
</tr>
<tr>
<td>$\leq 50$ $\times 10^9$/L</td>
<td>8/27</td>
</tr>
<tr>
<td>$\leq 20$ $\times 10^9$/L</td>
<td>10/27</td>
</tr>
<tr>
<td></td>
<td>9/27</td>
</tr>
<tr>
<td>Median time (months) of LOT development</td>
<td>3 (1-13)</td>
</tr>
</tbody>
</table>

Type of thrombocytopenia:
- fluctuating: 7%
- chronic: 82%
- transient: 11%

Causes of thrombocytopenia:
- cGVHD/cGVHD + infections: 37%
- relapse: 26%
- idiopathic: 11%
- CMV: 15%
- microangiopathy: 3%
- poor graft function: 7.5%

Zaja et al. Am J Hematology 2011
Patients with cGVHD: 32/71 (45%)

<table>
<thead>
<tr>
<th></th>
<th>N.</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with LOT</strong></td>
<td>13 (41%)</td>
<td>8 (61.5%)</td>
</tr>
<tr>
<td><strong>Patients without LOT</strong></td>
<td>19 (52%)</td>
<td>2 (10.5%)</td>
</tr>
</tbody>
</table>

Zaja et al. Am J Hematology 2011
Patho-physiology of post SCT LOT

• Pathogenic process of cGVHD-related thrombocytopenia complex and only partially understood.
• Biological and clinical evidence support an autoimmune-like thrombocytopenia with increased platelet destruction
• This is also supported by the response to some therapeutic strategies used to treat classical immune thrombocytopenia including steroids, high dose intravenous immunoglobulin, splenectomy, and rituximab
• Impaired platelet production has also been suggested.
TPO levels in ITP are not or only mildly elevated

TPO levels are inversely related to the platelet and megakaryocyte mass, because these cells bind and degrade TPO.

Kosugi et al. Br J Haematol1996

The ITP paradox

Where it should be

Where it is
In summary, post transplant prolonged thrombocytopenia is associated with complex mechanisms, including impaired thrombopoiesis (prevalent) and increased platelet turnover. GCI and TPO levels similar to aplastic anemia.
Romiplostim

- Extracellular domain
- TPOR inactive → TPOR active
- Cell membrane
- Cytoplasm
- Signal transduction
- Increased platelet production and MKC proliferation

Eltrombopag

- Transmembran domain
- TPOR inactive → TPOR active
- Cell membrane
- Cytoplasm
- Signal transduction
- Increased platelet production
Analysis of regulatory T-cell changes in patients with idiopathic thrombocytopenic purpura receiving B cell–depleting therapy with rituximab

Roberto Stasi,¹ Nichola Cooper,² Giovanni Del Poeta,³ Elisa Stipa,⁴ Maria Laura Evangelista,¹ Elisabetta Abruzzese,⁴ and Sergio Amadori³

Improved regulatory T-cell activity in patients with chronic immune thrombocytopenia treated with thrombopoietic agents

Welli Bao,¹ James B. Bussel,² Susanne Heck,³ Wu He,³ Marissa Karpoff,² Nayla Boulad,² and Karina Yazdanbakhsh¹
Patho-physiology of post SCT LOT

TPO MIMETICS

May improve platelet count

May improve cGVHD

May improve post SCT outcome
Prospective, multicenter, phase II study ITP0511

Target populations
Patients who underwent allogeneic SCT because of NHL/HL/MM/ALL and developed delayed cGVHD-related thrombocytopenia.

Primary endpoint
• Efficacy (increase in PLT count)

Secondary endpoints
• Overall survival (comparison with historical control)
• Bleeding events

Exploratory endpoints
• Relationship between baseline TPO serum level and response
• Modifications of T-reg activity during therapy
**Inclusion criteria**

- Patients who underwent allogeneic SCT because of NHL/HL/MM ALL
- Patients who developed delayed cGVHD-related thrombocytopenia
- Platelet count $\leq 50,000$/mm$^3$ from month 2 from SCT
- Sibling, MUD, aplo-identical donor

**Exclusion criteria**

- SCT from cord blood
- Progressive non stabilized cGVHD
- Active DVT/VOD/microangiopathy
- Grade 3-4 hyperbilirubinemia
- Hepatic cirrhosis
- Active infections
Treatment
• Eltrombopag 50 mg/d for a max 24 months in responders.
• Possible increase (up to 75 mg/d) or decrease (up to 25 mg every other day) according to PLT count.
• In order to keep a PLT count between 50 and 150 x 10^9/L.

Efficacy assessment
• PLT count \geq 50 \times 10^9/L and doubling of baseline platelet count, two months after treatment with eltrombopag.
• Registration of bleeding according to the WHO bleeding scale

Safety assessment
• According to CTCAE
**Prospective, multicenter, phase II study ITP0511. status of the protocol**

<table>
<thead>
<tr>
<th>Centers enrolling</th>
<th>pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Udine Clinica Ematologica</td>
<td>3</td>
</tr>
<tr>
<td>Policlinico Universitario 3 Bergamo A.O. Papa Giovanni XXIII</td>
<td>2</td>
</tr>
<tr>
<td>Ematologia con trapianto-Universita' degli Studi di Bari Aldo Moro</td>
<td>1</td>
</tr>
<tr>
<td>Catania Cattedra di Ematologia - &quot;Ospedale &quot;Ferrarotto</td>
<td>1</td>
</tr>
<tr>
<td>S.C. Ematologia ASO S. Croce e Carle</td>
<td>1</td>
</tr>
<tr>
<td>Milano Unita' Trapianto di Midollo Ist. Nazionale Tumori</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total patients enrolled</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>
Romiplostim in Patients Undergoing Allogeneic Stem Cell Transplantation: Results of a Phase I/II Multicenter Trial

Inclusion: 24 pts (13 AL) more than 45 days after HSCT with PLT count < 20 x 10^9/L sustained for 7 days (< 50 x 10^9/L with a history of bleeding) or if they were PLT transfusion dependent.

Treatment: Romiplostim 1 to 10 mcg/Kg sc x 12 weeks

The median time to reach a PLT > 50 x 10^9/L free of plt transfusion was 36 days, with required doses of 4 mcg/Kg.

15/19 (74%) evaluable pts obtained a durable PLT response.

No safety issues.

Peffault de Latour R et al, ASH 2016,65 oral
Admitted on day + 142 with worsening pancytopenia and new-onset hypertension. Mild oral chronic GVHD. Hb 8.3 g/dL, PLT 16 x 10⁹/L, WBC 1.9 x 10⁶/L. LDH 834 UI/L, total bilirubin 1.38 mg/dl, aptoglobine 129 mg/dl, 2% schistocytes, creatinine 1.5 mg/dL. Normal C3, C4, sC5b-9.

Assumed diagnosis of secondary poor graft function.

Interventions:
- tapered Cya
- stopped enalapril and administered amlodipine
- considered for eltrombopag protocol
- initiated deferasirox, when renal function was normalized
357 MDS pts undergoing myeloablative HSCT
Outcomes by iron-overload status measured by liver MR imaging.

A) Overall survival

B) cumulative incidence of NRM,

C) composite end point of NRM and complications

The possible effect of iron chelators on the transfusion independence and on restoration of normal hematopoiesis is well known in thalassemia, in MDS and in aplastic anemia.

The hypothesized mechanisms of actions are the reduction of reactive oxygen species or the redistribution of iron from storage to hematopoietic tissues, acting on hematopoietic stem cells or on microenvironment.
Deferasirox improves hematopoiesis after allo-SCT

Figure 1. (a) Hb after deferasirox administration. Patients at time 0 were transfusion dependent (Hb value at time 0 reflects the effects of transfusions). (b) Ferritin values after deferasirox administration. Patients at time 0 were transfusion dependent (ferritin value at time 0 reflects the effects of transfusions).
Conclusions

• PGF is diagnosis of exclusion and every patient has its own history.

• Treat with growth factors including TPO mimetics.

• Treat iron overload.

• Think to a second reinfusion of CD34+ selected CD34 + PBSC from the same donor.