Managing the Patient Refractory to Platelet Transfusion

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BLOOD MATTERS 2019
Objectives

Causes and clinical significance of refractoriness

Non immune mediated platelet refractoriness

Approaches to caring for patients with platelet refractoriness
50 year old female AML, admitted to ICU with tumor lysis syndrome

She requires mechanical ventilation, vasopressors and begins chemotherapy

Develops pneumonia treated with broad spectrum antibiotics and antifungals

Remains febrile

Day 13, platelet count is $3 \times 10^9$/L, she is not bleeding

24 hours following platelet transfusion, the count is $3 \times 10^9$/L
The next step is to:

Repeat the platelet count 10 minutes-1 hour after platelet transfusion.

Request HLA typing & antibody screen as she is refractory.

Administer fresh (<72 hours) platelets.

Administer ABO identical platelets.
WHO grading of bleeding

GRADE 1: petechiae, purpura localized to 1 or 2 dependent sites, epistaxis ≤30 min, oropharyngeal bleeding ≤30 minutes

GRADE 2: melena, hematemesis, hemoptysis, hematochezia, hemarthrosis

GRADE 3: Bleeding requiring RBC transfusion

GRADE 4: Fatal bleeding, bleeding with severe hemodynamic compromise (e.g. hypotension; >50mm/Hg fall or >50% decrease in either systolic or diastolic blood pressure)
Prophylactic platelet transfusion is intended to decrease the risk of hemorrhage

10-15% of platelets removed daily, predominantly by the spleen

7,000/µL for vascular integrity daily

1-hour post transfusion increment is ~30,000 to 60,000/µL

Shorter survival with lower counts: 7 days if 50 - 100,000/ µL vs. 5 days if < 50,000/ µL,

≤10,000/ µL is the prophylactic platelet count

Platelet refractoriness is defined as

Increment <10,000/µl 10-60 minutes after transfusion ≥ 2 occasions

Lack of an increment within 60 minutes suggests an immune etiology secondary to antibody mediated destruction

If there is an increment >10,000/ µL it is non immune

Refractoriness is predominantly, 80%, due to non immune factors

**Recipient related**

Platelet consumption

- Fever $1.6 \times 10^9/L \ (0.8, 2.3)$
- Bleeding $1.7 \times 10^9/L \ (0.6, 2.8)$
- Splenomegaly $3.5 \times 10^9/L \ (1.3, 5.8)$

Cytoreductive drugs/disease/antibiotics: e.g. linezolid, after 2 weeks of exposure in 2.4%

**Platelet product related**

Storage ≤ 48 hours $1.9 \times 10^9/L \ (1.1, 2.7)$, recovery similar in well vs 80% with older platelets and bacterial infection

Pathogen reduction RR 2.9 (2.1 to 4.2)

The inhibition of fibrinolysis by tranexamic acid to reduce the risk of bleeding may also decrease fibrinolysis.

Plasmin activated from plasminogen causes degradation of fibrin.

The process is facilitated by plasminogen binding to fibrin through lysine residues in fibrin that bind to lysine binding sites on plasminogen.

In the presence of TXA these lysine-binding sites are occupied: inhibition of fibrin binding to plasminogen and impairment of fibrinolysis.
Prophylaxis with antifibrinolytics appears to reduce platelet use: 4 ongoing studies will define their role

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<th>Tranexamic acid</th>
<th>Placebo</th>
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Bleeding events/participant

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Platelets/participant

Aiming for higher hemoglobin targets to reduce bleeding remains an unresolved question

**Supporting: Retrospective analysis of RCTs**

**Uhl et al, 2017** (n=1077): OR 4.9 (2.6, 9.9) of grade ≥ 3 bleeding with days with HCT ≤25% vs >29%

**Webert et al, 2006** (n=255) 10g/L increase in Hb, RR 0.8 (0.6, 1.0)

**Not supportive: Small RCTs**

**DeZern et al, 2016** (n=90) Hb 70 vs. 80 g/L: Frequency of bleeding, 32% vs. 37%

**Tay et al, 2016** (n=300): Hb 70 vs. 90 g/L, no difference

**Webert et al, 2008** (n=60): Hb 80 vs. 120 g/L, 86% vs. 90.3% had bleeding
Thrombopoietin receptor agonists increase the platelet count

Eltrombopag and romiplostim

- Bind to the thrombopoietin receptor
- Used for ITP refractory to other therapies
- Improve normal megakaryopoiesis
- Do they stimulate the growth of malignant blasts?
- Use in aplastic anemia suggests effect is on stem progenitor cells

Shastri A, Verma AK, Lancet Hematology
http://dx.doi.org/10.1016/S2352-3026(17)30229-6
Thrombopoietin receptor agonists are useful for SAA, early days for MDS/AML

Severe Aplastic Anemia: 6 month overall response, 80-90% eltrombopag vs. 66% historically

Low risk MDS: terminated early, transient increase in peripheral blast count > 10%: romiplostim 15% vs. placebo 4%, AML 12% vs. 11% at 5 yrs

MDS (IPSS1,2,high risk): terminated early, no difference transfusion independence, eltrombopag 16% vs. 40% placebo, trend of disease progression 14% vs. 9%

High risk MDS/AML: (life expectancy 6 months, untreated), clinical events from thrombocytopenia 54% eltrombopag vs. 69% p=0.03, weekly platelet transfusions/PFS unchanged

Platelet count after 1 hour was 10 x 10(9)/L, twice after fresh, ABO identical platelets, HLA antibody screen: cPRA is 20%

Request an HLA antigen negative product

The lack of response is not secondary to HLA antibody, request HPA antibody testing

The lack of response is not secondary to an HLA antibody, request partial splenic embolization

The lack of response is secondary to drugs, continue with the same product
Immune (ALLO/AUTO) etiologies account for 20% of lack of a sustained platelet increment

Alloimmune:
1. Class I HLA A, B antigens/epitopes
   Dependent on immune responsiveness, previous exposure to alloantigens by transfusion, pregnancy
   Leukoreduction: 18% alloimmunized, 3% refractory
2. Human Platelet Antigens (HPA) predominantly 1b, 5b
   Accounts for 2-8% of alloantibodies, refractoriness infrequent
3. ABO identical: $4 \times 10^9/L$

Autoimmune: Immune thrombocytopenia secondary to underlying disease e.g. lymphoma, leukemia or drugs

Immune mediated thrombocytopenia resolves within days of discontinuation of implicated drug

E.g. piperacillin/tazobactam in ≤ 1%

The decline is 5 - 10 days after daily exposure, or within hours after re-exposure

Platelet count decline < 20 × 10⁹/L

Rapid decline

Mucocutaneous bleeding symptoms often occur

Arnold D et al. TMR 2013; 27: 137–145. : 
Identifying platelet products for HLA alloimmunized

1. HLA epitope negative to the antibody:
   A. Identify the antibody: detection of antibody by solid phase assays
      Degree of HLA sensitization=Calculated Panel Reactive Antibody (cPRA): frequency of HLA epitope in the population/incompatibility
   B. Identify the epitope: molecular methods to detect epitopes +/- HLA Matchmaker

2. Crossmatching platelet products

She receives HLA antigen negative platelets to an antibody identified that result in minimal increases in platelet counts. She is not bleeding. Fever is resolved. Should daily platelet transfusion be discontinued?

Yes

No
Up to 20% may continue to have refractoriness

Expanding HLA antibodies

CD8+ T cells may mediate clearance independent of antibodies

IVIG does not appear effective (n=30) in immune refractoriness
Ongoing platelet refractoriness predisposes to bleeding: risk may differ according to disease

Bleeding: 25% of days with platelet ≤5000/µL vs. 17% when 6-80000/µL (p<0.001)

**Autologous stem cell transplant**

Similar bleeding rates in no prophylaxis (45%) vs. prophylaxis (47%) (Stanworth et al)

No grade 4 bleeding but grade ≥ 2: 8% prophylaxis vs. 28% therapeutic (p<0.001) (Wandt et al)

Thrombocytopenia in critically ill patients may be a marker of prognosis

Platelet transfusion may not improve outcomes

- Organ failure scores may not be improved
- Mortality may not be improved
- Receive more RBCs

Non Immune refractoriness (80% of platelet refractoriness)
Platelet count > 10, 10-60 minutes after a transfusion
Recipient/product related

ABO identical, fresh platelets (<72 hours)
Thrombopoietin mimetics for SAA
Remains refractory

Antifibrinolytics?
Immune refractoriness (20%)
- <10 x 10^9/L, 10-60 minutes following transfusion
- ABO identical, fresh platelet (<72 hours)

Remains refractory
- HLA antibody detection and typing/crossmatching

Remains refractory
- 1. Expanding HLA antibodies
- 2. HPA antibody
- 3. Autoantibody
- 4. Drug related antibody

Anti-fibrinolytics?
Anticipated developments/answers

Refractoriness

The role of anti-fibrinolytics for reduction of bleeding

Cold stored platelets

Prophylactic vs no transfusion according to disease or bleeding risk e.g. autologous transplant

Non Immune: The role for thrombopoietin agonists in MDS/AML and AA

Immune: The immune response and targeted therapies