Welcome

- Mute your microphone – To ensure no disruptions
- Turn off your video – This could affect your connection to the meeting
- If you have a question, when prompted please “Raise your hand” or write in the conversation
- This event will be recorded and can be used as an educational resource

The RTC Is Delighted to Present our "First West Midlands Virtual Conference"

**Dr Suzy Morton**
Consultant in Haematology & Transfusion Medicine (NHSBT/UHB)
12.00-12.30 - Granulocytes

**Dr Lorna Cain**
Haematology Registrar (UHBFT)
12.30-13.00 - MSBOS Regional Survey

TUE 03 NOV 2020
Granulocytes

Dr Suzy Morton
Consultant Haematologist
Case presentation

- 55yo with AML
- 2 x CPX then relapsed → FLAG-ida
- Failed to recover counts
- Recurrent positive blood cultures with *Enterococcus*
- Lesion suspicious for endocarditis on echo
- Fungal chest infection
- Embarking on unrelated bone marrow transplant...
Background

- Neutropenic sepsis is a major cause of morbidity and mortality for patients with bone marrow failure
- Supportive care improving but challenges e.g. antibiotic resistance
- Efficacy of granulocyte transfusion unclear (Estcourt, 2015 and 2016)
- Concerns over toxicity
- Previous RCTs failed to recruit (Price, 2015; Seidel, 2008)

Lack of evidence is a barrier to use but despite this NHSBT issue granulocytes to 8.6 new patients per month
Granulocytes, Pooled, Buffy Coat derived, in Platelet Additive Solution and Plasma, Irradiated

- 10 buffy coats, pooled in SSP+ and male plasma
- Hct 0.15
- 2.5 adult doses of platelets per pool
- Volume 207 mL
- Stored at 22°C without agitation
- Expire at midnight the day after donation
- ABO and D compatible, immediate spin “cross match compatible”
- CMV neg for CMV neg recipients if potential for SCT
Dosing and provision

- 10 donations; 0.9-1 x 10^{10} neutrophils
- **Dose**
  - 1-2 bags or 10-20ml/kg for children
  - Therapeutic dose unknown but considered to be in the region of
    - 0.5-1.0 x10^{9}/kg
    - i.e. for a 70kg patient, 3.5-7 x10^{10}
- **Availability** Tues-Sat
  - 4x O pos on Mondays, since Sept 2020

*Buffy coats* also sometimes available over weekends
*Apheresis granulocytes* no longer available
What are the indications?

NHSBT clinical guidelines

Red cell transfusion and red cell immunohaematology

2.1 Therapeutic granulocyte transfusions may be indicated for patients with severe neutropenia who fulfil all of the following criteria:

2.1.1 Severe neutropenia, defined as \( \text{ANC} < 0.5 \times 10^9/L \) [WHO 1999] due to congenital or acquired bone marrow failure syndromes.

2.1.2 Receiving active treatment in an attempt to achieve disease remission.

2.1.3 Proven or highly probable fungal or bacterial infection that is unresponsive to appropriate antimicrobial therapy as demonstrated by visible spreading lesions on skin, mucosa or radiological examination [Ascioglu et al 2002].

2.1.4 In whom neutrophil recovery is expected (\( \text{ANC} > 0.5 \times 10^9/L \)) in the near future and / or in whom definitive therapy of curative potential is planned.

2.2 Therapeutic granulocyte transfusions may also be indicated for patients with a known congenital disorder of neutrophil function [Kuijpers et al 1999] regardless of neutrophil count with proven or highly probable fungal or bacterial infection unresponsive to appropriate antimicrobial therapy, demonstrated by visible spreading lesions on skin, mucosa or radiological examination.

Guidelines don’t address
- Acquired neutrophil dysfunction
- Patients with no definitive treatment planned
- Prophylaxis
What are the potential adverse effects?

• Fever (FNHTR)
• TRALI
• HLA sensitisation
• TACO
• CMV transmission
• Red cell incompatibility considerations
Cochrane review of therapeutic granulocyte transfusions 2016

10 trials, 587 participants, 1975 to 2015

Quality of evidence low to very low

No difference in 30 day mortality, no difference in resolution of infection

Insufficient evidence to report on differences in adverse events

Similar in prophylaxis, with some suggestion of benefit for higher doses
The RING trial
(Resolving Infections in Neutropenia with Granulocytes)

• Price et al., 2015 *Blood*
• RCT, open label, phase 3
• Standard antimicrobial therapy +/- apheresis granulocytes (G-CSF/Dex)
• Daily transfusions up to 42 days, neutrophil recovery, resolution of the infection or life threatening toxicity
• Primary endpoint: survival and resolution of infection at 42 days
• Calculated sample size: 236 patients
RING study: results

- 114 subjects randomised
- Success rates and mortality at 42 days similar in both groups
- No association between the average post-transfusion neutrophil count and the primary outcome
- Post hoc analysis to evaluate effect of dose: $\geq 0.6 \times 10^9$ vs. $< 0.6 \times 10^9$ granulocytes/kg
- ??higher doses associated with better outcomes
Challenges for randomised trials

• RING study challenges
  • Believers vs. non-believers
  • Difficult to recruit donors
  • Lower mortality than anticipated in control arm
  • Intervention too early

• Unlikely that future RCT will be funded

Despite this NHSBT issue granulocytes to **8.6 new patients per month**
Why registries?

• “An organised system for the collection, storage, retrieval, analysis, and dissemination of information”

• *Detailed information* at patient, disease, and therapeutic intervention levels

• “Real-world” information, patients are not selected or excluded based on pre-stipulated protocols

• *Low frequency diseases* for which clinical trials would not be a feasible
Who needs granulocyte transfusions? Emerging findings from a national registry

### Disease

- **AML** 56%
- **ALL** 13%
- **Aplastic anaemia** 6%
- **Lymphoma** 6%
- **Myelodysplasia** 9%
- **Other** 11%

### Participants by age

- **<10**
- **10-19**
- **20-29**
- **30-39**
- **40-49**
- **50-59**
- **60-69**
- **70-79**

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<thead>
<tr>
<th>Age (years)</th>
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- 859 transfusions to 246 patients over 2.5 years

### Disease statistics

- **Mean age 43 years**
- **20% under 16 years**
- **30% undergoing bone marrow transplant**
Source of infection

- Lungs: 34%
- Other: 34%
- Skin: 11%
- Nose, sinus, oral cavity, throat: 5%
- Central Nervous System: 2%
- Unknown: 14%

Reason for stopping infusions

- Infection resolved but patient still neutropenic: 28%
- Patient no longer neutropenic: 46%
- Patient now for palliative treatment only: 7%
- Transfusions not tolerated: 5%
- Transfusions not tolerated due to febrile reaction: 1%
- Unknown: 4%
- No clinical response: 9%
12 patients = 1 GTX
10 patients = 0 GTX;
of these 22 patients, 14 died:
11 died within 3 days of referral
Source and dose of transfusions

Median 5.0 transfusions per episode
  • one per 2.3 days
  • median dose
    • $0.24 \times 10^9$/kg overall
    • $0.98 \times 10^9$/kg in children

Therapeutic dose unknown but considered to be in the region of
  $0.5-1.0 \times 10^9$/kg
i.e. for a 70kg patient, $3.5-7 \times 10^{10}$

12% GTX from buffy coats
(provided on Sundays and Mondays)
Clinician-reported outcomes

- Worsened outcome:
  - 1%
  - 5%
  - 10%
  - 15%
  - 20%
  - 25%
  - 30%
  - 35%
  - 40%

- Improved outcome:
  - 1%
  - 2%
  - 3%
  - 4%
  - 5%
ProGrES – day of first transfusion

(First 100 patients)
On a scale of 1 to 5, how important is it for granulocytes to be available on the same day you request them?

- 5 Extremely important
- 4 Important
- 3 Not very important
- 2 Not at all important
- 1 Not at all important

Which of the following concessions would you accept in order to facilitate same day or 7 days supply?

- a) Non ABO matched (but still compatible e.g. group O component to A patient)
- b) Non D matched - all patients e.g. D positive component to D negative patient
- c) Non D matched - for all patients except people of childbearing potential
- d) Non CMV selected - e.g. CMV positive or untested to CMV/gG negative recipient
• Continue to collect national data – THANK YOU

• Regular discussion with NHSBT re provision
  • Now 6 day granulocytes

• International collaboration through

• Collaboration with statisticians at London School of Hygiene and Tropical Medicine re novel techniques

• ??randomisation within the registry
Back to the case

• Granulocytes given for secondary prophylaxis throughout transplant Tues-Sat
• Increments ~0.1 \( \times 10^9 \)/L
• Many complications relating to transplant but nil additional infections
• Recovered counts after 3 weeks
• Ongoing complications from transplant
Summary

• Granulocytes are available
• Pooled component, short expiry
• Data are limited but studies ongoing with a goal of demonstrating whether there is benefit, or not
• Discuss if you have a patient you think may benefit
  • or if there are technical questions!
• Thank you for contributing data
• Ask for what you want, not what you think we can provide
Thank you

Trials team UK
Simon Stanworth
Charlotte Brierley
Emma Laing
Ana Mora
Chloe Fitzpatrick-Creamer
Eleanor Curnow
Joseph Parsons
Siobhan Martin
Suzy Morton (CI)

Patient facing NHSBT consultants - without whom we would have no patients

ProGrES

All the hospital teams who have contributed data

Components
Rebecca Cardigan
Edwin Massey
Kay Harding

Registry team BEST
Suzy Morton
Monica Pagano
Alan Tinmouth
Simon Stanworth