Granulocyte Transfusions: A Clinician’s Perspective
Is there a role for this therapy?

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Objectives

• Understand the rationale for granulocyte transfusion (GTX)
• Understand the controversy around efficacy and role of GTX
• Understand the ethical implications of the therapy
Outline

• Background and Rationale
  – Prophylactic vs Treatment
• Brief review/summary of data
• Cases
• Discussion
Background

From the gallery of Mikael Haggstrom
Neutrophil Chemotaxis

Neutrophil Crosstalk
Neutrophil Crosstalk
Innate Immunity

Nature Reviews | Immunology
Neutrophil Crosstalk Lymphocytes
Neutrophil Interaction with Pathogen

Phagocytosis

Examples of Neutrophil Disorders
Congenital/Hereditary

• Chediak-Higashi Syndrome (chemotaxis and killing)
• Chronic Granulomatous Disease (killing defect)
• Kostmann Syndrome (agenesis)
• LAD-I and II (chemotaxis defect)
Neutrophil Disorders
Acquired

• Neutropenia due to:
  – Medication induced
    • May be autoimmune or direct drug effect
  – Autoimmune
  – Aplastic Anemia (immune mediated)
  – Malignancy induced
  – Chemotherapy induced
Consequences

• Increased susceptibility:
  • Bacteria
  • Fungi
Standard Therapies

• Significant advances in anti-microbial therapy
  – Broad spectrum antibacterial prophylaxis
  – Broad spectrum antifungal prophylaxis
  – Better understanding of combination therapies and resistance

• Understanding who needs closer monitoring
  – Association of infection risk with therapy
    • AML vs ALL therapy
Rationale for GTX

• Neutropenia leads to these infections
• Antimicrobial resistance is always threatening
• Resistance is already present
• Mortality with advanced infections is high
• Why not replace the neutrophils/granulocytes?
  – We have the technology......we can replace them.
  – Should we prophylax or just treat?
Acquisition of Granulocytes

- ABO compatible donor
- HLA matched if recipient has HLA antibodies
- Donor questionnaire
- Steroid and GCSF stimulation
  - GCSF 600ug/Dex 8mg
  - 12-16 hrs pre-harvest
- Leukapheresis
- CMV status?
- No leukoreduction
- Irradiate
- HES (hydroxyethylstarch improves separation)
- Target 1-5x10e10 cells/collection
Dosing and Early studies

• Early studies suggested a dose response curve
  – Lowenthal et al. 1975 The Lancet
    • 4x granulocyte dose associated with response vs non-response
  – Alavi et al. NEJM 1977
    • Randomized to abx vs abx + GTX
      – 21 d survival 20% vs 75% in infected patients
      – 21 d survival 79% vs 88% if no confirmed infection
      – All got approx 5x10e10 cells per infusion

• Toxicities
  – Primarily pulmonary
  – GVHD if not irradiated
1980’s and 90’s

• Significant decrease in GTX
  – Questionable efficacy
  – Difficult to collect
  – Costly
  – Improvement in antimicrobial prophylaxis and therapy
Other Issues With GTX

• Donor Risks
  – GcSF
    • Bone pain
    • Headache
    • Fatigue
    • Myalgia
    • ? Postcapsular cataract

• Recipient Risks
  – Fever, chills, pulmonary edema
  – Hypotension, nausea/vomiting, TRALI

• Cost
  – Estimated $2000-4800/GTX
    • Kadri et al. Role of granulocyte transfusions in invasive fusariosis: systematic review and single-center experience. Transfusion 2015;55;2076-2085
Renewed Interest

• Improved yield
• More resistant infections
Prophylaxis- Evidence?

• Granulocyte transfusions for preventing infections in people with neutropenia...
  – Estcourt et al. Cochrane Database Review 2015
  – Eval’d 9 manuscripts of RCT’s/quasi RCT’s for meta-analysis
    • Patients received GTX or not
  – Results:
    • No difference in all cause mortality or mortality due to infection
    • Decreased bacteremia/fungemia and infection with intermediate dosing
    • Serious Adverse Events: Pulmonary; graft vs host disease x1 in unirradiated product.
  – Conclusion: There is low-quality evidence that prophylactic GTX decrease the risk of developing a bacterial or fungal infection
GTX for Treatment of Neutropenic Infections

- Stanworth et al. Cochrane Reviews 2005. July 20; (3)
- Evaluated 8 parallel RCT’s
- Inconclusive evidence to support or refute use of GTX in neutropenia due to chemotherapy
- Future studies should dose >1x10e10/transfusion
RING Study
(Resolving Infection in Neutropenia with Granulocytes)
Price et al. Blood, 29 October 2015 Vol 126, No 18

• Designed to eval effect of high-dose GTX
• Anti-microbials vs Anti-microbials + GTX
Primary Outcome

Figure 5. Survival to 90 days by treatment arm. Analyzed using Kaplan-Meier methodology. Three subjects were censored prior to day 90 due to missing information.
Sub-group Analysis

Figure 6. Survival to 42 days by dose group. Analyzed using Kaplan-Meier methodology. Two subjects were censored prior to day 42 due to missing information.
RING Study Conclusions

• Limitations:
  – Low accrual rate (Less than half of subjects needed to provide 80% power to detect 20% difference)
  – Dose of granulocytes
    • Targeted $4 \times 10^{10}$/dose
    • <75% got targeted dose

• If decision is made to provide GTX, ensure high doses of granulocytes
So What Should Clinicians Do?

• Prophylaxis?
• Treatment?
  – Certain populations?
• Ethical?
  – Resource intensive
  – Risk to donors
Cases
Possible Roles?

• Many attempts to understand the role of GTX
• No definitive answer
• Studies suggest there may be a niche for use of GTX in treatment
  – Surrogate markers for response?
    • CRP (c-reactive protein) decrease after GTX
  – Bridge to definitive therapy?
Personal Practice

• In the presence of neutropenia:
  – Definitive treatment plan in place or anticipated
  – Documented fungal infection that is life threatening and refractory to therapy
  – Wound/abscess that is healing poorly despite optimal medical therapy

• Very concerned about risks to donors given controversy

• Very open to constructive criticism and ideas for studies.
Thank You

• To the organizers
• To the investigators
• Especially to the donors

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