Published in final edited form as:
Curr Opin Hematol. 2009 January ; 16(1): 1–2. doi:10.1097/MOH.0b013e32831d7953.

Granulocyte Transfusion Therapy: A New Era?

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Keywords

Neutropenia; Granulocyte transfusions; Severe fungal infections; Granulocyte colony-stimulating factor

Granulocyte transfusion therapy is not a new idea; since the 1930's hematologists have tried to find ways to collect and transfuse enough granulocytes to prevent and treat infections in severely neutropenic patients. It has been a long road with periods of excitement and disappointment.

Without question, the availability of the myeloid growth factors, particularly granulocyte colony-stimulating factor (G-CSF), and new antibiotics and antifungal agents have improved supportive care. Nevertheless, severe neutropenia remains an important and serious complication of cancer chemotherapy and hematopoietic stem cell transplantation, and the mortality rate is still about ten percent for patients admitted to U S hospital with febrile neutropenia. (1) With prolonged neutropenia, fungal infections are still the most difficult clinical problem. The strongest predictor of recovery from invasive fungal infections in this setting is recovery of neutrophil production by the marrow and an adequate number of blood and tissue neutrophils. (2)

Neutrophil transfusion therapy represents a possible way to bridge the gap between marrow suppression and neutrophil recovery. In the early 1990's it was established that G-CSF is a powerful mobilizer of granulocytes from the marrow to the blood in normal donors for transfusion to severely neutropenic patients. (3) A study by Bensinger, et. al. then established that large numbers of neutrophils can be harvested by centrifuge leukapheresis from normal donors treated with a single dose of G-CSF. (4) When these cells were transfused to neutropenic recipients, they circulated normally and the effect of the transfusion lasted for at least 24 hours. Subsequent studies established that addition of dexamethasone to G-CSF enhanced the harvest almost two-fold, permitting the collection of approximately 8×10^{10} neutrophils, sufficient cells to raise the circulating count of a severely neutropenic patients to a normal level. (5) Further trials then showed that these cells also could migrate to a site of inflammation and had

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normal functional characteristics. (6) This was the start of a new era for neutrophil transfusion therapy.

Since these original trials, several studies have suggested that granulocyte transfusion from G-CSF/dexamethasone stimulated donors are effective for the treatment of infections in severely neutropenic patients, but there is not yet any definitive proof of clinical benefit. (7) Now for the first time, a phase III randomized controlled clinical trial is underway to evaluate the effectiveness of transfusing large numbers of G-CSF/dexamethasone mobilized granulocytes under sponsorship of the National Heart, Lung and Blood Institute, NIH, conducted by the Transfusion Medicine/Hemostasis Clinical Trials Network. The study will evaluate neutropenic patients who have undergone dose-intensive chemotherapy or hematopoietic stem cell transplantation within the last 60 days who have proven or probable infections. The objective is to evaluate the benefit of treating patients with G-CSF/dexamethasone mobilized granulocyte transfusion as an adjunct to organism-directed antimicrobial therapy. The control group will receive standard care with organism-directed antimicrobial therapy alone. Subjects in the granulocyte arm will receive daily transfusions for up to 42 days and all enrolled subjects will be followed for up to three months to evaluate survival benefits. The primary end point is a composite one: survival and a microbial response, both evaluated at 42 days after randomization.

One of the most important aspects of this study is the use of community donors. This part of the study plan is based upon observations in preliminary trials that allo-immunization occur slowly if at all in this patient population, permitting many days of transfusion of cells from a general donor population. Many other aspects of the trial, for example, the cytomegalovirus status of the donor and the recipient, collection techniques, storage duration of the granulocytes, need for irradiation of the cells to be transfused, timing of granulocyte transfusions in relationship to antimicrobial therapy and other factors have been worked out through careful studies over the last several years. This trial will also reinvestigate many of these factors and provide valuable information on contemporary patterns of infection in severely neutropenic patients, particularly on the diagnosis, treatment and outcomes for high risk fungal infections in this setting.

The study, called the RING (Resolving Infections in Neutropenia with Granulocytes) study, opened mid-year 2008 and aims to enroll 236 subjects (118 in each arm), based upon estimates of the effectiveness of current treatment and risk of mortality in this population. The Transfusion Medicine/Hemostasis Clinical Trials Network is interested in adding out-of-network participating centers and investigators. Interested parties should contact Dr. Thomas Price (thprice@psbc.org) or Julie Miller (JMiller@neriscience.com) at the New England Research Institue (the study's data coordinating center).

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