

INDICATIONS FOR GRANULOCYTE TRANSFUSIONS

Neutropenia-associated infection remains a limiting factor in the treatment of malignancy. Fungal infections account for approximately 40% of deaths in acute leukemia and marrow transplantation and their incidence is determined primarily by the degree and duration of neutropenia.¹

Transfusion of donor neutrophils is a logical approach to this problem. Initial clinical successes reported thirty years ago were followed by a series of controlled trials that, in aggregate, indicated a survival advantage for transfused patients. Nonetheless, granulocyte transfusion therapy all but disappeared from clinical use—attributable to a reduced incidence of refractory bacterial infection, reports of adverse effects, and because clinical results appeared marginal in patients receiving more advanced antibiotic regimens. The marginal efficacy likely was due to the low dose of neutrophils delivered. Optimal collections produced 20-30 x 10⁹ cells—a fraction of the expected need in the infected patient. Interest in granulocyte support therapy recently has been rekindled with the possibility of increased yields from donors stimulated with granulocyte colony-stimulating factor (G-CSF).

Traditional Granulocyte Transfusion Therapy

Donor Selection. In addition to meeting American Association of Blood Banks and Food and Drug Administration standards for blood donation, donors/recipients should be ABO compatible due to the large number of red cells in the concentrate. Cytomegalovirus (CMV) seronegative patients, particularly if immunocompromised, should receive granulocytes only from CMV seronegative donors.

In the non-alloimmunized patient, it is not necessary to select donors on the basis of leukocyte compatibility.² However, alloimmunized recipients are more likely to experience transfusion reactions if transfused with incompatible leukocytes, and the transfusion will be ineffective.²⁻⁴ Reliable detection of alloimmunization requires a panel of sophisticated tests, not available in most institutions. Alternatively, the likelihood of alloimmunization may be gauged by the patient's history of transfusion reactions, response to random donor platelets, and results of antibody screens.

Collection/Storage. For an adequate yield, the donor's neutrophil count must be increased. Stimulation with 60 mg prednisone or 8 mg dexamethasone is well tolerated and will raise the donor's neutrophil count 2-3 fold. Leukapheresis can be accomplished with any one of several available apheresis machines, processing 7-10 liters of blood over about three hours. A sedimenting agent is used for adequate separation of granulocytes from red cells. Two hydroxyethyl starch preparations are available. Hetastarch is effective but persists in the circulation. Pentastarch has a more rapid elimination time, but collection efficiencies are lower.⁵ These techniques will achieve mean yields of 20-30 x 10⁹ granulocytes. The granulocytes are suspended in 200-400 ml plasma and contain 10-30 ml red blood cells and 1-6 x 10¹¹ platelets. Granulocyte function is

TABLE I: Indications for Granulocyte Transfusions

Generally accepted indications

Documented severe bacterial infection unresponsive to 24-48 hours of appropriate antibiotic therapy in a patient with severe neutropenia/neutrophil dysfunction

Less Clear Indications

Documented severe fungal infection unresponsive to appropriate anti-fungal therapy in a patient with severe neutropenia

Not Indicated

Fever in the absence of documented infection
Prophylactic transfusion

normal or near normal.⁶ Granulocyte recovery and survival are adversely affected by as little as 8-24 hours storage.^{6,7} Therefore, granulocytes are administered immediately after collection. If this is not possible, the cells are stored at room temperature without agitation no more than 24 hours.⁸

Transfusion. Granulocytes are transfused daily until the patient's infection clears or until the neutrophil count exceeds 500/ μ l. A red cell crossmatch must be performed with each concentrate.

Granulocyte preparations contain viable lymphocytes, and graft versus host disease (GVHD) can occur. Although GVHD easily can be prevented by irradiation, routine irradiation is controversial. Some note that GVHD is rare, that irradiation may compromise the integrity of the cells, and that, as with any component, the decision to irradiate should be based on a clinical evaluation of the patient. However, most studies have suggested that irradiation does not impair neutrophil function, making it reasonable to routinely irradiate these cells.

Granulocytes are infused through a standard blood administration set filter (170 μ) over 1-2 hours. Premedication with antipyretics or corticosteroids is not needed routinely but is effective in patients with a history of reactions.

Clinical Efficacy. Seven controlled trials, reported between 1972 and 1982, assessed the efficacy of granulocyte transfusion in neutropenic adults with clinical evidence of infection.⁹ Three showed clear benefit, two showed benefit for certain patients, and two were negative. Subsequent analysis showed that the positive studies provided larger numbers of neutrophils and addressed leukocyte compatibility. The conclusion was that in the proper clinical circumstances granulocyte transfusion therapy is beneficial. Based on these trials, granulocyte transfusion can be considered for severely neutropenic patients with documented bacterial infection who have failed 24-48 hours of appropriate antibiotic therapy to which bacteria are susceptible. The prophylactic use of granulocyte transfusions

in neutropenic patients has been evaluated by several controlled trials and cannot be recommended.¹⁰

The role of traditional granulocyte therapy in fungal infection is not clear. One retrospective study failed to show benefit, but granulocyte dose was not determined and collections were suboptimal.¹¹ Studies in dogs suggest that granulocytes may be effective in treating candidal infection. In the absence of definitive data, it is reasonable to provide granulocytes for neutropenic patients with serious systemic fungal infection refractory to conventional therapy.

The efficacy of granulocyte transfusion therapy for neonatal sepsis has been evaluated in six controlled trials.¹⁰ In four of the six studies, a survival benefit was identified for transfused patients, although subsequent meta-analysis concluded that no definite conclusion could be reached. It is probably reasonable to recommend that in institutions experiencing high mortality in this clinical situation, granulocyte support be considered in septic neonates with blood neutrophil counts < 3000/ μ l.

Patients with severe neutrophil dysfunction also may benefit from granulocyte transfusions. Controlled trials have not been done, but there are several reports of clinical success in patients with chronic granulomatous disease and leukocyte adhesion deficiency. These indications are not firmly established and one should be conservative since these patients ordinarily have normal immune systems, and alloimmunization can be a significant problem.³

Adverse effects. Non-alloimmunized patients will experience mild to moderate fever and/or chills in about 10% of granulocyte transfusions. Pulmonary reactions can occur in these patients, but true transfusion reactions often are difficult to distinguish from other causes. Although a high incidence of severe pulmonary reactions has been reported in patients receiving granulocyte transfusions with amphotericin B, several investigators failed to confirm this phenomenon.¹² It remains common practice to separate the administration of amphotericin from granulocytes by several hours.

Use of G-CSF to Stimulate Donors

With the availability of recombinant G-CSF, increasing the dose of granulocytes suggested improved efficacy. Given to normal donors, G-CSF causes a dose-dependent increase in the neutrophil count within two hours that peaks at approximately twelve hours. G-CSF donor stimulation has been studied by several investigators.¹³ The dose of G-CSF ranged from 5-10 μ g/kg, resulting in average yields of 40-60 \times 10⁹ neutrophils. Higher yields, up to an average of 82 \times 10⁹ neutrophils, can be obtained by the addition of corticosteroids. Granulocytes obtained from these donors are functionally normal and may have improved phagocytic, bactericidal, and fungicidal activity.¹⁴ Administration of G-CSF, with or without corticosteroids, is well-tolerated. Most donors experience mild to moderate bone aching, headache, or insomnia.

Unlike traditional granulocyte therapy, neutrophil increments in patients receiving these increased doses of cells are quite large, and intravascular survival is prolonged. At the highest doses (>80 \times 10⁹) mean increments exceed 2 \times 10³ neutrophils/ μ l and next morning neutrophil counts average 2-3 \times 10³/ μ l.

The evidence that providing granulocytes from G-CSF stimulated donors is clinically efficacious is limited to case reports and small uncontrolled series. In most, the majority of patients were said to respond, including those with fungal infection. Controlled trials have not been done. Transfusion of granulocytes from G-CSF stimulated donors is well-tolerated by recipients. Mild to moderate febrile and pulmonary reactions are seen in approximately 10% and 0-5% of patients,

respectively. More severe pulmonary reactions are observed rarely.

Thus, administering G-CSF to donors, particularly with corticosteroids, permits the collection of large numbers of granulocytes. When transfused, these granulocytes circulate in patients and, on average, increase the patient's neutrophil count to normal or near normal levels. The cells are functionally normal and capable of migrating to tissue sites of inflammation.¹³ While preliminary data suggest that it now may be possible to provide meaningful neutrophil support to patients, large scale clinical trials are needed to determine efficacy.

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