Granulocyte transfusion therapy: randomization after all?

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MGUS outside the context of a clinical trial is not recommended because of the uncertain ratio between potential benefit and toxicity. Future studies should refine the risk factors for progression and develop criteria to identify people at high risk of progression who are candidates for preventive trials, as well as identify patients without any risk of progression who can be reassured.

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Severe neutropenia remains an important and serious complication of cancer chemotherapy and hematopoietic stem cell transplantation. A relation between the degree and duration of neutropenia and the risk of infections has been observed since the 1960's.[1] As the use of chemotherapy for the treatment of malignancy increased, the incidence of neutropenia and severe infections increased as well. The strongest predictor of recovery from infections is recovery of neutrophil production by the marrow and an adequate number of blood and tissue neutrophils.[2] This led to the concept of granulocyte replacement by transfusion therapy as a possible way to bridge the gap between marrow suppression and neutrophil recovery.

Granulocyte transfusions

Although the idea of replacing missing or dysfunctional granulocytes by transfusion from healthy donors originated already in the middle of the previous century, the efficacy of this therapy has still not been completely proven. The first reports on the use of granulocytes obtained from patients with chronic myeloid leukemia, who had high numbers of granulocytes due to their disease, were quite promising.[3] Several studies in the 1970s also showed positive results of using granulocytes from healthy donors.[4] However, other groups demonstrated only partial or no beneficial effect of granulocyte transfusions.[5] One of the explanations for these contradictory results was found to reside in the different dosages as well as the quality of the granulocytes transfused.[6] Healthy donors do not possess sufficient numbers of circulating neutrophils (2.5-7.5×10^9/L) to provide large enough granulocyte doses for transfusion. Moreover, the specific gravity of granulocytes and erythrocytes is similar, hampering optimal separation by centrifugation in sufficient quantities. Additionally, neutrophils are relatively short-living cells, and rapidly undergo apoptosis after collection, which precludes long-term storage.

The use of granulocyte colony-stimulating factor for collecting granulocytes in blood donors

In the early 1990s it was established that granulocyte colony-stimulating factor (G-CSF) is a powerful mobilizer of granulocytes from the bone marrow into the peripheral blood in normal donors. These granulocytes can then be harvested and transfused into severely neutropenic patients. A study by Bensinger *et al*.[7] showed that large numbers of neutrophils could be harvested by centrifuge leukapheresis from normal donors treated with a single dose of G-CSF. When these cells were transfused to the neutropenic patients, they circulated normally and could be detected for at least 24 h. Subsequent studies established that addition of dexamethasone to G-CSF enhanced the harvest almost another two-fold. Additional improvements in leukapheresis techniques and reduction of erythrocyte 'contamination' by the use of sedimenting agents (such as hydroxyethyl starch [HES]) during the apheresis procedure have resulted in a much more efficient and flexible process, enabling the collection of approximately 8×10^{10} neutrophils per procedure. This is a sufficient number to raise the circulating neutrophil count of severely neutropenic adults to almost normal levels,[8] and even above the doses recommended for pediatric patients.[9] Further studies showed that these cells also have normal functional characteristics and can migrate *in vivo* to the sites of inflammation.[10,11] Moreover, it was demonstrated that the neutrophils induced by G-CSF to circulate have a different transcriptional profile and, as a consequence of various pro-survival proteins, a much prolonged lifespan, which may be beneficial under clinical conditions.[12,13]

Side effects of the administration of granulocyte colony-stimulating factor to blood donors

Administration of G-CSF and dexamethasone and subsequent leukapheresis is usually well tolerated by donors, with the short-term side effects mainly consisting of mild symptoms, such as bone pain, headache and myalgia. Concerning the long-term side effects, Quillen *et al*. have recently published a study reporting a 10-year follow-up of unrelated, volunteer granulocyte donors who received multiple cycles of G-CSF and dexamethasone.[14] These investigators compared 83 granulocyte donors with a control group consisting of platelet donors, matched for sex and age. There was no difference in complete blood count or C-reactive protein levels between the two groups. Additional, predefined health events included the occurrence of malignancies, coronary artery diseases and thrombosis. At a median 10-year follow-up, there were seven such events in the granulocyte donors and five in the platelet donors. The authors consider the stimulation of donors with G-CSF and dexamethasone as safe, and not associated with long-term adverse vascular, hematologic or malignant outcomes. However, the authors were aware of the weaknesses of their study, including the relatively small numbers of donors, and other possible long-term adverse effects, such as those on bone metabolism or cataract development.

Concerning side effects in the patients receiving granulocyte infusion, the severe pulmonary complications that were seen in the past have not been reported in the recent studies since the introduction of new leukapheresis methods. There were mild pulmonary signs and symptoms that all resolved without late effects. Other complications were graft-versus-host disease and allergic reactions. After irradiation of the granulocyte products, the risk of graft-versus-host disease has become insignificant.[9] Although rather counterintuitive, the impact of the presence or formation of antibodies against neutrophils on both the recovery of neutrophils following infusion and the clinical response and outcome of the patient seems to be limited, as will be discussed below.

Clinical utility of transfusion of granulocytes obtained after granulocyte colony-stimulating factor and dexamethasone mobilization

Numerous clinical studies have been performed with granulocytes obtained after G-CSF and dexamethasone mobilization. Despite more than 15 years of experience with G-CSF-stimulated granulocyte transfusions, it is still unclear whether this therapy really affects the resolution of infection and reduces mortality. The existing evidence consists of case reports, case series and case-control studies. In some of these studies the results are compared with those of a control group, but these control groups are historical or case controls. Several of those studies were reported in the last decade.[15] In a case-control analysis of episodes of *Candida* species bloodstream infections, Safdar *et al*. detected better survival rates in high-risk patients who received granulocyte transfusions than in a control group of patients who did not.[16] Another single-center retrospective analysis included 47 patients with life-threatening infections. Granulocyte transfusions were given daily, and the patients who achieved neutrophil counts of more than 700 cells/μL after the transfusion (70% of the

cohort) had a significantly reduced infection-related mortality (27% *versus* 64.3%).[17]

In the current issue of the journal, Quillen *et al*. present their experience in using granulocyte transfusions as a supportive treatment for patients with severe aplastic anemia (SAA) suffering from bacterial and/or fungal infections.[18] In SAA the response to the immunosuppressive therapy for the disease can take up to 6 months or longer to develop, causing a neutropenic period that is typically longer than that seen after leukemia-induced chemotherapy or following hematopoietic stem cell transplantation. Infections, particularly those caused by fungi, constitute a major cause of death in patients with SAA. Any sign of infection in SAA patients is aggressively managed with the early use of broad-spectrum antibiotics and antifungal therapy. Nonetheless, invasive infections in SAA patients often progress and become fatal.

Despite the introduction of new anti-fungal agents in the last few years, the response rate in a trial comparing voriconazole and liposomal amphotericin was around 30% for both arms.[19] The purpose of the study by Quillen *et al*. was to analyze the institutional experience with G-CSF and dexamethasone-mobilized granulocyte transfusions in patients with SAA. During this study,[18] 32 SAA patients underwent granulocyte transfusions in addition to antimicrobial treatment. More than half of the patients included had an invasive fungal infection (with or without concurrent bacterial infections). The overall survival to hospital discharge was 44% for patients with fungal infections and 58% for those with bacterial infections, and was strongly correlated with hematopoietic recovery. The authors conclude that granulocyte transfusions may have an adjunctive role in severe infections in SAA patients. Moreover, therapy every other day was found to be as effective as daily transfusions. Finally, as was suggested previously as well,[20] HLA-immunized patients did not have lower neutrophil increaments or increased transfusion reactions.

On the other hand, not all studies have shown beneficial aspects of granulocyte transfusions.[21] This indicates the need for properly designed, well-randomized clinical studies. Thus far, only one randomized phase III study of therapeutic granulocyte transfusions in neutropenic patients has been reported.[22] Ten centers participated in the trial, but only five were able to recruit a total of 74 adult patients, which corresponded to less than half of the expected sample size. This study was closed prematurely due to the dramatic decrease in recruitment rate. Discussions during study committee meetings revealed the following obstacles to participation: patients' and physicians' refusal to randomization in a life-threatening situation, especially if a potentially life-saving strategy was available; lack of available donors; and introduction of modern antimicrobial drugs. The authors concluded that the data collected fail to confirm or refute the benefits of granulocyte transfusion treatment, as they did not observe significant differences between the two groups. However, only part of the patients included in the study were truly neutropenic at the time of randomization, and the patient population from either of the two groups – treated or untreated – recovered earlier than expected, representing a relatively *healthy cohort* without the typical patients who suffer from prolonged neutropenia and a high risk of fatal infections. Furthermore, not all patients included had a proven infection. Finally, the median cumulative dose of transfused granulocytes and the transfusion intervals were inefficient and non-informative when compared to those in existing reports. Given these problems, the data presented were of no use for rejecting or proving the clinical value of granulocyte transfusions.

Despite the lack of solid evidence, granulocyte transfusions are constantly being used as an additional treatment of severe, persistent or progressive infections in neutropenic patients. In most of the earlier studies, the authors suggested a beneficial role of this additive treatment. Response rates of 30-80% were observed in patients with severe, uncontrolled infections, but overall survival was, in most cases, determined by the underlying disease process and the time of the endogenous neutrophil recovery. Bacterial infections have consistently responded better than fungal infections. On the other hand, severe fungal infections in neutropenic patients are generally difficult to control and often fatal, even in the era of new antifungal agents. Half of the patients with invasive *Aspergillus* had progressive infections despite aggressive antifungal therapy. In neutropenic patients with refractory fungal infections granulocyte transfusions have shown a favorable outcome in 35-78% of patients. This observation confirms that granulocyte transfusions with sufficient cell doses and rapid availability are feasible and well-tolerated supplemental measures to fight severe infections in neutropenic patients.[15]

Prophylactic use of granulocyte transfusions

Granulocyte transfusions have also been used to prevent infections (primary prophylaxis) or the reactivation of infections (secondary prophylaxis) during periods of prolonged neutropenia. The role of prophylactic granulocyte transfusions in patients with expected prolonged neutropenia has been reviewed in a recently published meta-analysis.[23] No evidence to support the benefits of such a treatment was found, but the data included only randomized studies of which the vast majority had been performed before the introduction of G-CSF and the new leukapheresis methods. Adequate numbers of granulocyte were not, therefore, given to the patients. Only one study included was performed in the last 15 years. Oza *et al*. administered prophylactic transfusions to patients undergoing hematopoietic stem cell transplantation, each patient being given two transfusions from their HLA-matched donors.[22] Results were compared to those in a control group that did not receive granulocytes, consisting of the patients for whom no suitable donors were found. The clinical effect was rather modest; however, there were significant reductions in the fraction of patients with fever, median number of febrile days, days on antibiotics and the percentage of patients with bacteremia. There was no difference in duration of time spent in hospital or 100-day survival rate.[24] Granulocyte transfusions have also been used as second-

ary prophylaxis against fungal infections;[25,26] the results show that none of the patients included had reactivation of their previous infections. Voriconazole alone, however, was equally successful.[27] It is not, therefore, clear, so far, whether prophylactic granulocyte transfusions have beneficial effects.

Future prospects

For the future, the decision on whether to use granulocyte transfusions therapeutically should be made after a detailed assessment of the clinical state of the patient. Therapeutic granulocyte transfusions may be recommended for patients who meet the following criteria: severe isolated neutropenia (absolute neutrophil count $<0.5\times10^9$/L) or acquired bone marrow suppression (due to cytostatic chemotherapy and/or hematopoietic stem cell transplantation) with an expected duration of profound neutropenia of more than 10-15 days, or any bacteremia, fungemia, invasive bacterial or fungal infection in neutropenic patients unresponsive to proper antimicrobial therapy. Another possible group may be patients with granulocyte dysfunctions, such as chronic granulomatous disease, during episodes of severe, life-threatening infection.[28]

To date, the efficacy of granulocyte transfusions in different treatment settings is difficult to compare. Nevertheless, many clinicians emphasize that early initiation of granulocyte transfusions in neutropenic patients with severe infections who are not responding to proper antimicrobial treatment appears to be essential. Therefore, early identification of possible donors and confirmation of their availability may be appropriate. Early initiation of treatment appears to be mandatory and critical, especially for fungal infections.

All studies dealing with granulocyte transfusions indicate the need for well-designed, large-scale, randomized trials to prove the efficacy of such transfusions. However, it is unfeasible to enroll patients with life-threatening infections into a randomized trial. The major concern is that this approach may deprive some patients of a treatment that is potentially life-saving, which is considered to be unethical. The only recently published prospective randomized trial failed to reach its goal.[22]

The recently established National Heart, Lung and Blood Institute Transfusion Medicine/Hemostasis Clinical Trials Network has started a phase III randomized clinical trial (the RING study: 'Resolving Infections in People with Neutropenia') of high-dose granulocyte transfusion therapy. This trial has been opened and is currently recruiting patients. Fifteen to 20 centers are expected to participate, and the anticipated sample size required has been estimated at more than 200 patients, so the study will take several years to complete. In the meantime, granulocyte transfusions should be given in specific situations, according to well-established and preferably standardized operational procedures for both the donor and the patient.

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