Infections in Oncology

GRANULOCYTE TRANSFUSIONS: TIME FOR A SECOND LOOK

Stephen J. Chanock, MD, of the Pediatric Branch of the National Cancer Institute, National Institutes of Health, Bethesda, Md, and Jed B. Gorlin, MD, of The Children’s Hospital, Dana-Farber Cancer Institute, Boston, Mass

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Introduction

The patient who is profoundly neutropenic and expected to remain so for an extended period of time is at high risk for a serious bacterial or fungal infection.[1,2] In approximately one third of episodes of fever and neutropenia (absolute neutrophil count <500 cells/mm<sup>6</sup>), a diagnosis is documented, and of these, a small proportion is life threatening.[2,3] Successful therapy for documented infections is predicated on recovery from neutropenia and the efficacy of available antimicrobial agents. The morbidity and mortality are higher in patients with neutropenia that persists for more than a few days and results in progressive infection, as defined by lack of response to antimicrobial therapy.[2,4]

In the neutropenic patient, active, antimicrobial agents may not be sufficient to eradicate life-threatening infections. Therefore, accelerating recovery of neutrophils or replenishing the supply of circulating neutrophils are recent approaches in supportive care of the neutropic host. Reconstitution or replenishment of defective arms of the host defense matrix may improve outcome in neutropenic patients with a life-threatening infection.

Laboratory and clinical studies beginning in the 1970s showed that granulocyte infusions (GTX) could transiently increase the number of circulating granulocytes, suggesting a short-term clinical benefit for neutropic patients with a documented infection and particularly for those with a bacterial infection.[5] The data in favor of granulocyte transfusions for fungal infections were less compelling, albeit smaller in scope. Some went so far as to advocate the use of granulocyte transfusions as a preventive measure in neutropic patients (less than 0.5 x 109 polymorphonuclear leukocytes [PMNs] per liter of whole blood). The level of enthusiasm for granulocyte transfusion support of the neutropic patient led some to argue that controlled, clinical studies were no longer indicated and were perhaps unethical.[6,7] However, granulocyte transfusions have not been embraced by all, and in many quarters they have fallen into disrepute.

The impetus to pursue granulocyte transfusion has waned for two general reasons. First, alternatives to granulocyte transfusion improved. These include more effective antibiotics, earlier diagnosis and familiarity with specific clinical syndromes (eg, hepatosplenic candidiasis), and recombinant growth factors that increase the number of circulating granulocytes.[1,8,9] Second, concerns arose regarding the transfusions. These included fear of transfusion-associated infections (eg, human immunodeficiency virus, human T-cell lymphotropic virus I and II, and hepatitis B and C), risk of HLA alloimmunization, which could further complicate platelet support therapy, and acute toxicities associated with granulocyte transfusions (especially pulmonary).[10,11] Furthermore, granulocyte transfusions are complicated and time consuming, requiring considerable effort and coordination. Many centers do not consider granulocyte transfusions except as a desperate attempt to save a neutropic patient with a life-threatening infection.

The combination of improvements in alternatives and awareness of side effects and toxicities associated with granulocyte transfusions dampened the initial excitement, leading many experts to eschew their use in clinical practice.[12] However, new developments provide sufficient impetus to reevaluate granulocyte transfusions in neutropic patients. Specifically, the same growth factor — granulocyte-colony stimulating factor (G-CSF) — that can facilitate more rapid neutrophil recovery in a compromised host can mobilize an order of magnitude more cells from a healthy host and typically more promptly. In addition, granulocyte collection techniques have evolved to facilitate the collection of larger numbers of granulocytes. Hence, a reevaluation of the practice is warranted.

Granulocyte Transfusions in Neutropic Patients With Progressive Infection

A recent report[5] analyzed 32 studies of granulocyte transfusions in 944 neutropic patients receiving antibiotics, of whom 421 were evaluable for a meta-analysis (Table 1). The analysis illustrated the extent to which granulocyte transfusion therapy had once been considered an important therapeutic adjuvant. The data, though not conclusive, supported its use in selected circumstances, such as documented bacterial sepsis in oncology patients, especially those with progressive bacterial sepsis (ie, unresponsive to antimicrobial therapy). All patients included in this analysis were entered on the basis of manifesting an index infection or episode of prolonged fever/neutropenia. Patients were evaluable if sufficient information was available on the clinical course and mortality, regardless of the design of the study. Donor collection was not uniform, but in most cases, corticosteroids were given to increase the harvest; none of the patients received G-CSF–stimulated neutrophils. Patients with a fungal infection as the indication for granulocyte transfusions were pooled because adequate classification of the different types of infection (ie, pneumonia, sinusitis, and sepsis) was difficult. Definitions of therapeutic efficacy differed among the authors of the papers and were not uniform. The great variations in supportive care, patient condition at the time of GTX, and the quantity and quality of the collected neutrophils complicate interpretation of the data. The results of the analysis shown in Table 1 provide an overview of the relative efficacy of granulocyte transfusions in neutropic hosts with different types of infection.
In addition to the statistically significant results for treatment of patients with documented Gram-negative rod sepsis, several trends should be noted, despite an insufficient number of patient treatment episodes studied. The outcome following systemic fungal infection with or without granulocyte transfusion is uniformly poor. Hence, the efficacy of GTX for the indication of fungal infection in a neutropenic host appears to be less than 30%. Since patients who survive long enough to receive granulocyte transfusions may represent a subset of patients with a better prognosis, this figure may represent a generous indication of the overall the efficacy of GTX in neutropenic patients with an aggressive fungal infection. A recent retrospective study by Bhatia et al.[13] failed to discern a benefit for granulocyte transfusions in bone marrow recipients diagnosed with fungal infections. The results of the study are difficult to interpret because the approach to patient care was not uniform (eg, the decision to initiate and terminate granulocyte transfusions was individualized) and the provision of granulocyte transfusions was not randomized. In addition, the specifics of the granulocyte transfusion product were not well characterized, and no attempt was made to perform leukocyte typing or HLA crossmatching. This study did not support preliminary data reported by others as case reports or animal studies that observed a beneficial effect following GTX for fungal infections. Data are insufficient to recommend granulocyte transfusions as the standard of therapy for neutropenic patients with fungal infections, although the mortality of an invasive fungal infection warrants further investigation with high-dose GTX studies.[9,14]

Strauss delineated additional variables that may be critical for efficacy in his analysis of the seven controlled studies (Please see hard copy of journal for Table 2).[5,15-21] These variables include ABO matching/compatibility of donor and patient, degree of HLA matching or compatibility, specific granulocyte alloimmunization or crossmatching, bone marrow reserve, and dose of granulocytes transfused. The overall comparison between the control group (those who received supportive care) and those who also received granulocyte transfusions suggests a slight advantage for the group that received granulocytes. An advantage for granulocyte transfusions was demonstrated in five of the seven studies, significantly for three studies and partially for two.[15,17,20] In the two remaining studies for which no efficacy was reported, successful outcome with supportive care alone was sufficiently high (72% and 80%) that it may have been statistically difficult to demonstrate a clear advantage.[16,21]

Dosage and matching of granulocytes infused may be critical variables. The three groups reporting overall success transfused more neutrophils and collected from donors selected by a more rigorous leukocyte crossmatching.[18-20] Two studies showed mixed results; those who received three or more transfusions fared better than those who received fewer than three.[15,16] Bone marrow reserve has been reported to be a prognostic factor correlated with efficacy. Granulocyte transfusions administered to patients with either bone marrow failure or persistent neutropenia responded favorably compared with the control group. Some have interpreted this to mean that granulocyte transfusions may have a role in supporting the patient who will be neutropenic for an extended time. These groups may represent those who are in infectious trouble solely because they lack granulocytes, in contrast to septic patients in general who may have profound neutropenia as only one manifestation of multisystem failure. Granulocyte alloantigens may be induced during the course of leukocyte transfusions. Prospective matching of major alloantigens such as NA1/NA2 may be of prognostic or therapeutic significance.[22]

Granulocyte Transfusions in Other Clinical Settings

For patients with an inborn error in neutrophil function, such as chronic granulomatous disease, (CGD) or for neonates with immature granulocyte function complicated by limited marrow reserve, experience with granulocyte transfusions is also conflicting with regard to efficacy.[23] Anecdotally reports support granulocyte transfusions for CGD patients with unusually severe and progressive infections.[24-28] In principle, the theory of replacing defective neutrophils with functionally active neutrophils is sound. However, even for CGD patients, concern for alloimmunization and transfusion-associated infections limits their routine application. Due to the extremely short duration of circulation of transfused granulocytes, there is no role for prophylactic granulocyte transfusions in the CGD population. Interferon-gamma (IFN-gamma) has been licensed for prevention of severe infections in CGD patients and is the standard of care in most centers.29,30 Furthermore, gene therapy offers hope for effective correction of neutrophil dysfunction in CGD, and clinical trials are being initiated.

The use of granulocyte transfusions in neonates has gained acceptance in many centers.[31,32] Several controlled studies indicate efficacy for granulocyte transfusions in the neonate with an overwhelming bacterial infection, but even this conclusion is controversial.[32-34] Again, small numbers of patients have limited the strength of the studies. Similar to the experience with GTX in neutropenic patients, the use of GTX varies from center to center.

New Developments in Harvesting Granulocytes

Hematopoietic Growth Factors

The introduction of recombinant cytokines and growth factors into the clinical venue has led to their use in abbreviating the depth and duration of neutropenia induced by myelotoxic agents.[8,35] Even though the data do not strongly support the liberal use of growth factors in neutropenic patients, clinical practice has quickly adopted these factors as routine adjuvants for the neutropenic patient. Consequently, hundreds of patients are receiving G-CSF and granulocyte-monocyte colony-stimulating factor (GM-CSF) as part of their supportive care.[36] A committee assembled by the American Society of Clinical Oncologists has issued recommendations intended to assist the clinician in the judicious use of recombinant myeloid growth factors as a supportive adjuvant.[35,36]

The availability of these growth factors has created unique opportunities for manipulating the host defense matrix. By accelerating myelopoiesis following high doses of either chemotherapy or radiation, oncologists have pushed the concept of dose intensity further and thus have created a larger pool of profoundly neutropenic patients.[1] For example, current protocols for the treatment of solid tumors frequently include aggressive combination therapy and induce episodes of profound neutropenia and immunosuppression.[1,8,35] In this regard, dose intensity of these protocols overlaps with those used in transplantation and creates a wider spectrum of neutropenic patients. G-CSF given on four or five consecutive days mobilizes peripheral blood progenitor cells that may be collected and reinfused later in support following myeloablative therapy.[35,37-39] In most protocols, the ability to
mobilize sufficient progenitors consistently obviates the need to harvest bone marrow. Regardless of the dose of transfused progenitors, there is an absolute period of neutropenia, albeit much shorter than that for corresponding marrow transplant protocols.

The observation that G-CSF or GM-CSF could increase the number of circulating PMNs leads logically to their use to recruit PMNs for granulocyte transfusions. Increasing the number of available PMNs facilitates collecting more neutrophils. Whether higher doses of granulocytes infused will result in greater efficacy is an issue that is technically possible to address.

Two landmark studies document that G-CSF given to normal volunteer donors increases the total number of granulocytes collected to a mean of over 4 x 1010 PMNs compared with the quantities reported following stimulation with corticosteroids (1 to 2 x 1010).[40,41] In the study by Casper et al.[41] G-CSF was given to normal volunteers and granulocyte collection was an endpoint, whereas the study conducted by Bensinger et al.[40] reported the infusion of collected granulocytes into recipients suffering from a severe infection. The Bensinger study represents a unique circumstance in that marrow donors served as granulocyte donors for the respective recipients. In this setting, GTx is especially very well matched immunologically (although not necessarily for granulocyte antigens, which were not assessed). As many as 14.4 x 1010 granulocytes were collected from one donor following administration of G-CSF.

In addition to increasing the number of collected granulocytes, G-CSF and GM-CSF may also prime or activate neutrophils.[42] Ample in vitro data suggest that the microbicidal activity of the PMNs may be augmented by treatment with G-CSF or GM-CSF. In vitro G-CSF has been shown to prime PMNs. The phenomenon of priming illustrates the ability of a cytokine or proinflammatory molecule to prepare a system, such as the respiratory burst, to respond more vigorously to a second stimuli. Thus, G-CSF may activate PMNs and provide better activity against an infection.[43,44] However, the relative contribution of these in vitro observations to in vivo microbicidal activity remains to be established.

The higher number of neutrophils transfused provided a greater duration of coverage. In the study by Bensinger et al.[40] the mean granulocyte level 24 hours after infusion was 954/mm3 compared with 50/mm3 in the historical control group. Historically, transfused granulocytes have a half-life of approximately six hours and are largely undetectable 24 hours later. In addition to a larger dose, immunologic and physiologic reasons may result in longer circulation times. The fact that the granulocyte donor was also the marrow donor represents a most favorable donor recipient pair. The observation that granulocyte transfusions stimulated by G-CSF or GM-CSF may persist longer in circulation is consistent with recent laboratory data demonstrating that cytokine-mobilized granulocytes may be more resistant to apoptosis (programmed cell death).[45-47] A study by Adachi et al.[48] has shown that the in vivo administration of G-CSF to both normal volunteers and patients receiving chemotherapy promotes neutrophil survival in vitro. Survival in vitro was prolonged by as much as 24 hours, which the authors attribute to the inhibition of programmed cell death. Similar findings have been reported with GM-CSF and IFN-gamma pretreatment of freshly isolated neutrophils.[46,49] The combination of G-CSF and IFN-gamma may, at minimum, additively retard apoptosis, thus extending the life-span of the neutrophil. Also, IFN-gamma pretreatment of human neutrophils may protect isolated neutrophils from deterioration during storage and thus prolong the shelf-life of the neutrophil collection product.[50]

**Advances in Collection Technology**

Technologic advances in apheresis collection procedures have improved both the quantity (number of cells collected) and the quality of collection product (the collection process does not cause significant PMN activation). The original method of running PMNs over glass wool results in the activation of neutrophils and may shorten the subsequent half-life of a neutrophil in circulation.

Granulocyte collection and transfusion are regulated as a blood bank technology. The American Academy of Blood Banks (AABB) has established standards stating that the granulocyte apheresis unit shall include at least 1 x 1010 granulocytes,[51] which represents an amount far below that achieved by a G-CSF-mobilized collection. Collections must be tested for all the same infectious agents as other blood products and must clear testing prior to transfusion. Collections must be stored at 20 degrees to 24 degrees C and must be used within 24 hours. Since viral testing in most centers usually requires a one day turnover time, the typical algorithm is to perform viral testing on the prospective donor prior to performing the granulocyte collection and to consider the results valid for the duration of the collections, as long as this period does not exceed two weeks from the initial viral testing. Red cells within granulocyte collections must be compatible with the recipient’s plasma. (Most transfusion centers interpret this standard as a requirement to formally crossmatch the donor plasma with the granulocyte collection.)

Granulocytes have a median density of 1.080, greater than that of reticulocytes and neutrophils (young red cells). Hence, apheresis techniques that collect granulocytes by establishing a density gradient by centrifugal force results in collecting many red cells with the granulocytes. To maximize the efficiency of the collection, agents that enhance density gradient formation (eg, starch) are often infused into the donor. Starch facilitates sedimentation of red cells, and both pentastarch and hetastarch have been advocated as agents to facilitate granulocyte collection. While pentastarch has been associated with fewer donor reactions, one recent study[52] presented in abstract form observed "significantly higher granulocyte collection efficiency" resulting in larger yield using hetastarch without concurrent adverse effects. Pentastarch itself is not without side effects. In the study by Bensinger et al,[40] seven of 58 collection procedures omitted the pentastarch (the usual dose is 200 to 800 mL) due to weight gain and edema.

Typically, granulocyte collections are performed using conventional apheresis technology. Specifically, the same equipment used for collecting platelets or peripheral blood stem cells, such as a COBE Spectra (COBE BCT, Inc, Lakewood, Colo) or Baxter-CS-3000 (Baxter Health Corp, Deerfield, Ill), can be used for granulocyte collection. Usually, collections are performed using leukopheresis tubing sets. Access may be by peripheral vein, although serial daily collections may result in sufficient damage to peripheral veins such that central venous access is required. In the Bensinger study,[40] either surgically placed right atrial or percutaneously placed subclavian catheters provided access. Collections were performed over a three- to four-hour period processing seven to 12 liters of blood, longer than a typical platelet donation. To prevent citrate toxicity, a combination of lower-dose citrate and heparin were used as anticoagulants.

Because of the requirement for special access and mobilization with infused starch and cytokines, granulocyte transfusion studies are unlikely to recruit pediatric granulocyte donors, even if they are already the bone marrow donor.

**Considerations in Granulocyte Transfusions**

The decision to initiate granulocyte transfusions is not straightforward in the age of managed care. The financial cost and potential liability of a controversial therapy are formidable, thus requiring the clinician to consider the benefits and the risks carefully. The coordination required to identify, solicit, and test donors adds to the complexity of care for an acutely ill patient. It remains to be determined what effect the high cost of granulocyte transfusions will have on their availability. In the meantime, it is safe to assume that granulocyte transfusions will be limited to large medical centers and most likely under the auspices of a clinical trial.
Lack of efficacy from studies prior to the modern era of G-CSF–mobilized granulocytes. G-CSF–stimulated granulocyte transfusion therapy is still investigational; hence, the specific indication for granulocyte transfusion should be determined on the basis of previous experience treating patients with comparable infections in the same institution. If the local experience of treating profoundly neutropenic patients with antibiotics and biologic modifiers approaches 100% success, then granulocyte transfusions are not indicated because the risks outweigh the potential benefit. If the overall success rate is considerably lower, a granulocyte transfusion therapy should be considered as an adjuvant to standard care. Consideration of granulocyte transfusions will arise in a subset of patients, primarily those with a poor prognosis (ie, bacterial sepsis or fungal infection in the profoundly neutropenic patient who will remain neutropenic for an extended period of time). In any patient considered to be a candidate for GTX, other measures should be delivered at maximum intensity. In this regard, granulocyte transfusion therapy is indicated when outcome is uncertain and when the risks are outweighed by the benefits.

At present, there is little justification for the prophylactic use of granulocyte transfusions for patients with neutropenia or for those without a microbiologic diagnosis. The hazards of prophylactic granulocyte transfusions — particularly the high incidence of transfusion reactions, especially febrile reactions — argue strongly against this approach.

In the 1990s, the risk of transfusion-transmitted infection from granulocyte transfusions after proper screening of the donors should be minimal. Although G-CSF is commercially available, it should not be used to stimulate the donor except under the aegis of a study or as a special exception with local institutional review board approval. Ongoing studies will determine the proper role of G-CSF–stimulated granulocytes in supporting the neutropenic patient with a severe infection.

**Administration of Granulocyte Transfusions**

Once the decision has been made to administer granulocyte transfusions, proper arrangements should be made for identification and collection of granulocytes from suitable donors. In neutropenic patients, the expectation is that multiple daily transfusions will be required, whereas a single transfusion may be indicated for a neonate. Consultation with a local transfusion center is critical to coordinate the collection, processing, and timely administration of granulocyte products. In preparation for granulocyte transfusion therapy, it is crucial to consider that granulocytes have a finite half-life measured in hours and that they cannot be safely stored overnight. Therefore, each granulocyte transfusion must be infused without delay. As previously mentioned, ABO compatibility and crossmatching are required.

The total number of granulocytes administered to a neutropenic patient should be at least 2 to 3 x 10^10 PMNs and not less than 1 x 10^10 PMNs. For children, the preferred dose should be in the range of 1 x 10^9/kg per day. The standard of therapy has been to use corticosteroids and starch to increase donor collection from normal individuals by apheresis. A leukocyte depletion or microaggregate (20µm) filter must not be used during GTX; a standard 170µm filter is recommended.

In practice, transfusions are administered daily until there is evidence of recovery of peripheral counts (ie, absolute neutrophil count of more than 500/mm3) or clinical evidence of recovery from the infection. At no time should the administration of a granulocyte transfusion be considered a substitute for supportive care. Antibiotics, growth factors, intravenous gammaglobulin therapy, and other supportive measures should continue, usually without delay. One major exception to this practice is amphotericin B, which requires modification in the time of administration. If amphotericin B is to be given, the administration of granulocyte transfusions and amphotericin B should be separated by at least four to six hours. This exception is based on the clinical observation that the simultaneous administration of the two agents is associated with a severe, life-threatening pulmonary reaction.

Since the recipient may already be sensitized to blood products due to previous transfusions, donor selection should be directed at identifying the most appropriate candidates by HLA matching and, if available, by leukocyte crossmatching. This is particularly important for a patient with a history of alloimmunization (eg, platelet refractoriness, febrile transfusion reactions, pulmonary infiltrates posttransfusion, or the presence of antileukocyte antibodies). Despite attempts to optimally match donor and recipient, the success of granulocyte transfusions in alloimmunized patients has not been conclusively established, although most centers attempt to do so. Still, some have advocated that in the presence of high-titer anti-HLA antibodies, granulocyte transfusions are contraindicated except from a closely matched donor. A lesson from the earlier studies, including several of the controlled studies, is that the selection of donors on the basis of erythrocyte compatibility was insufficient and was associated with the lack of success of granulocyte transfusions.

It is necessary to irradiate freshly isolated neutrophils prior to infusion in an immunocompromised host. The recommended dose is 2500 cGy (or rad), which is sufficient to prevent induction of transfusion-associated graft-versus-host disease. A number of small studies have shown that treatment of normal PMNs with 1500 to 2500 cGy (1500 used to be the recommended radiation dose) is not deleterious to the oxidative respiratory burst or chemotactic response. Preliminary data suggest that IFN-gamma may offset the possible acceleration of apoptosis induced by irradiation.

**Future Considerations**

Before G-CSF (and possibly GM-CSF) is used routinely in the stimulation of PMN donors in blood banking, the safety and efficacy of this agent must be well established. First, the effects of G-CSF or GM-CSF on normal donors require further investigation, particularly the long-term effects. A single dose of 5 µg/kg of G-CSF administered subcutaneously is associated with minimal toxicity or discomfort, but with daily doses, the likelihood of toxicity increases. Toxicities associated with G-CSF administration include bone pain, muscle aches, insomnia, headache, nausea/vomiting, and pain the site of injection or in their long bones. A preliminary study indicates that the difference in side effects between administering 5 µg/kg and 10 µg/kg is minimal if given for one day. However, in studies designed to evaluate the kinetics of mobilization of peripheral stem cells (or so-called CD34+ cells), both 5 and 10 µg/kg mobilized neutrophils quickly, but daily administration of G-CSF was associated with the above toxicities. In fact, 10 µg/kg appeared to have more toxicity, and sooner. Rare side effects of G-CSF have been reported in ill patients receiving other medications, which may contribute to these unusual side effects. So far, serious adverse reactions associated with the use of G-CSF in noncritically ill individuals have not been reported.

GM-CSF is reported to have greater toxicity. On the basis of this observation, G-CSF is preferred over GM-CSF for increasing donor collection in normal volunteers and is the agent used in most ongoing studies.

Ongoing investigations of the collection process include the optimization of mobilization agents, schedules of harvest, comparison of red cell sedimentation agents, and route of access. Given the improvements in techniques and equipment for granulocyte collection, the relevance of historical controls is questioned. Properties of G-CSF–primed granulocytes may differ from those collected by standard techniques. Therefore, it is important to establish that the biologic activity of PMNs stimulated in vivo with G-CSF have comparable or perhaps enhanced activities, such as microbicidal activity. While preliminary data suggest this may be true, this work needs to be confirmed in several laboratories. It is also critical to investigate the toxicity profile of G-CSF–stimulated PMNs in patients who are not on recombinant growth factors and in those receiving G-CSF.

An intriguing anecdote of exceptionally prompt engraftment was recently reported following infusion of pooled buffy coats from random donors into marrow transplant recipients.
The authors speculate that the resultant cytokine release from mutually stimulated lymphocytes may have facilitated engraftment. Whether their speculation has any scientific basis is questionable, although the study may be worth independent validation to confirm their results.

**Consideration of Monocyte Transfusions**

With the development of an improved technique for collecting pure preparations (>98%) of circulating monocytes from peripheral blood, consideration of allogeneic monocyte transfusions in immunocompromised patients is now possible.[63-65] Monocytes, like neutrophils, are phagocytic cells that ingest and kill microbes. However, the contribution of monocytes in fighting infections, especially during periods of neutropenia, is less well established. Nonetheless, monocyte transfusions are attractive for several reasons. Monocytes can transform into tissue-specific macrophages, cells that may survive for months. In circulation, the half-life of a monocyte is longer than that of a neutrophil. Recent reports that monocytes may concentrate antibiotics such as macrolides also raise the theoretical possibility of enhanced drug delivery to the target site.[66] However, it has not been established that monocytes traffic efficiently to the site of infection.

**Conclusions**

The rekindling of the debate concerning the role of granulocyte transfusions follows from the logical yet simplistic view that temporarily providing allogeneic neutrophils will substitute for the absent host neutrophils. This concept, first proposed years ago, is based on the assumption that neutrophils as effector cells are necessary for controlling and eventually eradicating life-threatening infections. At the same time, it is critical to recognize that the margin between beneficial effects of exogenous neutrophils and dangerous side effects is thin. To this end, transfusion medicine consultation is imperative prior to embarking on a course of granulocyte transfusions. Attention must be paid to blood banking practices, rules, and regulations to ensure patient safety and compliance with regulatory restrictions. In addition, clinical endpoints should be considered prior to initiating therapy because the risks are high and the procedure is costly in time and expense.

The emergence of bacteria and fungi that are resistant to available antimicrobial agents looms as a significant problem that will not go away for the foreseeable future.[1] Because the development of new, effective antibiotics designed to counter resistant organisms is not keeping pace with the emergence of dangerous strains, alternative strategies to augment or substitute for defects in host defense may assume a greater role in the care of immunocompromised patients. In this regard, we must not only consider a second look at granulocyte transfusions as necessary, but also investigate whether infusion of granulocytes may be an effective alternative to failed antimicrobial agents.

The advent of hematopoietic growth factors G-CSF and GM-CSF, which increase the number of circulating granulocytes available for collection and subsequent donation, has lead to a renewed interest in this therapeutic intervention. The availability of and familiarity with the hematopoietic growth factors make it easy to consider their application to neutrophil transfusions as a logical and necessary extension of their clinical use. However, a number of issues must be addressed before embracing G-CSF-stimulated granulocyte transfusions as a standard of therapy (Table 3). We must beware of the technical imperative to use these agents freely. In other words, we must be cautious and recognize that just because it can be done does not mean that it should be done. Hence, we conclude that given the largely unproven but strongly suggested benefit of granulocyte transfusions, properly designed clinical trials are necessary to determine the efficacy (or lack thereof) for specific indications (eg, bacterial or fungal infections unresponsive to optimal therapy).

**Table 3.** Future Considerations in Granulocyte Transfusion Therapy

| Determination of the efficiency of G-CSF-stimulated granulocyte transfusions in controlled trials in neutropenic patients with documented bacterial or fungal infection. |
| Efficiency of granulocyte transfusions in patients on immunosuppression and growth factors. |
| Study of the biologic profile of G-CSF-stimulated neutrophils, including changes in circulating half-life of neutrophils and leukocytes. |
| Extension of shelf life for neutrophil collection product. |
| Optimal dose and duration of G-CSF for neutrophil collection. |
| Improvements in leukocyte crossmatching. |
| Optimization of granulocyte transfusion for specific indications or therapeutic use. |

**References**


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