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Granulocyte transfusion therapy 2006: The comeback kid?

CHARLES A. SCHIFFER

Division of Hematology/Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan, USA

There has been an increased interest in the use of therapeutic granulocyte transfusion in recent years because premedication of donors with granulocyte colony stimulating factors produces much higher doses of granulocytes for transfusion. Other factors which influence the outcome of transfusion include the types of infection being treated, the likelihood of recipient marrow recovery and recipient alloimmunization. This review provides a historical perspective on these issues.

Keywords Granulocyte transfusion, G-CSF, CML donors, alloimmunization, granulocyte dose

There has been a recent renewal of interest in the use of granulocyte transfusion, largely because of the observation that premedication of donors with granulocyte colony stimulating factor (G-CSF) permits the collection of large numbers of granulocytes resulting in higher post transfusion granulocyte increments, which are sometimes sustained for a few days post transfusion [1,2]. This 'resurrection' follows a period of more than 15 years in which granulocyte transfusions were used very sparingly. In the following, some of the reasons for this fluctuation over time will be addressed.

A brief history of the use of granulocyte transfusion

Granulocyte transfusions were first utilized in the early 1960s in an era characterized by a high incidence of refractory infections with gram negative bacteria, due in part to the absence of effective antibiotics and the long periods of neutropenia related to the lack of effective therapies for acute leukemia [3]. In addition, technology was not available to efficiently separate granulocytes from the upper layer of red blood cells after centrifugation. In response to this problem, investigators at the National Cancer Institute studied the transfusion of leukocytes collected from patients with chronic myelogenous leukemia (CML), initially by simple centrifugation [4], and subsequently with the use of a continuous flow blood cell separator collaboratively developed by the NCI and the IBM Corporation [5].

Two important principles were established by these early studies, both of which were somewhat ignored in subsequent decades. First, there was a direct relationship between the dose of leukocytes administered and the post transfusion increments with a suggestion that improved response rates were also associated with higher doses [4]. Secondly, increments were lower and the incidence of transfusion reactions was increased in recipients who were alloimmunized, as documented by the presence of leukoagglutinating antibodies. Because immature myeloid progenitors were obtained from CML donors, sustained levels of circulating granulocytes were commonly seen for a number of days after single transfusions owing to continued differentiation of the myeloid precursors. Interestingly, it was also shown that the leukocyte alkaline phosphatase levels were markedly increased in the granulocytes tested *ex vivo* after circulation in the infected host, whereas they were characteristically decreased in the CML donors [6].

Although the CML transfusions were well tolerated and demonstrably of benefit, there was increasing reluctance to utilize donors with 'cancer', with a shift towards the collection of cells from normal donors. In parallel, in the early 1970s, both continuous flow (CFC) and intermittent flow centrifugation (IFC) apheresis devices were developed which utilized rou-

Correspondence: Charles A. Schiffer, Division of Hematology/Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA. E-mail: schiffer@karmanos.org

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leauxing agents, most particularly hydroxyethyl starch, to increase the efficiency of separation, and stimulation of donors with corticosteroids to increase their circulating granulocyte count. These were wonderful engineering feats which facilitated the collection of single donor platelets and hematopoietic stem cells which are in routine practice today. However, the granulocyte yields were suboptimal, ranging from $\sim 10 \times 10^9$ (IFC) to $15–20 \times 10^9$ (CFC) compared to $>10^{11}$ from patients with CML. Simultaneously, a technique termed continuous flow filtration leukopheresis was developed, in which donors were heparinized with passage of blood over nylon fiber filters with adherence of the granulocytes to the fibers with subsequent elution of the granulocytes after the donor was disconnected. Although the yields were higher with this technique, the process of adherence and release produced some damage to these cells with associated higher rates of infusion reactions [7].

A series of randomized trials focusing on patients with refractory bacterial infections were conducted during this decade, most of which were 'positive' as evidenced by improved survival in the granulocyte transfusion recipients [8–13]. In hindsight, by contemporary statistical standards, these trials were underpowered with relatively small numbers of patients and were somewhat heterogeneous in their design. Nonetheless, they carried the day and, with the proliferation of IFC separators in blood centers, the use of granulocyte transfusions increased substantially.

However, usage dropped over the following years. Although there are no certain explanations for this trend, it is the author's suspicion that hematology clinicians, and the infectious disease specialists who belatedly entered this arena, voted with their feet and stopped ordering transfusions because they were unimpressed with the clinical outcome and concerned about the transfusion reactions which they observed. The crowning blow was a 'negative' randomized trial using very low doses of granulocytes obtained by IFC from non steroid stimulated donors [14] such that, with occasional exceptions, transfusions were utilized only by more specialized centers until recently. This trial proved little, however, except that inadequate doses are not likely to be ineffective.

In addition to ignoring the historical lessons of the importance of dosage, scant attention was paid to issues of recipient alloimmunization and donor/recipient histocompatibility. During these same years, multiple publications documented the adverse consequences of recipient alloimmunization on increments following platelet transfusion [15]; however, the logical extension of these results was not applied to granulocyte transfusion recipients, in part because of the difficulties in quantifying changes in granulocyte count post-transfusion. Undoubtedly, since many transfusion recipients were alloimmunized, it is likely that histocompatibility issues were the cause of some transfusion 'failures' and certainly contributed to many, if not most, of the transfusion reactions.

Studies in dogs indicated impaired migration of transfused granulocytes in sensitized recipients [16]. Two studies in humans using indium^{111} labeled documented the importance of immune factors on the outcome of transfusion [17,18]. Both demonstrated that there was rapid migration of labeled granulocytes to known sites of infection in non-alloimmunized recipients, but no migration of incompatible granulocytes in alloimmunized patients, with alloimmunization documented by the presence of either lymphocytotoxic (anti HLA) antibodies or antibodies directed against leukocyte specific antigens. These studies clearly indicated that non-matched transfusions are not likely to be of benefit in alloimmunized recipients, although it is not clear what type of *in vitro* cross-matching technique is preferable to select donors for such patients. It is our practice to utilize HLA matched donors and to monitor platelet count increments as an indirect measure of compatibility. ABO matching is sufficient for non-alloimmunized patients who have good responses to platelet transfusions.

The present and the future

Other advances in supportive care also decreased the need for granulocyte transfusions in the 1990s. These included: improvements in the quality of broad spectrum antimicrobial agents; a shift in the type of bacterial infections, with lower virulence gram positive organisms now predominating; the increased use of fluconazole as prophylaxis against yeast infections; the availability of newer antifungal agents with more favorable side effect profiles; some improvements in chemotherapy resulting in higher remission rates and fewer patients with prolonged neutropenia; a possible effect of the increased use of myeloid colony stimulating factors with resultant shorter durations of neutropenia; replacement of bone marrow as the source of stem cells for transplantation with peripheral blood collections; concomitant advances in platelet transfusion therapy and antiemetics, the latter being of particular importance in allowing maintenance of adequate nutrition.

So, is there a role for the transfusion of the higher granulocyte doses ($>40 \times 10^9$) now routinely obtained with G-CSF donor stimulation? The answer is certainly

'yes', and indeed, there have been a number of case series reported in recent years [19–29]. In this regard, the indications for transfusion would appear to be similar to those articulated in the past – bacterial or fungal infection which is not responding to appropriate antimicrobial treatment in a patient whose underlying cancer is still responsive to treatment and in whom severe neutropenia ($< 100–200/mm^3$) is expected to persist for $>5–7$ days. We frequently obtain bone marrows from potential recipients to determine the persistence of leukemia and/or the likelihood of endogenous marrow recovery. In this manner, donors are spared the inconvenience and side effects of apheresis/G-CSF and recipients are not exposed to the risks of potential CMV transmission [29] and alloimmunization [30].

Although arguments have been raised that randomized trials should now be conducted to 'prove' the benefit of these higher dose transfusions, my concern is that this approach would deprive some patients of a treatment which has been proved to be of value in the past, in a clinical setting in which treatment failure often results in patient death. It now seems wiser for large treatment centers to develop the administrative steps which would permit the rapid availability of granulocyte transfusions for the small, but real population of patients who might benefit from them.

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