Granulocyte Transfusions

To the Editor:

We wish to provide some additional information not covered in the review of granulocyte transfusions by Dr. Higby and Dr. Burnett. First, we and other investigators of granulocyte transfusions are still very preoccupied in research attempting to demonstrate whether granulocyte transfusions work. Most of our efforts have been stimulated by the vulnerability of previously published studies of granulocyte transfusion therapy to critical analysis and the fact that most infected neutropenic patients will respond to appropriate antimicrobial therapy alone. Criticisms against studies of granulocyte transfusion therapy to critical analysis and to demonstrate whether granulocyte transfusions work. Most of our efforts include: (1) the marked variability in the patients studied with respect to age, reversibility of underlying disease, the degree of neutropenia, and the types of infections and causative organisms; (2) the variation in the types and duration of antimicrobial therapy; and (3) the application of different criteria for evaluating response to therapy. Moreover, none of these studies included more than 20 patients in either the transfused or control group. The analysis of relatively few patients with very complex underlying illnesses and infections may only allow slight differences in prognostic factors between the transfused and control groups to bias the results. In most of these studies, the positive effect of transfused granulocytes was frequently short-lived, and a significant number of transfused patients died shortly after they were released from the study. For all of the above persons, a multicentered, controlled trial both therapeutic and prophylactic granulocyte transfusions sponsored by the National Heart, Lung and Blood Institute is now being carried out in order to accumulate the large number of patients needed to assure better comparability of transfused and control patients in terms of important prognostic factors and to provide data indicating which patients, if any, might benefit from granulocyte transfusions. This ongoing study should be completed soon.

Second, the data on granulocyte procurement provided by Dr. Higby and Dr. Burnett may not be representative of most transfusion centers. Indeed, in a survey of 10 centers located in Southern California, we found that the mean cost of a granulocyte transfusion to the patient or his medical insurer is $468.00 (range, $280.00–$600.00). The Haemonetics Model 30 blood processor is used almost exclusively by all the centers for collection of granulocytes. The Haemonetics Model 30 blood processor is used almost exclusively by all the centers for collection of granulocytes by intermittent flow centrifugation. Only 4 of the centers stimulate the donors with both corticosteroids and hydroxyethyl starch, and a mean granulocyte yield per procedure of 1.3 x 10^10 (range, 0.6–3.0 x 10^10) is obtained. The other 4 centers are reluctant to use corticosteroids in their donors and thus obtain a mean granulocyte yield per procedure of only 0.55 x 10^10 (range, 0.1–2.0 x 10^10).

Third, serious side effects of granulocyte transfusions may not be relatively rare. In a recently completed study of prophylactic granulocyte transfusions in bone marrow transplant recipients, oral-nonabsorbable antibiotics alone were as effective as oral-nonabsorbable antibiotics plus granulocyte transfusions in preventing serious infections. However, recipients of prophylactic granulocyte transfusions experienced a significantly greater number of cytomegalovirus (CMV) infections, including fatal interstitial pneumonia. Wright and colleagues have reported lethal pulmonary reactions associated with the combined use of amphotericin B and leukocyte transfusions. We have also observed a higher incidence of interstitial pneumonias in acute leukemic patients undergoing induction chemotherapy and receiving prophylactic granulocyte transfusions. This higher incidence was independent of amphotericin B administration.

Finally, while transfused granulocytes appear to maintain their functional integrity after collection, neutropenic patients may lack the serum opsonic activity necessary for their optimal function. Three separate studies have found deficient serum opsonic activity in infected neutropenic patients, and in two of the studies, the opsonic deficiency correlated with an impaired response to transfused granulocytes. Animal experiments have also demonstrated an improved response to granulocyte transfusions when they are combined with passive immunization against the infecting organism.

In summary, we believe that several critically important questions about the effectiveness and safety of granulocyte transfusions need to be answered before they can be accepted as standard or routine therapy. We support Dr. Higby's and Dr. Burnett's plea for continued research in this area.

Drew J. Winston, M.D.
Winston G. Ho, M.D.
Robert Peter Gale, M.D., Ph.D.
Divisions of Infectious Diseases and Hematology/Oncology
Department of Medicine
UCLA Center for the Health Sciences
Los Angeles, Calif. 90024

REFERENCES

6. Ho WG, Winston DJ, Gale RP: Unpublished data
10. Winston DJ, Ho WG, Gale RP: Unpublished data

12. Winston DJ, Huang S, Young LS: Decreased serum opsonization and impaired response to transfused granulocytes during gram-negative septicemia. Presented at the 18th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga, October 1978 (abstr 502)


Reply:

We appreciate the comments of Drs. Winston, Ho, and Gale. Our article was based on the premise that the wide availability and increasing use of granulocyte transfusions is evidence that most physicians are convinced from the published literature and personal experience (as we are) that granulocyte transfusions are of benefit to at least a subgroup of patients with neutropenia and infection. The debate as to whether or not they work was deliberately not addressed.

We, and indeed many other investigators, see serious side effects rarely.4 However, it may be that these surface clinically in prophylactically treated patients more often than in patients who are already infected and seriously ill. We do not advocate routine prophylactic granulocyte transfusions and took pains to indicate our reasons in our article. Drs. Winston, Ho, and Gale, we are sure, do not mean to compare side effects in bone marrow transplant patients receiving prophylactic granulocyte transfusions with those seen in acute leukemia patients receiving therapeutic granulocyte transfusions.

Wright and his colleagues suggested an alarming possibility—that there may be a lethal effect related to combining amphotericin B with leukocyte transfusions.5 While this possibility certainly deserves further investigation, the authors of the original report stressed the preliminary nature of their data, and it is certainly clear that a patient for whom amphotericin B has been prescribed cannot be directly compared with an age, sex, disease, or otherwise matched control in whom amphotericin B has not been prescribed. Thus, to attribute synergism between amphotericin B and leukocytes is premature.

We have evidence that not only opsonic activity, but indeed, serum chemotactic activity correlates with the outcome of infection in patients with neutropenia, whether or not they receive granulocyte transfusions.4 Again, these data and those cited by Winston et al.5,6 simply indicate that a large-scale randomized study of granulocyte transfusion therapy is not appropriate at this time because we do not know enough about other factors influencing outcome.

Donald J. Higby, M.D.
Department of Medical Oncology
Roswell Park Memorial Institute
Buffalo, N. Y.

REFERENCES


6. Winston DJ, Huang S, Young LS: Decreased serum opsonization and impaired response to transfused granulocytes during gram-
Granulocyte transfusions [letter]

DJ Winston, WG Ho and RP Gale