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Single Donor Platelet Transfusion

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Cytopheresis equipment from a number of manufacturers now permits the rapid, safe, and efficient procurement of functionally normal platelets from single donors. There has been an extensive proliferation of these blood cell separators and virtually all large blood collection centers and most large hospitals have at least one blood cell separator in operation. Transfusions from single donors selected by HLA typing are a well-accepted feature of the management of alloimmunized patients [1, 2]. In addition, occasional centers located at a distance from regional blood transfusion centers utilize nonmatched transfusions from single donors as a major part of their "regular" platelet supply. Because most single donor transfusions are not obtained from "closed systems" however, these collections cannot be stored for more than 24 h, making it more difficult to utilize such products rationally as a form of long-term platelet inventory. Furthermore, the availability of newer plastic bags now allows storage of platelet concentrates at ambient temperatures with preservation of normal post-transfusion recovery after 7 days of storage [3]. Thus, there should be few such "geographic peculiarities" which necessitate the widespread use of single donor platelets as "random donor platelets" in the future.

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Alloimmunization with refractoriness to random donor platelet transfusions remains the major complication of any type of platelet transfusion therapy. There has been considerable interest in the last 5 years in the use of single donor platelets as a means of preventing or delaying immunization in transfusion recipients. There are a number of scientific, theoretic, and practical considerations which are implicit in such an approach. These will be discussed in detail with evidence presented which on balance will support the approach of reserving single donor platelet transfusion for alloimmunized patients.

The "scientific" evidence is perhaps the simplest of the issues to deal with. There has only been a single evaluable study done comparing the use of single donor with pooled random donor platelets performed in a prospectively randomized fashion in a homogeneous patient population. This was a small study performed in Zurich by Gmur and colleagues in which patients with acute leukemia were randomized to receive either platelets prepared solely from single donors or pooled random donor platelet concentrates [4]. A total of 54 patients were studied and life table analysis suggested that alloimmunization was significantly delayed in the group of patients receiving single donor platelets. Both serologic and clinical criteria were used to document alloimmunization and in this study, as in previous observations from our institution, lymphocytotoxic (anti- HLA) antibody served as an excellent marker for the presence of alloimmunization [5, 6]. All patients re-

ceived leukocyte-poor red blood cells (RBC). Although the study was very carefully performed and analyzed, there are a number of questions about the interpretation of the data, including: (a) the inclusion of patients who had received granulocyte transfusions; (b) the failure to censor patients who had early deaths; (c) and the possibility that a genetically more homogeneous Swiss population might not be representative of the donor gene pool in a country with more racial heterogeneity such as the United States. Only a small number of patients were studied and statistically significant benefit was most prominent in women who had had prior exposure to histocompatibility antigens through pregnancy, a somewhat surprising finding. In addition, entry to the study was limited to patients with no past or recent transfusions. This is not necessarily representative of the leukemia patient population, however. In a recent study at our referral center, 10/56 evaluable leukemia patients had received packed RBC transfusion immediately prior to transfer from other hospitals with an additional 8 patients having received RBC for other illnesses in the past [7]. Whether such patients would benefit from single donor platelets is unknown.

Nonetheless, this is an important and provocative study which represents the only observation of its kind in humans to satisfy these important study guideline criteria:

1. Prospective randomization
2. Serologic criteria for alloimmunization
3. Homogeneous patient group in terms of diagnosis and chemotherapy received
4. Use of leukocyte-poor RBC
5. Analysis over the entire course of induction therapy
6. Minimal number of protocol violations

Other studies which have attempted to address this issue fail to meet most if any of these criteria. Thus, although Sintnicolaas et al. [8] purport to demonstrate a benefit for single donor platelets in a randomized study, the results must be viewed with care because of: (a) the relatively small number of patients (34) with a variety of diagnoses; (b) the absence of serologic data in many patients; (c) the inclusion of patients with prior random donor transfusions in the single donor group; and (d) perhaps most critically, only the first two random or single donor transfusions received by the patient were compared rather than the entire transfusion history.

There are a number of theoretic considerations which must also be kept in mind about which there are relatively few data available. One could conceive of different strategies of using either multiple "random" single donors, repeated transfusions from small numbers of single donors, or repeated transfusions from small numbers of HLA-matched single donors. Because of the relatively small number of HLA-matched donors available per patient, even in centers with large numbers of typed donors [9], the latter approach would be extremely difficult to implement and furthermore could reduce the number of donors available for patients who are already alloimmunized. Furthermore, if only closely HLA-matched donors are utilized, it is possible that one could select for the development of antibody against platelet-specific antigens which are extremely difficult to detect reliably at this time. Despite the proliferation of an enormous number of different techniques for detection of antiplatelet antibody, none of these are reliably applicable to donor cross-matching at this time [10, 11]. Experiments in dogs by O'Donnell and Slichter have indicated that platelet transfusions from DLA-matched littermates can result in a high incidence of refractoriness, probably due to platelet-specific antigens [12]. Although platelet-specific antigens tend to be found in the overwhelming majority of the population in humans (greater than 95%–99% for most antigens), there are no comparable post-transfusion data available in humans and one must be cognizant of this theoretical concern when utilizing HLA-matched platelets alone.

The repeated use of a small number of single donors is predicated on the theorem that should refractoriness develop to one donor, it should be relatively simple to switch to another donor of a totally different HLA type. There is however considerable serologic cross-reactivity within

the HLA system [1] and it is probable that recipients exposed to even a few HLA antigens would also develop antibody directed against the large number of HLA antigens that may be antigenically similar. The development of multispecific antibody of this pattern was noted in a small study performed at our institution many years ago [13]. Similar observations were also noted in the canine studies already mentioned [12]. Overall, the alloimmunization rate was similar using either pooled random donor platelets or a sequence of transfusions from single donor dogs.

It is perhaps the practical problems which represent the most compelling barrier to the exclusive use of single donor platelet transfusions. Obviously, cost features are an important factor. All patients with leukemia and thrombocytopenia also require RBC transfusions. It would be illogical to utilize a "clean" platelet product while providing large amounts of antigenic material from leukocytes and platelets contaminating packed RBC obtained from "random" RBC donors. Leukocyte-poor blood or perhaps more ideally frozen RBC will increase the cost of RBC transfusions by a factor of 2–3. Such a program would also markedly increase the procedural burdens on any blood center involved in the supportive care of large numbers of such patients. Furthermore, platelet concentrates are a relatively inexpensive by-product of RBC donations which are constantly occurring in large blood centers. The charge to the patient for single donor platelets is greater in most hospitals and does not include the "cost" to society of donors missing work for at least half a day because of travel and donation time. Lastly, donor morbidity must be considered. Although available blood cell separators have an excellent safety record, there are side effects associated with platelet pheresis which include the frequent occurrence of reactions to the citrate anticoagulant, the annoyance of multiple venipunctures and the possible immunologic consequences of removing circulating lymphocytes with long-term immunologic "memory" which can occur with frequent donations processed through the cytopheresis machines. Newer equipment [14, 15] and modification to older equipment [16] will make this less of an issue in the future, however.

An additional problem is that it would be difficult if not impossible for most blood centers to adhere to the rigorous requirements of supplying only single donor platelets on weekends and during emergencies. The study by Gmur et al. [4] was performed in a small pheresis center in which the blood bank physicians were also primarily responsible for the patient care. This is similar to the arrangement in our own center and in studies that we have carried out in the past, it has often been extremely difficult to coordinate the scheduling of single donors with the patient's requirements for transfusion. I am aware of at least two studies in large centers in which the investigators found it impossible to provide either the single donor platelets or the leukocyte-poor blood cells at all times for the patients randomized to these products. "Protocol violations" occurred in up to 50% of the patients on study. It would obviously be inappropriate to utilize an expensive modality such as single donor platelets only part of the time. Thus, implementation of any approach to modify or prevent alloimmunization will require much greater coordination between blood transfusion services and clinicians than exists at most centers at this time. Indeed, it could be suggested that the energy required for improving such coordination could be best directed at improving the quality control and clinical usage of the random donor platelet concentrates provided in many blood banks.

Lastly, there is a misconception in many centers that alloimmunization is an inevitable consequence of the administration of repeated platelet transfusions. On the contrary, data from a number of centers indicate that in cancer patients receiving cytotoxic and immunosuppressive therapy, alloimmunization develops in a minority of patients [4, 6, 17, 18]. In large studies of more than 200 leukemia patients treated with standard, intensive induction chemotherapy at our institution, only about 40% –50% of patients became immunized as documented by the development of lymphocytotoxic antibody [6]. In most of these patients, alloimmunization did not develop

until 3–5 weeks after initial antigenic exposure (i.e., at a time when patients would be entering remission) so that alloimmunization is even less common in patients undergoing remission induction therapy. In a recent study completed at the University of Maryland Cancer Center, only 19% of 100 platelet transfusion recipients actually required HLA-matched platelet transfusions during their initial induction therapy [7]. Similar findings were noted by Gmur et al. [4]. Additional data from our center demonstrate that patients who become alloimmunized develop antibody within 3–8 weeks after their initial platelet transfusion. If antibody does not develop at this time, then it is quite unusual for such patients to become alloimmunized in the future despite the administration of further platelet transfusions [18].

With this background in mind it is of interest to consider exactly how many patients with leukemia might be benefited from any approach by which alloimmunization may be reduced. If one begins with 100 newly diagnosed patients with acute leukemia, approximately 10% of such patients will be alloimmunized on admission or become alloimmunized following their first transfusion as a result of an anamnestic antibody response due to prior transfusions or pregnancies. This would leave a total of 90 patients who might benefit from any approach to modify alloimmunization. If one assumes a final alloimmunization rate of approximately 50%, then the number of patients is reduced to 45. All patients receiving therapy do not achieve complete remission. Assuming a remission rate of 70%, the figure is reduced to approximately 30 patients. Not all patients who achieve complete remission are candidates for aggressive subsequent therapy. If one assumes (perhaps somewhat liberally) that 80% of such patients would receive repeated intensive therapy, the number of patients is further reduced to 24. In our experience, approximately 10%–20% of patients receive granulocyte transfusions because of infections not responsive to antibiotic therapy alone, reducing the number of potential "beneficiaries" to approximately 20 patients. Lastly, it is unlikely that any approach to modify alloimmunization would be 100% effective. If one generously assumes a halving of the immunization rate, then one is left with a figure of approximately 10–15 patients who might benefit from any such approach. Short-term benefit is even lower because, as noted, only 20% of patients require HLA-matched platelets during induction. Unfortunately, it has been impossible to distinguish prospectively between patients who are more or less likely to become immunized. Thus, it would be necessary to "treat" 100 patients for what at this time remains the theoretic possibility of benefiting only some 10%–15% of such patients. Furthermore, most of these alloimmunized patients can be managed successfully with HLA-matched volunteer donors or family members.

In summary, it is likely that the exclusive use of single donor platelets would strain the apheresis capabilities of most centers so that it would be more difficult to supply histocompatible platelets and granulocytes for patients who clearly need and could benefit from them. In addition, because the number of HLA-typed donors available for patients is usually limited, one has to question if this is the appropriate use of this valuable resource compared with saving these donors for alloimmunized patients. It is also unlikely, because of the issues raised, that such an approach could even be carried out at most blood centers. Thus, the current practice of administering random donor platelets followed by single donor platelets should alloimmunization develop is justified by both economic and scientific reasoning at this time [19]. Further scientific documentation of the potential effectiveness of the use of single donor platelets alone is required before this therapeutic modality is utilized, even in specialized transfusion centers.

References

1. Duquesnoy RJ, Filip DJ, Rodey GE, Rimm AA, Aster RH (1977) Successful transfusion of platelets "mismatched" for HLA antigens to alloimmunized thrombocytopenic patients. Am J Hematol 2:219–226
2. Yankee RA, Grumet FC, Rogentine GN (1969) Platelet transfusion therapy – the se-

lection of compatible platelet donors for refractory patients by lymphocyte HL-A typing. N Engl J Med 281:1208–1212
3. Hogge DE, Thompson B, Schiffer CA (1985) Platelet storage for seven days in second generation CLX blood bags. Transfusion (In press)
4. Gmur J, Von Felten A, Osterwalder B, Honegger H, Hormann A, Sauter C, Deubelbeiss K, Berchtold W, Metaxas M, Scali G, Frick PG (1983) Delayed alloimmunization using random single donor platelet transfusion: A prospective study in thrombocytopenic patients with acute leukemia. Blood 62:473–479
5. Daly PA, Schiffer CA, Aisner J, Wiernik PH (1980) Platelet transfusion therapy – One-hour posttransfusion increments are valuable in predicing the need for HLA-matched preparations. JAMA 243:435–438
6. Hogge DE, Dutcher JP, Aisner J, Schiffer CA (1983) Lymphocytotoxic antibody is a predictor of response to random donor platelet transfusion. Am J Hematol 14:363–369
7. Schiffer CA, Dutcher JP, Aisner J, Hogge D, Wiernik PH, Reilly JP (1983) A randomized trial of leukocyte-depleted platelet transfusion to modify alloimmunization in patients with leukemia. Blood 62:815–820
8. Sintinicolaas K, Sizoo W, Haije WG, Abels J, Vriesendorp HM, Stenfert Kroese WF, Hop WCJ, Lowenberg B (1981) Delayed alloimmunisation by random single donor platelet transfusions – A randomised study to compare single donor and multiple donor platelet transfusions in cancer patients with severe thrombocytopenia. Lancet 1:750–754
9. Schiffer CA, Keller C, Dutcher JP, Aisner J, Hogge D, Wiernik PH (1983) Potential HLA-matched platelet donor availability for alloimmunized patients. Transfusion 23:286–288
10. Aster RH (1978) Matching of blood platelets for transfusion. Am J Hematol 5:373–378
11. Schiffer CA (1980) Clinical importance of antiplatelet antibody testing for the blood bank. In: Bell CA (ed) A seminar on antigens on blood cells and body fluids. American Association of Blood Banks, Washington, DC, pp 189–208
12. O'Donnell MR, Slichter SJ (1979) Platelet alloimmunization: correlation with donor source. Clin Res 27:390
13. Schiffer CA, Aisner J, Daly PA, Schimpff SC, Wiernik PH (1979) Alloimmunization following prophylactic granulocyte transfusion. Blood 54:766–774
14. Katz AJ, Genco PV, Blumberg N, Snyder EL, Camp B, Morse EE (1981) Platelet collection and transfusion using the Fenwal CS-3000 cell sorter. Transfusion 21:560–563
15. Hester JP, Kellogg RM, Mulzet AP (1982) Platelet collection in the dual stage channel. In: Vogler WR (ed) Cytapheresis and plasma exchange: clinical indications. Liss, New York, pp 143–151
16. Hogge DE, Schiffer CA (1983) Collection of platelets depleted of red and white cells with the "surge pump" adaptation of a blood cell separator. Transfusion 23:177–181
17. Holohan TV, Terasaki PI, Deisseroth AB (1981) Suppression of transfusion-related alloimmunization in intensively treated cancer patients. Blood 58:122–128
18. Dutcher JP, Schiffer CA, Aisner J, Wiernik PH (1981) Long-term follow-up of patients with leukemia receiving platelet transfusions: Identification of a large group of patients who do not become alloimmunized. Blood 58:1007–1011
19. Schiffer CA, Slichter SJ (1982) Platelet transfusion from single donors. N Engl J Med 307:245–248