High-Dose Intravenous Gamma Globulin Improves Responses to Single-Donor Platelets in Patients Refractory to Platelet Transfusion


Ten patients, with bone marrow failure or malignant disorders, became refractory to platelet transfusions using random, as well as partial or fully HLA-matched, single-donor platelets. To determine its effect on platelet refractoriness, intravenous gamma globulin (IV IgG) was administered at 400 or 800 mg/kg/d for five days, and postinfusion platelet responses were monitored. Platelet transfusion responses following intravenous gamma globulin (IV IgG) were graded as follows: Excellent, 48-hour posttransfusion count > 50,000/µL; good, 48-hour count > 20,000 but < 50,000/µL; Fair, increased increment, 48-hour count < 20,000; and failed, no increased increment. Six of ten patients (60%) had improved responses to selected single-donor platelets (two were excellent, three were good, and one was fair). The time to achieve a platelet transfusion count > 25,000/µL ranged from one to nine days of IgG therapy. One individual had sustained benefit (> 1 year); the remaining responses persisted for 6 to 8 weeks. These results suggest that IV IgG may be useful in the management of platelet refractoriness, especially in patients receiving single-donor platelets.

PLATELET refractoriness represents a life-threatening complication in patients with bone marrow failure who have platelet counts < 10,000/µL. Poor platelet increments occur in two situations and may have different pathogenic mechanisms. In outpatients with chronic aplasia, poor responses probably reflect alloimmunization. In contrast, in febrile patients following chemotherapy-induced aplasia, factors related to infections may contribute to poor transfusion responses. In these patients, it is difficult to discern the relative contribution of allosensitization and/or other factors.

High-dose intravenous gamma globulin (IV IgG) is effective in the treatment of autoimmune thrombocytopenia purpura and posttransfusion purpura. Results are conflicting, however, in the management of platelet alloimmunization. IV IgG is potentially suitable for the management of platelet refractoriness because it has a rapid onset of effect (two to five days) and does not suppress bone marrow. We report the beneficial effects of IV IgG in the management of a cohort of platelet-refractory patients.

MATERIALS AND METHODS

Patients. Ten patients who became refractory to platelet transfusion, defined as a one-hour posttransfusion increment of < 15,000/µL, participated in this study. All ten had failed to respond to 24 to 110 U random-donor platelets, (administered as 6- to 10-U platelet transfusions) and to platelet transfusions from donors who were HLA-identical, partially matched, or selectively mismatched, for cross-reactive HLA antigens. Each patient gave informed consent for participation in this study. The protocol was approved by the Institutional Review Board of Montefiore Hospital, University of Pittsburgh School of Medicine.

The clinical characteristics of the patients are shown in Table 1; four patients (patients no. 1 through 4) had chronic aplastic anemia and became refractory to prophylactic transfusion of selected single-donor platelets. Patient no. 4 developed pneumonia five days after initiation of IV IgG therapy; the other patients with aplasia were afebrile. Three patients (patients 5 through 7) had bone marrow failure due to lymphoma and developed refractoriness to chronic platelet transfusion therapy; one (patient no. 7) was receiving active chemotherapy. The remaining patients failed to obtain platelet responses to transfusion while undergoing induction therapy for acute nonlymphocytic leukemia (ANLL).

Patients varied in the duration of blood support (2 weeks to 3 years) and the number of unit exposures (13 to 735 U). Generalized alloimmunization, as judged by HLA-antibody screening, was detected in eight patients; these patients showed antibodies against > 75% of screening cells. Six had fever, two had enlarged spleens, and 1 (patient no. 5) had undergone splenectomy earlier in her treatment course. HLA-identical platelets were available and ineffective in six of the ten patients. Five had gastrointestinal (GI) bleeding (melena, hematemesis, or rectal bleeding), and one suffered limited hemmorhage into the CNS during the time of study. Three patients (patients no. 2, 5, and 6) who failed to respond died of uncontrolled bleeding.

IgG infusion. All patients received IgG (Sandoglobulin) as an IV infusion over six to eight hours at a dose of 400 mg/kg/d for five days. This dose was chosen to correspond to that recommended for the treatment of immune thrombocytopenia purpura. If no response occurred during the five-day course of therapy, the dosage was increased to 800 mg/kg/d until a posttransfusion platelet count ≥ 25,000/µL was obtained or for an additional five days. Single-donor platelets were given within one to ten hours of the IgG infusion if the platelet counts were <20,000/µL. Random-donor platelets were not given unless the patient was actively bleeding and single-donor platelets were ineffective.

Definition of platelet responses. One-hour posttransfusion platelet counts were performed by chamber analysis using the method of Brecher and Cronkite.

Responses to single-donor platelets were graded as follows: Excellent, increased increment, 48-hour count > 50,000/µL; good, increased increment, 48-hour count > 20,000 but < 50,000/µL; fair, increased increment, 48-hour count < 20,000/µL; and failed, no increased increment.

For single donors that were used repetitively for a given patient, the degree of HLA match to the patient was determined. This was based on HLA-A and HLA-B loci and published cross-reactivity information. The match categories were defined as follows: A

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Table 1. Platelet Refractory Patients: Clinical Characteristics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Blood Support (mos)</th>
<th>Blood or Platelets Administered (U)</th>
<th>HLA Screen No. Positive/No. Screening Cells</th>
<th>Temperature &gt; 100°F</th>
<th>Spleen</th>
<th>A-match Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>14</td>
<td>Chronic aplastic anemia</td>
<td>5.0</td>
<td>735</td>
<td>+ 28/30</td>
<td>N</td>
<td>NP</td>
<td>NA</td>
</tr>
<tr>
<td>M</td>
<td>57</td>
<td>Chronic aplastic anemia</td>
<td>13.0</td>
<td>149</td>
<td>+ 40/48</td>
<td>N</td>
<td>NP</td>
<td>NA</td>
</tr>
<tr>
<td>M</td>
<td>59</td>
<td>Chronic aplastic anemia</td>
<td>1.0</td>
<td>115</td>
<td>+ 29/30</td>
<td>N</td>
<td>NP</td>
<td>Failed</td>
</tr>
<tr>
<td>F</td>
<td>56</td>
<td>Chronic aplastic anemia</td>
<td>5.0</td>
<td>191</td>
<td>+ 17/20</td>
<td>Y</td>
<td>NP</td>
<td>NA</td>
</tr>
<tr>
<td>F</td>
<td>62</td>
<td>Lymphoma</td>
<td>17.0</td>
<td>315</td>
<td>+ 21/48</td>
<td>N</td>
<td>Splenex</td>
<td>Failed</td>
</tr>
<tr>
<td>F</td>
<td>53</td>
<td>Lymphoma</td>
<td>15.0</td>
<td>477</td>
<td>+ 21/24</td>
<td>Y</td>
<td>Enlarged 6 cm</td>
<td>Failed</td>
</tr>
<tr>
<td>F</td>
<td>60</td>
<td>Lymphoma</td>
<td>1.0</td>
<td>59</td>
<td>+ 36/48</td>
<td>Y</td>
<td>Enlarged 3 cm</td>
<td>Failed</td>
</tr>
<tr>
<td>M</td>
<td>24</td>
<td>Acute aplasia ANLL</td>
<td>3.5</td>
<td>156</td>
<td>+ 36/48</td>
<td>N</td>
<td>NP</td>
<td>Failed</td>
</tr>
<tr>
<td>F</td>
<td>60</td>
<td>Acute aplasia ANLL</td>
<td>1.0</td>
<td>174</td>
<td>+ 27/30</td>
<td>Y</td>
<td>NP</td>
<td>Failed</td>
</tr>
<tr>
<td>F</td>
<td>77</td>
<td>Acute aplasia ANLL</td>
<td>0.5</td>
<td>13</td>
<td>+ 10/48</td>
<td>Y</td>
<td>NP</td>
<td>NA</td>
</tr>
</tbody>
</table>

N, no; Y, yes; NP, not palpable; Splenex, splenectomy; NA, not available.

match, HLA-A and HLA-B antigen identical; B match, three donor antigens matched and the fourth unknown or cross-reactive, or two donor antigens matched and the third and fourth unknown or cross-reactive; C match, three donor antigens matched and one mismatched; and D match, two or more donor antigens mismatched.

Platelet-associated IgG levels. Platelet-associated IgG levels were measured by the immunodiffusion assay of Morse et al. Levels were monitored before and during the administration of IgG, and at times before the next transfusion, when the platelets were <15,000/µL. This was done so that changes would not be due to an increase in the platelet count.

RESULTS

Platelets from random donors were without benefit in six patients after administration of IV IgG. The results obtained with selected single donors are summarized in Table 2. The total amount of IV IgG administered varied from 2.0 to 6.0 g/kg. One patient (no. 4) continued to receive booster doses of 800 mg/kg before each platelet transfusion because of the fair response and the clinical judgment that continued IgG improved platelet increments. The other patients received only the initial course of IgG.

In this series, six patients had improved responses to platelet transfusion of selected single-donor platelets. Two of the responses were excellent, three were good, and one was fair. The time to a transfusion-related platelet count of >25,000/µL ranged from one to nine days. In patients in whom the duration of response could be evaluated, most responses persisted from 6 to 8 weeks; however, one patient (patient no. 4) had excellent responses to platelet transfusions in >1 year of observation.

The best response is summarized for patient no. 4 (Table 3), who had been supported by selected single donors for 5 months because of failure to respond to 30 U random-donor platelets. On three successive days, transfusion of platelets from donors that had been effective failed to provide adequate increments. The patient was admitted (October 10, 1984) for IV IgG in an attempt to improve platelet support. The first dose of IgG was administered, followed by platelet transfusion from donor no. 4, which provided a transfusion increment of 40,000/µL, but a markedly shortened survival (the 24-hour count was <16,000/µL). Platelets from donor no. 4, on the seventh day of IV IgG, survived better, with a 48-hour count of 39,000/µL. Improved increments are shown in Table 3 for each of the three donors used for this patient during the platelet refractory period.

Responses to platelets from single donors who were known to be effective before the refractory state were retested after IgG in three patients (patients no. 1, 4, and 8). The data from these seven donors is shown in Fig 1. For comparison, the 1-hour posttransfusion increment observed the first time a donor was used for that patient was considered to be 100%;
the remaining results are expressed as a percentage of that baseline increment. Following IV IgG therapy, one-hour increments averaged 107.5% ± 16.7% (n = 16) of baseline as compared with 22.8% ± 2.8% (n = 8) in the refractory period of time, P < .001. The degree of HLA match between the donor and recipient did not appear to influence the results; improved increments occurred with grades of HLA match ranging from A through D.

Platelet associated-IgG (PA-IgG) levels were measured before transfusion and before and during therapy with IgG. Baseline values were elevated in seven of eight patients (Fig 2) and did not discriminate between responders and nonresponders. In contrast, a correlation was observed between responder responses and PA-IgG level obtained on days 7 through 15 of IV IgG therapy. In responders, values ranged from 3 to 11.4 fg/platelet; in nonresponders, the PA-IgG values ranged from 12 to 100. Responders showed a decline in PA-IgG; in contrast, nonresponders either showed no change or an increase in their levels.

**DISCUSSION**

Although scattered reports describe favorable responses to IV IgG in alloimmunized platelet transfusion recipients, the prevailing data are negative. Studies by Schiffer et al and Knupp et al indicated no improvement in platelet transfusion responses to IV IgG. Thus, their results differ from those in this study.

From the present data, determination of the reasons for these discrepant results is impossible. Most of the patients reported herein received higher doses of IgG than were used in previous studies. Because the same preparation of IgG was used in both this study and that reported by Schiffer et al, the choice of preparation does not appear to explain the difference. In this study, patients were given platelet transfusions in conjunction with the IgG therapy rather than having platelets administered after a course of IV IgG. Moreover, all the present patients were given the best HLA-matched single-donor platelets available. Further observations will be necessary to determine which, if any, of these differences are important in reversing the platelet-refractory state.

In this series, patients had improved responses to selected single-donor platelets; however, random-donor platelets were tried without benefit. Therefore, this therapy may not improve responses to random platelets in most cases, as has been noted previously. That transfusion responses were restored to HLA-D-matched platelet products suggests that some responses to random products may be anticipated.

Although IV IgG improved responses to transfused platelets in selected patients, the mechanisms involved are unclear. In contrast to immune thrombocytopenic purpura in which data suggest that platelet destruction is due to
reticuloendothelial clearance of antibody-coated cells, the mechanism of destruction of allogeneic platelets is not established. Beneficial effects of IV IgG may also result from delayed clearance of sensitized cells. An analogy can be drawn to the findings of Grumet and Yankee, who demonstrated that corticosteroids or splenectomy could improve transfusion increments to HLA-compatible, but not random-donor, platelets in alloimmunized aplastic patients.

The present observations suggest that IV IgG may be able to interfere with antibody coating of platelets. Decreased PA-IgG levels were observed as early as 1 day after institution of IgG therapy (data not shown). This decreased antibody binding continued throughout the study and correlated with response. PA-IgG levels on days 7 through 15 of therapy remained high in nonresponders and fell in responders. These results are similar to those of Becton et al, who noted a decline in surface-associated IgG in two alloimmunized children with aplastic anemia that responded to IV IgG therapy. Moreover, Kekomaki et al showed that the addition of IgG, but not buffer, reduced alloantibody binding in vitro. Higher drug levels may be important for this mechanism as compared with those necessary to produce reticuloendothelial blockade.

REFERENCES

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In conclusion, high-dose IgG therapy improved platelet support, with use of single donors, in six of ten platelet-refractory patients. Even though the effect was usually transient (6 to 8 weeks), improved responses may provide valuable time needed for bone marrow recovery following therapy of acute leukemia or aplastic anemia. The use of IV IgG to improve responsiveness to transfused platelets is certainly expensive. In our hospital, 1 g of IV IgG costs $100.00; thus, the average cost for a single course of 400 mg/kg for five days is ~$14,000.00. Because of this, IV IgG is not a means of maintaining platelet counts >20,000/µL prophylactically; however, this therapy might be considered if a patient is experiencing uncontrollable bleeding and is no longer supportable with single-donor platelet products.

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High-dose intravenous gamma globulin improves responses to single-donor platelets in patients refractory to platelet transfusion

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