Prevention of HLA Immunization With Leukocyte-Poor Packed Red Cells and Platelet Concentrates Obtained by Filtration


HLA immunization is a common complication of transfusion therapy in 30% to 60% of oncohematologic patients. Evidence shows that leukocytes present in cellular blood products are the main component involved in the occurrence of HLA immunization, and several studies showed that leukocyte-poor blood products are less able to induce it. However, leukocyte-poor platelet concentrates obtained by conventional techniques, ie, centrifugation, frequently have a high level of remaining leukocytes. Cotton wool filter Imugard IG 500 can be used to obtain leukocyte-poor cellular blood products. The technique is easy to perform, even in an emergency, and can be used with either packed RBCs or platelet concentrates. Means of leukocyte depletion, Imugard IG 500 exhibits the ability to retain leukocytes with a minimal loss of We found this technique easy to perform even in an emergency.

During the past 10 years, evidence obtained from animal experiments and human transfusions supports the fact that posttransfusion alloimmunization against the major histocompatibility complex is induced by the contaminating leukocytes in blood products. Pure platelet preparations in rats and mice could not induce alloimmunization against class I antigens. A body of studies conducted in humans showed that the rate of HLA immunization can be reduced with the use of leukocyte-poor blood products. However, statistical methodology can be criticized in some of these studies. Eernisse and Brand made an historical comparison, and Murphy et al included patients in a given protocol according to the availability of leukocyte-poor and HLA-matched platelet concentrates. The study of Schiffer et al, although methodologically satisfactory, remains statistically inconclusive despite an important difference in the rates of alloimmunization—20% in the leukocyte-poor group vs 42% in the control group.

Leukocyte-poor RBCs can be easily obtained with most of the commercially available blood filters. Residual leukocytes are usually less than 10^6/U, with a minimal loss of RBCs. In contrast, leukocyte-poor platelet concentrates classically obtained by low-spin centrifugation, frequently contain more than 10^6 residual leukocytes per unit transfused in adult patients. Among the available filters for leukocyte depletion, Imugard IG 500 exhibits the ability to retain leukocytes with a minimal loss of platelets. We found this technique easy to perform even in an emergency.

The aim of our study was to determine whether or not the use of leukocyte-poor blood products, either packed RBCs or platelet concentrates, obtained with the Imugard IG 500 filter, could significantly reduce the rate of HLA alloimmunization in polytransfused oncohematologic patients. The study was conducted in four centers between August 1985 and September 1986.

MATERIALS AND METHODS

Patients

Patients eligible for randomization were to receive standard (control group) or filtered (leukocyte-poor group) cellular blood products when they satisfied the following three inclusion criteria: high probability of being multitransfused with cellular blood products from at least ten donors; not given on a minimum of three different days and within a maximum of 6 months; fewer than 10 prior exposures to HLA antigens, either by blood transfusion or pregnancies; no detectable anti-HLA (A and B) at entry. Since the result of a pre-transfusion anti-HLA antibody screening was available only after the first transfusion took place, patients were usually randomized before the result was known and eventually excluded later. In the same manner, complete information about previous stimulations was not always available at the time of randomization.

Exclusion criteria were as follows: positive anti-HLA screening at entry; insufficient number of cellular blood products transfused, ie, fewer than ten; fewer than three separate days during which a transfusion took place; inadequate anti-HLA antibody screening during and after transfusion (see later); no adherence to the randomization (standard blood products given to a patient randomized in the leukocyte-poor group or vice versa) regardless of the reason; severely immunocompromised patients, either spontaneously or...
therapeutically, ie, bone marrow transplantations and severe autoimmune diseases treated with high doses of corticosteroids and/or immunosuppressive therapy; and leukocyte transfusions.

Patients were advised of the protocol at entry and informed consent was obtained for all.

Transfusion Policy

RBC transfusion. All patients received packed RBCs; some were phenocompatible in the Rh and Kell systems, and others were not. In all patients, transfusions were performed to maintain the hemoglobin concentration above 8 g/100 mL.

Platelet transfusion. In one center, some patients received single-donor platelet concentrates as first-line therapy, depending on the underlying disease and on the availability of blood products. Single-donor platelet concentrates consisted of platelets obtained with Fenwal CS 3000 or Haemonetics V 50 cell separators with "leukocyte-poor" or "surge" protocols. These protocols provided platelet concentrates with a leukocyte contamination similar to that obtained in pools of six to ten standard platelet concentrates. No special selection of donors was made in regard to recipients' HLA phenotype. In the three other centers, patients received pooled multiple-donor platelet concentrates at entry. The usual dose was one platelet concentrate/7 kg of recipient body weight. Indications for platelet transfusion were mainly prophylactic, the platelet count threshold in peripheral blood being 20 x 10^9/L. Single-donor platelet concentrates were transfused, according to French regulations, after a short storage time (less than 24 hours). Standard platelet concentrates were prepared in five-day storage plastic bags and could be used for transfusion after one to five days. Transfusion efficacy was assessed by platelet counts performed on the transfused products, in the patients before transfusion, and 12 to 18 hours after.

In vivo recovery was evaluated by using the following formula: R (%) = (platelet count increment/total platelets infused) x blood volume x 100. Normal 18 hour posttransfusion recovery of stored platelets is found to be between 25% and 60% efficient. Platelet transfusion refractoriness was defined when two successive transfusions had an R value <20%.

Preparation of Leukocyte-Poor Blood Products

The technique used was similar for packed RBCs, single-donor platelet concentrates, and pooled multiple-donor platelet concentrates: the Imugard IG 500 filter is primed with 150 to 200 mL of 0.9% saline solution, and the excess saline is collected in a waste bag. In the case of platelet transfusion were mainly prophylactic, the platelet count threshold in peripheral blood being 20 x 10^9/L. Single-donor platelet concentrates were transfused, according to French regulations, after a short storage time (less than 24 hours). Standard platelet concentrates were prepared in five-day storage plastic bags and could be used for transfusion after one to five days. Transfusion efficacy was assessed by platelet counts performed on the transfused products, in the patients before transfusion, and 12 to 18 hours after.

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Anti-HLA Antibody Screening

Each unabsorbed serum was tested against a panel of 30 lymphocytes sharing all known HLA-A and -B specificities at least once by the lymphocyte microcytotoxicity test, either trypan blue or eosin dye uptake by dead cells was used to assess cytotoxicity.

Anti-HLA antibody screening was performed at least once a week in intensively multitransfused patients such as those with acute nonlymphocytic leukemia (ANLL) induction therapy. In patients with a chronic transfusion regimen such as those with refractory anemia, the test was performed at least on each pretransfusion serum. At the end of the transfusion period studied, anti-HLA antibody screening was performed between the tenth and the 20th day after the last transfusion because previous studies have shown that this is the best time for detection.

When the screening test was positive, ie, when at least 10% of the panel (three cells) showed reproducible cytotoxicity, an attempt to identify HLA specificities was always made. Up to 100 cells could be used for that purpose.

Quality Control During the Study

Each center had a regular control program for the products transfused, either controls or filtered, and no significant differences were noted between the centers. All counts were performed with an automatic technique (Coulter S Plus). Results of quality control were expected to meet the official French requirements for platelet and leukocyte content of cellular blood products:

Standard packed RBCs, no requirement defined; standard platelet concentrates, platelets ≥5 x 10^11 and leukocytes ≤2 x 10^9/U; single-donor platelet concentrate, platelets ≥4 x 10^11 and leukocytes ≤1 x 10^9/U; "leukocyte-free" packed RBCs, leukocytes ≤1 x 10^9/U in at least 75% of the production; filtered platelet concentrates, although there is no official specific requirements, we expected these products to fit with the leukocyte-free packed RBC requirements: (a) single-donor platelet concentrate, leukocytes ≤1 x 10^9/L; and (b) pooled multidonor (ten or fewer) platelet concentrates, leukocytes ≤1 x 10^9/L.

For several months before the study started filtration was used for packed RBCs and found to be efficient; therefore, only routine quality control was performed. In contrast, filtration of platelet preparations, which was more recently introduced, was monitored very closely.

The leukocyte-poor group received a total of 403 packed RBC concentrates, 2,503 platelet concentrates in 334 pools (mean number of units per pool, 7.5), and 54 single-donor platelet concentrates. Of these, 35 packed RBC concentrates (8.7%), 224 pooled multidonor platelet concentrates (67%), and all the 54 single-donor platelet concentrates (100%) were controlled. In addition, during the same period 232 pooled multidonor platelet concentrates and 34 single-donor platelet concentrates prepared for patients not included in the protocol were controlled as well. The mean leukocyte depletion was 97% for packed RBC concentrates, 90% for pooled platelet concentrates, and 76% for single-donor platelet concentrates. Seven of 35 filtered packed RBCs (20%), 40 of 456 (8.8%) pooled multidonor platelet concentrates, and 33 of 88 (37%) single-donor platelet concentrates contained more than 1 x 10^9 contaminating leukocytes. Because filtered products were transfused before the quality control counts were available, some patients in the leukocyte-poor group received blood products with leukocyte contamination outside the stated limits. The complete results of quality control counts are given in Table 1.

End Point of the Study

For each patient included, the study was stopped on the following grounds: at the end of the transfusion period in the case of intensive transfusion therapy, after 6 months in the case of chronic transfusion, or when anti-HLA immunization occurred. In this situation, immunization was always confirmed at least on a second sample. Moreover, in the case of initial narrow specificity, the test was repeated to study the extent of immunization.
Statistical Analysis

The immunization rate and specificity were compared by using the chi-square and the Fisher's exact test, respectively. The immunization rate as a function of time was estimated for each group by using the Kaplan-Meier method, and both groups were compared with the log rank test. The confidence limit of the estimated immunization rate was calculated according to Rothman.

RESULTS

Patient Population

One hundred twelve patients were randomized in the study, 55 in the control group and 57 in the leukocyte-poor group. Forty-three patients were nonevaluable. The main reasons for exclusion are given in Table 2. Eleven patients were excluded when complete information of their pretransfusion status was available (presence of anti-HLA antibody and/or more than ten previous stimulations by transfusions or pregnancies at entry). Fourteen patients were excluded for insufficient blood transfusion due to an incorrect evaluation by the investigators at entry. Early death during induction therapy as well as loss to follow-up and incorrect follow-up made impossible the posttransfusion anti-HLA screening test in 14 patients. Finally, four patients were excluded after transgression of transfusion protocol or receiving a leukocyte transfusion.

Sixty-nine patients remained evaluable, 35 in the control group and 34 in the leukocyte-poor group. These two groups were very similar in regard to underlying disease, sex ratio, age, and previous stimulations with transfusions or pregnancies as shown in Table 3. All 59 patients with ANLL, acute lymphocytic leukemia (ALL), and lymphomas were previously untreated patients, and their treatment could differ from one center to another. Chronic myelogenous leukemia (CML) patients were all treated for their first blast crisis.

Table 2. Patients Excluded From Evaluation: Their Distribution in the Two Randomized Groups: Control and Leukocyte-Poor

<table>
<thead>
<tr>
<th>Exclusions From Evaluation</th>
<th>Number of Patients per Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Anti-HLA at entry</td>
<td>3</td>
</tr>
<tr>
<td>Previous stimulations &gt; 10</td>
<td>3</td>
</tr>
<tr>
<td>Early death</td>
<td>4</td>
</tr>
<tr>
<td>Days of transfusion &lt;3</td>
<td>4</td>
</tr>
<tr>
<td>Blood products transfused &lt;10</td>
<td>2</td>
</tr>
<tr>
<td>No adherence to transfusion protocol</td>
<td>2</td>
</tr>
<tr>
<td>No adherence to anti-HLA screening</td>
<td>1</td>
</tr>
<tr>
<td>Leukocyte transfusion</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
</tr>
</tbody>
</table>

Abbreviations: PRBC, packed RBCs; PC, platelet concentrates.

AntihLA Immunization

Characteristics of antihLA immunization in the leukocyte-poor and the control groups are shown in Table 5. Eleven patients (4 ANLL, 3 ALL, 2 CML, 2 refractory anemias) became immunized in the control group and four (2 ANLL, 1 ALL, 1 CML) in the leukocyte-poor group. The immunization rate was significantly lower in the leukocyte-poor group (P < .05), as well as the development of broad immunization (P < .05). Of the 11 immunized patients in the control group, nine developed broad specific antibodies

Table 3. Evaluable Patient Populations: Characteristics of the Two Groups Concerning Diagnosis, Sex, Age, and HLA Stimulation Before the Transfusion Period Studied

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Control</th>
<th>Leukocyte Poor</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANLL</td>
<td>17</td>
<td>19</td>
<td>36</td>
</tr>
<tr>
<td>ALL</td>
<td>10</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>CML</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Refractory anemia</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Sex ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>14</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>M</td>
<td>21</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>43 ± 18</td>
<td>46 ± 19</td>
<td>44 ± 19</td>
</tr>
<tr>
<td>Range</td>
<td>16-82</td>
<td>14-84</td>
<td>14-84</td>
</tr>
<tr>
<td>Number of patients with previous stimulations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusions</td>
<td>12</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Pregnanacies</td>
<td>6</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Transfusions + pregnancies</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>
Filtration of blood products and HLA immunization

Different according to the log rank test ($P$ or associated specificity and one anti-A2). In the control group, 14 of 30 group; six (21.4%) were found refractory, of whom four were exceptions. In vivo platelet transfusion recovery was available for 22.7% to 56.5%). These two rates are not statistically different according to the log rank test ($P = .07$).

Platelet transfusion refractoriness was defined as a platelet in vivo recovery $\leq 20\%$ in at least two successive transfusions. In vivo platelet transfusion recovery was available for all the transfusions in 28 patients in the leukocyte-poor group; six (21.4%) were found refractory, of whom four were nonimmunized and two were immunized patients (one broad specificity and one anti-A2). In the control group, 14 of 30 evaluable patients (46.6%) became refractory, ten being immunized. Again, this difference between the two groups is significant ($P < .05$). Table 6 gathers information about platelet transfusion refractoriness in the two groups.

**DISCUSSION**

Repeated transfusions of standard packed RBCs alone$^{3,12}$ or associated with platelet concentrates$^{4,17,20}$ lead to HLA immunization in a mean of 40% of patients (28% to 71%). When leukocyte-depleted cellular products are used, the rate of HLA immunization is reduced to 21% (15% to 28%).$^{3,5}$ These results are extremely diverse. Elghouzzi et al$^3$ randomized surgical patients to receive either standard packed RBCs or those passed through the Organon Erypur filter and observed a decrease in HLA immunization from 28% to 15%. Eernisse and Brand$^4$ did not randomize patients and compared an historical group receiving standard blood products with a group transfused with filtered packed RBCs (Organon Erypur filter) and low-spin centrifuged platelet concentrates. Since all the patients mentioned in the study were not evaluable for HLA immunization, this could explain the extremely high immunization rate reported, at least as regards the HLA screening technology used. Schiffer et al$^5$ presented rigorous data according to statistical methodology, but despite a striking difference between the two groups, 42% vs a 20% HLA immunization rate, they did not differ statistically. Their study was focused on the effect of platelet transfusion alone; all patients received leukocyte-poor packed RBCs.

Our study, which was based on a methodology similar to that of Schiffer et al (except for the RBC transfusion policy), shows a statistical significance of the HLA immunization reduction from 31.4% in the control to 11.7% in the leukocyte-poor group. This significance could be related to the number of evaluable patients, 69 in our study vs 56 in Schiffer’s. However, another important difference between the two studies is the leukocyte contamination in platelet concentrates. Standard preparations have almost identical leukocyte contamination per unit: $0.12 \times 10^8$ in ours, 0.65 $\times 10^8$ in Schiffer’s and $0.64 \times 10^8$ in Schiffer’s. In contrast, there is a mean of 0.12 $\times 10^8$

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (N = 35)</th>
<th>Leukocyte-Poor (N = 34)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunized patients</td>
<td>11 (31.4)</td>
<td>4 (11.7)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Broad specificity</td>
<td>11 (81.8)</td>
<td>1/4 (25)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Mean Range</td>
<td>Mean Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of appearance after first transfusion</td>
<td>21 8-49</td>
<td>20 12-33</td>
<td>NS</td>
</tr>
<tr>
<td>Number of blood products received before immunization</td>
<td>62 14-220</td>
<td>70 31-103</td>
<td>NS</td>
</tr>
</tbody>
</table>

The rate of immunization and broad specificity are significantly different in the two groups as tested by chi-square and Fisher’s exact test, respectively.
60 x 10^9 in Schiffer's leukocyte-poor group and 0.06 x 10^9 in ours. Schiffer et al did not present data about reproducibility (no SD mentioned) of the centrifugation technique they used. Our own experience with centrifugation is very similar to that of Schiffer et al for mean leukocyte elimination, with a wider range than the filtration technique has. In our experience, filtration of pooled multidonor platelet concentrates always leads to a leukocyte contamination <0.2 x 10^9/U and only 7.9% contain more than 0.12 x 10^9 residual leukocytes.

The number of leukocytes present in cellular blood products is a critical factor for induction of HLA immunization. Transfusion of highly purified platelet preparations to previously nontransfused patients awaiting renal transplantation showed that three successive transfusions containing 0.15 x 10^9 leukocytes were able to induce HLA immunization in three of 12 patients, while preparations containing less than 0.05 x 10^9 leukocytes could not elicit HLA immunization. This extremely low threshold may be modified in patients undergoing chemotherapy or immunosuppressive treatment as suggested by the observation of Holohan et al that, for a similar number of blood products transfused, the HLA immunization rate is lower in patients undergoing chemotherapy than in untreated patients.

Quality control showed that compared with the excellent performance with pooled multidonor platelet concentrates filtration of single-donor platelet concentrates is less efficient, with 76% leukocyte elimination. Inasmuch as the prefiltration leukocyte content in both products was equivalent, this difference may be due to the fact that single-donor platelet concentrates are filtered a few hours after preparation while most of the pooled multidonor platelet concentrates are filtered after two to three days of storage at 22°C, which favors some degree of microaggregate formation.

We stress the fact that quality control of filters must be managed carefully and constantly. Pooled multidonor platelet concentrates filtered with Imugard IG 500 were studied for 18 months, and no significant variation in leukocyte depletion was observed during this period. After the completion of our study, a modified filter, Imugard IG 500 Y, was investigated in our institutions. This new device gave a shorter filtration time, mainly for packed RBCs, and was supposed to give similar leukocyte elimination. Analysis of 108 packed RBCs and 256 pooled multiple-donor platelet concentrates showed that the new filter, although it had a shorter filtration time, was less efficient. The elimination of leukocytes was only 84% in multiple-donor platelet concentrates and 92% in packed RBCs as opposed to 92% and 97%, respectively, with Imugard IG 500.

One feels that the use of leukocyte-poor blood products does not lead to a true HLA immunization rate reduction but rather to a delayed immunization. Our work clearly shows that, as a function of time, the kinetics of HLA immunization are quite the same in both groups; the mean time of detection of immunization is the same (20 to 22 days), and the majority of patients (nine in the control and three in the leukocyte-poor group) are detected before 3 weeks. This unchanged pattern supports the fact that the number of leukocytes injected at each transfusion is a more important factor to elicit HLA immunization than is the overall number of stimulations.

In transfusion practice, filtration seems to be an efficient and reliable technique that is easy to perform in any blood bank. Packed RBC filtration is already possible with numerous filters, some of them giving highly reproducible results and extremely low numbers of residual leukocytes. In the case of platelet concentrate filtration, the use of filters other than Imugard IG 500 has been reported, but with a significantly higher loss of platelets, up to 20%. We think a given filter can be considered for routine use in blood banks if it gives a leukocyte reduction above 90% and 10% loss of platelets without affecting platelet functions.

In our study platelet transfusion refractoriness has been reduced from 46.6% in the control group to 21.4% in the leukocyte-poor group. One must keep in mind that these results concern a relatively small and heterogeneous patient population (mainly ANLL and ALL) and that factors other than filtration could play a role in reducing the HLA immunization and platelet transfusion refractoriness rates. For example, the therapeutic regimen could be of great importance as suggested by Holohan et al and improvement of cell separator technology to provide leukocyte-poor platelet concentrates could also be of interest.

Prevention of HLA immunization is an important goal for transfusion support of patients with leukemia. It is well established that among immunized patients, up to 90% become refractory to multidonor platelet concentrates. In contrast, approximately 80% of nonimmunized patients have good platelet recoveries. The management of platelet transfusion of patients with anti-HLA antibodies is sometimes extremely difficult and always adds considerably to the cost of transfusion support. Therefore, we think that any new patient with acute leukemia who is potentially eligible for subsequent bone marrow transplantation (either allogeneic or autologous) should be transfused with special consideration for HLA immunization prevention.

Some extremely interesting methods to inhibit major histocompatibility complex immunization by transfusion are now emerging and involve UV irradiation. However, these techniques are unusable in transfusion practice, and meanwhile, filtration remains a practical and efficient means to reduce HLA immunization in humans.

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