To the Editor:

Novotny et al described the results of prestorage leukocyte depletion of blood products on the occurrence of refractoriness and development of HLA-antibodies in patients with aplastic thrombocytopenia. The reason for filtration of fresh blood is mainly derived from experiments in animals in which refractoriness and HLA-alloimmunization occurred more frequently when blood products were transfused that were leukocyte-depleted after a period of storage. This was explained by the passage of leukocyte fragments, which arise during storage, through the filter. It is also supposed that, in humans, these fragments are so immunogenic that they give rise to HLA-immunization. We used many years for all hematologic patients citrate-phosphate-dextrose-adrenaline (CPDA-1) red blood cell concentrates (RBC; buffy coat included) filtered after a storage time of 3 to 4 weeks and found a percentage of refractoriness and HLA-alloimmunization that is comparable with the results showed by Novotny et al.

From 1987 to 1992, 90 untreated acute leukemia patients received remission induction chemotherapy. All patients received leukocyte-poor RBC (LPRBC) when the hemoglobin concentration decreased to less than 80 g/L or sooner if anemic complaints made it necessary. Blood was collected in CPDA-1 solution, centrifuged, and separated in RBC and platelet-poor plasma, or platelet-rich plasma (PRP). RBC stored for 3 to 4 weeks is depleted of leukocytes by the use of a polyester filter (Sepacell R-500; Asahi Med Co, Tokyo, Japan) and transfused within 24 hours. After filtration, LPRBC contained 0.05 ± 0.11 × 10^9/L (mean ± SD) leukocytes. PRP is centrifuged and the platelets are stored in 50 mL plasma at room temperature for up to 5 days. Each donor unit contained at least 0.55 × 10^11 platelets and 1.8 ± 0.1 × 10^8 leukocytes. When the platelet count decreased to less than 10 × 10^9/L a pool of 6 donor units that had been mostly stored for 3 to 5 days was transfused. The effect of the platelet transfusion was evaluated by the corrected count increment (CCI), which is defined as the ratio of the platelet increment × body surface area and the number of platelets transfused. Patients who were clinically refractory (repeatedly poor 1-hour platelet CCI less than 10 that could not be attributed to sepsis, fever, splenomegaly, bleeding, or DIC) and had HLA-antibodies received HLA-compatible platelet concentrates. The presentation and thereafter at regular intervals (1 to 4 weeks), serum samples from all patients were tested for HLA-antibodies by the standard National Institutes of Health complement-dependent microlymphocytotoxicity test against a panel of 40 donors representing most of the defined HLA-A and B specificities.

Ninety patients with acute leukemia (49 with acute myeloid leukemia [AML; age 45 ± 17 years; range, 18 to 73 years] and 41 with acute lymphoid leukemia [ALL; age 29 ± 14 years; range, 15 to 60 years]), were treated with remission induction chemotherapy. None of them received transfusions before; women with previous pregnancies were excluded. These 90 patients (69 men and 21 women) received 28 ± 14 U of leukocyte-poor RBC (AML, 31 ± 15; ALL, 24 ± 13) and 88 ± 57 platelet concentrates (AML, 102 ± 60; ALL, 71 ± 49). Two of 90 patients became refractory (2.2%). Including the two refractory patients, 4 of 80 patients developed HLA antibodies (4.4%). There were no statistically significant differences in the incidence of refractoriness and development of HLA-antibodies between AML and ALL patients. These results suggest that primary alloimmunization can be prevented by the use of RBC filtered after a storage period of 3 weeks and that fragments seemingly are not immunogenic in humans. Our results are in agreement with findings that antibody formation requires viable allogeneic HLA-class I and II bearing antigen-presenting cells and not just fragments of cells. Remarkable in our results is the low incidence of refractoriness despite the use of non-leukocyte-depleted platelets, which contained ±1.0 × 10^9 leukocytes/pool of 6 concentrates. The only difference with the transfusion practice of Novotny et al is that the platelet concentrates we use are stored for up to 5 days. Fiebig and Lane showed a significant downregulation of surface molecules such as CD14 on monocytes during storage (50% reduction at day 5). Because these molecules are important for antigen presentation, this might be the explanation for the poor immunogenicity of the leukocyte-containing platelet concentrates we used. In conclusion, RBC can be filtered after a storage period up to 4 weeks without the induction of HLA-alloimmunization in aplastic leukemia patients.

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The message of our study was (1) that, with prestorage filtered red blood cell (RBC) and platelet transfusions, primary HLA immunization was prevented (2.7%; 95% confidence interval [CI], 0.6% to 7.8%); (2) that patients with a risk history of a prior allogeneic contact still develop HLA antibodies; and (3) that, with this transfusion policy, the need for HLA-matched platelet transfusions, because of broad HLA-reactive antibodies, was less than 5% of the patients.

Other approaches to reduce HLA immunization include UV light treatment of antigen-presenting cells (APCs), photoinactivation, storage-induced inability of APCs to activate an adequate second costimulatory signal, or transfusion of viable DR-sharing mononuclear cells probably establishing microchimaerism and acting as veto cells cytotoxic to the recipient cells responding to alloantigens expressed by the donor.

De Wolf et al, applying poststorage (3 to 4 weeks) filtered RBCs and non–leukocyte-depleted platelet transfusions stored for 3 to 5 days, observed a similar incidence of primary HLA alloimmunization (4.4%; 95% CI, 1.2% to 10.9%).

Leukocyte-depleted blood does not induce primary HLA-immunization, does not induce allograft tolerance, and does not induce blood transfusion-mediated immunosuppression.

Immunomodulatory approaches with damaged or nonviable APCs or viable MHC-sharing APCs tolerate against allo-MHC antigens and suppress the immune response against solid allografts. Consequences of such immunomodulation, for instance, for cancer immunosurveillance, autoimmunity, and susceptibility for infections, are incompletely investigated and still debated. It is, in our opinion, too early to conclude that transfusion-mediated immunosuppression does no harm. It cannot be concluded that both approaches (leukocyte-depletion vs immunosuppression), while equally effective to prevent primary immunization, are equally safe. Another aspect not mentioned by de Wolf et al is whether their transfusion policy is equally convenient for the patient with regard to pyrogenic transfusion reactions, observed quite frequently (20% to 70%) after stored leukocyte-contaminated blood products and are rare with prestorage leukocyte-depleted RBC and platelet transfusions. It would be more interesting how the results of the transfusion policy of de Wolf et al were in patients with prior pregnancy. For this population, allogenic HLA-antigens are presented by self-MHC molecules. If this secondary response can be downregulated by nonviable allo-MHC presenting cells, an immunosuppressive approach can be considered for these patients at higher risk for alloimmunization.

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Prestorage leukocyte depletion is not necessarily required for the prevention of refractoriness to platelet transfusion [letter; comment]

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