Journal of Hematology
volume 83 – number 8 – August 1998

Haematologica 1998; 83:673-675 editorial

Primum non nocere: balancing allogeneic and autologous transfusion risks with a 'society perspective'

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Following the principle of *primum non nocere*, prudent doctors avoid unnecessary patient exposure to blood products. This is done by taking advantage of the tolerance of the human body to blood values below the lower boundaries of normality. For these reasons the triggers for red cell and platelet transfusion in uncomplicated patients have been set at hemoglobin values of 70-80 g/L and at platelet counts of 10-20×10^9/L, respectively. In addition, other strategies specifically developed to avoid exposure to allogeneic blood are available, that rely on the patient's ability to donate his or her own blood prior to the occurrence of an anticipated need. These procedures, which are known as autologous transfusion, are usually perceived as risk-free.

In this issue of Haematologica, Pedrazzoli *et al.*[1] report their recent experience with a refined autologous platelet transfusion program which takes advantage of the platelet count rebound occurring in patients suffering from stage II-III high-risk breast cancer and undergoing autologous peripheral blood stem cell transplantation after high-dose chemotherapy. All the 32 consecutive patients enrolled in the study achieved a platelet count greater than 250×10^9/L and underwent a single platelet apheresis at a median of three weeks after chemotherapy, which allowed the collection of platelet concentrates with a median platelet count of 6.6×10^{11}. The patients' platelets were cryopreserved and used at a later time on a prophylactic basis in 28 patients, when the platelet count was below 20×10^9/L, or during bleeding episodes. A median of 3.8×10^{11} platelets per transfusion were reinfused, as 37% of those collected were lost due to the freeze-thaw-wash procedure. Four of the 28 patients required additional platelets that were provided by allogeneic donors. Two patients escaped the thrombocytopenic phase without reaching a platelet count nadir below the transfusion trigger, thus avoiding any transfusion exposure. Very appropriately, Pedrazzoli *et al.* were concerned that the apheretic product could contain tumor markers. This concern prevented the infusion of two platelet concentrates that were initially found to contain CK19 mRNA by RT-PCR, although none of the platelet products tested positive when re-examined later with a new, more sensitive method free of false positive results. In the control group of 16 consecutive patients treated in the same institution just before the onset of the study, 15 patients received a total of 17 allogeneic transfusions.

The data reported by Pedrazzoli *et al.* may be considered from two perspectives. One perspective is to appreciate that avoidance of allogeneic donor exposure is technically feasible in a large proportion of these patients. Another perspective is to ask ourselves: should this become a standard of care for the breast cancer patient? Before we try to answer this question I would like to raise a few points that may be relevant to the final answer.

The first issue regards the current risks associated with allogeneic blood transfusion, which are exceedingly low.

Transmission of viral infections – a complication affecting in the 1980s more than 10% of the recipients in our country – is declining sharply to levels below those commonly accepted for a number of ordinary avoidable and unavoidable life activities.[2] More encouraging, a number of experts believe that the HIV and hepatitis window periods will be definitely closed in the near future by the adoption of nucleic acid amplification tests.[3] Other potential transfusion associated side effects such as non-hemolytic, febrile and allergic transfusion reactions can generate discomfort and morbidity and cause waste of limited and expensive transfusion resources, but are very unlikely to cause life-threatening harm to the patients. Conversely, transmission of bacterial infections with platelet concentrates is still a matter of concern, because the growth of bacteria that may have inadvertently found access into the platelet storage bag – either via a donor skin biopsy at the time

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of venipuncture or because of poor sterility control during manipulation – is facilitated by the 20-24°C storage of platelet concentrates. Similar concern regards the development of anti-HLA alloimmunization, which is a potential cause of platelet refractoriness. Finally, it appears that either unit or patient misidentification causing the transfusion of the wrong unit to the wrong recipient – a human error affecting both allogeneic and autologous transufion practices – is a commonly overlooked cause of transfusion accidents. The latter include a number of fatalities, which are almost totally confined to red cell containing blood components.[4-6]

A second issue should be considered if the proposed approach entails any potential drawbacks.

Although it is encouraging to note that none of the patients treated by Pedrazzoli *et al.* reported any untoward effects due to the apheresis procedures, the very small but measurable risk of apheresis must be considered when proposing this option to patients. Figures concerning both donor and patient apheresis procedures were recently reviewed by Simon and McLeod.[7] In general, it seems that most of the severe complications relate more to the donor/patient conditions rather than to accidents caused by technical failures of the apheretic systems or their disposables, although the already mentioned possibility of human errors causing actual transfusion of the *autologous* component to the wrong patient should not be overlooked.[4-6] It thus appears that carefully selected patients who are treated in settings with adequate experience and organization do not run significant risks.

From the administrative point of view, another issue requiring consideration is the cost of the procedure and its organization.

Although it can be expected that the cost of an apheresis procedure carried out in patients such as those studied by Pedrazzoli *et al.* is not significantly different from that of collections performed with ordinary blood donors, one should consider the costs of platelet freezing/thawing. The current national reimbursement fee for a freezing/thawing procedure is 399,000 Italian lire (US$228 with an exchange rate of 1,750 lire/US$).

Other issues regard possible strategies to decrease the needs for platelet support and to improve identification of the patients who will actually need it, independently of its allogeneic or autologous source.

First, it should be investigated whether the platelet transfusion trigger can be safely lowered for breast cancer patients as was shown to be the case for patients with other conditions,[8] so that some patients can completely escape any transfusion needs. This seems to be possible if one considers the studies of Hanson and Slichter, who showed that approximately 7,500 platelets per microliter are sufficient for endothelial repair and prevention of spontaneous bleeding.[9] In this regard, it is interesting to note that none of the patients treated by Pedrazzoli *et al.* showed pretransfusion platelet counts below 8,000 per microliter, although the occurrence of fever above 38°C in 23 out of 28 autologous recipients might prevent the use of a lower trigger in a proportion of the cases.

Second, specific programs aimed at preventing impairment of physical performance by aerobic exercise could be considered for these patients, as suggested by the outcomes of the studies of Dimeo *et al*.[10] These authors found that duration of neutropenia and thrombocytopenia, severity of diarrhea, severity of pain and duration of hospitalization were significantly reduced in 33 patients on high dose chemotherapy (including 16 with breast cancer) who did training with aerobic exercise, as compared to 37 controls. The former group used an average of 19.5 platelet units as compared to 26.9 in the control group.

Third, in order to reduce the chance of wasting costly autologous resources, attempts could be made to identify patients who may have an increased probability of requiring platelet support. From the studies of Bolwell *et al.*,[11] who evaluated a large group of patients including 154 with breast cancer, it appears that platelet transfusion requirements during autologous peripheral blood progenitor cell transplantation correlate with the pretransplant platelet count and that this correlation is independent of the dose of $CD34^+$ cells infused.

Finally, the results of the present study should be considered in view of new possibilities offered by *ex vivo* generation of megakaryocytic progenitors to reduce platelet support requirements in these patients, that have been recently successfully explored in a feasibility clinical study reported by a group of investigators including Pedrazzoli and others who share the authorship of the present report.[12] Of course, the economic impact of such approaches will again be an issue, as would other possible applications of the recently developed thrombopoietic factors.

Can we now answer the question of whether allogeneic platelet support should be replaced by autologous transfusion for all breast cancer patients undergoing high dose chemotherapy and autologous stem cell rescue? The advantages of the approach described by Pedrazzoli *et al.* are evident for patients who are refractory to random donor support and when the number of available platelets is not sufficient to cover patients' needs. As far as concerns the other patients, the report by Pedrazzoli *et al.* triggers further debate that must involve not only the scientific community, but the society at large. This is necessary to take the economic decisions with the so-called *society perspective*.[13] For example, to cite a recent real case related to blood transfusion risks, how will the average citizen and tax-payer react to the report that the HIV p24 antigen test costs United States blood centers more than US$ 24 million per year and

yet only four HIV p24 antigen-positive, HIV antibody-negative donations have been detected in the American Red Cross system since implementation of the test in March 1996?[3] Where do we place a boundary to risks that we consider acceptable? How much money and efforts is our society willing to spend to reduce the very low risks of allogeneic blood transfusion yet further?

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