



Prophylactic platelet transfusion in acute leukemia: which threshold should be used?

GUIDO FINAZZI

Divisione di Ematologia, Ospedali Riuniti, Bergamo, Italy

Prophylactic platelet transfusion is a common practice in patients with acute leukemia and severe thrombocytopenia consequent to myelo-suppressive therapy. However, the threshold of the platelet count under which prophylactic transfusion should be given is controversial. Traditionally, a level of 20,000/ μ L has been used, on the basis of a study by Gaydos *et al.*¹ carried out in 1962, that reported an increase in hemorrhagic episodes at platelet counts below 20,000/ μ L. The presence of a threshold value was not, however, clearly demonstrated in that study. Further observations questioned this platelet level^{2,3} and in 1986 a Consensus Conference on Platelet Transfusion Therapy⁴ suggested that “the value of 20,000 platelets/ μ L might safely be lower for some patients”.

In subsequent years, the safety of a stringent prophylactic platelet transfusion policy was investigated in non-randomized clinical studies. In 1991 Gmür *et al.*⁵ described their experience with an algorithm of different thresholds: when the count was below 5,000/ μ L platelets were administered routinely; if fever or minor hemorrhagic manifestations were present, platelet transfusions were administered if the count was below 10,000/ μ L; prophylactic platelets were administered to patients with counts in the 10,000 to 20,000 range only if heparin was being administered or coagulation disorders were present. Treatment of 102 patients receiving induction therapy for acute leukemia showed this approach to be safe. Three deaths due to bleeding occurred, but review of the data makes it clear that none of these would have been prevented by prophylactic administration of platelets at the 20,000/ μ L level. An observational study with historical controls was performed by Gil-Fernandez *et al.*⁶ in 190 patients who underwent bone marrow transplantation at one institution during one period in which the transfusion threshold was 10,000/ μ L and a second period in which the threshold was 20,000/ μ L. The frequency of bleeding was not sig-

nificantly different in the two periods, although the median platelet requirement during the first 100 days after transplantation was reduced by about 26% when the 10,000/ μ L trigger was used. In this issue of Haematologica, Navarro *et al.*⁷ report a similar study on 48 patients with *de novo* acute myeloid leukemia diagnosed in a single institution over a nine year period. The trigger for prophylactic platelet transfusions was 20,000/ μ L during the years 1989-1993 and 10,000/ μ L afterwards. Again, no difference in major bleeding between groups was observed. The definitive demonstration that 10,000 platelets/ μ L is a safe threshold was achieved in two recent randomized clinical trials. An Italian multicenter study⁸ evaluated 255 adults with acute myeloid leukemia randomly assigned to receive a transfusion when their platelet count fell below 10,000/ μ L (or 10,000 to 20,000/ μ L in those with fever, active bleeding or before invasive procedures) or below 20,000/ μ L. Major bleeding occurred in 21.5 and 20 percent of patients in the two groups respectively and only one case of fatal hemorrhage was registered in a patient with a platelet count of 32,000/ μ L. Platelet use was reduced by 21% in the group with the lower threshold. The second randomized trial⁹ was a single-institution study comparing the 10,000 vs. the 20,000/ μ L trigger in 78 patients undergoing induction therapy for acute leukemia. Once again, no significant differences in the total number of bleeding episodes per patient, red blood cell transfusion requirements, remission rate or death during induction chemotherapy were reported. In this study, too, platelet utilization was reduced by about 36% in the 10,000/ μ L trigger group. Summing up, all comparative studies consistently show no significant difference in major bleeding between patients receiving prophylactic platelet transfusions below 10,000 or below 20,000 platelets/ μ L. Most importantly, there were no deaths directly attributable to the use of the more restrictive level in over 600 patients studied.

The advantages of this restrictive but safe platelet transfusion policy are relevant. Reducing patient's exposure to blood products is expected to lower the

Correspondence: Guido Finazzi, M.D., Divisione di Ematologia, Ospedali Riuniti, largo Barozzi 1, 24128 Bergamo, Italy.

potential risks of transmitting viral and bacterial infections as well as other potential transfusion associated side effects such as non-hemolytic, febrile and allergic reactions. These risks are very low, nowadays, but a prudent use of allogeneic blood transfusion remains recommendable.¹⁰ One must also consider the risk of sensitization. Although the relationship between the number of units of platelets received and the development of refractoriness is controversial, the possible development of anti-HLA alloimmunization, which is a potential cause of platelet refractoriness, should be considered. Finally, platelet transfusion is an expensive procedure. In the USA, the cost of providing platelets to an average patient admitted with a hematologic or oncologic condition is over \$2,000; in a patient refractory to platelet transfusion who is undergoing a bone marrow transplantation, the mean cost rises to nearly \$15,000.¹¹

In conclusion, balancing benefits and risks, eminent authorities currently recommend that we "*abandon the irrational practice of transfusing patients whenever the platelet counts decreases to less than 20,000*"¹² and "*embrace the use of a lower platelet-transfusion trigger*".¹³ Based on the results of the largest randomized clinical trial hitherto published,⁸ a threshold of 10,000 platelet/ μ L should be used for administering prophylactic platelet transfusion in stable patients with acute leukemia undergoing conventional chemotherapy. The 20,000/ μ L threshold is recommended for febrile patients ($>38^\circ$), or in the presence of fresh bleeding or if invasive procedures are foreseen. Importantly, these recommendations do not apply to patients with acute promyelocytic leukemia, whose bleeding risk and platelet transfusional requirements remain higher even in the retinoic acid era,¹⁴ or to patients with other cancers, not yet evaluated in appropriate clinical trials. In the future, alternative approaches such as the administration of thrombopoietin may radically change our approach to platelet transfusion. At the moment, the results of the clinical trials should be followed in the management of the single patient.

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