Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Mini Review

Usefulness of Platelet Count as Parameter to Decide on Administering Platelet Transfusions to Hemato-Oncology Patients at Risk of Bleeding

Batman B[1], Urbanus RT[1-3], Fijnheer R[1,4] and Korporaal SJA[1,5]*

[1]Center for Circulatory Health, Department of Clinical Chemistry and Hematology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[2]Van Creveld Laboratory, University Medical Center Utrecht, Utrecht, the Netherlands
[3]Van Creveld Clinic, University Medical Center Utrecht, Utrecht, the Netherlands
[4]Department of Internal Medicine, Meander Medical Center, Amersfoort, The Netherlands
[5]Laboratory of Experimental Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands

***Corresponding author:** Korporaal SJA, Center for Circulatory Health, Department of Clinical Chemistry and Hematology, and Laboratory of Experimental Cardiology (G03.550), UMC Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands

Received: August 19, 2019; **Accepted:** November 07, 2019; **Published:** November 14, 2019

Abstract

Bleeding is a common side-effect in hemato-oncology patients and assumed to be due to chemotherapy-induced thrombocytopenia, a problem observed in many cancer patients. Current guidelines demand that patients receive prophylactic platelet transfusions when their platelet count drops below the threshold of 10x10^9 platelets/L to preserve hemostasis. However, there is ample evidence from large clinical trials that platelet count correlates poorly with bleeding risk in this group of patients as bleeding occurs both above and below the transfusion threshold.

Hence, platelet count cannot reliably predict which thrombocytopenic patient develops a bleeding tendency and requires platelet transfusions. Hence, administering platelet transfusions based on platelet count alone is not sufficient. Consequently, there is a desperate and immediate need for a novel diagnostic parameter that will predict the bleeding risk in thrombocytopenic patients and discriminate between those patients in need of a platelet transfusion and those who are not.

Keywords: Platelet function; Platelet transfusion; Hemato-oncology; Thrombocytopenia; Platelet count; Flow cytometry

Introduction

Platelets are anucleate blood cells that play a key role in the maintenance of vascular integrity. They continuously monitor the vascular wall for breaches and are able to respond rapidly upon encountering defects. In case of such an event, platelets will adhere to the site of injury despite the shear forces of the circulating blood to form an aggregate. The resulting primary haemostatic plug prevents blood loss and remains in place to be reinforced with a strong fibrin network [1]. Failure to form an adequate platelet plug may result in a bleeding tendency [2].

Clinically significant bleeding is a frequent and often major complication in patients with hematological malignancies such as acute leukemia. The link between bleeding and chemotherapy induced thrombocytopenia has been described as early as 1962 [3]. Shortly after this landmark study, bleeding was described to be the leading cause of death in those patients with haematological malignancies who did not receive platelet transfusions [4].

Consequently, transfusion regimens gradually switched from being therapeutic towards being prophylactic in nature, in an attempt to prevent bleeds by increasing the platelet count in patients at risk, which was supported by three small-randomized trials in patients undergoing high-dose chemotherapy for acute leukemia [5-7]. These studies showed that the number of bleeding events were lower and periods between events were shorter in patients receiving prophylactic platelet transfusions below a platelet count threshold of 20x109 platelets/L [5,7]. Such studies were the basis of the current platelet transfusion guidelines that are meant to prevent and treat bleeding complications in patients with thrombocytopenia due to myelosuppressive treatment [8-10].

Platelet count – the current guide for platelet transfusion

The platelet count in healthy individuals is high, lying between 150-400x109 platelets/L, and signs of bleeding are not expected before the platelet count falls to a number below 30-50x109 platelets/L. Over time, the platelet count threshold to guide transfusion was lowered to 10x10^9 platelets/L, which markedly reduced the platelet transfusion demand, without compromising safety when considering incidence, severity and fatality of bleeding [11-13].

However, over time it became apparent that patients may become refractory to platelet transfusions, progressively decreasing the post-transfusion platelet count increments as well as the time interval between transfusions [14].

Interestingly, there is ample evidence from several large clinical trials that bleeding occurs both below and above the platelet transfusion threshold, and that not all patients experience bleeding episodes at low platelet counts [10,15,16], indicating that bleeding risk correlates poorly with platelet count and questioning the benefit of prophylactic platelet transfusions for patients with severe thrombocytopenia [17-19]. A number of randomized controlled trials addressed this issue by comparing bleeding risk in patients receiving prophylactic platelet transfusions with bleeding risk in patients subjected to a therapeutic strategy. The outcome was contradictory, with some trials concluding that a policy of giving platelet transfusions only as treatment for bleeding should become the new standard of care for selected patient groups only [8,20,21], while other trials showed that prophylactic

Citation: Batman B, Urbanus RT, Fijnheer R and Korporaal SJA. Usefulness of Platelet Count as Parameter to Decide on Administering Platelet Transfusions to Hemato-Oncology Patients at Risk of Bleeding. Ann Hematol Oncol. 2019; 6(9): 1269.

platelet transfusions were still likely to prevent bleeding [22]. Strikingly, the rate of bleeding events of World Health Organisation (WHO) grade II, III, or IV [17,23] remained high (43%), despite administration of prophylactic platelet transfusions.

Consequently, the absence of a clear relation between severity of thrombocytopenia and the occurrence of significant bleeding episodes has resulted in a debate on the appropriateness of platelet count in guiding platelet transfusion policy. Adding to the debate is the fact that transfusions are not harmless [24,25], and carry multiple risks for the receiving patients [26]. The associated adverse events range from mild to moderate reactions to platelet transfusions including rigors, fever, and urticaria. These reactions are not life-threatening but can cause extreme distress for the patient. Rarer, but more serious sequelae include anaphylaxis, transfusion-transmitted infections, transfusion-related acute lung injury, and immunomodulatory effects [27]. Because of these side-effects, unnecessary transfusions should be avoided.

Platelet function – a better predictor of bleeding?

Bleeding in patients with immune mediated destruction of platelets depends on platelet function, rather than count [28]. Moreover, acute coagulopathy after trauma was observed to be the result of platelet dysfunction [29]. These observations underline the need to also focus on platelet function, in addition to platelet count to guide the administration of platelet transfusions to prevent bleeding episodes. However, qualitative analysis of platelet function in thrombocytopenic samples has long been impossible with the currently available diagnostic tools. For instance, the gold standard in platelet diagnostics, light transmission aggregometry, is unable to accurately assess platelet function in samples with a platelet count below 50x10^9 platelets/L [30]. Similarly, despite indications of a possible correlation with bleeding events, feasibility of Multiplate® impedance aggregometry is also debatable at low platelet count [31]. We improved and standardized a flow cytometry based platelet function test that can readily detect platelet function defects in patients with a bleeding tendency, including thrombocytopenic patients. The test is therefore superior to the current gold standard, light transmission aggregometry [32,33], and makes it a suitable test for platelet function diagnostics in leukemia patients on chemotherapy. Using this test, we established an inverse relation between platelet function and the risk of bleeding in a phase I single center study amongst 21 leukemia patients with a platelet count below 30% of normal due to chemotherapy. Results showed that patients with a high platelet function score were 5 times less likely to bleed than patients with a low platelet function score, providing evidence that platelet function is a better predictor of bleeding risk than platelet count in thrombocytopenic patients [34]. We are currently confirming these observations in a phase II multicenter trial.

Additional factors influencing bleeding risk

Several factors contribute to hemostasis: in addition to platelets, the vascular endothelium is increasingly being recognized for its important role in this process. Endothelial cells covering the vessel wall release inhibitors that prevent platelet activation and aggregation when the vessel wall is intact. Moreover, the endothelium expresses proteins that inhibit the coagulation system, and synthesizes components that stimulate the degradation of a fibrin clot. Damage to the vascular endothelium can occur as a result of chemotherapy [35], and markers of vessel wall damage, such as von Willebrand factor, are likely to influence the bleeding tendency [1,36]. This way, the degree of damage to the vascular endothelium may affect the incidence and severity of bleeding in a manner independent of platelet count, and may explain the differences in bleeding outcomes between patients. It is therefore necessary to keep in mind to also evaluate and correct for other factors that may put patients at risk for bleeding independent of platelet count and platelet transfusions.

Concluding Remark

Using platelet function as a transfusion parameter rather than or in combination with platelet count will lead to a more efficient use of resources by safely decreasing the need for prophylactic platelet transfusions in hemato- oncological patients, which will concomitantly have significant clinical (fewer donor expositions/ side effects of transfusion) and economical (fewer transfusions/costs) consequences.

References

1. de Groot PG, Urbanus RT, Roest M. Platelet interaction with the vessel wall. Handb Exp Pharmacol. 2012; 210: 87-110.
2. van Ommen CH, Peters M. The bleeding child. Part I: primary hemostatic disorders. Eur J Pediatr. 2012; 171: 1-10.
3. Gaydos LA, Freireich EJ, Mantel N. The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. N Engl J Med. 1962; 266: 905-909.
4. Han T, Stutzman L, Cohen E, Kim U. Effect of platelet transfusion on hemorrhage in patients with acute leukemia: An autopsy study. Cancer. 1966; 19: 1937-1942.
5. Murphy S, Litwin S, Herring LM, Koch P, Remischovsky J, Donaldson MH, et al. Indications for platelet transfusion in children with acute leukemia. Am J Hematol. 1982; 12: 347-356.
6. Solomon J, Bofenkamp T, Fahey J, Chillar R, Beutler E. Platelet prophylaxis in acute non- lymphoblastic leukaemia. Lancet. 1978; 1: 267.
7. Higby DJ, Cohen E, Holland JF, Sinks L. The prophylactic treatment of thrombocytopenic leukemic patients with platelets: a double blind study. Transfusion. 1974; 14: 440-446.
8. Stanworth SJ, Estcourt LJ, Powter G, Kahan BC, Dyer C, Choo L, et al. A no-prophylaxis platelet- transfusion strategy for hematologic cancers. N Engl J Med. 2013; 368: 1771-1780.
9. Estcourt LJ, Stanworth SJ, Murphy MF. Platelet transfusions for patients with haematological malignancies: who needs them? Br J Haematol. 2011; 154: 425-440.
10. Stanworth SJ, Hudson CL, Estcourt LJ, Johnson RJ, Wood EM. Risk of bleeding and use of platelet transfusions in patients with hematologic malignancies: recurrent event analysis. Haematologica. 2015; 100: 740-747.
11. Wandt H, Frank M, Ehninger G, Schneider C, Brack N, Daoud A, et al. Safety and cost effectiveness of a 10 × 109/L trigger for prophylactic platelet transfusions compared with the traditional 20 × 109/L trigger: A prospective comparative trial in 105 patients with acute myeloid leukemia. Blood. 1998; 91: 3601-3606.
12. Navarro JT, Hernandez JA, Ribera JM, Sancho JM, Oriol A, Pujol M, et al. Prophylactic platelet transfusion threshold during therapy for adult acute myeloid leukemia: 10,000/microL *versus* 20,000/microL. Haematologica. 1998; 83: 998-1000.
13. Zumberg MS, del Rosario MLU, Nejame CF, Pollock BH, Garzarella L, Kao KJ, et al. A prospective randomized trial of prophylactic platelet transfusion and bleeding incidence in hematopoietic stem cell transplant recipients: 10,000/L *versus* 20,000/microL trigger. Biol Blood Marrow Transplant. 2002;

8: 569-576.

14. Slichter SJ, Davis K, Enright H, Braine H, Gernsheimer T, Kao KJ, et al. Factors affecting posttransfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. Blood. 2005; 105: 4106-4114.

15. Nevo S, Fuller AK, Zahurak ML, Hartley E, Borinsky ME, Vogelsang GB. Profound thrombocytopenia and survival of hematopoietic stem cell transplant patients without clinically significant bleeding, using prophylactic platelet transfusion triggers of 10x10(9) or 20x10(9) per L. Transfusion. 2007; 47: 1700-1709.

16. Nevo S, Fuller AK, Hartley E, Borinsky ME, Vogelsang GB. Acute bleeding complications in patients after hematopoietic stem cell transplantation with prophylactic platelet transfusion triggers of 10x10(9) and 20x10(9) per L. Transfusion. 2007; 47: 801-812.

17. Slichter SJ, Kaufman RM, Assmann SF, McCullough J, Triulzi DJ, Strauss RG, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med. 2010; 362: 600-613.

18. Triulzi DJ, Assmann SF, Strauss RG, Ness PM, Hess JR, Kaufman RM, et al. The impact of platelet transfusion characteristics on post transfusion platelet increments and clinical bleeding in patients with hypoproliferative thrombocytopenia. Blood. 2012; 119: 5553-5562.

19. Estcourt LJ, Heddle N, Kaufman R, McCullough J, Murphy MF, Slichter S, et al. The challenges of measuring bleeding outcomes in clinical trials of platelet transfusions. Transfusion. 2013; 53: 1531-1543.

20. Wandt H, Schaefer-Eckart K, Wendelin K, Pilz B, Wilhelm M, Thalheimer M, et al. Therapeutic platelet transfusion *versus* routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. Lancet. 2012; 380: 1309-1316.

21. Wandt H, Schaefer-Eckart K, Frank M, Birkmann J, Wilhelm M. A therapeutic platelet transfusion strategy is safe and feasible in patients after autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2006; 37: 387-392.

22. Stanworth SJ, Estcourt LJ, Llewelyn CA, Murphy MF, Wood EM. Impact of prophylactic platelet transfusions on bleeding events in patients with hematologic malignancies: a subgroup analysis of a randomized trial. Transfusion. 2014; 54: 2385-2393.

23. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981; 47: 207-214.

24. Slichter SJ. Eliminate prophylactic platelet transfusions? N Engl J Med. 2013; 368: 1837-1838.

25. Schiffer CA. They took a mulligan and mostly got it right ... the issue of prophylactic platelet transfusion for patients receiving autologous stem cell transplantation. Transfusion. 2014; 54: 2372-2374.

26. Lerner NB, Refaai MA, Blumberg N. Red cell transfusion. In: Williams Hematology 8th ed. USA. McGraw-Hill. 2010; 2287-2300.

27. Crighton GL, Estcourt LJ, Wood EM, Trivella M, Doree C, Stanworth S. A therapeutic-only *versus* prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. Cochrane Database Syst Rev. 2015: CD010981.

28. van Bladel ER, Laarhoven AG, van der Heijden LB, Heitink-Polle KM, Porcelijn L, van der Schoot CE, et al. Functional platelet defects in children with severe chronic ITP as tested with 2 novel assays applicable for low platelet counts. Blood. 2014; 123: 1556-1563.

29. Wohlauer MV, Moore EE, Thomas S, Sauaia A, Evans E, Harr J, et al. Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. J Am Coll Surg. 2012; 214: 739-746.

30. Hayward CP, Moffat KA, Pai M, Liu Y, Seecharan J, McKay H, et al. An evaluation of methods for determining reference intervals for light transmission platelet aggregation tests on samples with normal or reduced platelet counts. Thromb Haemost. 2008; 100: 134-145.

31. Opheim EN, Apelseth TO, Stanworth SJ, Eide GE, Hervig T. Multiple electrode aggregometry and thromboelastography in thrombocytopenic patients with haematological malignancies. Blood Transfus. 2019; 17: 181-190.

32. van Asten I, Schutgens REG, Baaij M, Zandstra J, Roest M, Pasterkamp G, et al. Validation of flow cytometric analysis of platelet function in patients with a suspected platelet function defect. J Thromb Haemost. 2018; 16: 689-698.

33. van Asten I, Schutgens REG, Urbanus RT. Toward flow cytometry based platelet function diagnostics. Semin Thromb Hemost. 2018; 44: 197-205.

34. Batman B, van Bladel ER, van Hamersveld M, Pasker-de Jong PCM, Korporaal SJA, Urbanus RT, et al. Agonist-induced platelet reactivity correlates with bleeding in haemato-oncological patients. Vox Sang. 2017; 112: 773-779.

35. Cameron AC, Touyz RM, Lang NN. Vascular complications of cancer chemotherapy. Can J Cardiol. 2016; 32: 852-862.

36. van Mourik JA, Boertjes R, Huisveld IA, Fijnvandraat K, Pjakrt D, van Genderen PJ, et al. von Willebrand factor propeptide in vascular disorders: A tool to distinguish between acute and chronic endothelial cell perturbation. Blood. 1999; 94: 179-185.