

Thrombopoiesis in Chemotherapy-Induced Thrombocytopaenia Using *Carica Papaya* Leaf Extract: An Attentive Clinical Observation

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Received on 06.04.2019, **Accepted on** 20.06.2019

Abstract

Chemotherapy induced thrombocytopaenia is difficult to manage due to limited number of therapies available. A clinical experiment using *Carica papaya* leaf extract helped to overcome the low platelet count in 3 to 4 days. New agents for correcting thrombocytopaenia take 3 weeks to correct the platelet count. The *Carica papaya* leaf extract contains large amounts of ascorbic acid (Vitamin C) and Calcium which are essential not only for proplatelet production but also for normal platelet function.

Keywords: Thrombopoiesis; Chemotherapy; Thrombocytopaenia; *Carica Papaya* Leaf.

How to cite this article:

PK Prem Ravi Varma. Thrombopoiesis in Chemotherapy-Induced Thrombocytopaenia Using *Carica Papaya* Leaf Extract - An Attentive Clinical Observation. Indian J Canc Educ Res. 2019;7(2):49-53.

Introduction

Thrombocytopenia creates a number of problems in the care of a cancer patient. At platelet counts $<10,000/\mu\text{L}$, spontaneous bleeding is increased. At platelet counts $<50,000/\mu\text{L}$, surgical procedures are often complicated by bleeding. At platelet counts $<100,000/\mu\text{L}$, chemotherapy and radiation therapy are administered with caution for fear of worsening the thrombocytopenia and increasing the risk of bleeding.¹ Therapeutic and prophylactic platelet transfusions create the additional risk of infusion complications. Thrombocytopenia can also occur with any infection or adverse drug reaction associated with cancer treatment. Finally, a diagnosis of thrombocytopenia exacerbates the patient's sense of anxiety and fear beyond that associated with the cancer diagnosis itself.

Papaya leaf extract has been known to increase platelet counts with varied results.² Patients

undergoing chemotherapy for solid tumours, haematological malignancies or myelodysplastic syndromes develop thrombocytopaenia at some point during their chemotherapy. Random donor platelet concentrates are used locally to correct thrombocytopaenia along with plasma and packed red cells in a 1:1:1 or 1:2:1 ratio when platelet counts went below $50,000/\mu\text{L}$. Patients with platelet counts below $80,000/\mu\text{L}$ will have their chemotherapy cycles postponed. This leads to inferior treatment results as the chemotherapy cannot be administered according to protocol.

Rationale

Transfusing random donor platelet concentrates repeatedly may stimulate production of antiplatelet antibodies causing destruction of the transfused platelets.³ Newer agents for correcting thrombocytopaenia like Romiplostim require a three-week period to correct thrombocytopaenia

when patients receive upfront Romiplostim.⁴ Eltrombopag takes 3 to 6 weeks to achieve a rise in platelet count.⁵ Although few studies have been completed to demonstrate their ability to treat chemotherapy-induced thrombocytopenia, these agents may be useful in treating this condition in some situations. Chemotherapy dose reduction and platelet transfusions remain the major treatments for affected patients. Moreover the number of therapies that prevent platelet-related bleeding are few and far between. *Carica papaya* leaf extract was instituted as an option due to difficulty in obtaining platelet rich plasma locally.

Materials and Methods

Participants: Twenty-nine patients who developed thrombocytopenia following chemotherapy for solid tumours, haematological malignancies and myelodysplastic syndromes were randomly observed from April 2017 to April 2019 for at the Cochin Cancer Research Centre.

Ethics committee of the Cochin Cancer Research Centre advised that no prior approval is required for analysis of routine data in April 2017.

Materials: Following chemotherapy patients were seen in the medical oncology out-patients on the 10th day following chemotherapy and prior to the next cycle of chemotherapy with a complete blood count that included a platelet count.

Design: The design is a 2×2 within-subjects design and the volume of *Carica papaya* leaf extract consumed is a within-subjects variable. The independent variables

were age, tumour type and chemotherapy regimen used.

Procedure: Patients who refused platelet transfusions following the development of chemotherapy induced thrombocytopenia were informed of the useful nature of the papaya extract that raises platelet counts in a three to four days' time. They were advised to drink 300 ml freshly made papaya extract in the morning and in the evening till the platelet counts were more than 80,000/ μ L. Patients were advised to consume a piece of cane sugar or honey after drinking the *Carica papaya* leaf extract.

Patients with platelet counts less than 50,000/ μ L were otherwise administered packed red cells, plasma and platelets in a ratio of 1:1:1 or 1:2:1 which is the protocol widely recommended in clinical guidelines to prevent severe thrombocytopenia or haemodilution of coagulation factors.

Results

A dramatic increase in the platelet count was seen following the administration of *Carica papaya* leaf extract. Patients with platelet counts below 80,000 cells/ cu mm would experience a rise of up to more than 150,000/ μ L in 3 to 4 days' time (Fig. 1). This increase did not depend on the initial platelet count or the chemotherapy regime administered. In patients presenting with pancytopenia consuming the papaya extract did not interfere with responses to packed cell transfusions or that of the granulocyte-colony stimulating factor. An increase of five times the presenting platelet count was observed.

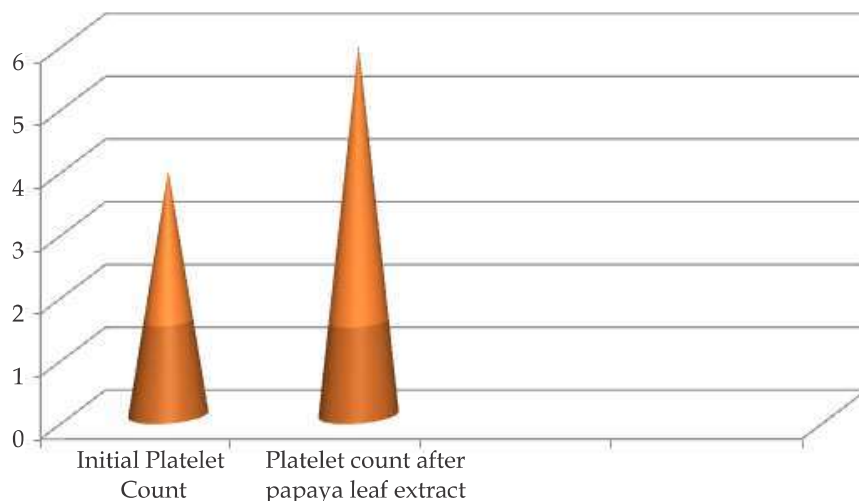


Fig 1: Platelet counts show dramatic increase within 3 days' after consuming papaya leaf extract.

However 11 patients presented with twice the presenting platelet count. A detailed history revealed that they drank less than 300 ml of papaya leaf extract and sometimes 300 ml of papaya leaf extract once daily due to the unpleasant taste of the extract. When they resorted to drinking papaya

leaf extract at the prescribed dose of 300 ml twice daily the platelet counts rose dramatically to almost 150,000/ μ L in 3 to 4 days' time (Fig. 2).

Drinking less than 300 ml of papaya leaf extract over seven days caused a rise of platelet count to twice the presenting platelet count.

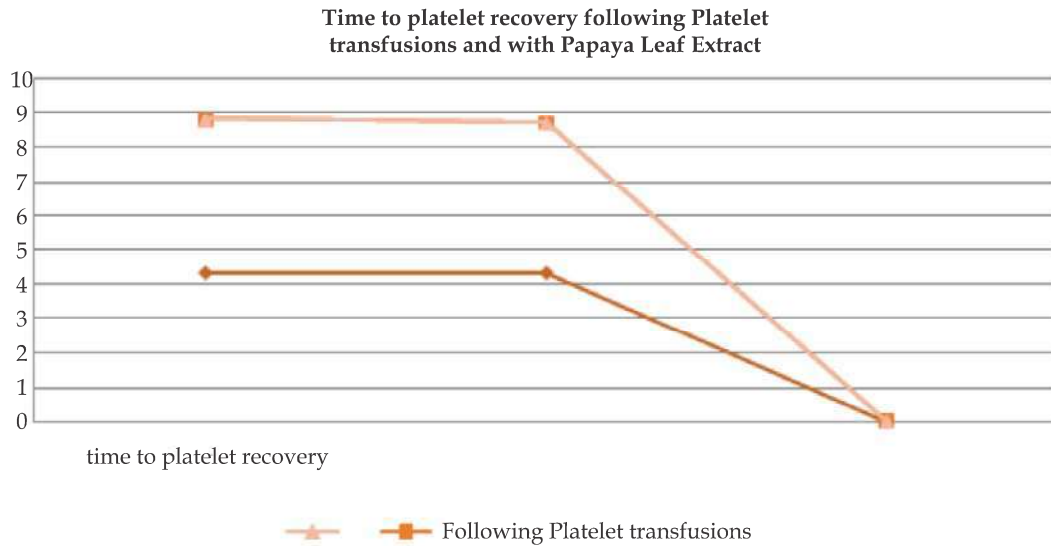


Fig. 2: Comparing time to platelet recovery in days following platelet transfusions and consumption of papaya leaf extract.

Discussion

Not all chemotherapy drugs cause thrombocytopenia in the same way. Stem cells differentiate into cells committed to megakaryocyte differentiation (megakaryocyte colony-forming cells [Mk-CFCs]). At some stage, these cells stop their mitotic divisions and enter a process called "endomitosis," in which DNA replication occurs without subsequent division of the nucleus or the cell. This gives rise to polyploid precursor cells with 2, 4, 8, 16, or 32 times the normal diploid DNA content. These polyploid megakaryocyte precursor cells then stop DNA synthesis and mature into large, morphologically identifiable megakaryocytes.

Mature megakaryocytes then produce platelets by a mechanism that is still poorly defined. In its simplest iteration, mature megakaryocytes extrude long cytoplasmic processes through endothelial cells, and large strands of platelet material (proplatelets) are released into the circulation, eventually becoming mature platelets, possibly through fragmentation in the lung.⁶ If not consumed in haemostasis, the mature platelet undergoes programmed cell death (apoptosis), determined by a "platelet clock"²⁸. This platelet clock depends

on the presence of an anti-apoptotic protein called Bcl-x(L), a protein that restrains the pro-apoptotic proteins Bax and Bak.⁷⁻¹⁰ When levels of Bcl-x(L) decline, Bax and Bak activity increase and trigger platelet apoptosis. The apoptotic platelets are cleared by the reticuloendothelial cell system; the spleen plays only a limited role in normal platelet homeostasis.¹¹

Different chemotherapy drugs affect the megakaryocyte and platelet production pathway at different stages. Alkylating agents such as busulfan affect pluripotent stem cells.^{12,13} Cyclophosphamide spares hematopoietic stem cells because of their abundant levels of aldehyde dehydrogenase, but affects later megakaryocyte progenitors.¹⁴ Bortezomib has no effect on stem cells¹⁵ or megakaryocyte maturation but does inhibit nuclear factor kappa B, a critical regulator of platelet shedding.¹⁶ This probably explains the relatively short duration of thrombocytopenia following its administration.¹⁶

Not all chemotherapy drugs reduce platelet production; some can actually increase the rate of platelet destruction. Indeed, platelet survival itself may be altered by some agents. The experimental chemotherapy agent ABT-737 reduces the activity

of the platelet clock Bcl-x(L) and rapidly induces platelets to undergo apoptosis.^{8,17} After a single dose of ABT-737, platelet levels dropped to 30% of baseline by 2 hours, dropped to 5% of baseline by 6 hours, started to recover to 10% of baseline by 24 hours, and returned to baseline after 72 hours.¹⁷ This was not due to platelet activation; rather, caspase-mediated apoptosis was induced, with a rapid appearance of phosphatidylserine on the platelet surface and clearance of these cells from the circulation by the reticuloendothelial system in the liver. Although this mechanism has not been evaluated for most standard chemotherapy drugs, etoposide also increases platelet apoptosis by reducing Bcl-x(L) activity.¹⁷

Finally, chemotherapy may enhance platelet clearance by immune mechanisms. In the treatment of many lymphomas, administration of single-agent fludarabine has been noted to produce an immune thrombocytopenia in up to 4.5% of patients.¹⁸ This ITP typically responds to rituximab¹⁹ Platelet destruction is also increased when chemotherapy drugs produce a drug-dependent secondary immune thrombocytopenia, but this effect is uncommon.

Drug-associated thrombotic microangiopathy is seen with Gemcitabine, antibodies to red cells and platelets are seen in patients treated with Oxaliplatin, and, a drug-associated Haemolytic Uraemic Syndrome-like picture may occur in patients undergoing treatment with vascular endothelial growth factor inhibitors.²⁰ All of these chemotherapy interventions and at times bone marrow failure can cause thrombocytopenia.

The haematopoietic growth factor thrombopoietin is the key regulator of platelet production. In animals or humans deficient in thrombopoietin or its receptor, the platelet count is 10% to 15% of normal values.^{21,22} Megakaryocyte, erythroid, and myeloid precursor cells are all reduced in such knock-out animals, but the white blood cell (WBC) and RBC counts are normal.²³

Thrombocytopenia results from platelet activation leading to irreversible shedding of its receptors. This results in an increased susceptibility to bleeding. However, shedding of GPIIb/IIIa ectodomain forming the glycoalbumin fragment and platelet desialylation triggers hepatic thrombopoietin production in most patients.²⁴ Thereafter for haemostasis platelet receptors must be expressed. This occurs only when new platelets are produced and released into the circulation which may take days to weeks. Calmodulin (calcium modulated protein) is required to prevent platelet activation.

Moreover type IV collagen, fibrinogen and fibronectin stimulate proplatelet formation²⁵ and Ascorbic acid is required for the production of all types of collagen including type IV collagen.²⁶

Calcium is present at a concentration of 344 mg and Vitamin C (Ascorbic Acid) at 140 mg in 100 gm of *Carica papaya* leaves.²⁷ This probably triggers megakaryocyte maturation in the bone marrow to form proplatelets and expression of platelet receptors.

Conclusion

Therapies to improve platelet counts are less than a handful. In resource poor settings *Carica papaya* leaf extract has been useful to raise platelet counts in 3 to 4 days' time. The principle behind this dramatic platelet response is poorly understood. Further experimental studies and clinical trials are warranted in assessing comparative effectiveness to real-world solutions for a quality improvement in personalized medicine.

References

1. Kuter DJ. General aspects of thrombocytopenia, platelet transfusions, and thrombopoietic growth factors. In: Kitchens C, Kessler C, Konkle B, editors. Consultative Hemostasis and Thrombosis. Philadelphia: Elsevier Saunders; 2013.pp.103-16.
2. Ahmad N, Fazal H, Ayaz M, *et al.* Dengue fever treatment with *Carica papaya* leaves extracts. Asian Pac J Trop Biomed. 2011;1:330-333.
3. Catalano, P M. (1992). NMS Hematology. Malvern, Pennsylvania. Harwal Publishing Company.
4. Soff GA, Miao Y, Devlin SM, *et al.* Romiplostim for chemotherapy-induced thrombocytopenia (CIT). 2017.p.289.
5. Noris P and Pecci A. Hereditary thrombocytopenias: a growing list of disorders. Hematology. American Society of Hematology Education Program. 2017.pp.385-99.
6. Machlus KR, Thon JN, Italiano JE, Jr. Interpreting the developmental dance of the megakaryocyte: a review of the cellular and molecular processes mediating platelet formation. Br J Haematol. 2014;165:227-36.
7. Dowling MR, Josefsson EC, Henley KJ, *et al.* Platelet senescence is regulated by an internal timer, not damage inflicted by hits. Blood. 2010;116:1776-8.
8. Josefsson EC, James C, Henley KJ, *et al.*

- Megakaryocytes possess a functional intrinsic apoptosis pathway that must be restrained to survive and produce platelets. *J Exp Med.* 2011;208:2017–31.
9. Josefsson EC, White MJ, Dowling MR, *et al.* Platelet life span and apoptosis. *Methods Mol Biol.* 2012;788:59–71.
 10. White MJ, Schoenwaelder SM, Josefsson EC, *et al.* Caspase-9 mediates the apoptotic death of megakaryocytes and platelets, but is dispensable for their generation and function. *Blood.* 2012;119:4283–90.
 11. Berger G, Hartwell DW, Wagner DD. P-Selectin and platelet clearance. *Blood.* 1998;92:4446–52.
 12. Fitchen JH, Deregnacourt J, Cline MJ. An in vitro model of hematopoietic injury in chronic hypoplastic anemia. *Cell Tissue Kinet.* 1981;14:8590.
 13. McManus PM, Weiss L. Busulfan-induced chronic bone marrow failure: changes in cortical bone, marrow stromal cells, and adherent cell colonies. *Blood.* 1984;64:1036–41.
 14. DeZern AE, Petri M, Drachman DB, *et al.* High-dose cyclophosphamide without stem cell rescue in 207 patients with aplastic anemia and other autoimmune diseases. *Medicine (Baltimore).* 2011;90:89–98.
 15. Fitzgerald M, Fraser C, Webb I, *et al.* Normal hematopoietic stem cell function in mice following treatment with bortezomib. *Biol Blood Marrow Transplant.* 2003;3:193.
 16. Lonial S, Waller EK, Richardson PG, *et al.* Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed, refractory multiple myeloma. *Blood.* 2005;106:3777–84.
 17. Zhang H, Nimmer PM, Tahir SK, *et al.* Bcl-2 family proteins are essential for platelet survival. *Cell Death Differ.* 2007;14:943–51.
 18. Leach M, Parsons RM, Reilly JT, *et al.* Autoimmunethrombocytopenia: a complication of fludarabine therapy in lymphoproliferative disorders. *Clin Lab Haematol.* 2000;22:175–8.
 19. Hegde UP, Wilson WH, White T, *et al.* Rituximab treatment of refractory fludarabine-associated immune thrombocytopenia in chronic lymphocytic leukemia. *Blood.* 2002;100:2260–2.
 20. Scully M. Thrombocytopenia in hospitalized patients: approach to the patient with thrombotic microangiopathy. *Hematology. American Society of Hematology Education Program.* 2017. pp.651–659.
 21. de Sauvage FJ, Carver-Moore K, Luoh SM, *et al.* Physiological regulation of early and late stages of megakaryocytopoiesis by thrombopoietin. *J Exp Med.* 1996;183:651–6.
 22. de Sauvage FJ, Villeval JL, Shivdasani RA. Regulation of megakaryocytopoiesis and platelet production: lessons from animal models. *J Lab Clin Med.* 1998;131:496–501.
 23. Carver-Moore K, Broxmeyer HE, Luoh SM, *et al.* Low levels of erythroid and myeloid progenitors in thrombopoietin- and c-mpl-deficient mice. *Blood.* 1996;88:803–8.
 24. Montague SJ, Andrews RK and Gardiner EE, Mechanisms of receptor shedding in platelets. *Blood.* 2018;132(24):2535–45.
 25. Farooq T. Phytochemical and Pharmacological Investigation of the Leaves of *Carica Papaya* Linn. 2009. Dissertation. Department of Pharmacy, East-West University, Dhaka, Bangladesh. 23.
 26. Cristina D'Aniello, Cermola F, Patriarca EJ, *et al.* Vitamin C in Stem Cell Biology: Impact on Extracellular Matrix Homeostasis and Epigenetics. *Stem Cells International.* 2017, Article ID 8936156, 16 pages.
 27. Van der Meijden PEJ, Heemskerk JWM. Platelet biology and functions: new concepts and clinical perspectives. *Nature.* 2019;16:166–79.
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