

Original Research Article

A post marketing randomized placebo controlled study to evaluate the efficacy of study product UPLAT® (*Carica papaya* leaf extract + *Tinospora cordifolia* extract) in the cancer patients with thrombocytopenia induced by chemotherapy

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ABSTRACT

Background: Thrombocytopenia refers to abnormal decrease in platelet count in an individual. The condition may rise at different grades of severity in cancer patients under chemotherapy. In most of the cases, thrombocytopenic condition of cancer patient becomes a major therapy limiting factor. Generally, the treatment of thrombocytopenia lies in dose reduction and/or dose delay but this may adversely affect the treatment plan of cancer. Therefore, managing chemotherapy induced thrombocytopenia is still a challenge. This study was conducted to examine the platelet count improving effect of marketed product UPLAT® (*Carica papaya* leaf extract + *Tinospora cordifolia* extract) in cancer patients with chemotherapy induced thrombocytopenia (CIT).

Methods: Forty (40) subjects were recruited as 'case' and twenty (20) as 'control'. 'Cases' were cancer patients with chemotherapy induced thrombocytopenia. UPLAT® containing following active ingredients; *Carica papaya* leaf extract: 350 mg (standardized to 2% flavonoids) and *Tinospora cordifolia* extract: 150 mg (standardized to 3% bitters) was given twice daily (2 units each) for 10 consecutive days. Platelet count was observed at baseline and day 15 (end of the study). Then pre and post-treatment platelet counts were compared individually in both arms by statistical tests. Response was evaluated in forty (40) 'cases' and twenty 'control'y.

Results: Mean change for platelet count in case group (93990.00±63896.73) was much higher than control group (27600.00±29758.42). No adverse events with the treatment were observed.

Conclusions: This study proves the effectiveness of platelet booster UPLAT® (combination of *Carica papaya* leaf extract and *Tinospora cordifolia*) as it significantly increased thrombocytes/platelet count in post-chemotherapy cancer patients.

Keywords: *Carica papaya*, *Tinospora cordifolia*, Chemotherapy, Thrombocytopenia

INTRODUCTION

Thrombocytopenia is a common problem in patients with cancer and is characterized by platelet count less than 150,000/ μ L.¹ It can result from chemotherapy or radiation treatment, or from the underlying disease itself.

Thrombocytopenia creates a number of problems in the care of a cancer patient. At platelet counts <10,000/ μ L, spontaneous bleeding is increased. At platelet counts <50,000/ μ L, surgical procedures are often complicated by bleeding. At platelet counts <100,000/ μ L, chemotherapy and radiation therapy are administered

with caution for fear of worsening the thrombocytopenia and increasing the risk of bleeding.²

In a survey, the incidence of immune thrombocytopenia among adults in United States was estimated to be 3.3 per 100,000 adults/year. On the other hand prevalence of thrombocytopenia was found to be 9.5 cases per 100,000. The annual prevalence of the disorder was estimated to be 5.3 per 100,000 among children; because children in Immune thrombocytopenic purpura (ITP) usually recover, the number of children who have ITP at any one time is about equal to those diagnosed annually.³

Therapeutic and prophylactic platelet transfusions may lead to additional risk of complications associated with infusion. Thrombocytopenia is not only caused due to chemotherapy but may also occur due to adverse drug reaction or infection. Precipitation of thrombocytopenia during the treatment of cancer can lead to more anxiety than diagnosis of cancer itself. Response of treatment of thrombocytopenia in a patient may vary to great extent. Some of the common remedies for management of thrombocytopenia may include; reduction of the dose intensity, use of the radiation, avoiding of treatment regimens that have thrombocytopenia as a side effect or sometimes completely avoiding the treatment. For some patients, treatment of the underlying cause of thrombocytopenia (e.g., stopping therapy with the offending antiviral drug) may work. Platelet transfusion is often the only readily available treatment.⁴

With the discovery of thrombopoietin in 1994, great expectations were generated that it would play a role in preventing or treating thrombocytopenia in cancer patients, just as erythropoietin and granulocyte colony-stimulating factor (G-CSF) have played roles in reducing anemia and neutropenia, respectively.⁵ The first-generation recombinant thrombopoietins reduced chemotherapy-related thrombocytopenia in early clinical trials, but their subsequent development was halted due to antibody formation against endogenous thrombopoietin.⁶ While two second-generation thrombopoietin receptor agonists have now been developed that are potent stimulators of platelet production, neither has yet been tailored for treating thrombocytopenia in patients with cancer.^{5,7}

Management of CIT includes dose reduction and/or delay in initiation of further cycles of chemotherapeutic regime, platelet transfusion, and use of thrombopoietic agents. There are no guidelines to treat CIT; it is based on the patient factors such as risk of bleeding tendency and co-existing morbidities. At present, the US Food and Drug Administration has approved recombinant interleukin (IL)-11 (oprelvekin) for thrombocytopenia induced by chemotherapeutic agents. However, its use is not justified because of its side effect profile and as it demonstrates only modest efficacy.^{8,9} Over the years, there have been many thrombopoietic drugs evaluated for supportive therapy in CIT. One such novel agent is thrombopoietin

receptor agonists like eltrombopag, romiplostim with promising results and lesser potential for immunogenicity. On the other hand, it remains unclear whether use of this agent during chemotherapy is beneficial for cancer outcome due to its adverse effects, cost limits, affordability and accessibility.^{10,11} Therefore, optimizing the management of CIT remains a significant area of research due to unmet need of patients with thrombocytopenia.

Carica papaya belongs to the plant family *Caricaceae*, is an economically important fruit crop worldwide. Many scientific works have been carried out to evaluate the benefit of different parts of papaya plant including fruits, seeds, leaves, rind, shoots, roots or latex.¹² The leaf is considered non-toxic as its lethal dose is >15 g/kg body weight.¹³ Recent studies showed that *C. papaya* leaf extract has potential anti-sickling (inhibition of sickle cell formation) properties.¹⁴

The capacity of papaya leaf extract to reverse the lowering of blood cells, especially platelets, is gaining attention in recent times. A study was aimed to investigate the potential role of fresh *Carica papaya* leaf extract on hematological and biochemical parameters and toxicological changes in a murine model.¹⁵ Fresh *C. papaya* leaf extract significantly increased the platelet and RBC counts in the test group as compared to controls.¹⁵ Therefore, it is very important to identify those phytochemicals of *C. papaya* leaves as it can be recommended to be used as a medication to boost thrombopoiesis and erythropoiesis in humans and in animals in which these cell lineages have been compromised.^{14,16}

Tinospora cordifolia commonly named as “Guduchi” in Sanskrit belongs to family *Menispermaceae*. A variety of active components derived from the plant like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides have been isolated from the different parts of the plant body, including root, stem, and whole plant. Recently, the plant is of great interest to researchers across the globe because of its reported medicinal properties like anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritis, anti-oxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective, immunomodulatory and anti-neoplastic activities.¹⁷ A study performed on busulfan induced thrombocytopenia in rabbits showed that *Tinospora cordifolia* was able to improve platelet count in the test animals.¹⁸

Some studies have been published previously using *Carica papaya* and *Tinospora cordifolia* to analyze their therapeutic potential in thrombocytopenia but none of them have checked therapeutic effect in CIT patients. We here performed a clinical trial on patients with different type of cancer to show the beneficial effect of UPLAT in CIT patients.

METHODS

The study was conducted on 60 (40+20) subjects; 40 subjects consumed UPLAT and 20 consumed placebo at two different study sites (Table 1 and Figure 2). Subject study completion was considered once subject has completed all mandatory visits till visit 7 (Day 16) with all procedures done as per protocol (Table 2). Subjects were identified by unique subject identification (ID) number that remained consistent for the duration of the study. Upon completion of all the required screening/baseline assessments, eligible subjects were enrolled in the study, allocated and treated as per the procedures mentioned in the protocol by the investigator or authorized site staff (Figure 1). All participating investigator took respective ethics committee approvals

before initiating study at the site. All the documents (Protocol, ICF, CRF, any other study related document being utilised in the study) were approved by IEC/IRB. Informed consent was obtained from all the subjects before any study related procedures were carried out. In obtaining and documenting informed consent, the investigator complied with applicable regulatory requirements, and adhered to ICMR Ethical Guidelines for Biomedical Research on Human Participants, International Conference on Harmonisation Guideline-Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. Subject confidentiality was maintained throughout the study by study specific codes. Study was registered on CTRI with CTRI number CTRI/2018/02/012064 [Registered on: 21/02/2018].

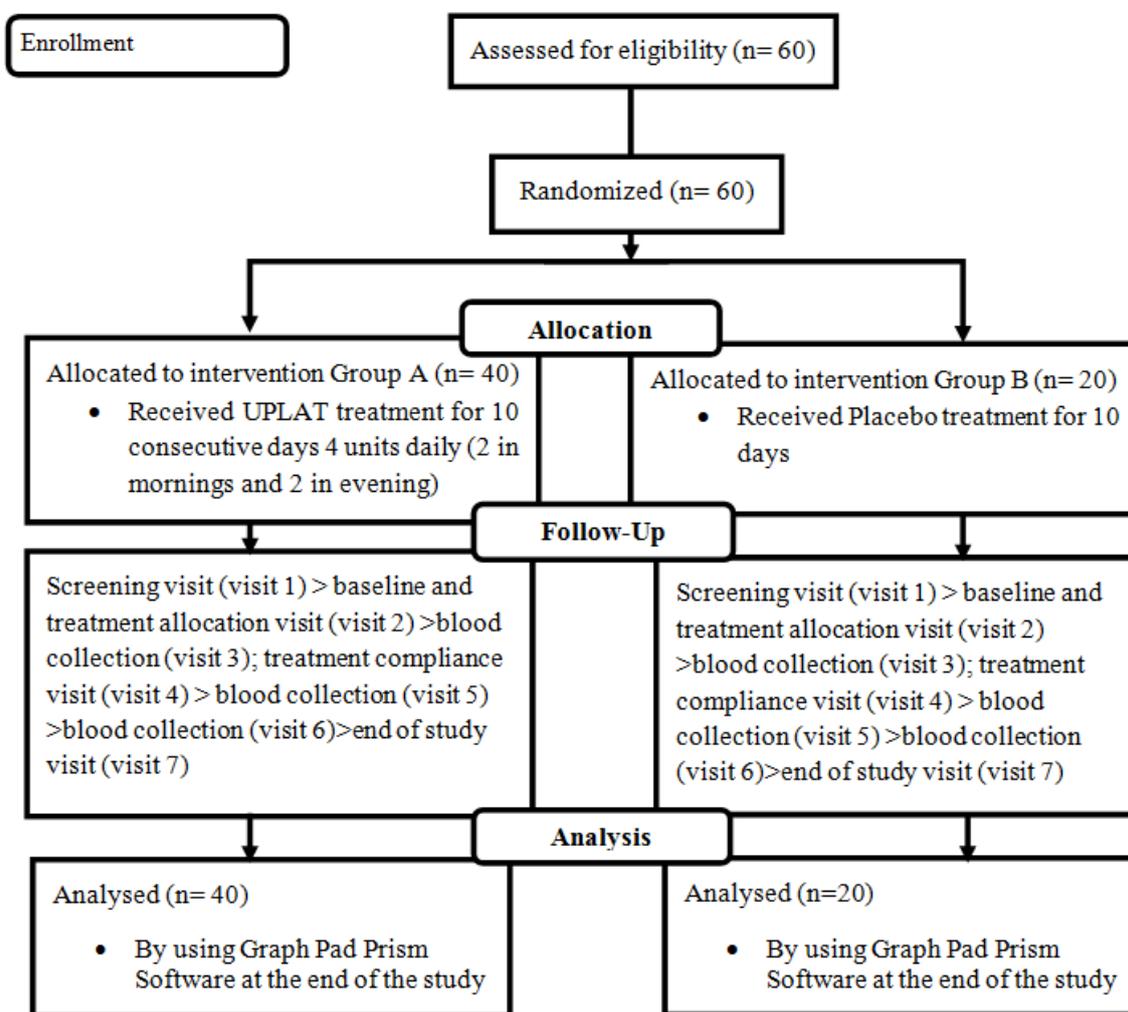


Figure 1: Flow diagram of study conducted in accordance with CONSORT guidelines.

Table 1: Sites where the studies were conducted.

S. No	Site ID	Hospital name
1	UPLAT101	North East Cancer Centre Hospital and research Institute, Jarobat, Guwahati, Assam, India
2	UPLAT102	Aman Hospital And Research Center 15, Shashwat, Opp E.S.I Hospital, Vadodara, Gujarat, India

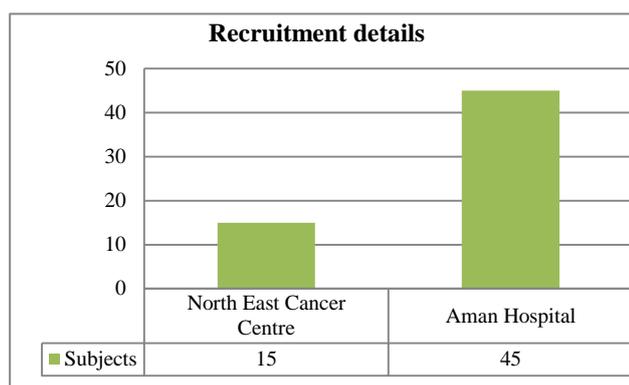


Figure 2: Study recruitment details site wise.

Table 2: Study timelines for enrolled subjects.

Study timelines	Date
First subject first visit (FSFV)	18-Jul-2017
Last subject last visit (LSLV)	09-Dec-2017
Study duration (Days)	145

Pre-treatment screening (visit 1)

A screening/baseline visit was performed within 30 days of the scheduled treatment allocation visit. If eligibility criteria were met, the subject was approached to obtain written informed consent. The purpose of the study participation, benefits and risks of the procedures were explained to the subject. Subjects who agreed to study participation signed an EC approved consent form.

The following assessments were performed on screening visit and the results were recorded on the appropriate subject case report form (CRF):

- Informed consent
- Review of inclusion/exclusion criteria
- Demographics
- Medical/history (including chemotherapy received)
- Physical examination (baseline vital signs, height and weight). At minimum, heart, lung and systems were examined.
- Concomitant medications
- History of alcohol and substance abuse
- Subject’s surgical history
- Haematology: following clinical laboratory tests were done
 - Blood group & Rh typing
 - Haemoglobin
 - Total RBC count
 - Total WBC count
 - Differential count
 - Platelet count
 - Haematocrit
 - ESR
- Urine pregnancy test

After screening visit, each subject was advised to return facility/clinic for baseline and treatment allocation visit.

Baseline and treatment allocation visit (visit 2)

After screening evaluations were conducted and the subject was declared eligible for inclusion into the study, the subject was asked to report to the clinic for treatment allocation. The investigator evaluated the health status of the subjects. Randomization was conducted prior to the treatment allocation visit. Each subject was dispensed two strips for morning and evening dose along with treatment compliance card. Each subject was advised to return to clinic/facility for blood collection visit to central lab. Appropriate details of treatment label were recorded on the appropriate subject (CRFs).

Blood collection visit (visit 3, 5 and 6)

Blood sample collection of each subject was done at this visit. Complete blood count of each subject was performed at central lab and results were recorded on the appropriate subject CRFs. Each subject was advised to return facility/clinic for treatment compliance visit.

Treatment compliance visit (visit 4)

Compliance card was issued to subjects in order to ensure that study product have been ingested timely and accurately. All subjects were encouraged to fill compliance card after ingestion of each dose (by marking as tick). Subjects were advised to return filled compliance card and empty strips along with unused units (if any) in strips at scheduled compliance visit. If a subject missed any of doses during study treatment period, same was captured as cross mark on compliance card and next dose was doubled to make up per day requirement. Compliance card and strips (product accountability) was retained from each subject at this visit. All information was documented in CRF. Each subject was advised from return to clinic/facility for blood collection visit to central lab.

End of study visit (visit 6)

End of Study CRF section was completed for each subject included in the study. Reason for study exit as well as the date of study exit was documented in CRF. Subjects were advised that they may voluntarily withdraw from the study at any time and were instructed to notify their investigator of their decision immediately. Subjects had the liberty to choose to withdraw for any reason and were not obligated to reveal their reasons for withdrawal to study treatment.

Data analysis and statistical considerations

Statistical analysis was done as per the Statistical Analytical plan (SAP) of the study. All statistical tests were performed using SAS® Version 9.1.

RESULTS

A total of 60 patients were recruited after consideration of all the clauses mentioned in the inclusion-exclusion criteria. Patients were randomized and were divided into two groups; Group A (n=40) which received the test product UPLAT and Group B (n=20) which was administered placebo. The platelet count was measured at Day 1 and Day 15.

Demographic characteristics

Subjects in the age group of 30-60 years were considered for study. In group A comprised of; 21 males (52.5%) and 19 females (47.5%) while in group B; 11 males (55.0%) and 9 females (45.0%) were included (Table 3). The mean value of age distribution in both the groups was calculated to be approximately 48 years (Figure 3). The study included patients from vast range of cancer types to obtain unbiased results (Figure 4).

Table 3: Gender distribution between the groups.

Gender	Group A (n=40)		Group B (n=20)		P value ¹
	No.	%	No.	%	
Male	21	52.5	11	55.0	0.85
Female	19	47.5	9	45.0	

¹Chi-square test.

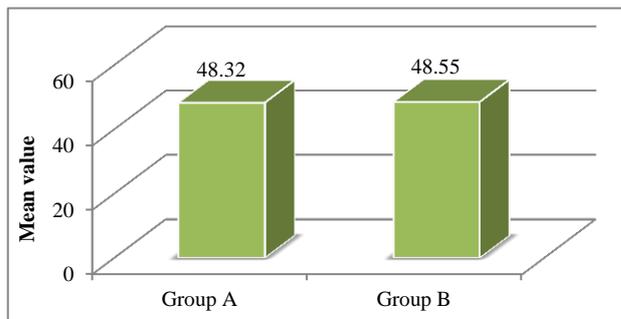


Figure 3: Age distribution between the groups.

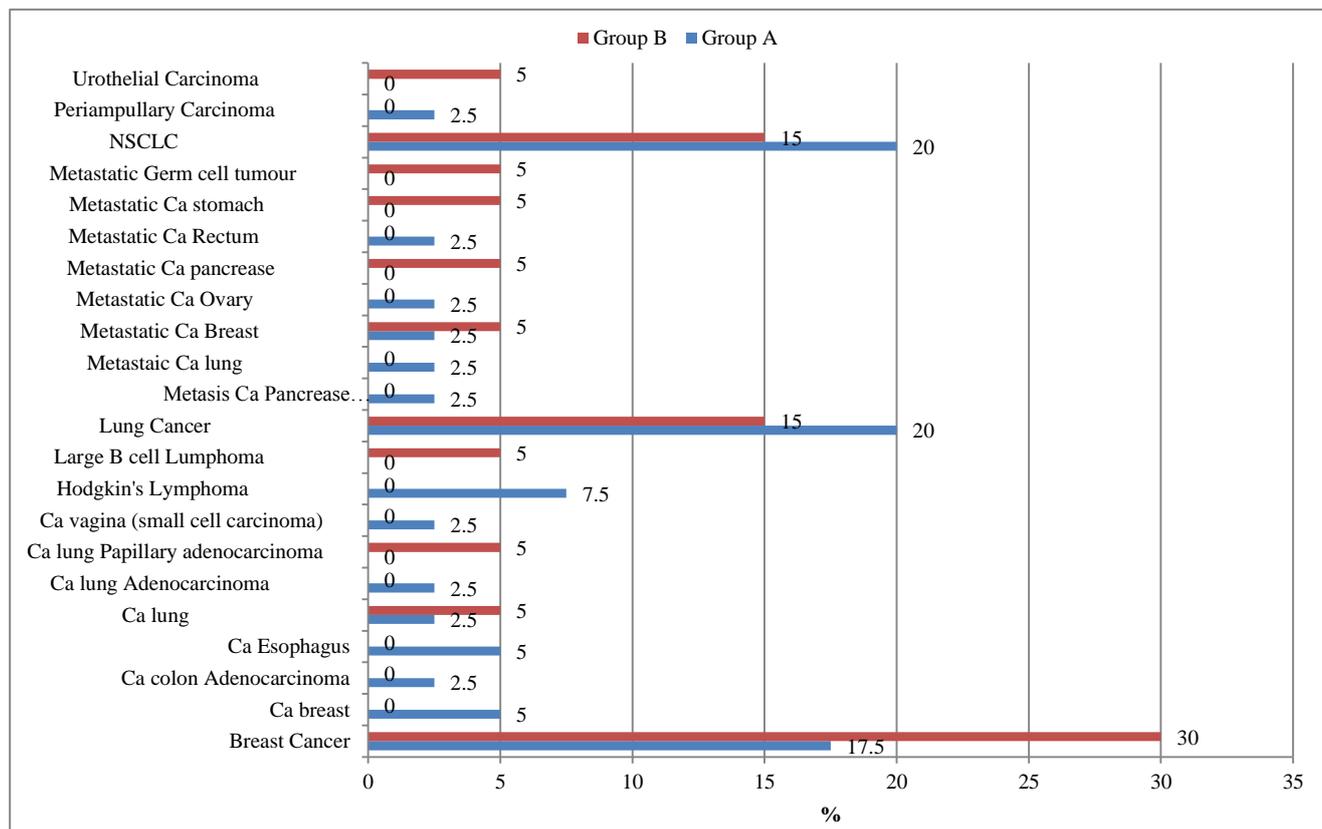


Figure 4: Distribution of type of cancer between the groups.

Table 4: Comparison of platelet count between the groups at Day 1 and Day 15.

Time period	Group A	Group B	P value ¹
Day 1	95849.75±29209.31	103129.00±31404.60	0.37
Day 15	189843.80±48500.88	130730.00±34736.32	0.0001*

¹Unpaired t-test, *Significant.

Table 5: Comparison of mean change in platelet count from day 1 to day 15 in Group A and Group B.

Groups	Mean change	P value ¹
Group A	93990.00±63896.73	0.0001*
Group B	27600.00±29758.42	0.001*
P value ²	0.0001*	

¹Paired t-test, ²Unpaired t-test, *Significant.

Change in platelet count

After the execution of the study plan, it was observed that there was significant increase in the number of platelets in Group A after the oral administration of UPLAT as compared to the placebo Group B (Table 4). The mean changes in platelet counts of both the groups from day 1 to day 15 are shown below. It is evident that the subjects in the intervention group who received UPLAT could attain significantly higher increase in platelet count when compared to the control group (Table 5).

DISCUSSION

Thrombocytopenia is one of the major medical side effect encountered in cancer patients during the administration on chemotherapy. It usually occurs after 6-10 days of the chemotherapy session and its severity depends on the dose and type of the chemotherapeutic drug. When a patient becomes susceptible to the thrombocytopenia after administration of chemotherapy, continuing the therapy becomes equally dangerous to the severity. As, low count of platelet in the blood increases the risk of bleeding in the patient.⁹

This side effect not only affects the treatment regimen but also pose financial burden on the patient. The treatment of CIT either involves altogether stopping or delaying the chemotherapy or use of management regimen which includes platelet transfusion or administration of recombinant thrombopoietin analogs. Treatment with thrombopoietin analogs has its own limitations which include generation of autoantibodies which can further worsen thrombocytopenia. Even platelet transfusion can lead to infusion reactions thereby making this mode of therapy too unreliable. It would not be wrong to say that CIT is still an unmet medical need and requires extensive research to develop natural/alternative medicines that would help in management of CIT.⁹

The test formulation was able to justify its effect by inducing an increase in number of the platelet count in the blood of the treated group. The effect produced is supported by a study performed on dengue patients in whom platelet count was improved by administration of using *Carica papaya* leaf extract.¹⁶ Similar results were also produced in a study performed earlier by sole use of *Carica papaya* leaf extract in CIT patients as well as in patients with viral infection further supporting its positive effect in platelet compromised patients.^{19,20} Similarly, *Carica papaya* and *Tinospora cordifolia* in combination

was also able to elevate the liver cirrhosis induced thrombocytopenia, there by further establishing its effect in platelet compromised patients.²¹

This study was performed to test efficacy of marketed formulation of UPLAT capsules; 350 mg of *Carica papaya* and 150 mg of *Tinospora cordifolia* in Cancer patients suffering from thrombocytopenia as a side effect of chemotherapy. The results show that UPLAT can be given as a supporting therapy to CIT patients to minimize the bleeding possibilities without compromising with the chemotherapy regimen, to support better treatment and reduce the financial burden on patients.

CONCLUSION

The result of the study showed that study product UPLAT increased level of platelet count with no noticeable adverse events within 1-15 days. No significant change was found in pre and post-treatment level of biochemical values other than hematology panel. No sign or symptom of UPLAT related injury was found over the treatment period and there was no treatment related death. Thus oral use of UPLAT® was found to be safe and demonstrated a clinically & statistically noteworthy outcome in raising platelet count on chemotherapy induced thrombocytopenia.

Funding: Study was sponsored by Sanat Products Ltd.

Conflict of interest: None declared

Ethical approval: The study was approved by IEC/RBC and registered on CTRI with CTRI number CTRI/2018/02/012064

REFERENCES

- Liebman HA. Thrombocytopenia in cancer patients. *Thromb Res*. 2014;133:63-9.
- Kuter DJ. General aspects of thrombocytopenia, platelet transfusions, and thrombopoietic growth factors. *Consultative Hemostasis and Thrombosis: Third Edition*. 2013: 103-116.
- NORD (National Organization of Rare Disorders). Available at: <https://rarediseases.org/rare-diseases/immune-thrombocytopenia/>. Accessed on 3 March 2018.
- Refaai MA, Phipps RP, Spinelli SL, Blumberg N. Platelet transfusions: impact on hemostasis, thrombosis, inflammation and clinical outcomes. *Thrombosis research*. 2011;127(4):287-91.
- Kuter DJ. Milestones in understanding platelet production:a historical overview. *Br J Haematol*. 2014;165:248-58.
- Kuter DJ, Begley CG. Recombinant human thrombopoietin:basic biology and evaluation of clinical studies. *Blood*. 2002;100:3457-69.
- Kuter DJ. The biology of thrombopoietin and thrombopoietin receptor agonists. *Int J Hematol*. 2013;98:10-23.

8. Xiao Y, Liu J, Huang XE, Guo JX, Fu PC, Huang XH, et al. A Clinical Study on Juheli (Recombinant Human Interleukin- 11) in the Second Prevention of Chemotherapy Induced Thrombocytopenia. Asian Pac J Cancer Prev. 2016;17(2):485-9.
9. Lei W, Liang J, Chen WG, Ma XZ, Xu M, Du LL. Effectiveness and safety of recombinant human interleukin-11 in the treatment of chemotherapy-induced thrombocytopenia. Zhonghua Zhong Liu Za Zhi. 2006;28(7):542-4.
10. Kuter DJ. What is the potential for thrombopoietic agents in acute leukemia? Best Pract Res Clin Haematol. 2011;24:553-8.
11. Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. Oncology (Williston Park). 2015;29(4):282-94.
12. Ong H, Chua S and Milow P. Ethno-medicinal plants used by the Temuan villagers in Kampung Jeram Kedah Negeri Sembilan Malaysia. Ethno Med. 2011;5:95-100.
13. Sathasivam K, Ramanathan S, Mansor SM, Haris MR and Wernsdorfer WH. Thrombocyte count in mice after administration of papaya leaf suspension. Wien Klin Wochenschr. 2009;121:19-22.
14. Dharmarathna SLCA, Wickramasinghe S, Waduge RN, Rajapakse RPVJ, Kularatne SAM. Does Carica papaya leaf-extract increase the platelet count? An experimental study in a murine model. Asian Pacific J Tropical Biomed. 2013;3(9):720- 4.
15. Yadav J et al. Effect of Carica Papaya Leaf Extract On Platelet Count In Dengue Patient. Int J Recent Sci Res. 2017;8(11):21762-5.
16. Gadhwal AK, Ankit BS, Chahar C, Tantia P, Sirohi P, Agrawal RP. Effect of Carica papaya Leaf Extract Capsule on Platelet Count in Patients of Dengue Fever with Thrombocytopenia. J Assoc Physicians India. 2016;64(6):22-6.
17. Saha S, Ghosh S. Tinospora cordifolia: One plant, many roles. Ancient Science of Life. 2012;31(4):151-9.
18. Chauhan DS, Lata S, Sharma RK, Jindal M, Gupta AK, Suman A, Rehman S, Malik P. Evaluation of role of Tinospora Cordifolia (T.cord.) in experimentally induced (busulfan induced) thrombocytopenia in rabbits. Paripex-Indian J Res. 2016;5(6).
19. Sundarmurthy D, Jayanthi CR, Lakshmaiah KC. Effect of Carica papaya leaf extract on platelet count in chemotherapy-induced thrombocytopenic patients: A preliminary study. Natl J Physiol Pharm Pharmacol. 2017;7(7):685-92.
20. Chinnappan S, Ramachandrappa VS, Tamilarasu K, Krishnan UM, Pillai AK, Rajendiran S. Inhibition of Platelet Aggregation by the Leaf Extract of Carica papaya During Dengue Infection: An in Vitro Study. Viral Immunol. 2016;29(3):164-8.
21. Panda AK, Bhuyan G, Dattatray D, Rao MM. Phytoextracts of carica papaya and Tinospora cordifolia can correct thrombocytopenia in alcoholic decompensate liver cirrhosis: case series. Ayurveda Integr Med Sci. 2018;1:99-101.

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