RESEARCH ARTICLE

Effect of *Carica papaya* leaf extract on platelet count in chemotherapy-induced thrombocytopenic patients: A preliminary study

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ABSTRACT

Background: Chemotherapy-induced thrombocytopenia (CIT) is a detrimental side effect of cancer chemotherapy. Several pharmacologic agents have been evaluated, but their thrombopoietic activity is modest and often associated with unfavorable side effects. *Carica papaya* leaf extract (CPLE) is shown to overexpress ALOX-12 and platelet-activating factor receptor gene which stimulates the megakaryopoiesis. **Aims and Objectives:** To evaluate the efficacy and safety of CPLE in CIT. **Materials and Methods:** A total of 40 patients diagnosed to have CIT were randomized to two groups of 20 subjects each. Interventional group received CPLE 1100 mg TID for 7 days post chemotherapy day 7-14 and non-interventional group did not receive any active treatment. Complete hemogram was done at post chemotherapy day 7, 10, 13, and 16. Patients were followed up for 28 days for adverse effects. **Results:** The mean platelet count in interventional group was $49.700 \pm 12.649/mm^3$, which increased to $55.350 \pm 15.131/mm^3$ ($P > 0.05$), $147.540 \pm 54.359/mm^3$ ($P < 0.01$), and $200.585 \pm 51.893/mm^3$ ($P < 0.01$) on post chemotherapy day 7, 10, 13 and 16, respectively. The mean platelet count in non-interventional group was $47.361 \pm 13.110/mm^3$, $42.580 \pm 12.108/mm^3$, $46.367 \pm 14.776/mm^3$, and $54.238 \pm 16.053/mm^3$ on post chemotherapy day 7, 10, 13, and 16, respectively, with no statistically significant improvement (ANOVA, P). Increment in white blood cell from baseline to day 7 was statistically significant ($P < 0.001$) as compared to control. **Conclusion:** CPLE statistically increased platelet count by day 13 of post chemotherapy along with other hematological parameters. Hence, CPLE could be a viable option for treatment of CIT.

KEY WORDS: *Carica papaya* Leaf Extract; Chemotherapy Induced Thrombocytopenia; Platelet Count; White Blood Cell Count

INTRODUCTION

Chemotherapy-induced thrombocytopenia (CIT) is a major clinical problem affecting nearly 3 lakhs people/annum worldwide.[1] It is defined as a drop in platelets below 1 lakh cells/μl, as a result of the use of conventional chemotherapy that is when clinical evaluation is to be considered.[2,3] Its incidence varies greatly depending on the treatment used, i.e., highest with gemcitabine and platinum-based regimens. However, the overall prevalence of CIT in solid tumors ranges from 1% to 25%.[4] Severe or persisting CIT is associated with the risk of hemorrhage, affects the quality of life and may warrant change in dosing schedule.[5] Chemotherapy drugs differ in their mechanism of causing thrombocytopenia. Studies have shown that alkylating agents affect pluripotent stem cells, cyclophosphamide affect megakaryocyte progenitors.

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 coexisting morbidities. At present, the US Food and Drug Administration has approved recombinant interleukin (IL)-11 (oprelvekin) for thrombocytopenia induced by chemotherapeutic agents. Its use is however not justified because of its side effect profile. 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 besides, adverse effects and cost limits its affordability and accessibility.[3] Hence, there is a need to explore other alternatives to treat CIT.

Amidst years of research and testing, many natural agents from plants or herbs have shown some effect on cancer, but none have shown as much promise as the papaya leaf. *Carica papaya* belongs to plant family Caricaceae.[6] It has established its use in dengue-induced thrombocytopenia as shown by many studies.[7-9] Researchers have found that *C. papaya* leaf extract (CPLE) can mediate Th1-type shift in human immune system, which could potentially help regulate the immune system, treat or prevent cancer, and also serve as an immune adjuvant for vaccine therapy.[10] Furthermore, it is shown to influence platelet production and aggregation by activating arachidonate 12-lipoxygenase (ALOX 12) and platelet-activating factor receptor (PTAFR) genes. Animal toxicity studies for CPLE conducted according to Organization for Economic Co-operation and Development guidelines have shown it to be safe for human consumption.[11,12]

Therefore, this preliminary study was conducted to evaluate the efficacy and safety of CPLE in CIT.

MATERIALS AND METHODS

An open-label, randomized prospective study was conducted during December 2015 and June 2016 on outpatient basis in oncology clinic at Bengaluru. After obtaining written informed consent and ethics clearance, the outpatients at the oncology clinic, diagnosed to have CIT and fulfilling the inclusion/exclusion criteria were enrolled in the study.

Patients aged above 18 years irrespective of the sex were included in this study. Patients diagnosed with CIT, i.e., platelet count ranging from 30,000 to 100,000/µl with diagnosis of solid tumors such as Ca Colon, Ca breast, Ca lung, soft tissue or bone sarcoma or carcinoma and epithelial tumors with adequate renal, and liver function (defined as serum creatinine ≤1.5 and liver function tests ≤2.5 times normal) were included. Patients with primary diagnosis of hematological tumors, with platelet count <30.000/µl or who

have received blood or blood product transfusion during this episode or those with a history of congestive heart failure, arrhythmia, thromboembolic events in past 6 months or with platelet disorder, pregnant, and lactating women were excluded. Patients fulfilling the above eligibility criteria, with nadir low platelet count on day 7-10 of post chemotherapy cycle were included in this study. Patients were randomized using computer-generated table in a 1:1 ratio to receive 1100 mg tablet of CPLE 3 times daily, for 7 days before the initiation of next chemotherapy cycle (intervention group). The decision on dose was made based on the previous study in dengue-induced thrombocytopenic patients.[8] Standardized CPLE 1100 mg is available in market. In non-interventional group, patients were not on any active intervention for CIT.

Demographic data, medical history, concomitant medications, details of general and systemic examination, and laboratory investigations (complete blood count, liver function test, renal function test, and ultrasonography) were recorded on post chemotherapy day 7 ± 3 (visit 1/baseline). Follow-up was done at post chemotherapy day 10 ± 3 (visit 2), day 13 ± 3 (visit 3), and day 16 ± 3 (visit 4) after study drug administration in both groups (Figure 1).

Efficacy Parameters

Primary endpoint of our study was to evaluate the mean change in platelet count on visit 2 from baseline. Secondary endpoint was to assess the mean change in platelet count on visit 3 and 4 from baseline, mean change in other hematological parameters on visit 3 and safety, tolerability of the study medication.

Statistical Analysis

Platelet count, white blood cell (WBC), red blood cell (RBC), hemoglobin, and age are expressed as a mean ±
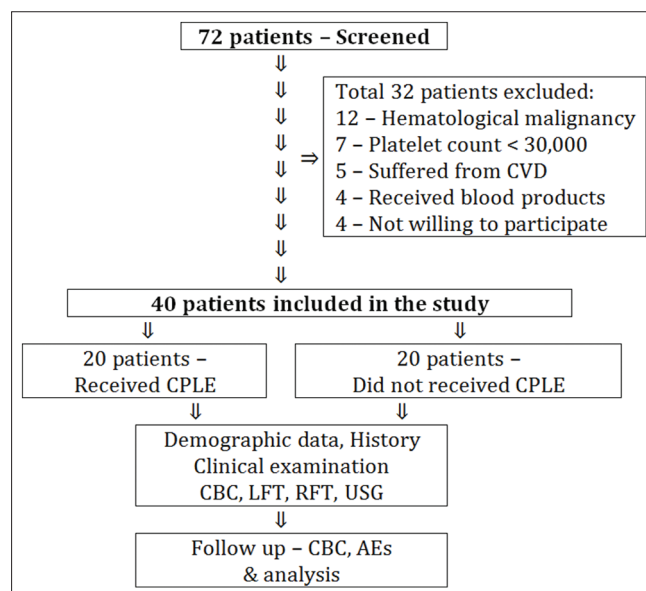

Figure 1: Inflow of study patients

standard deviation. One-way ANOVA followed by *post-hoc* analysis, Tukey's test was performed for platelet count improvement within group. For comparison of mean values of WBC, RBC, and hemoglobin between groups unpaired *t*-test was used. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 72 patients were screened, of which 32 patients were excluded and remaining 40 patients were randomized in a 1:1 ratio into two groups of 20 each. There were no drop outs, and all the 40 patients completed the study (Figure 1).

Baseline Demographic Characteristics

Table 1 represents the demographic profile of the patients included in the study. Both groups were matched with respect to demographic characteristics at baseline ($P > 0.05$).

The cancer profile among study cohort is shown in Figure 2.

The spectrum of chemotherapeutic regimens used among study population is given in Table 2.

The mean platelet count in interventional group and non-interventional group on visit 2, was 55350 ($P > 0.05$) and 42580.6 ($P > 0.05$), on visit 3 was 147.540 ($P < 0.01$) and 46367.1 ($P > 0.05$), and on visit 4 was 200.585 ($P < 0.01$) and 54238.8 ($P > 0.05$) from baseline. In interventional and non-interventional groups, the increase in platelet count between the follow-up visits was statistically significant ($P < 0.001$ vs. $P < 0.05$) (Figure 3).

The mean difference in the platelet count (/μl) on visit 2, 3, and 4 from baseline/visit 1 in interventional versus non-interventional groups was 5650 versus −4781.05 ($P < 0.001$), 97840 versus −994.55 ($P < 0.001$), and 150.885 versus 6.877 ($P < 0.0001$), respectively (Figure 4).

WBC count ($\times 10^9$/μl) on visit 1/baseline and visit 3 in interventional and non-interventional groups is as shown in Figure 5.

RBC count ($\times 10^6$/mm³) on visit 1 and 3 in interventional and non-interventional groups is shown in Figure 6.

Hemoglobin (g/dl) level on visit 1 and 3 in interventional and non-interventional groups is given in Figure 7.

Treatment with CPLE tablet 1100 mg, showed a time-dependent increase in platelet count, WBC, RBC, and hemoglobin which was statistically significant ($P < 0.05$) with respect to non-interventional group.

CPLE given for seven days was well tolerated among the study participants with few side effects which were of mild to moderate in severity and were comparable with a non-interventional group (Table 3).

DISCUSSION

Thrombocytopenia is a significant medical problem encountered in clinical practice among cancer patients on intensive chemotherapy.[4] Chemotherapy-related hematological adverse events pose a significant economic burden on patients, payers, caregivers, and society at large.[13] The treatment of CIT mainly depends on the disease severity with options being delay in reinitiation of chemotherapeutic regime or to stop the use of culprit drug, platelet transfusion if platelet count is below 20.000/μl and recombinant thrombopoietin (rhTPO).[3] However, the use of rhTPO was marred by autoantibodies to thrombopoietin that further exacerbated their thrombocytopenia.[14] Platelet transfusion serves as a temporary solution but is associated with complications such as infusion reactions and platelet transfusion purpura.[3]

Hence, CIT is an unmet medical need and also is of major concern as it not only increases the risk of bleeding but also, importantly, leads to a reduction in chemotherapy dose and frequency which are associated with poorer outcomes. Considering the burden, frequency, and severity of these toxicities selection of optimal treatment is the need of the hour.

CPLE has shown to contain many active components that increase the total antioxidant activity in blood and

| Table 1: Demographic and baseline data of study participants			
Characteristics	**Non-interventional group (*n*=20)**	**Interventional group (*n*=20)**	*P* **value unpaired *t*-test**
Age (years) (mean±SD)	44±8.8	41.5±11.5	0.26
Sex (M/F)	14/6	11/9	
Hematological parameters (mean±SD)			
Platelet count (/μl)	47.361±13.110	49.700±12.649	0.28
WBC ($\times 10^9$/μl)	3.57±0.80	3.9±1.26	0.13
RBC ($\times 10^6$/mm³)	4.42±0.48	4.39±0.61	0.43
Hemoglobin (g/dL)	9.85±1.29	9.87±2.01	0.4

SD: Standard deviation, WBC: White blood cell, RBC: Red blood cell

| Table 2: Spectrum of chemotherapy regimens			
Chemotherapy regimen	Carcinoma	Interventional group (%)	Non-interventional group (%)
Gemcitabine+carbo/ cisplatin	Ca Breast, Ca pancreas	10	12.5
ABVD, ICE	Hodgkins lymphoma	7.5	7.5
ECF	GIT tumors	7.5	5
Etoposide+carboplatin, Docetaxel+carboplatin, Bleomycin+etoposide	Germ cell tumor	5 0 0	0 5 2.5
FEC+docetaxel	Ca breast	7.5	2.5
Chlorambucil+prednisolone	Follicular lymphoma	2.5	5
IA	Sarcoma	2.5	2.5
CHOP	Non-Hodgkin's lymphoma	0	5
Docetaxel	Ca prostate	2.5	2.5
FOLFOX	Ca colon	2.5	0
IAP	Osteosarcoma	2.5	0

ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine, ICE: Ifosfamide, carboplatin, etoposide, ECF: Epirubicin, cisplatin, 5-fluorouracil, FEC: 5-fluorouracil, epirubicin, cyclophosphamide, IA: Idarubicin, Cytarabine, CHOP: Cyclophosphamide, hydroxyl-daunorubicin, oncovin, prednisone, FOLFOX: Fluorouracil, leucovorin, oxaliplatin, IAP: Oxaliplatin, epirubicin, ifosfamide
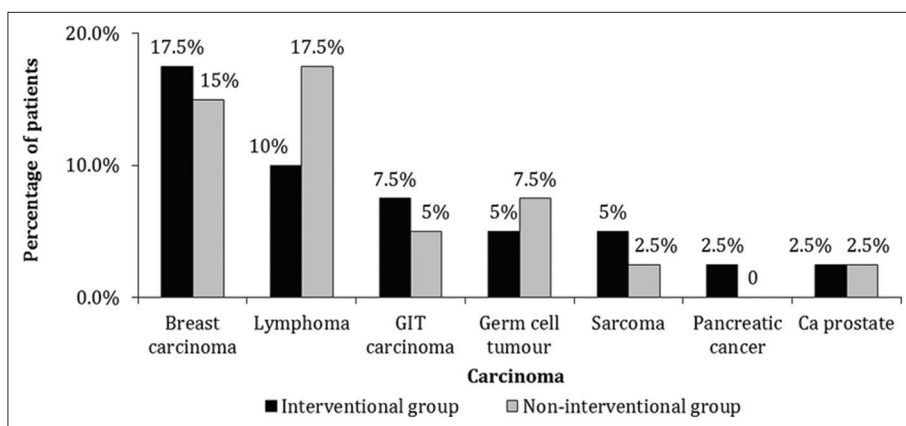
Figure 2: Profile of cancers in study cohort
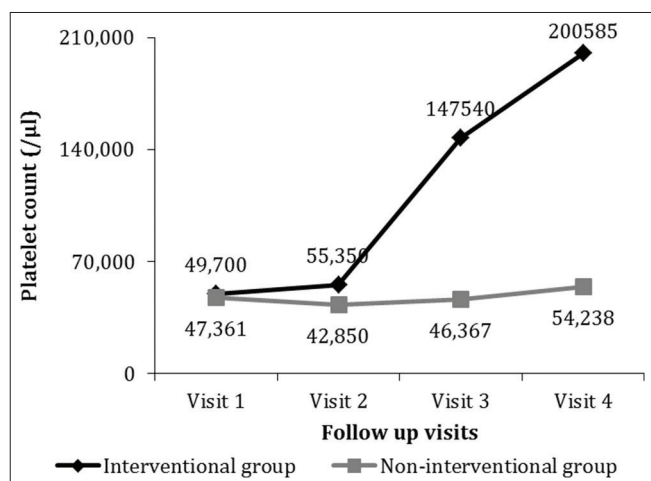
Figure 3: Mean platelet count (ANOVA: Interventional group - $P < 0.001$ and non-interventional group - $P < 0.05$)
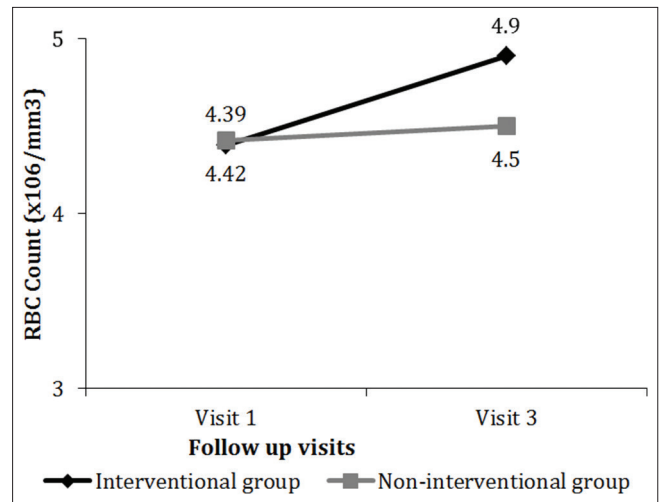
reduce lipid peroxidation, such as papain, chymopapain, cystatin, tocopherol, ascorbic acid, flavonoids, cyanogenic - glucosides, and glucosinolates. The alkaloids, flavonoids, saponins, tannin, and glycosides are related with anti-inflammatory activity. CPLE is also found to have antitumor and immunomodulator activities.[15] Proteolytic enzymes like papain and chymopapain may help increase platelet count, and alkaloid fraction (carpaine) has shown to be responsible for the anti-thrombocytopenic activity. The flavonols and flavonoids have stimulant effect on blood cell production. CPLE has been categorized as nontoxic because its LD_{50} >15 g/kgBW.[16]
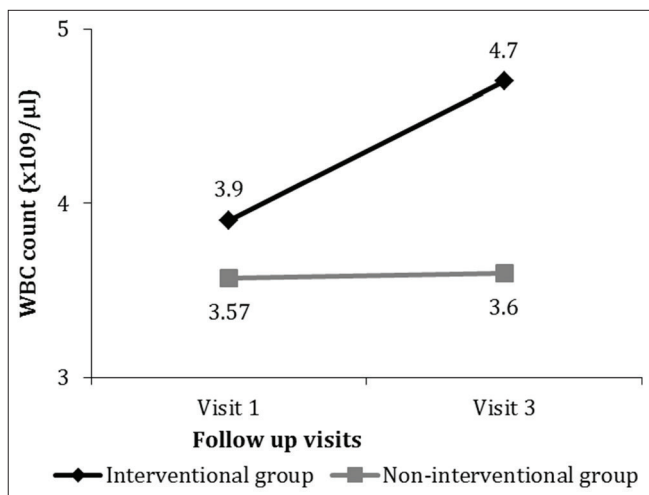
The active ingredients of CPLE are known to upregulate ALOX 12 and PTAFR genes which in turn are responsible for increased production of megakaryocytes and its conversion into platelets. Clinical evidence shows that CPLE increases ALOX 12 activity 15-fold and PTAFR activity 13.42-fold which is responsible for increased platelet production in patients with dengue fever and dengue hemorrhagic fever.[11] Hence, this study was planned to explore the possibility of using CPLE in the treatment of CIT.
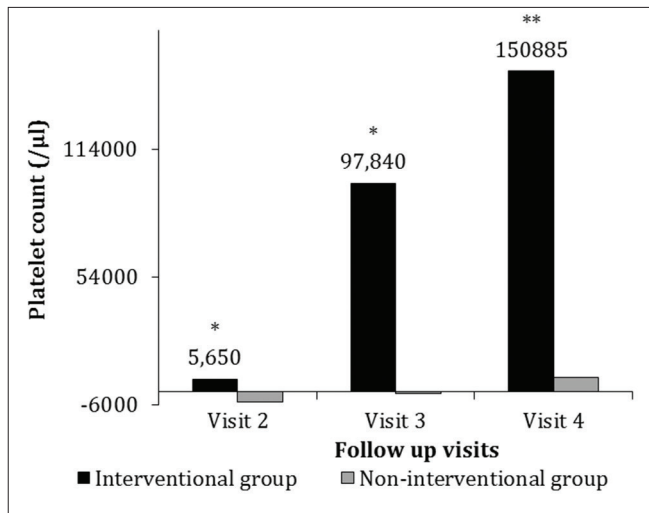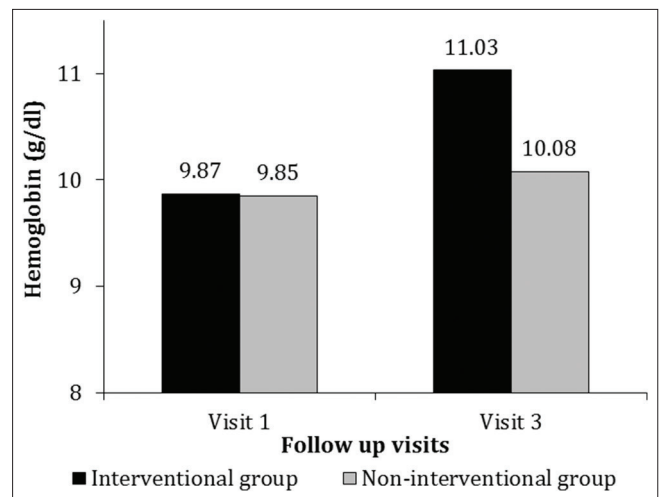
Figure 4: Increment in platelet count from baseline (unpaired *t*-test: *P* < 0.001, **P < 0.0001)

Figure 5: Mean white blood cell count (unpaired *t*-test: *P* < 0.001)

Figure 6: Mean red blood cell count (unpaired *t*-test: *P* < 0.01)

Figure 7: Mean hemoglobin level (unpaired *t*-test: *P* < 0.05)

The prevalence and severity of CIT depends on dose, duration and therapy with chemotherapeutic agents, type of tumor, concomitant drugs causing thrombocytopenia and comorbidities irrespective of age and sex.[3,4] In this study, we encountered patients with a mean age in years of 42.5 ± 10.2 with 25 (62.5%) and 15 (37.5%) male and female subjects, respectively.

Nearly 10-25% of patients with solid tumor on intensive chemotherapy regime develop CIT[4] and a similar picture was reflected in this study with most common carcinoma encountered being breast carcinoma (17.5% vs. 15%) followed by lymphoma (10% vs. 17.5%), gastro intestinal tract tumors (7.5% vs. 5%) in interventional and non-interventional groups, respectively.

The chemotherapeutic regime used influences the occurrence of CIT and is said to be highest with the use of platinum-based compounds (60-80%),[3] followed by those receiving combination therapies with carboplatin, gemcitabine or

Table 3: Adverse effects in study subjects		
Adverse effects	***n* (%)**	
	Interventional group	**Non-interventional group**
Nausea	0	1 (5)
Diarrhea	3 (15)	4 (20)
Dizziness	2 (10)	1 (5)
Vomiting	3 (15)	5 (25)
Headache	2 (10)	2 (10)
Dysgeusia	4 (20)	2 (10)

taxanes. The frequently used regimes in this study were gemcitabine with platinum compounds (10 vs. 12.5%) adriamycin, bleomycin, vinblastine, dacarbazine, ifosfamide, carboplatin, etoposide (7.5 vs. 7.5%), epirubicin, cisplatin, 5-fluorouracil (7.5 vs. 5%) in interventional and non-interventional groups.

Monitoring platelet count (/μl) in patients with CIT is of utmost importance as consequences like bleeding and decision to

reduce the dose of chemotherapy agent can be minimized. The drop in platelet count following a chemotherapy cycle starts by day 7 and reaches its nadir by day 14 with a gradual return to baseline by day 28-35.[3] In this study, platelet counts were recorded on post chemotherapy day 7 ± 3 (visit 1/baseline), day 10 ± 3 (visit 2), day 13 ± 3 (visit 3), and day 16 ± 3 (visit 4). The increase in mean platelet count in interventional group on visit 2 from baseline was not statistically significant, but there was a statistically significant improvement on subsequent visits (visit 3 and 4). In non-interventional group, there was a very minimal change in platelet counts between visits and was not statistically significant.

In a study conducted by Vadhan-Raj et al., rhTPO was administered on days 2, 4, 6, and 8 after a second cycle of carboplatin chemotherapy for patients with gynecologic malignancy, as compared with the first cycle, during which no rhTPO was administered. It was reported that the mean platelet count nadir was higher ($44.000/\mu L$ vs. $20.000/\mu L$; $P = 0.002$), the number of days with platelet count $<20.000/\mu L$ was lower (1 vs. 4 days; $P = 0.002$); and the number of days with a platelet count $< 50,000/\mu L$ was lower (4 vs. 7 days; $P = 0.006$) in the second cycle. The need for platelet transfusion in the group receiving rhTPO was reduced from 75% of patients in cycle 1-25% of patients in cycle 2 ($P = 0.013$). Administration of rhTPO improved recovery to a platelet count $\geq 100.000/\mu L$ (20 days for rhTPO in cycle 2 vs. 23 days without rhTPO in cycle 1; $P < 0.001$).[17] In another study conducted by Basser et al., advanced cancer patients were treated with pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) subcutaneously on 1, 3, and 7 days after chemotherapy (carboplatin, cyclophosphamide, and filgrastim). Compared with cycle 1, those receiving the same chemotherapy dose on a subsequent cycle had a significantly higher platelet nadir ($47.500/\mu L$ vs. $35.500/\mu L$; $P = 0.003$). Administration of PEG-rhMGDF before chemotherapy did not show any benefit. [18] Because of concerns over neutralizing antibody formation the further development was reported to be halted.[14]

The role of thrombopoietin receptor agonist, romiplostim, and eltrombopag was also evaluated for preventing CIT. In a retrospective study conducted by Parameswaran et al., cancer patients with platelet count $<100.000/\mu L$ and who had >4-week delay in their chemotherapy or had dose reductions/modification in >2 prior cycles were treated with romiplostim at 2 $\mu g/kg$ weekly. Platelet counts improved in all of them, i.e., 19 of 20 had platelet counts $\geq 100.000/\mu L$. A total of 15 patients resumed chemotherapy, and all but one continued for two or more cycles without dose modifications.[19] In a Phase I dose escalation study of eltrombopag in patients with advanced soft tissue sarcoma receiving doxorubicin and ifosfamide disclosed that the platelet counts increased in all patients receiving eltrombopag on day 1 of cycle 2 compared to day 1 of cycle 1 in patients not receiving eltrombopag.[20]

At present, thrombopoietin agonist has orphan drug status as a third-line agent in the treatment of patients with chronic immune thrombocytopenia. Based on the available evidence thrombopoietin receptor agonist could be considered for CIT, myelodysplastic syndrome, hereditary and acquired bone marrow failure, hepatitis C infections, or liver cirrhosis.[21]

The anti-thrombocytopenic activity claim of CPLE in CIT was scientifically validated in animal models and was shown to be beneficial. CPLE treated cyclophosphamide-induced thrombocytopenic rat, and carboplatin-induced thrombocytopenic mice showed increase in platelet counts ($P < 0.01$) on day seven onward which was statistically significant.[22,23] Another study conducted on hydroxyurea-treated Wistar albino rat by Guruprasad et al. showed that CPLE increased platelet count on day 5 ($P < 0.05$).[24] In this study, CPLE increased platelet count from day 7 onward in a time-dependent manner similar to that reported in aforementioned animal studies.

In this study, CPLE has shown to have beneficial effects on other hematological parameters also. WBC ($\times 10^9/\mu l$), RBC ($\times 10^6/mm^3$), and Hemoglobin (g/dL) levels significantly increased on day 6 in interventional group ($P < 0.05$). A study conducted by Guruprasad et al. showed that CPLE in addition to platelet count likewise improved RBC count and hematocrit in a time-dependent fashion on day 5 which was statistically significant.[24]

Safety profile was another important objective of this study. The most commonly encountered adverse effects were vomiting, diarrhea, headache, dysgeusia, dizziness, and nausea which were of mild to moderate severity. In contrast, adverse effects encountered by recombinant human thrombopoietin (first generation) were antibody reactions.[3] Thrombopoietin receptor agonists, eltrombopag, and romiplostim (second generation) had risks of developing hepatotoxicity, bone marrow fibrosis, malignancy, thrombosis, and withdrawal thrombocytopenia.[25,26] Recombinant human IL-11 (oprelvekin) is known to cause fluid retention with dilutional anemia, peripheral edema, pleural effusions, papilledema, and atrial arrhythmias which is severe and life-threatening in nature.[27]

The major hurdle with the use of thrombopoietin agonist and oprelvekin was cost, romiplostim ($1400), eltrombopag ($2000), and oprelvekin ($2366) for the management of CIT per week, respectively.[3]

To the best of our knowledge this study is the first of its kind which evaluated the therapeutic role of CPLE in CIT patients, while the previous studies have evaluated the prophylactic role of thrombopoietic agents. The study subjects were randomized in 1:1 which minimized the selection bias. In addition to platelet count, other hematological parameters and safety of CPLE were also evaluated. All the above added

to the strength of the study. However, patients were followed up for a shorter duration, i.e., 28 days, track on chemotherapy response or dose reduction or occurrence of thrombocytopenia in next cycles of chemotherapy was not looked for. Patients were not evaluated for the nutritional status. These potential limitations are to be borne in mind while considering further studies in future.

CONCLUSION

Considering its modest efficacy and safety, CPLE may be a feasible option in treating CIT, however further studies are required to validate its beneficial effects.

ACKNOWLEDGMENTS

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