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Original Research Article

Effect of an Ayurveda antidote *Dooshivishari Agada* in carboplatin induced myelosuppression in Male Wistar rats

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ABSTRACT

Background: Carboplatin is one of the common chemotherapeutic agents in the management of various malignant conditions. Myelosuppression remains one of the major adverse effects of it that leads to compromised quality of life and can procrastinate or cease the chemotherapy regimen. Increasing shreds of evidence suggest the role of Complementary and alternate medicine in palliative cancer care. Ayurveda has prescribed *Dooshivishari Agada* (DVA) as an anti-dote for similar conditions mentioned above which arise out of sub-lethal toxic substances called *Dooshivisha* (DV).
Objective: The present study was carried out to evaluate the role of DVA in myelosuppression among rats.
Method: Male Wistar rats weighing 250–275 g were divided into three groups, Group I was administered normal saline and acted as Normal control. Group II and III received a single dose of carboplatin (60 mg/kg through the tail vein) on day one and acted as disease control. Group III received experimental drug DVA 256 mg/kg orally for the next 18 days. Animals were bled on days 0, 3, 6, 9, 12, 15, 18 for hematological analysis.
Results: DVA prolonged the nadir time for Hb, RBC, and WBC counts from day 9 to day 12 when compared to the carboplatin group. In terms of Platelet count, there was no significant difference over carboplatin. Group III showed a significant increase in Total reticulocyte count in comparison to group II.
Conclusion: Present study showed that DVA may help in delaying the myelosuppression which needs further evaluation.

1. Introduction

Carboplatin is one of the commonly used cytotoxic chemotherapeutic agents across the world. It offers considerable effect in ovarian cancer and cancers of the lung, along with endometrial, esophageal, breast, head, and neck cancers [1]. However, carboplatin comes with a known set of toxicities like nausea, vomiting, dyspepsia and abdominal pain. Series of studies warn of its hematotoxic association. This toxicity reflects as anemia, neutropenia, and thrombocytopenia, which leads to compromised quality of life like dizziness and fatigue [2]. Adverse effects also cause undue hospitalization due to infection or hemorrhagic episodes, which cause out-of-pocket expenses. Nearly 20–40% of patients and more than 90% of patients experience these toxicities when treated with conventional and high-dose carboplatin drugs respectively. This can procrastinate or cease the continuum of chemotherapy regimens [3].

Currently, such events are managed through frequent blood transfusions, granulocyte colony-stimulating factor [GM-CSF], erythropoiesis-stimulating agents [ESA], and bone marrow transplants. These supportive measures come with risks [blood transfusions leading to reactions and infections, GM-CSF causing bone pain and ESA carrying the risk of thrombotic events], economic burden, and above all, the current guidelines don't consider all aspects of patient care which makes the situation a challenging one [4–7]. In such a scenario exploring new therapeutic drugs for preventing and improving myelosuppression induced by chemotherapeutic agents becomes warranted [8]. Increasing evidence suggests the role of Complementary and

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Alternate Medicines like *Ayurveda* and the Chinese system in cancer either as therapeutic or palliative care [9–13]. Few studies indicate that the use of complementary and alternative medicine can be cost-effective and even cost-saving [14,38].

In Ayurveda, such toxic conditions are explained under *Dooshivisha (DV)* [15]. DV is a state where poison originating from inanimate and animate sources or any artificial poison, is retained in the body after partial or incomplete expulsion or which has provisionally undergone detoxification by anti-poisonous/antidote therapy or any poison that's been battered by forest fire, wind or sun externally and then enters the body or has inherent low potency and settles in body.

DV can produce on and often aliments like *Avipaka* [Indigestion], *Moha* [Delirium], *Murccha* [Giddiness], *Paadakarsya Shopa* [Dependent edema], *Vishmajwara* [fever], *Dhatukshaya* [Debilitation] and *Mandala* [urticaria], etc [16]. *Achayara Charaka* says that *rakta* [blood] will be the major substrate for disorders arising out of DV [17]. Chemotherapy-induced side effects are similar to the symptoms mentioned in DV. In such conditions, it is advised and treated with *Dooshivishari agada* (DVA) [an antidote] along with other *panchakarma* measures. DV is a herbomineral compound containing 13 drugs among which few [18] [Table 1] drugs like *Jatamamsi* [19], *Gokshura, Shyonaka, and Yasthimadhu* [20] have shown bone marrow protective activity against agents like cyclophosphamide and cisplatin. While others have shown significant anti-inflammatory and immunomodulatory activities [21–26].

The involvement of Rakta dhatu [blood] in *Dooshivisha* and chemotherapy-induced side effects inspires one to explore *Dooshivishari agada* for understanding its role in myelosuppression. Hence the present study is carried out to evaluate the role of DVA in myelosuppression induced by carboplatin.

2. Materials and methods

2.1. Study drug

Experimental drug *Dooshivishari Agada* (manufactured by GMP certified Vaidyaratnam Oushadhi pharmacy bearing batch number: 19C0415) and Honey (vehicle) were purchased from KLE Ayurveda Hospital.

2.2. Chemicals

Carboplatin [Therapeutic grade] was procured from a licensed dealer [batch number 8790129A01] manufactured by FRESE company and marketed by Nexus lifecare Pvt Ltd, Mumbai, Maharashtra.

2.3. Animals

After Ethical clearance (BMK/IAEC/Res.No.18/2018-01), healthy adult Male Wistar rats weighing 250-275 gms were procured from Sri Raghavendra enterprise [Bengaluru, Karnataka]. Standard polypropylene cages were used to house the rats. The bedding was changed every day. Adequate access to rat pellet food and water was given to the rats throughout the experimental study. The rats were housed in an air-conditioned room [24–28 °C] and a 12-h light–dark cycle was maintained. All the rats were maintained and experimented under standard conditions as per the guidelines of the committee for the purpose of control and supervision of experiments (CPCSEA). All the rats were acclimatized for 7 days before the experiment was initiated.

2.3.1. Experimental design

The rats were randomly divided into three groups [Table 2] Group I- Normal control group (n = 9) received no intervention. Group II- active control; was treated with a single dose of Carboplatin (60 mg/kg body weight through intravenous.) (n = 18). Group III- experimental group treated with a single dose of Carboplatin (60 mg/kg body weight through intravenous) (n = 18) followed by administration of *Dooshivishari agada* in a dose of 256 mg/kg body weight per rat per orally for the next 18 days. The dose of DVA was extrapolated from the human dose [classical human dose is one aksha pramana which weighs approximately 12 gm per day] [27] to the rat dose as per the Paget and Barnes conversion table, 1964 [28].

2.3.2. Estimation of complete blood count [CBC]

Further the Rats in each group were divided into 3 subsets (six each) for blood withdrawal purposes, on an alternate rotational basis on 0, 3rd, 6th, 9th, 12th, 15th and 18th day. A slight modification was made in the model where the blood withdrawal was done through retro-orbital puncture instead of the tail vein [29]. Complete Blood Count [Hemoglobin, Total count, Red blood cell count, and Platelet count] was carried out at KLE Ayurveda Hospital, Belagavi, Karnataka using an automated blood cell analyzer.

2.3.3. Estimation of total reticulocyte count percentage

Total Reticulocyte count percentage was assessed on days 0, 9, and 18 at Jeevan Diagnostics, Belagavi, Karnataka. It was assessed by adding 3–4 drops of reticulocyte stain to collected blood [EDTA tube] which was mixed well. Then it was kept in the incubator for 15–20 min at 37 °C. After incubation, the test tube was slightly shaken to mix well and smears were prepared ~~to~~ for observation ~~e~~ under a microscope, and the score was calculated in percentage.

2.3.4. Histopathology of femur bone for bone marrow

On day 20th, the femoral bone of rats was collected, fixed, sectioned, and stained with hematoxylin and eosin. The histological description was made by a pathologist; photographs were taken under a microscope at 10x and 40x.

2.4. Statistical analysis

All data were statistically analyzed using GraphPad Prism version 5 for windows. A two-way Analysis of variance and Bonferroni's multiple comparison test [post hoc] was applied to data-

Table 1
Ingredients of *Dooshivishari Agada*.

Sl.no	Plant	Scientific name	Part used
1.	Pippali	*Piper longum* Linn.	Phala (Fruit)
2.	Pippalimula	*Piper longum* Linn.	Mula (root)
3.	Dhyamaka	*Cymbopogon martinii* (Roxb.) Wats.	Patra (Leaves)
4.	Jatamamsi	*Nardostachys jatamamsi* DC(*N. grandiflora*)	Mula (Root)
5.	Lodra	*Symplocos racemosa* Roxb.	Twak (Stem Bark)
6.	Ela	*Elettaria cardamomum* Maton	Phala (Fruit)
7.	Suvarchika	*Tribulus terrestris* Linn.	Phala (Fruit),
8.	Katunnatum	*Oroxylum indicum* (Linn) Benth.Ex Kurz.	Mulatwak (Root bark)
9.	Natam	*Valeriana wallichii* D.C.	Mula (Root)
10	Kusta	*Saussurea lappa* C.B. Clarke.	Mula (Root)
11.	Yastimadhu	*Glycyrrhiza glabra* Linn.	Mula (Root)
12.	Rakhtachandana	*Pterocarpus santalinus* Linn. f.	Khanda (Heartwood)
13.	Gairika	Red ochre	

Table 2
Study groups with Induction and Intervention agent.

Group	No. of Animals	Intervention
Normal Control Group I	9 (divided as 3 subsets of three each as A, B & C)	Saline was injected 0.6 ml IV on day
Carboplatin Control Group II	18 (divided as 3 subsets of six each as A, B & C)	Single dose of Carboplatin 60 mg/kg I.V on 1st day of Study
Experimental group or DVA Treated Group III	18 (divided as 3 subsets of six each as A, B & C)	Single dose of carboplatin 60 mg/kg I.V on 1st day of Study + 270 mg/kg/day DVA per orally for 18 days

Human dose of DVA is one Aksha praman i.e 12 gm/day, based on Paget and Barnes conversation table the dose of rat was extrapolated as 1.08/kg b.wt. Powdered DVA was mixed with honey as a vehicle and then administered in a divided dose.

keeping $p \leq 0.05$ as a level of significance. Entire data were expressed in terms of Mean ± S.E.M.

3. Results

3.1. Effect of DVA on hemoglobin [gm/dl] at different time intervals between the groups

There was no significant difference [$p > 0.05$] observed in Hb count between the groups. However, the lowest count was on the 9th day in the carboplatin group [9.53 ± 5.49] and the 12th day in DVA treated group [9.83 ± 5.30] [Table 3]. Interestingly Hb count recovered by the 18th day in DVA treated group [13.13 ± 0.80] which was comparable to the normal group [13.16 ± 1.28], while it was on the lower side in the Carboplatin group [10.60 ± 0.98].

3.2. Effect of DVA on total count [WBC - 10*9 L] at different time intervals between the groups

There was no significant difference [$p > 0.05$] observed in WBC count between the groups [Table 3]. The count was lowest on the 9th day in the carboplatin group [7.12 ± 6.21] and the 12th day in DVA treated group [5.99 ± 2.39]. The total count in both the group came to baseline value by 18th day.

3.3. Effect of DVA on red blood cells [RBC- 10*12 L] at different time intervals between the groups

There was no significant difference [$p > 0.05$] observed in RBC count between the groups. RBC showed bi-phasic decline [Table 3] on 9th [5.05 ± 2.83] and 15th day [4.58 ± 2.53] in the carboplatin group, while in the DVA treated group the lowest count was observed on 12th day [5.09 ± 2.75]. On the 18th day, RBC in each group was in the recovery phase.

3.4. Effect of DVA on platelets at different time intervals between the groups

There was no significant difference [$p > 0.05$] in carboplatin and DVA treated group on platelet value [Table 3] Both the groups showed a similar pattern of reduction and rebound increase in count. However, there was a significant difference [$p < 0.001$] between the normal group [Day 9, 686.66 ± 67.00] and Carboplatin [Day 9, 105.33 ± 76.02] and DVA treated group [Day 9, 79.66 ± 11.37] indicating there is no action of DVA on platelet count.

3.5. Effect of DVA on Total Reticulocyte count at different time intervals between the groups

There was a significant difference [$p < 0.01$] observed in the Total Reticulocyte Count percentage [Table 3] on the 18th day of study between carboplatin [1.7 ± 0.28] and DVA treated group [5.8 ± 3.53].

4. Discussion

The present study findings were similar to the results reported by Woo S et al., 2008, where the Hb, RBC, WBC, and Platelet Counts reached the lowest by the 9th day of study in the carboplatin group [Table 3].

No significant difference [$p > 0.05$] was observed in above parameters between carboplatin and DVA treated group except the Total Reticulocyte count percentage [$p < 0.05$]. However, it is of interest to note that in the DVA treated group the Hemoglobin, RBC,

Table 3
Effects of DVA on Hb, WBC, RBC, Platelet and Total Reticulocyte count at different time points in carboplatin induced myelosuppression.

Parameters	Groups	Days						
		0	3	6	9	12	15	18
Hb (gm/dL)	Normal	13.95 ± 4.27	14.93 ± 0.12	15.33 ± 0.32	14.53 ± 0.15	12.93 ± 1.70	13.70 ± 0.78	13.17 ± 1.29
	Carboplatin	14.78 ± 0.42	14.67 ± 0.70	12.17 ± 0.67	9.53 ± 5.49	12.67 ± 0.40	8.97 ± 4.48	10.60 ± 0.99
	Carboplatin + DVA	15.43 ± 1.34	13.57 ± 4.30	14.93 ± 0.84	12.33 ± 0.50	9.83 ± 5.31	10.40 ± 1.87	13.13 ± 0.81
WBC (10 x 9) L	Normal	10.81 ± 3.57	14.29 ± 1.04	29.88 ± 5.22	15.60 ± 6.42	18.16 ± 1.00	13.25 ± 0.25	11.65 ± 4.08
	Carboplatin	20.96 ± 5.16**	13.62 ± 4.20	8.17 ± 3.96***	7.13 ± 6.21	9.30 ± 2.54	12.63 ± 4.70	18.51 ± 2.05
	Carboplatin + DVA	11.28 ± 5.60	10.93 ± 3.25	8.90 ± 0.97	11.31 ± 2.87	5.99 ± 2.39	13.31 ± 3.53	10.30 ± 1.70
RBC (10*12) L	Normal	7.73 ± 2.09	7.66 ± 0.06	8.55 ± 0.32	7.63 ± 0.24	6.77 ± 0.87	7.12 ± 0.56	7.38 ± 1.02
	Carboplatin	8.18 ± 0.45	7.91 ± 0.37	6.96 ± 0.59	5.05 ± 2.84	6.82 ± 0.37	4.58 ± 2.54	5.12 ± 0.11
	Carboplatin + DVA	8.24 ± 0.47	7.017 ± 2.10	8.03 ± 0.27	6.83 ± 0.28	5.10 ± 2.75	5.50 ± 1.27	6.28 ± 0.42
Platelets (10*9) L	Normal	506.50 ± 202.31	499.67 ± 86.93	491.33 ± 68.25	686.67 ± 67.00	761.33 ± 39.58	670.00 ± 77.66	486.00 ± 205.94
	Carboplatin	631.17 ± 53.30	512.33 ± 64.05	149.67 ± 51.83*	105.33 ± 76.03***	156.00 ± 45.04***	608.67 ± 254.72	1303.50 ± 54.45***
	Carboplatin + DVA	699.67 ± 119.10	541.67 ± 137.29	177.33 ± 20.53	79.67 ± 11.37	136.67 ± 144.76	604.67 ± 391.80	1094.33 ± 216.02
Total Reticular count %	Normal	2.25 ± 0.32	–	–	4.4 ± 0.26	–	–	3.3 ± 0.98
	Carboplatin	1.96 ± 0.47	–	–	2.53 ± 1.05	–	–	1.7 ± 0.28
	Carboplatin + DVA	2.31 ± 0.68	–	–	3.96 ± 0.11	–	–	5.8 ± 3.53 **

*p < 0.05, **p < 0.01, ***p < 0.001 compared to normal.

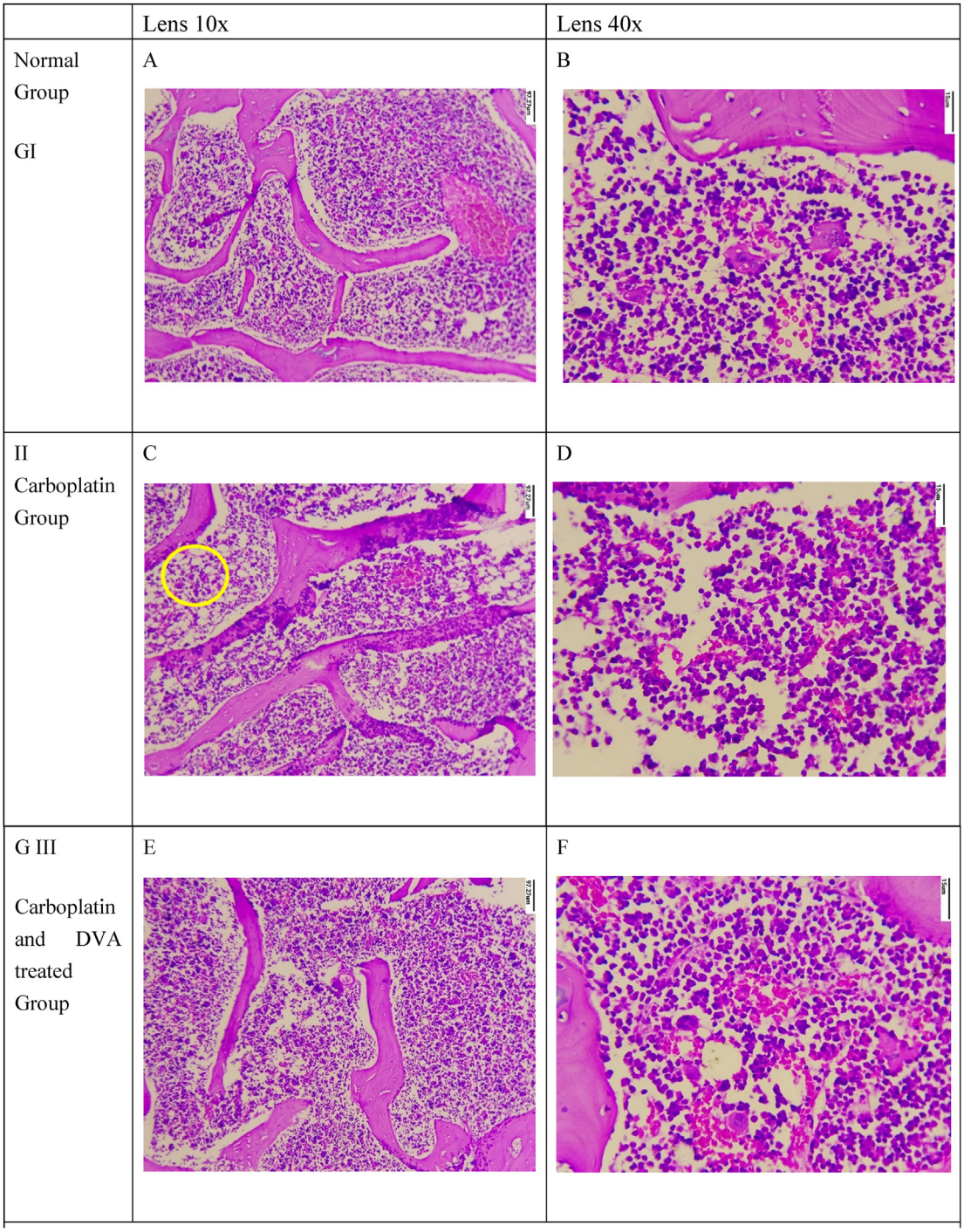

Fig. 1. Histopathology of bone marrow.

and WBC count reached the nadir on the 12th day. Subsequently, these hematological values showed better recovery at day 15 when compared to the carboplatin group and reached near normalcy by day 18 when compared to the normal group. While there was a lag seen in the carboplatin group.

An increase in Total reticulocyte count percentage was seen at day 9 in all groups, however, on day 18 the count was stable in normal, decreased in carboplatin, and increased in DVA treated group indicating that bone marrow was active in DVA treated group to replenish the cells and this was also in concordance with drop and rebound phenomenon [29].

The hematopoietic system delivers through cells like Hematopoietic Stem Cells (HSC) which initiate the chain by self-renewal, proliferation, and differentiation into multiple peripheral blood cells via hematopoietic progenitor cells (HPC). The HSC is dormant, in a steady-state, and arrives to serve when there is exhaustion under various stressful conditions However, they are very less influenced by chemotherapeutic drugs. In contrast, HPC is self-

limiting in the renewal phase and rapidly proliferating in case of normal hematopoietic crises like infection, blood loss, and hemolysis. In the case of Chemotherapy-induced acute myelosuppression, the HPC's get depleted and paves way for HSC to drive the damage control. If HSCs are affected by chemotherapeutic drugs, then the myelosuppression could be long term like bone marrow failure. The acute or late myelosuppression could be due to ~~be~~ apoptosis, senescence, or damage to bone marrow stromal cells [30].

Reticulocytes produced in the bone marrow mature peripherally in a day or two. An increase or decrease in reticulocyte count can be a surrogate for erythropoiesis activity in conditions like anemia and bone marrow dysfunction [31,32].

The bone marrow assay Fig. 1 showed normal cellularity in respect to erythroid and myeloid series in DVA treated group with minimum adipocyte distribution indicating it was active. In the carboplatin group, the cellularity was comparatively less and adipocyte distribution was slightly increased.

Delay in Hb, RBC nadir, increasing reticulocyte count percentage on 18th day and balanced bone marrow cytology in the DVA group indicates that the test drug might be having a direct or indirect role in erythropoietin utilization or production since it is a major factor in utilizing iron stores and leading to erythropoiesis [33].

Among many pathways for cytotoxic effects, the generation of radical oxygen species (ROS) is considered as the root cause, which paces up during chemotherapy. It is also established that antioxidants can help to prevent cell death and serve for adequate cell proliferation [34,35]. Preliminary studies for standardizing DVA had shown presence of flavonoids and phenolics. Crude water extract of DVA has shown appreciable anti-oxidant and free radical scavenging activity, which could be a reason for the DVA treated group to reach the nadir by the 12th day in comparison to Carboplatin group 9th day. Hence the role of antioxidants may be considered in preventing, preserving, controlling, and improving myelosuppression.

In DVA treated group, WBC cell counts were well within the normal range and showed nadir on day 12 [5.99 ± 2.39] but then returned to the normal range by day 15 [13.30 ± 3.53] and remained normal until the 18th day [10.3 ± 1.70]. While in the Carboplatin group the nadir was on day 9 [7.12 ± 6.21] and returned to pretreatment values at day 18 [18.51 ± 2.05] which is in agreement with Siddik et al., [29,36]. Few preclinical studies on DVA have shown immunomodulatory, anti-microbial and anti-fungal that indicate it has an undeniable role in managing leucocyte count which may be attributed to the phytochemical profile of formulation.

Platelet reached the nadir on day 9 in both carboplatin group [105.33 ± 76.02] and DVA treated group [79.66 ± 11.37] was significant ($p < 0.001$) in comparison to the normal [686.66 ± 67.00]. However, the drop and rebound were also seen in both the carboplatin group and DVA treated group. The platelet returned to pretreatment values by day 15 and showed a rebound increase till day 18. This gradual decrease in platelet is due to the cell cycle nonspecific agents like carboplatin which affect the proliferating platelets precursors rather than mature platelets [37]. However, in this study, the DVA has no activity in withholding the developing thrombocytopenia due to carboplatin.

5. Conclusion

In the present study, the DVA was able to prolong the nadir time of RBC, WBC, and Hb with early recovery in comparison to carboplatin and the normal group. However, further study for revalidation and mode of action through anti-oxidant and erythropoietin assay can warrant its use. This experimentation takes into account the effect of one dose of chemotherapy agent while a model of multiple doses can be chosen for better evaluation.

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Author contributions

Patil S F: Conceptualization, Funding acquisition, Methodology, Investigation, Writing - Original draft preparation, Writing Review & Editing.

Shahpurkar V V: Investigation and formal analysis.

Khanal P: Data curation, Writing Review & Editing.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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