A COMPARATIVE STUDY: EFFECT OF PLATINUM COMPOUNDS VIZ. CISPLATIN, CARBOPLATIN AND OXALIPLATIN ON BLOOD PARAMETERS

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ABSTRACT:

Aim: *Studied the effects of commonly used three platin derivative namely cisplatin, carboplatin and oxaliplatin, on hematogenesis, for any damage done by the three drugs on the functions of important body systems.*

Material and Method: *Total 150 patients of either gender were in the age group of 18-60 years were analyzed for various hematological parameters. We collected blood sample from each patient on the first day of beginning of each drug cycle and the sample were analysed.*

Result and Discussion: *In this study Total red blood cell count, packed cell volume (PCV) and hemoglobin levels were found significantly decreased in cisplatin group, were as TRBC and PCV were significantly lower in carboplatin group while in oxaliplatin only PCV was found decreased. ESR levels in all the three study groups were significantly higher indicating toxic effect of the drugs on the hepatic functions. Three platin drugs i.e. cisplatin, carboplatin and oxaliplatin produce a fall in total leucocyte count (TLC). A significant decreased in Absolute eosinophil count and thrombocytopenia in carboplatin group. Bleeding time was found significantly increased in the patients of carboplatin group.*

Conclusion: *An observation points out that all platin drugs are myelosuppressive. In which cisplatin and carboplatin are toxic drug to the bone marrow whereas oxaliplatin is comparatively safer.*

Keywords: *Platin derivative, hematogenesis, myelosuppressive*

INTRODUCTION

Chemotherapy employs systemically administrated drugs that directly damage cellular DNA (and RNA). They kill cells by promoting apoptosis and sometimes frank necrosis. The chemotherapeutic drugs are not cancer cell specific; therefore, they kill cancer as well as normal cells/tissues. The dose and schedule of chemotherapy is limited by the tissue tolerance, especially in those more proliferative tissues of the bone marrow and gastrointestinal tract mucosa.[1]

We have used these three DNA cross-linking - platinum compounds drugs namely cisplatin, carboplatin and oxaliplatin in the treatment of our cancer patients. These platinum compounds share some structural similarities. However, there are marked differences between them in therapeutic use, pharmacokinetics and adverse effect profiles. Since myelosuppression effects of these drugs are known, the first objective of the study was to compare the toxic effect of these three drugs on blood parameters in patients with malignancy and second was to study the difference in the magnitude of myelosuppression by these drugs.

MATERIALS AND METHODS

This study was carried out in the Department of Physiology in close collaboration with Acharya Tulsi Regional Cancer Treatment and Research Institute, Sardar Patel Medical College, Bikaner, Rajasthan, India. Institutional ethical clearance was obtained before commencement of the study from the ethical committee of S.P. Medical College, Bikaner, Patients were informed about the investigative nature of this study and obtained written consent and willingness to participate prior to initiation of therapy. This is in accordance with institutional and Govt. of India guidelines.

All 150 patients were divided into three equal study groups i.e. 50 in each group and they were planned for either of cisplatin, carboplatin or oxaliplatin based chemotherapy. All the three study groups were examined for their different hematological parameters and their results were collected for final analysis. A complete medical history with clinical examination was recorded for every subject with respect to their occupation, demographic data, clinical examination and laboratory investigation.

PATIENT SELECTION

All patients included in this study were suffering from histo-pathologically proved malignancy and received no treatment for malignancy before they registered at Acharya Tulsi Regional Cancer Treatment and Research Institute. All cases were given 3 cycles of chemotherapy.

Criteria of patient selection:

1. Patient with adequate renal functions and hematological values
2. No other serious medical or psychiatric illness that would limit the ability of the patient to receive protocol therapy or provide informed consent.
3. Women/men of reproductive age group must agree to use effective contraceptive methods.

Patient with Cases of urogenital tract cancer, Cases of systemic diseases, Cases of renal failure, Chemotherapy or radiotherapy treated patients, Pregnant or lactating women, Inability to eat orally, Cases of malabsorption syndrome, Patient require more than 6 weeks' time to recover from side effects of drugs, Other serious medical or psychiatric illness were excluded from this study.

TREATMENT AND DOSE SCHEDULE

Platin based chemotherapy with or without any other nephron sparing therapeutic agent was planned. Before the therapy cycle started, minimum level of the leucocyte count (3000 /cumm), the platelet count (1, 00,000 lac/cumm), Hb (9 gm/dl) and the liver and renal functions were done to satisfy the eligibility criteria (with in minimum reference level). Chemotherapy was administered to the study groups with the given protocol.

Study group was sub divided into three groups:

- Group I : The patients were given cisplatin Cisplatin (50-75 mg/m^2) + 5-fluorouracil, i.v. , repeated in a cycle of 3-4 weeks
- Group II : The patients were given carboplatin Carboplatin (400 mg/m^2) + 5-FU, i.v. repeated in a cycle of 3-4 weeks
- Group III : The patients were given oxaliplatin Oxaliplatin (85 mg/$m^{2)}$ + 5-FU + leucovorin , i.v., repeated in a cycle of 2 weeks

TREATMENT OF SIDE EFFECTS

Many patients showed fall in hemoglobin level, loose motions, nausea, vomiting and stomatitis. Following WHO (World Health Organization) common toxicity criteria (CTC) blood transfusion was given when hemoglobin level was less than 6.5 gm/dl. For non haematological side effects supportive treatment such as I.V. infusion of DNS (Dextrose and sodium chloride), injection antiemetic drugs such as perinorm and ondansetron was given. All patients were advised to take high protein diet, multivitamins, haemetinics, adequate water intake and maintain proper oral hygiene.

COLLECTION OF SAMPLES

Blood sample were collected in morning after overnight fasting or two hours after ingestion of light meal of vegetarian diet from each of the patients before the starting of first, second and third cycle of treatment. We used venipuncture method to draw blood samples in a plastic vial and used the for following hematological parameters investigations: Total RBC count, total leucocyte count, total platelet count, differential leucocyte count, packed cell volume and hemoglobin by CBC Automated Hematology Analyzer, Absolute eosinophil count by using improved Neubauer's counting chamber and Pilot's solution, determination of ESR by Westergreen's method, bleeding time by Duke's method, clotting time by capillary glass tube method.

For statistical analysis of data, appropriate statistical models were applied. Since the study was conducted at one place only, hence geographical and climatic conditions were similar in all cases. The study variables were summarized by mean and standard deviation. For comparison of mean, ANOVA and student's t-test was employed wherever applicable.

OBSERVATION AND RESULT

Table 1: Age distribution

AGE (YEARS)	STUDY GROUP		
	GROUP I	GROUP II	GROUP III
18- 30	1	2	7
31-40	13	1	7
41-50	19	19	17
51-60	17	28	19
TOTAL	50	50	50

Table 1 shows the age distribution of patients included in this study. There are three study groups. Total number of patients in each group was 50. Their age ranged from 18 to 60 years and most of them were in 5^{th} and 6^{th} decade of life.

Table 2: Gender and Age wise distribution of total study subjects

Sex	Group I (n=50)		Group II (n=50)		Group III (n=50)		P
	Male	Female	Male	Female	Male	Female	
Number (n)	37	13	34	16	28	22	NS (P>0.05)
Age (Years)	47.86 ±8.93	44.54 ±7.32	51.11 ±8.27	48.62 ±5.08	46.14 ±12.10	46.23 ±10.71	

Data presented are mean±SD. NS – non-significant.

Table 2 shows the comparison between three study groups according to their age and gender. Perusal of data reveals that the mean age among different groups was nearly same and there was no statistically significant difference ($p > 0.05$) in the mean age among the three groups.

Table 3: Primary site of malignancy

Primary Site	**Study Group**		
	Group I	**Group II**	**Group III**
Head and neck	38	16	-
Thoracic	11	4	-
Git	-	10	41
Pelvic	-	-	2
Hepato-biliary	1	20	7
Total	**50**	**50**	**50**

Table 3 shows the distribution of patients according to primary site of malignancy. Among the study groups 38 (76%) of patients in group I comprised of head and neck cancers and 11 (22%) had thoracic cancers. In group II, 20 (40%) patients had hepato-biliary cancers, 16 (32%) patients had head and neck cancers and 10 (20%) patients had gastro-intestinal tract (GIT) cancers. While in group III there were 41 (82%) patients of gastro-intestinal tract (GIT) cancers, 7 (14%) patients of hepato-biliary and only 2 (4%) patients were of pelvic cancers.

Table 4: Red blood cell, Packed cell volume, Haemoglobin and Erythrocyte sedimentation rate in the study groups receiving chemotherapy in cycles

GROUPS (n=50)	RBC (million/cumm)			PCV (%)			Hb (gm%)			ESR (mm in 1st one hour)		
	BL	C I	CII	BL	C I	C II	BL	C I	C II	BL	C I	C II
G I	4.24 ±0.69	3.93* ±0.47	3.77* ±0.59	36.43 ±6.11	33.91* ±5.19	32.12* ±4.59	11.03 ±1.40	10.20* ±1.22	9.63*† ±1.30	30.78 ±22.48	38.74 ±26.38	39.98† ±19.02
G II	4.18 ±0.21	4.07 ±0.39	3.91* ±0.43	36.35 ±5.68	33.55*† ±4.71	33.58* ±4.19	10.76 ±1.95	10.75 ±1.67	10.70 ±1.48	30.36 ±26.56	42.96* ±16.26	49.36* ±15.59
G III	4.11 ±0.62	3.82† ±0.53	3.81 ±0.84	35.01 ±4.83	30.02*† ±5.51	31.17 ±7.67	10.53 ±1.63	10.14 ±1.88	10.47 ±1.59	31.12 ±13.60	48.46* ±18.28	46.26* ±22.84

n = Number of subjects; BL = Baseline; CI = Cycle I; CII = Cycle II; GI = Group I; GII = Group II; GIII = Group III; *p<0.05 compared with in group; † p<0.05 compared in between groups

Table 5: Total leucocyte count, Total Eosinophil count, Total platelet count and Bleeding time in the study groups receiving chemotherapy in cycles

GROUPS (n=50)	TLC (per cumm)			TEC (per cumm)			TPC (Lac/cumm)			BT (in minute)		
	BL	C I	C II	BL	C I	CII	BL	C I	C II	BL	C I	C II
G I	8691.48 ±2215.7	6339.20* ±2425.2	6374.84* ±2786.3	140.00 ±84.51	139.00 ±77.78	130.00 ±61.44	2.32 ±0.88	2.08 ±0.99	1.74* ±0.72	2.05 ±0.59	1.80 ±0.45	1.84 ±0.51
G II	8797.54 ±2270.3	6820.20* ±1685.1	5260.70*† ±1428.4	142.00 ±64.96	138.00 ±72.53	99.00* ±44.59	2.71 ±0.79	2.26 ±0.88	1.75* ±0.57	1.88 ±0.49	2.32*† ±0.52	2.82*† ±0.53
G III	8516.44 ±1659.0	7492.36 ±3271.4	6806.68* ±3345.2	129.00 ±33.63	113.00† ±50.31	136.00 ±59.79	2.53 ±0.96	2.41 ±0.89	2.07* ±0.80	1.94 ±0.50	1.88 ±0.34	2.01 ±0.38

n = Number of subjects; BL = Baseline; CI = Cycle I; CII = Cycle II; GI = Group I; GII = Group II; GIII = Group III; *p<0.05 compared with in group; † p<0.05 compared in between groups.

The table 4 shows in rows the baseline values before the starting of treatment (1st dose) of total red blood cell count (TRBC), Packed cell volume (PCV), Haemoglobin (Hb) and Erythrocyte sedimentation rate (ESR) also at the end of cycle I and II. The data shows that the mean values of TRBC in group I of cycle I ($p = 0.026$) and cycle II ($p = 0.000$) were significantly lower than that of

baseline. The data for group II shows that mean in cycle II were significant lower (p =0.001) than that of baseline. However, in group III statistical analysis shows no significant difference in the magnitude of mean values. Comparison of data in between the groups reveals that on cycle I, the mean value of TRBCs in group III (3.82±0.53) was significantly lower (p =0.027) than group II (4.07±0.39).

Comparison of mean values of PCV reveals that values in cycle I (p =0.05) and cycle II (p =0.000) were significantly lower than that in baseline. Statistical analysis of group II data makes it clear that the mean values of PCV in cycle I 33.55±4.71 (p =0.014) and cycle II 33.58±4.19 (p =0.016) were significantly lower than those in baseline (36.35±5.68). Group III data shows that comparison of mean values reveals that value in cycle II was significantly lower (p =0.01) than that of baseline. The comparison of data in between the groups reveals that mean value (30.02±5.51) in cycle I of group III was significantly lower than those in group I (p =0.001) and group II (p =0.002).

Mean values of Hb in group I hemoglobin values in cycle I (10.20±1.22; p =0.005) and cycle II (9.63±1.30; p =0.000) were significantly lower that than of baseline (11.03±1.40). However, the data of Hb levels for group II in different cycles of treatment showed no significant variation. Similarly, in case of group III no significant variations in the values were observed. The comparison of data in between the groups reveals that in cycle II of group I was significantly lower than those in group II (p =0.001) and group III (p =0.011). However, comparison of mean values in baseline and cycle I of different groups exhibited no significant variations.

Table 4 depicts the mean values for erythrocyte sedimentation rate (ESR) in study group I, II and III. In group I the magnitude of difference in ESR mean values of baseline (30.78±22.48), cycle I (38.74±26.38) and cycle II (39.98±19.02) were statistically non-significant. In group II, comparison of data in different cycles demonstrate that the mean values were significantly increased in cycle I (42.96±16.26; p =0.006) and cycle II (49.36±15.59; p =0.000) with respect to that of baseline (30.36±26.56). The data of group III ranged between 31.12±13.60 to 48.46±18.28 mm in 1st one hour. In cycle I (48.46±18.28) and cycle II (46.26±22.84) the magnitude of difference of ESR valves was statistically significant higher (p =0.000) than that of baseline (31.12±13.60). The data further shows that in cycle I, mean values of three study groups shows no significant difference. However, the mean values of ESR in cycle II (49.36±15.59) of group II was significantly higher (p =0.05) than that of (39.98±19.02) group I.

Table 5 shows the comparison of total leucocyte count (TLC), Total Eosinophil count (TEC), Total platelet count (TPC), Bleeding time and clotting time in study groups on different cycles of chemotherapy given. In group I the mean values of TLC in cycle I (6339.2±2425.2) and cycle II (6374.84±2786.3) were significantly lower (p =0.000) when compared with the mean values (8691.48±2215.7) of baseline. In the group II on comparison of mean values we found that values in cycle I and cycle II were significantly lower (p =0.000) than that of baseline. Even in group II mean values of TLC in cycle II was significantly lower (p =0.000) than that of cycle I. Examination of data for group III reveals TLC values were (7492.36±3271.4) in cycle I, cycle II (6806.68±3345.2) and in baseline (8516.44±1659.0). The mean values of TLC in cycle II was significantly lower (p =0.010) than that of baseline. When we compare magnitude of difference the mean value in the cycle II of group II (5260.70±1428.4) was significantly lower (p =0.012) than that of group III (6806.68±3345.2).

As shown in table that the mean value of absolute eosinophil count was statistically significant lower in cycle II (99.00±44.59) was than those in baseline (142.00±64.96; p =0.002) and cycle I (138.00±72.53; p =0.006) in group II. While comparing the magnitude of difference, the mean value in cycle II of group II (99.00±44.59) was significantly lower than those in group I (130.00±61.44; p =0.003) and group III (136.00±59.79; p =0.019).

The total platelet count (TPC) in group I the mean values in cycle II (1.74±0.72) was statistically significantly lower (p =0.004) than that of baseline (2.32±0.88). In group II the mean values in cycle I (2.26±0.88; p =0.010) and cycle II (1.75±0.57; p =0.000) were statistically significantly lower than that of baseline (2.71±0.79). We also observed a significant difference (p =0.006) between the mean values of cycle I and cycle II of group II. In group III the mean value in cycle II (2.07±0.80) was statistically significantly lower (p =0.003) than that of baseline (2.53±0.96). We analyzed and compared all other mean values on baseline, cycle I and cycle II in all the groups. We found no significant difference in mean values and magnitude.

As depicted in table the mean values of bleeding time shows that in group I, the mean values ranged between 1.80±0.45 to 2.05±0.49 and were not statistically significant. In group II the mean values of bleeding time were in baseline (1.88±0.49), cycle I (2.32±0.52) and cycle II (2.82±0.53). Comparison of these mean values revealed that the values in cycle I and cycle II were statistically significantly higher (p =0.000) than those in baseline and there was significant variation (p =0.000) between cycle I and cycle II with respect to this parameter. In group III no significant difference was observed in mean values of different cycles of chemotherapy given. The

comparison of data in between the groups reveals that mean values in cycle I of group II (2.32±0.52) was significantly higher (p =0.000) than that of group I (1.80±0.51). Similarly, the mean value of cycle II of group II (2.82±0.53) was significantly higher (p =0.000) than those in group I (1.84±0.51) and group III (2.01±0.38).

But no significant difference was observed in values of clotting time values obtained from cancer patients of all these groups receiving different cycles of chemotherapy. We found no significant difference when mean values were compared with one another.

Table 6 demonstrate the percentage of neutrophil, lymphocyte, monocyte and eosinophil. In group I the mean value of neutrophil in cycle I (47.54±15.57) and cycle II (46.08±16.76) were significantly lower (p =0.000) than the mean value (64.48±9.72) of baseline. Of the group II data the mean values of neutrophil in cycle I (55.40±16.80; p =0.027) and cycle II (45.94±13.60; p =0.000) were statistically significantly lower than that (62.92±11.85) of baseline. Even we also found that value of cycle II was significantly lower (p =0.003) than that in cycle I. In group III mean value of neutrophil in cycle I (54.72±11.32) and cycle II (52.54±11.89) were significantly lower (p =0.000) than that of baseline (64.06±9.14). We noticed that baseline mean values did not differ significantly among the groups. The mean value in cycle I of group I (47.54±15.57) was statistically significantly lower than the mean values in cycle I of group II (55.40±16.80; p =0.026) and of group III (54.72±11.32; p =0.048).

The mean percentage of lymphocyte in group I revealed that the mean value of lymphocyte percentage in cycle I (45.24±14.64) and cycle II (46.60±15.96) were significantly higher than that (29.28±9.04) of baseline. Of the group II data the mean value of lymphocyte percentage in cycle I (37.60±11.90; p =0.026) and cycle II (49.68±13.29; p =0.000) were significantly higher than that (31.10±11.29) of baseline. We also found that value of cycle II was significantly higher (p =0.000) than that of cycle I. Similarly, the mean values of lymphocyte in cycle I (38.32±10.13) and cycle II (40.36±11.07) of group III were significantly higher (p =0.000) than that (29.58±9.14) of baseline. On comparing the mean values in cycle I (45.24±14.64) of group I was significantly higher than those of cycle I (37.60±11.90; p =0.007) of group II and the cycle I (38.32±10.13; p =0.017) of group III. The lymphocyte mean value in cycle II of group II (49.68±13.29) was significantly higher (p =0.002) than the mean values in cycle II (40.36±11.07) of group III.

Table also shows a mean value of monocyte percentage in group II were 3.04±2.53 for baseline, 4.62±2.28 for cycle I and 3.96±2.27 for cycle II. Comparison of data reveals that the mean value in cycle I was significantly higher (p =0.003) than that of baseline. We found that cycle II of group I (5.72±3.55) was significantly higher (p =0.011) than that of cycle II of group II (3.96±2.27). All other values were found insignificant when compared with baseline values, and those with one another.

Mean percentage values of eosinophils in group II data reveals that the mean value of eosinophil percentage were (1.04±0.75) in cycle II when compared with baseline (1.72±1.30) which was found to be significantly (p =0.006) different. While comparing the eosinophil mean percentage values we observed that values in cycle I of group II (1.26±1.10) was significantly lower (p =0.025) than that in cycle I of group II (1.82±1.16). Even we found that in cycle II of group II (1.04±0.75) mean values significantly differ (p =0.000) from cycle II of group III (2.02±1.56).

The differential leucocyte count depicts basophil percentage. The data shows no significant variations among the mean values in all the different groups.

Table 6: Differential leucocyte count in the study groups receiving chemotherapy in cycles

GROUPS (n=50)	DIFFERENTIAL LEUCOCYTE COUNT											
	(N %)			(L%)			(M%)			(E%)		
	BL	C I	C II	BL	C I	C II	BL	C I	C II	BL	C I	C II
G I	64.48 ±9.72	47.54*† ±15.57	46.08* ±16.76	29.28 ±9.04	45.24* ±14.64	46.60* ±15.96	4.10 ±3.96	5.40 ±3.12	5.72 ±3.55	2.12 ±1.59	1.82 ±1.16	1.60 ±1.32
G II	62.92 ±11.85	55.40* ±16.80	45.94* ±13.60	31.10 ±11.29	37.60*† ±11.90	49.68* ±13.29	3.04 ±2.53	4.62* ±2.28	3.96† ±2.27	1.72 ±1.30	1.26† ±1.10	1.04* ±0.75
G III	64.06 ±9.14	54.72* ±11.32	52.54* ±11.89	29.58 ±9.14	38.32*† ±10.13	40.36* ±11.07	4.32 ±3.07	5.30 ±3.32	5.08 ±3.02	2.04 ±1.85	1.64 ±0.85	2.02 ±1.56

n = Number of subjects; BL = Baseline; CI = Cycle I; CII = Cycle II; GI = Group I; GII = Group II; GIII = Group III; *p<0.05 compared with in group; † p<0.05 compared in between groups.

DISCUSSION

In our study there were 118 males and 82 females and most of the subjects were of age group between 51 and 60 years (Table 1 and 2). We included biopsy proved carcinoma occurring in lung, GIT, head and neck regions. Cisplatin + 5-fluorouracil, carboplatin + 5-fluorouracil and oxaliplatin + 5-fluorouracil + leucovorin are common combination of drug regime used for the treatment. The main adverse side effects of 5-fluorouracil are the oral mucositis and diarrhea. However, this drug shows lower hematotoxicity and very rarely nephrotoxicity.

In colorectal cancer along with oxaliplatin+ 5-fluorouracil, leucovorin calcium is used as a protection agent to overcome 5-fluorouracil toxicity. However, leucovorin does have some anticancer activity yet it does not have any effect on renal functions and haemopoiesis.

Standard premedication procedure was used to avoid toxicity which may hamper the further treatment. Adequate supportive care during chemotherapy infusion and between the cycles of chemotherapy was employed to help the patients to complete their treatment protocol with good quality of life. In our study, Age and gender distribution among all the groups was almost equal therefore we presume that the entire body organ including kidney and bone marrow would be uniformly affected. However, no significant difference was observed in drug effects in terms of age and gender in our patients.

Anemia in cancer patients is multifactorial, resulting from nutritional deficiencies, decreased production of red blood cells, and/or increased loss /destruction of blood and may occur as a either a direct effect of the cancer or due to chemical factors produced by the cancer.[119] In our study we observed a significant fall (p =0.000) in total red blood cell count and packed cell volume in all the cancer patients in comparison to base line (before starting the chemotherapy).

In present study total red blood cell count shown a significant fall in cisplatin and carboplatin treated groups. Whereas significant fall in packed cell volume were observed in all the three study group in successive cycles of treatment.

We also observed that Hb concentration was significantly decreased only in cisplatin treated group. The significant fall in TRBC, PCV and Hb was observed specially after the second course of therapy. Such observation, point's that myelogenic depression is a progressive effect of these drugs. Our study involves a large number of cancer patients undergoing chemotherapy treatment and we found evidence of progressive bone marrow suppression by the use of platin drugs, shown by reduction in TRBC, PCV and Hb levels. As the chemotherapy moves from cycle I to the cycle II anemia became more severe (Table 4).

Our observations are corroborated by the earlier study done[**90**] on tumor bearing mice and it was reported that cisplatin treatment causes anemia as a result of fall in the levels of Hb, PCV and TRBC. In the same study it was reported that the reduction of glutathione level in the blood and tumor cells was attributed to the development of anemia. In other studies[2,3] on mice it was found that cisplatin was more toxic to earlier haemopoietic progenitor cells then the mature ones. It was suggested that the anemia could be due to difference in time of maturation of the erythroid series. However, in a recent study[4] hemolysis was blamed for the production of anemia. It has been proved[5] that cisplatin therapy inhibits the production of renal erythropoietin which results in a lower RBC production. Cisplatin is said[6] to cause anemia by interfering in the iron metabolism. On comparing the magnitude of myelosuppression (Table4) we found that carboplatin produced a highest degree of fall in TRBC, PCV and cisplatin in Hb levels than those produced individually by other platins. [5,7,8]

In cancer the ESR is often elevated, particularly with widespread disease; in some neoplasms it can be a valuable prognostic marker when assessed prior to treatment. In our study we observed a significant increased (p =0.000) in ESR in all the cancer patients at base line in comparison to normal healthy persons.[9] In our study we observed that there was a gradual increase in ESR value with successive cycles of chemotherapy in all three groups. But carboplatin and oxaliplatin produced a significant effect on raising ESR in comparison to cisplatin (Table 4). These rise in ESR in response to platin drugs may be due to reactive change in plasma proteins occurring as a result of the breakdown of tumor and normal tissue cells.[9] Our observation corroborate with recent study[10] done in 2010 where oxaliplatin used for adenocarcinoma of colon and there was a significant elevation of ESR (74 mm/hour) attributed with changes in plasma proteins and role of diet in GIT cancer.[11]

White blood cells are mobile defense units of the protective system of the body. Leucocytosis is very common in acutely ill patient. We found a significant rise in total leucocyte count in all the three study group of cancer patients in comparison to normal healthy person at base line. In our study we observed that the TLC was significantly lower in all the patients in the baseline, cycle I and cycle II. We also observed that the fall from baseline was higher in carboplatin group in comparison to those with cisplatin and oxaliplatin groups (Table 5). A significant fall in TLC in all patients receiving chemotherapy is an important finding in our study. Our observation was supported by the earlier

finding[12,13] where it was reported that cisplatin can cause leucopenia if it is given with high dose in patients of nephrotoxicity and reduced hydration. And similar leucopenia was reported[14] following oxaliplatin therapy with dose of 90mg/sqm.

A significant fall was observed in platelet count in all the cycles of three groups and especially after second cycle of chemotherapy. We also recorded a significant fall in cycle I and cycle II of carboplatin treated group. It is evident from observation (Table 5) that all three drugs are toxic to platelet progenitor cells of megakaryocytes and carboplatin turned to the most toxic drug in comparison to other two. In earlier studies[15] it was observed that cisplatin and carboplatin are most toxic to platelet precursor. Similarly, in another studies[16,17] thrombocytopenia was commonly observed in response to platin drugs.

We estimated bleeding time at baseline and in successive cycles of three study groups receiving chemotherapy. In all cycles of all the groups no significant change in the bleeding time was observed except in carboplatin group which shows a significant increase in bleeding time in all the cycles (Table 5). It is interesting to note that carboplatin causes a significant fall in the platelet count which is an important factor in stoppage of bleeding. We suggest that increase in bleeding time in carboplatin group could be due to the myelosuppressive effect of carboplatin on megakaryocytes leading to thrombocytopenia and increased bleeding time. In reference to bleeding time we found no earlier reference to support our claim.

We estimated clotting time in all patients of three groups in all the cycles. In our study we did not observed any significant difference in clotting time in normal healthy subjects and all the patients in three groups and chemotherapy cycles. Since the coagulation time depends on several coagulation factor and most of them are produced in the liver. We suppose that platin drugs did not cause much toxic effect on the liver which continued to produce coagulation factor.

In addition to our observation, myelosuppression affects all the platin drugs more on the leucocyte count. We also observed the effect of these drugs on differential leucocyte counts in cycles of chemotherapy. We noted that neutrophil count was decreased significantly in all three platin groups, especially in cisplatin as compared to carboplatin and oxaliplatin [Table 6].

In an earlier study[18] a significant neutropenia in carboplatin and cisplatin therapy was observed. Similarly in another study[14] neutropenia was also observed following oxaliplatin therapy. We cannot explain the mechanism of myelosuppression leading to neutropenia. But we agree with the suggestion of earlier workers[2,3] who explained that cisplatin is more toxic for the earlier granulocytic progenitor cells leading to production of neutropenia.

It is commonly seen in clinical practice that most of malignancy in the body are associated with some kind of chronic infections. In the present study we found that the lymphocyte count in all chemotherapy cycles of all the groups was significantly higher than. [Table 6]. On perusal of Tables on leucocytes count (Table 5) and lymphocyte [Table 6] we found that there is no absolute lymphocytosis. Nevertheless, we speculate that the relative lymphocytosis could be due to leucocytopenia and neutropenia or it could be due to no effects of platin drugs on the production of lymphocytes or both. No reference on lymphocytosis in chemotherapy is available to support or repudiate our claim.

In our study we count eosinophil in hundred WBCs in all the cycles in three study groups and significant difference was observed only in carboplatin treated group [Table 6], due to specific suppressive effect of carboplatin on the bone marrow[19]. and may be due to its effect on granulocyte progenitor cells as well as delayed maturation[3]. whereas, monocyte n basophil shows no significant differences in any group.

CONCLUSION

We concluded that hematotoxicity is the major side effects of the platin drugs and these side effects limit the use of these drugs. We strongly propose that further studies should be done to improve their therapeutic value and minimize toxicity by trying various cytoprotective agents. A try could be done in collaboration with pharmaceutical industry to change the chemistry of the platin drugs in order to increase the efficacy and reduce the level of toxicity.

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