AN OBSERVATIONAL STUDY TO ASSESS THE ADVERSE DRUG REACTIONS OF CISPLATIN-ETOPOSIDE VS CARBOPLATIN-ETOPOSIDE IN LUNG CANCER PATIENTS IN A TERTIARY CARE HOSPITAL OF KOLKATA

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ABSTRACT

BACKGROUND

Lung cancer is the commonest cancer having high mortality- it accounts for 13% of all new cancer cases and 19% of cancer related deaths worldwide. In India, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in both sexes; it is the commonest cancer and cause of cancer related mortality in men.

MATERIALS AND METHODS

Total 115 lung cancer patients (71 in Cisplatin-Etoposide arm and 44 in Carboplatin-Etoposide arm) were recruited in the study over a period of 1 year with follow up for another 4 months after receiving their written informed consent. Selection of chemotherapy regimen was done by treating Oncologist. Patients having severe haematological, renal and hepatic impairment were excluded. All ADRs were graded according to ECOG-CTC criteria- Grade 3&4 were considered serious. Data were analysed using GraphPad Prism version 5 [San Diego, California: Graph Pad Software Inc., 2007] software. Summary statistics were expressed using mean and standard deviation (SD) for numerical variables (median and interquartile ranges when skewed) and counts and percentages for categorical variables. Numerical variables were compared between subgroups by Mann-Whitney U test (for variables with skewed distribution) and unpaired T test (for variables with normal distribution). Fisher's exact test was employed for intergroup comparison of categorical variables.

RESULTS

Majority were male [89 (84%)]. Median [inter quartile range (IQR)] age was 69 (61 -72) years. Majority belongs to upper lower and lower middle socioeconomic group Histologically SCLC were more common [n=79(75%)] followed by NSCLC [n=27(25%)]. All patients were diagnosed at an advanced stage (stage IIIB/IV). The majority was belonging to stage IV [n=67 (63%)] followed by stage IIIB [n=39 (37%)]. History of smoking revealed that a substantial number of patients (95.28%) consumed tobacco in any form.

CONCLUSION

The study demonstrated higher incidence of Haematotoxicity and Hepatotoxicity in Carboplatin and that of nephrotoxicity, neurotoxicity and Emetotoxicity in Cisplatin. Statistically significant higher incidence of leucopenia, thrombocytopenia and severe thrombocytopenia is seen in Carboplatin, whereas statistically significant higher incidence of nausea, vomiting, nephrotoxicity (↑BUN, ↑Creatinine) is seen in Cisplatin group. A further multicentric Interventional study needs to be conducted on a larger number of populations to confirm these findings.

KEYWORDS

Lung Cancer, Chemotherapy, ADR, Haematotoxicity, Nephrotoxicity, Neurotoxicity, Emetotoxicity, Hepatotoxicity.

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BACKGROUND

An adverse drug reaction (ADR) is defined by world health organization as "any response to a drug which is noxious, unintended & occurs at doses used in man for prophylaxis, diagnosis or therapy".[1]

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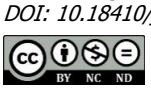


It has been seen that health care cost increases to great extent due to ADRs[2] as they are so serious and severe at sometimes, that cost needed to treat morbidity & mortality due to it is more than the cost needed to treat the actual condition of interest.[3] Cancer chemotherapeutic drugs are the commonest to produce serious and life threatening ADRs.[4]

Lung cancer is the commonest cancer and commonest cause of cancer related deaths all over the world. It accounts for 13% of all new cancer cases and 19% of cancer related deaths worldwide. There were 1.8 million new lung cancer cases estimated to occur in 2012.[4] In India, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in both sexes; it is the

commonest cancer and cause of cancer related mortality in men.[5]

Lung cancer is divided into two groups - Non Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). NSCLC constitutes the majority (75-80%), the rest being contributed by SCLC (20%). In both the situations, the majority of the patients is diagnosed at an advanced stage, probably due to their aggressive nature and delayed presentation of clinical symptoms. The 5 year survival rate is only 14% & it has not changed significantly in last decades.[6]

In NSCLC, early stages (I or II) undergo potentially curative surgical resection followed by adjuvant chemotherapy. Advanced but potentially resectable (IIIA, N2) disease undergoes systemic therapy (chemotherapy and radiotherapy) in spite of low survival rates. Locally advanced unresectable disease (stage IIIA/B) are treated with multimodality approach utilizing various combination platinum based doublets. Combination doublet chemotherapy is also the accepted standard of care for stage IV disease.[7]

In contrast to NSCLC, SCLC is staged as either limited-stage disease (LD) or extensive-stage disease (ED). Chemotherapy remains the essential component for treatment of all patients with SCLC, regardless of stage or performance status. In LD, the addition of radiation therapy improves survival over chemotherapy alone.[8] Thus, it is evident that chemotherapy remains the integral part of treatment in all stages and subtypes of lung cancer.

Chemotherapy kills cells at a faster rate than the re-growth of the cells. All chemotherapeutic agents known to date are toxic for the tumours as well as the host. The limitations of chemotherapy are their ADRs. When cure is possible, treatment may be undertaken despite the certainty of severe life threatening adverse drug reactions. When the clinical goal is palliation – as in the majority of lung cancer cases, careful attention to minimize the ADRs of treatment becomes a significant goal.[4]

Amongst the chemotherapeutic agents, platinum based chemotherapy is commonly used (Cisplatin, Carboplatin) along with other agents specially Etoposide in lung cancer (both NSCLC & SCLC).[8,9]

The incidence of Emetotoxicity (nausea, vomiting), nephrotoxicity, ototoxicity is more in Cisplatin. Thrombocytopenia is much more in Carboplatin, whereas the incidence of anaemia, leucopenia, neutropenia, neurotoxicity is not different in these two drugs. The overall toxicity of Cisplatin is much more than that of Carboplatin.[10,11] However, severe toxicities are comparable in these two regimens.[12]

Different studies demonstrated that Carboplatin has comparable survival benefit to Cisplatin in lung cancer;[9] but some studies indicated slightly superior response rate and survival benefit of Cisplatin over Carboplatin.[10,12] However Cisplatin is cheaper compared to Carboplatin. Both are used as a 1st line chemotherapeutic agent in the treatment of lung cancer in this Hospital. Cisplatin is the preferred regimen if cure is the ultimate goal of therapy. When the target of treatment is palliation as in the majority of lung cancer patients, Carboplatin based chemotherapy is the preferred regimen.[9,11]

However the data in Indian population regarding ADRs of Cisplatin & Carboplatin in lung cancer patients are sparse. To our knowledge, there are no published studies in this aspect in the past 5 years in Eastern India. From the above discussion, it is evident that both Cisplatin-Etoposide and Carboplatin-Etoposide combination has comparable survival benefit in the majority of situations, but regarding ADR profile there is controversial reports. As acceptability and continuation of chemotherapy is dependent on ADR profile and there is lack of adequate studies comparing ADRs of the two regimens, it is thought prudent to compare the ADR profile of these two combinations.

Objectives

1. To study the different types of adverse drug reactions seen in patients of lung cancer who are receiving either Cisplatin –Etoposide or Carboplatin- Etoposide regimen.
2. To assess the severity of the ADRs by grading them according to common toxicity criteria (CTC) ECOG guidelines.

MATERIALS AND METHODS

Study Type

Prospective observational study.

Place of Work

Pharmacology and Radiotherapy department of R. G. Kar Medical College.

Duration of Study

One year from February 2014 to January 2015. Follow up was continued for another 4 months up to May 2015.

Study Population

All lung cancer patients attending RADIOTHERAPY department & receiving either Cisplatin-Etoposide or Carboplatin-Etoposide therapy during this study period following inclusion and exclusion criteria were included in this study.

Ethical Consideration

- Study protocol was submitted to the Institutional Ethics Committee (IEC), R.G. Kar Medical College and Hospital, Kolkata for approval. Subject recruitment commenced only after approval of the Institutional Ethics Committee.
- Administration of blood, its consequences & adverse profile were not evaluated in the present study.

Recruitment of Patients

Patients satisfying the following criteria was enrolled, observed and assessed during the study period.

Inclusion Criteria

1. All histologically proven lung cancer patients who are receiving either Cisplatin – Etoposide or Carboplatin – Etoposide regimen.
2. Previously untreated patients of all ages and both sexes.

Exclusion Criteria

1. Those who are not willing to participate.
2. Those receiving other chemotherapeutic agents.
3. Post-surgical patients.
4. Those who are receiving concomitant radiotherapy.
5. Pregnant women.
6. Haematopoietic, hepatic & significant renal impairment.

(Hb-<10 g/dl, Platelet count-<1 lakh/, Total leukocyte count <4000, SGOT & SGPT >45 U/L, Creatinine clearance <30 ml/min)

- A prior written informed consent was obtained from all the patients.
- The ADRs of the following parameters were observed in the two groups – one group receiving Cisplatin – Etoposide & other group receiving Carboplatin – Etoposide ->>

1. *Emetotoxicity*- was assessed from history.
2. *Neurotoxicity*- was assessed on the basis of deep tendon reflexes, touch and pain sensation.
3. *Nephropathy*- was assessed on the basis of BUN & Creatinine reports.
4. *Haematotoxicity*-was assessed on the basis of blood Hb%, Platelet count, and Total leukocyte count.
5. *Hepatotoxicity*-was assessed from Liver Function Test
   - All ADRs were graded according to ECOG-CTC 13 criteria. Grade 3 & 4 were considered as severe ADRs.
   - Apart from these ADRs, other ADRs were also assessed.
   - The patients were assessed at the onset of chemotherapy for baseline clinical and investigational parameters.
   - They were reassessed during their subsequent visits for development of ADRs & if any were graded.
   - Clinical parameters were assessed during next review visits & the biochemical parameters were evaluated as prescribed by the physician. Investigation parameters were compared to their normal values.[14,15] for development of ADRs.
   - Each patient was followed for 4 contentious chemotherapy cycles.

Statistical Analysis

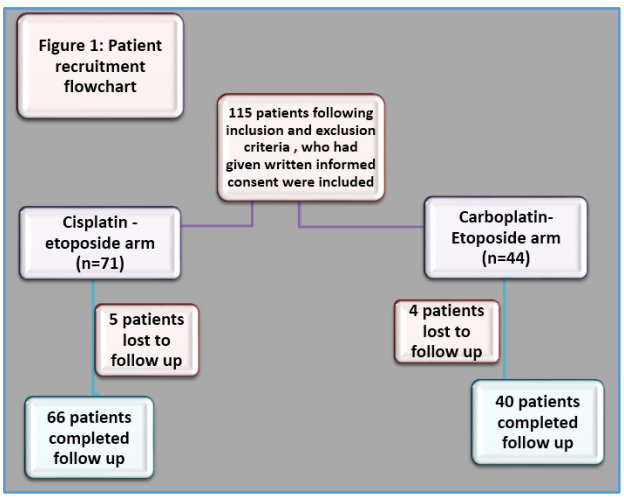
Data were analysed using GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007] software. Summary statistics were expressed using mean and standard deviation (SD) for numerical variables (median and interquartile ranges when skewed) and counts and percentages for categorical variables. Numerical variables were compared between subgroups by Mann-Whitney U test (for variables with skewed distribution) and unpaired T test (for variables with normal distribution). Fisher's exact test was employed for intergroup comparison of categorical variables.

Data Archiving

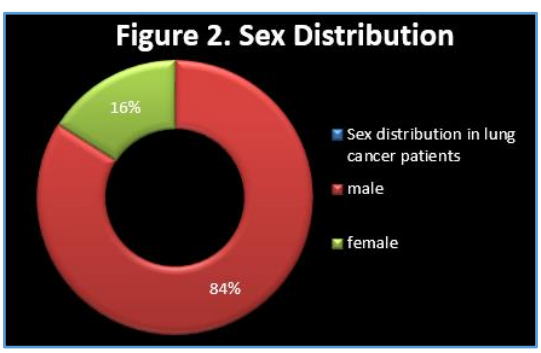
Archiving of study documents were done by the principal investigator at the Department of Pharmacology, R.G Kar Medical College, and Kolkata.

RESULTS

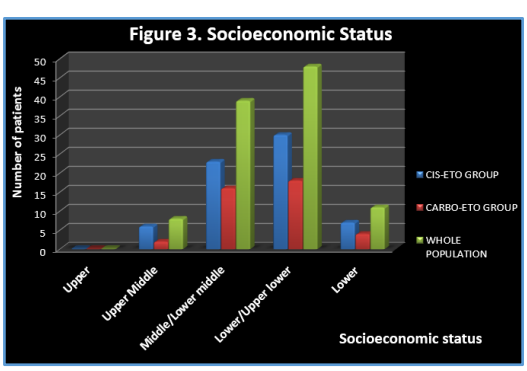
Total 115 lung cancer patients (71 in Cisplatin-Etoposide arm and 44 in Carboplatin-Etoposide arm) were recruited in the study over a period of 1 year starting from February 2014 to January 2015. Follow up was continued for another 4 months up to May 2015. Selection of chemotherapy regimen was done by treating Oncologist. Total 9 patients were lost to follow up (5 in Cisplatin-Etoposide arm and 4 in Carboplatin-Etoposide arm). Final analysis was done on 106 patients (66 in Cisplatin-Etoposide arm and 40 in Carboplatin-Etoposide arm). (See figure 1)



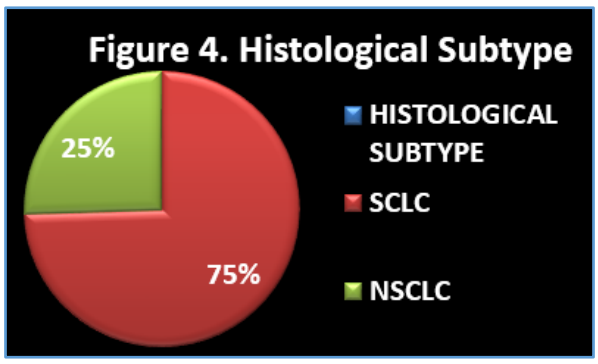
- Median [inter quartile range (IQR)] age were 69 (61 - 72) years.
- Majority were male [89 (84%)]. (See figure 2).



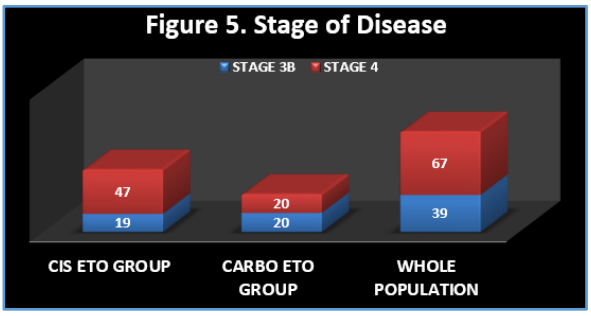
Majority belongs to upper lower and lower middle socioeconomic group as per revised Kuppuswamy's socioeconomic status scale 2012.[16] (See figure 3).



Histologically SCLC were more common [n=79(75%)] followed by NSCLC [n=27(25%)]. (See figure 4).



All patients were diagnosed at an advanced stage (stage IIIB/IV). The majority was belonging to stage IV [n=67 (63%)] followed by stage IIIB [n=39 (37%)]. (See figure 5).



History of smoking revealed that a substantial number of patients consumed tobacco in any form. Smoking was the most common form of tobacco consumption. Bidi was the most common form of smoking. Majority were heavy smoker followed by moderate smoker (See table 1) as per pack year consumption. (See annexure page x).

Tobacco Consumption(n)	**Yes [n (%)]**		**No [n (%)]**	
	101 (95.28)		**5 (4.72)**	
Route of tobacco consumption (n)	Smoking [n (%)]	Other forms [n (%)]		Both [n (%)]
	75 (70.75)	5 (4.72)		21 (19.81)
Form of smoking (n)	Bidi [n (%)]	Cigarettes [n (%)]		Both [n (%)]
	49 (46.23)	28 (26.42)		19 (17.92)
Degree of smoking as per pack year consumption (n)	Non-smoker [n (%)]	Light smoker [n (%)]	Moderate smoker [n (%)]	Heavy smoker [n (%)]
	10 (9.43)	8 (7.55)	27 (25.47)	61 (57.55)

Table 1. Tobacco Usage Pattern

All baseline demographic and investigational parameters were comparable in Cisplatin-Etoposide arm vs. Carboplatin-Etoposide arm (P value >0.05). (See table 2)

Parameter	**Cisplatin-Etoposide group (n=66)**	**Carboplatin- Etoposide group (n=40)**	**P value**
Age in years [median(IQR)]	69	68.5	0.7715
Socioeconomic status score (as per modified Kuppuswamy's scale 2012) [median(IQR)]	10 (9-14)	10 (9-15)	0.7047
Body mass index in Kg/m2 [mean(SD)]	22.45 (2.55)	22.85 (2.07)	0.3768
Creatinine clearance (ml/min/1.73m^2 BSA) [median(IQR)]	66.51 (63.26-73.92)	68.00 (47.29-84.21)	0.737
Baseline creatinine(mg/dl) [median(IQR)]	0.85 (0.7-0.9)	0.9 (0.7-0.11)	0.2215
Baseline BUN(mg/dl) [median(IQR)]	16 (14 -17)	15.5 (14 -17)	0.897
Haemoglobin (gm/dl) [median(IQR)]	13.35 (12.90-13.67)	13.60 (13.15- 13.82)	0.06
Total count (×10^3/cumm) (mean±SD)	7.09 (1.08)	6.8 (1.09)	0.9314
Neutrophil count(×10^3/cumm) [median(IQR)]	3.7 (3.3-4.1)	3.9 (3.1-4.1)	0.7655
Platelet count (×10^3/cumm) [median(IQR)]	246 (221.75-265.75)	240 (209-261.75)	0.4178
Serum bilirubin(mg/dl) [median(IQR)]	0.8 (0.7 -0.9)	0.8 (0.7 – 1.0)	0.4574
SGOT (U/L) [median(IQR)]	29 (27-32)	31 (27 – 33.25)	0.3796
SGPT (U/L) [median(IQR)]	34 (31-36)	35 (32 – 36.25)	0.0932
Alkaline Phosphatase(microgram/l) [median(IQR)]	74 (65.25-85)	74 (67.75 – 84.25)	0.934

Table 2. Baseline Demographic and Investigation Parameter

Patients were followed up for 4 continuous chemotherapy cycles, each at an interval of 3-4 weeks in both Cisplatin-Etoposide and Carboplatin-Etoposide arm. Adverse drug reactions were assessed and graded from history, clinical examination and laboratory investigational parameters by ECOG-CTC criteria. Worst grade of any adverse drug reactions was considered for statistical analysis.

Different dosage of chemotherapy regimen administered were as follows-

Non-Small Cell Lung Cancer	Etoposide: 100 mg/m^2 IV on days 1–3 Cisplatin: 100 mg/m^2 IV on day 1 Repeat cycle every 21 days
Small Cell Lung Cancer	Etoposide: 80 mg/m^2 IV on days 1–3 Cisplatin: 80 mg/m^2 IV on day 1 Repeat cycle every 21 days
	Etoposide: 100 mg/m^2 IV on days 1–3 Carboplatin: AUC of 6, IV on day 1 Repeat cycle every 28 days (see annexure page xi for the calculation of Carboplatin dose)

Table 3. Dosage of Different Chemotherapeutic Regimens

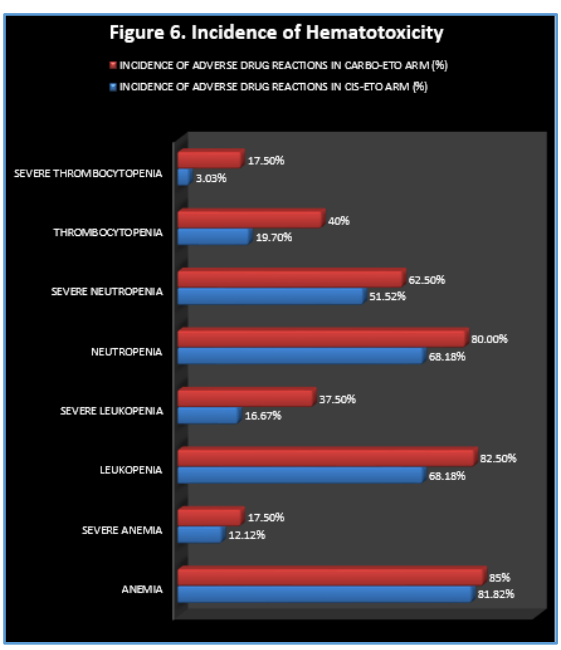
Incidence of adverse drug reactions

Incidence of different ADRs were as follows-

Haematotoxicity

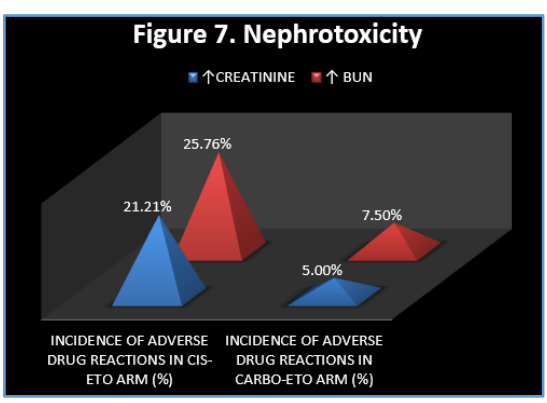
- The incidence of Anaemia was higher in Carboplatin group (85%) compared to Cisplatin (81.82%) group.
- The incidence of severe Anaemia (Grade 3 & 4) were higher in Carboplatin group (17.5%) compared to Cisplatin (12.12%) group.
- The incidence of Leucopenia were higher in Carboplatin group (82.5%) compared to Cisplatin (68.18%) group.
- The incidence of severe Leucopenia (Grade 3 & 4) were higher in Carboplatin group (37.5%) compared to Cisplatin (16.67%) group.
- The incidence of Neutropenia was higher in Carboplatin group (80%) compared to Cisplatin (68.18%) group.
- The incidence of severe Neutropenia (Grade 3 & 4) were higher in Carboplatin group (62.5%) compared to Cisplatin (51.52%) group.
- The incidence of Thrombocytopenia was higher in Carboplatin group (40%) compared to Cisplatin (19.70%) group.

The incidence of severe Thrombocytopenia (Grade 3 & 4) were higher in Carboplatin group (17.5%) compared to Cisplatin (3.03%) group. (See figure 6).



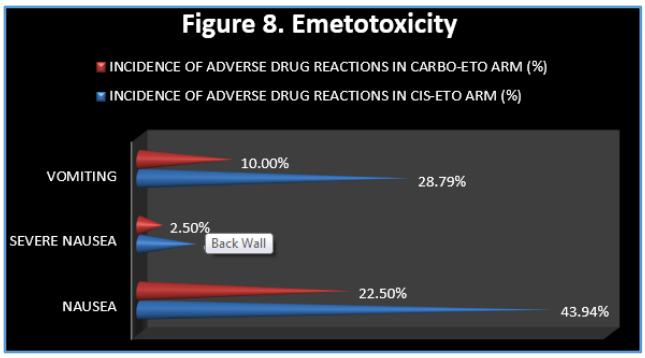
Nephrotoxicity

- Incidence of rise in serum creatinine level above normal were higher in Cisplatin group (21.21%) compared to Carboplatin (5%) group.
- Incidence of rise in the serum BUN level above normal were higher in Cisplatin group (25.76%) compared to Carboplatin (7.5%) group.
- None of the patients in either arm developed severe (grade 3 & 4) nephrotoxicity. (See figure 7)



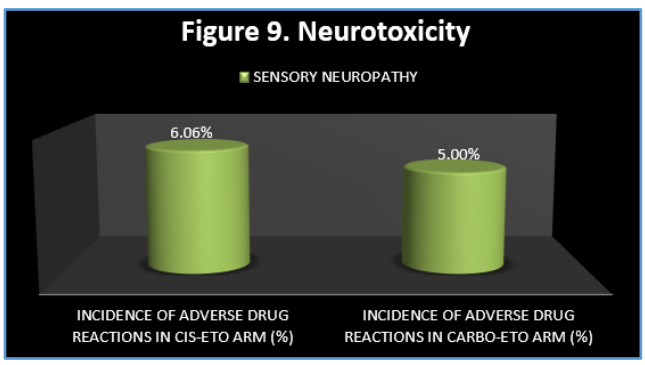
Emetotoxicity

- The incidence of nausea was higher in Cisplatin group (43.94%) compared to Carboplatin (22.5%) group.
- The incidence of severe nausea (grade 3 & 4) were higher in Cisplatin group (6.06%) compared to Carboplatin (2.5%) group.
- The incidence of vomiting was higher in Cisplatin group (28.79%) compared to Carboplatin (10%) group.
- None of the patients in either arm developed severe (grade 3 & 4) vomiting. (See figure 8).



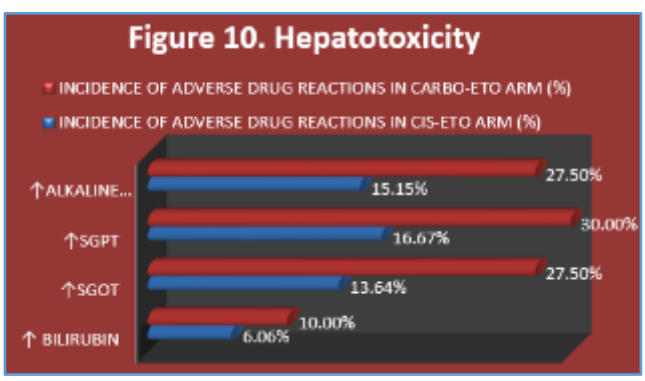
Neurotoxicity

- The incidence of sensory neuropathy was higher in Cisplatin (6.06%) compared to Carboplatin (5%). They were mild in severity (all grade 1). (See figure 9).



Hepatotoxicity

- Incidence of rise in the serum Bilirubin level above normal were higher in Carboplatin group (10%) compared to Cisplatin (6.06%) group.
- Incidence of rise in the serum SGOT level above normal were higher in Carboplatin group (27.5%) compared to Cisplatin (13.64%) group.
- Incidence of rise in the serum SGPT level above normal were higher in Carboplatin group (30%) compared to Cisplatin (16.67%) group.
- Incidence of rise in the serum Alkaline Phosphatase level above normal were higher in Carboplatin group (27.5%) compared to Cisplatin (15.15%) group. (See figure 10)
- None of the patients developed severe (grade 3 & 4) Hepatotoxicity.



So, the above results indicate that incidence of Haematotoxicity and Hepatotoxicity was more in those patients who received Carboplatin, whereas nephrotoxicity, Emetotoxicity and neurotoxicity were more in patients who had received Cisplatin.

Comparison of Adverse Drug Reactions between Cisplatin-Etoposide vs. Carboplatin-Etoposide

- Adverse drug reactions were categorized on the basis of their presence or absence and analysed using Fischer's exact test.

Haematotoxicity

- The incidence of anaemia was higher in Carboplatin [34 out of 40 (85%)] compared to Cisplatin [54 out of 66 (81.82%)], however the difference was statistically not significant (P=0.7925).
- The incidence of severe anaemia (grade 3 & 4) was higher in Carboplatin [7 out of 40] compared to Cisplatin [8 out of 66]. The difference was statistically not significant (P=0. 5667).
- The incidence of leucopenia was higher in Carboplatin [33 out of 40 (82.5%)] compared to Cisplatin [45 out of 66 (68.18%)], however the difference was statistically not significant (P=0.1179).
- The incidence of severe leucopenia (grade 3 & 4) was higher in Carboplatin [15 out of 40 37.5%)] compared to Cisplatin group [11 out of 66 (16.67%)], however the difference was statistically significant (P=0.0204).
- The incidence of neutropenia was higher in Carboplatin [32 out of 40 (80%)] compared to Cisplatin [45 out of 66 (68.18%)], however the difference was statistically not significant (P=0.2612).
- The incidence of severe neutropenia (grade 3 & 4) was higher in Carboplatin [25 out of 40 (62.5%)] compared to Cisplatin [34 out of 66 (51.52%)], however the difference was statistically not significant (P=0.3162).
- The incidence of thrombocytopenia was higher in Carboplatin group [16 out of 40 (40%)] compared to Cisplatin group [13 out of 66 (19.7%)], however the difference was statistically there was statistically significant higher incidence of severe leucopenia, thrombocytopenia and severe thrombocytopenia significant (P=0.0269).
- The incidence of severe thrombocytopenia (grade 3 & 4) was higher in Carboplatin group [7 out of 40 (17.5%)] compared to Cisplatin group [2 out of 66 (3.03%)], however the difference was statistically significant (P=0.0251).
- So, the above results clearly indicate that in Carboplatin compared to Cisplatin. (See table 4)

	Cis – Eto arm (n=66)		Carbo – Eto arm (n=40)		P value (two tailed)	Statistically Significant
	No	Yes	no	Yes		
Anaemia (any)	12	54	6	34	0.7925	No
Severe anaemia (grade 3 & 4)	58	8	33	7	0.5667	No
Leucopenia (any)	21	45	7	33	0.1179	No
Severe leucopenia (grade 3 & 4)	55	11	25	15	0.0204	Yes
Neutropenia (any)	21	45	8	32	0.2612	No
Severe neutropenia (grade 3 & 4)	32	34	15	25	0.3162	No
Thrombocytopenia (any)	53	13	24	16	0.0269	Yes
Severe thrombocytopenia (grade 3 & 4)	64	2	33	7	0.0251	Yes

Table 4. Haematotoxicity

Nephrotoxicity

- Incidence of rise in creatinine level above normal were higher in Cisplatin [14 out of 66 (21.21%)] compared to Carboplatin [2 out of 40 (5%)]. This difference was statistically significant (P=0.0264).
- Incidence of rise in BUN level above normal were higher in Cisplatin [17 out of 66 (25.76%)] compared to Carboplatin [3 out of 40 (7.5%)]. This difference was statistically significant (P=0.0220).
- None of the patients developed severe nephrotoxicity (grade 3 & 4). (See table 5)

	Cis – Eto arm (n=66)		Carbo – Eto arm (n=40)		P value (two tailed)	Statistically Significant
	No	Yes	No	Yes		
Raise in creatinine (any)	52	14	38	2	0.0264	Yes
Raise in BUN (any)	49	17	37	3	0.0220	Yes

Table 5. Nephrotoxicity

Neurotoxicity

- Incidence of sensory neuropathy were higher in Cisplatin [4 out of 66 (6.06%)] compared to Carboplatin [2 out of 40 (5%)], but this difference was statistically not significant (P=1.00). (see table 6)

	Cis – Eto arm (n=66)		Carbo – Eto arm (n=40)		P value (Two Tailed)	Statistically Significant
	No	Yes	No	Yes		
Sensory Neuropathy	62	4	38	2	1.000	No

Table 6. Neurotoxicity

Emetotoxicity

- Incidence of nausea were higher in Cisplatin [29 out of 66 (43.94%)] compared to Carboplatin [9 out of 40 (22.5%)], this difference was statistically significant (P=0.0362).
- Incidence of severe nausea (grade 3) were higher in Cisplatin [4 out of 66 (6.06%)] compared to Carboplatin [1 out of 40 (2.5%)]. This difference was statistically not significant (P=0.6478).
- Incidence of vomiting were higher in Cisplatin [19 out of 66(28.79%)] compared to Carboplatin [4 out of 40 (10%)], this difference was statistically significant (P=0.0285). (See table 7).

	Cis – Eto arm (n=66)		Carbo – Eto arm (n=40)		P value (two tailed)	Statistically significant
	No	Yes	No	Yes		
Nausea (any)	37	29	31	9	0.0362	**Yes**
Severe Nausea (grade 3 & 4)	62	4	39	1	0.6478	No
Vomiting (any)	47	19	36	4	0.0285	**Yes**

Table 7. Emetotoxicity

Hepatotoxicity

- Incidence of rise in bilirubin level above normal were higher in Carboplatin [4 out of 40 (10%)] compared to Cisplatin [4 out of 66 (6.06%)]. This difference was statistically not significant (P=0.4722).
- Incidence of rise in SGOT above normal were higher in Carboplatin [11 out of 40 (27.5%)] compared to Cisplatin [9 out of 66(13.64%)]. This difference was statistically not significant (P=0.1227).

- Incidence of rise in SGPT level above normal were higher in Carboplatin [12 out of 40 (30%)] compared to Cisplatin [11 out of 66 (16.67%)].This difference was statistically not significant (P=0.1446).
- Incidence of rise in Alkaline Phosphatase level above normal were higher in Carboplatin [11 out of 40 (27.5%)] compared to Cisplatin [10 out of 66 (15.15%)]. This difference was statistically not significant (P=0.1380). (See table 8).

	Cis – Eto arm (n=66)		Carbo – Eto arm (n=40)		P value (two tailed)	Statistically Significant
	No	Yes	No	Yes		
↑Bilirubin (total)	62	4	36	4	0.4722	No
↑SGOT	57	9	29	11	0.1227	No
↑SGPT	55	11	28	12	0.1446	No
↑ALKALINE PHOSPHATASE	56	10	29	11	0.1380	No

Table 8. Hepatotoxicity

DISCUSSION

Majority of lung cancer patients were male (84%) which support a previous study in India where male (77.7%) outnumbered female.[17] This finding is also supported by a Meta-analysis by Ardizzoni et al. which showed male predominance (62%-91%).[12]

Histologically SCLC was the predominant variety (75%). However, this finding differs from the previous findings where NSCLC were the predominant variety (92%).[17] The possible reasons behind this difference could be due to exclusion of majority of NSCLC patients as they were treated with concomitant radiotherapy and different chemotherapeutic regimens.

A substantial number of lung cancer patients were diagnosed at the stage of metastasis (stage IV=63%) which supports the previous literature (69%).[12]

A large number of patients had history of tobacco consumption (95.28%) with majority being smoking (70.75%), in the form of bidi. Majority were heavy smokers. This is in line with recent epidemiologic and experimental findings which consistently concluded the positive causal relationship between tobacco smoking and development of lung cancer.[18]

Regarding ADRs, the study clearly illustrated the higher incidence of Haematotoxicity and Hepatotoxicity in Carboplatin and higher incidence of nephrotoxicity, neurotoxicity and Emetotoxicity in Cisplatin. Statistically significant higher incidence of leucopenia, thrombocytopenia and severe thrombocytopenia is seen in Carboplatin, whereas statistically significant higher incidence of nausea, vomiting, nephrotoxicity (↑BUN, ↑Creatinine) is seen in Cisplatin group.

There is no significant difference regarding the incidence of Anaemia between Cisplatin and Carboplatin groups (81.82% in Cisplatin, 85% in Carboplatin). Majority of observations demonstrated higher incidence of anaemia in Carboplatin group,[12,19] but some research work had also elucidated higher incidence of anaemia in Cisplatin group.[20] Although, the incidence of severe anaemia (17.5% in Carboplatin, 12.12% in Cisplatin) were higher in Carboplatin, this finding was statistically not significant, which supports the previous observation.[12,19,20]

Anaemia related to cancer has multiple aetiologies including bleeding, marrow infiltration, anaemia of chronic disease and the effect of chemotherapy and/ radiotherapy on bone marrow/renal function.[21] Progressive decline in haemoglobin level were seen with both types of platinum-based chemotherapy.[22] Clinical data suggested that mild to moderate chemotherapy induced anaemia results in perceptible reduction in energy level and quality of life.[23]

Incidence of leucopenia (82.5% in Carboplatin, 68.18% in Cisplatin) was higher in Carboplatin. However, the difference was statistically not significant which supports the previous studies.[19,20,24] Severe leucopenia was much more common in Carboplatin (37.5%) compared to Cisplatin (16.16%). This difference was statistically significant, which corroborates with some of the previous studies,[20,24] however other differs.[19] Carboplatin is known to cause myelosuppression in dose dependent manner.[25,26]

Incidence of neutropenia (80% in Carboplatin, 68.18% in Cisplatin) and severe neutropenia (62.5% in Carboplatin, 51.52% in Cisplatin) were higher in Carboplatin, but the difference was statistically not significant which endorse the previous studies.[19,20,24]

Incidence of thrombocytopenia (40% in Carboplatin, 19.70% in Cisplatin) and severe thrombocytopenia (17.5% in Carboplatin, 3.03% in Cisplatin) were higher Carboplatin. The difference was statistically significant in both cases. This is in line with previous studies.[19,20,24]

Statistically significant higher incidence of nephrotoxicity (↑BUN, ↑Creatinine) is seen in Cisplatin, compared to Carboplatin, which corroborates with previous studies.[20,24] None of the patients in this study developed severe nephrotoxicity. Cisplatin induced nephrotoxicity can present in number of ways, however most serious and one of the common presentation being Acute Kidney Injury (AKI).[27,28] None of the patients in the study developed AKI. Nephrotoxicity increases with the dose and frequency of administration and cumulative dose of Cisplatin.[29] Progressive and permanent nephrotoxicity can result with successive treatment courses despite preventative measures.[30,31]

Sensory neuropathy was the only type of neuropathy seen in this study. In spite of higher incidence of neuropathy in Cisplatin (6.06%) compared to Carboplatin (5%), the difference was statistically not significant which substantiates some of the previous studies.[19,20] however other differs.[24] Among the platinum compounds in clinical

use, Cisplatin is the most neurotoxic, inducing mainly sensory neuropathy of the upper and lower extremities. Carboplatin is generally considered to be less neurotoxic than Cisplatin, but it is associated with a higher risk of neurological dysfunction if administered at high dose or in combination with agents considered to be neurotoxic.[32]

Cisplatin was more emetogenic compared to Carboplatin and the difference was statistically significant, which supports the previous studies.[20,24] Severe nausea was more common in Cisplatin, but the difference was statistically not significant. None of the patient developed severe vomiting. However, incidence of nausea and vomiting were much less compared to previous studies[19,20,24] presumably due to aggressive use of antiemetic drugs like– Ondansetron, Palanosetron, Apripitant, Dexamethasone and many others. Evidence suggests that good control of acute nausea and vomiting, particularly during the initial treatment received by chemotherapy naïve patients correlates with the delayed and by extrapolation anticipatory symptoms, as well as acute and delayed onset emesis associated with subsequent cycles of treatment.[33-36]

Hepatotoxicities were mild in nature (grade 1) with asymptomatic rise in bilirubin and liver enzymes. Incidences of Hepatotoxicity were higher in Carboplatin compared to Cisplatin, but the difference was statistically not significant, which corroborates with the previous study results.[19,24]

The study evaluated and compared the incidence and severity of different ADRs of Cisplatin and Carboplatin. Majority of the findings were in line with previous studies; however, some differs, most likely due to genetic, metabolic, racial, individual, dietary variation and population heterogeneity.

There was a paucity of literature about the incidence and severity of ADRs in Cisplatin and Carboplatin in lung cancer patients especially in Indian population. In this context, the present study had attempted to illuminate the real scenario and bridge the deficit in literature.

No study is devoid of shortcomings. The scope of the study was limited due to its observational nature, single centre patient recruitment and small number of sample size. Quality of life and survival analysis was not performed due to logistic and time constraints. A further multicentric Interventional study needs to be conducted on a larger number of populations to confirm these findings.

CONCLUSION

The study demonstrated higher incidence of Haematotoxicity and Hepatotoxicity in Carboplatin and higher incidence of nephrotoxicity, neurotoxicity and Emetotoxicity in Cisplatin. Statistically significant higher incidence of leucopenia, thrombocytopenia and severe thrombocytopenia is seen in Carboplatin, whereas statistically significant higher incidence of nausea, vomiting, nephrotoxicity (↑BUN, ↑Creatinine) is seen in Cisplatin group. There is a need for evaluation of safety on the background of efficacy of these chemotherapeutic agents, in order to reduce morbidity without affecting survival, which is the ultimate goal of palliation therapy. A further multicentric Interventional study needs to be conducted on a larger number of populations to confirm these findings.

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