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COMPARING A STANDARD 3-WEEKLY PACLITAXEL AND CARBOPLATIN TO WEEKLY PACLITAXEL AND CARBOPLATIN (SAME AS IN THE 3-WEEKLY ARM) IN STAGE IV METASTATIC NSCLC

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ABSTRACT

AIM: Purpose of this study is to compare the efficacy of standard 3-weekly Paclitaxel and Carboplatin to weekly Paclitaxel and Carboplatin (same as in the 3-weekly arm) in Stage IV Metastatic NSCLC"

MATERIALS AND METHODS: It is a two arm Prospective Randomized Controlled Trial. Twenty patients were randomized each to the control as well as the study (experimental) arm, fulfilling all the Inclusion criteriae. Eligible patients were either assigned to:

- Arm1- Paclitaxel 75mg/m2 weekly on Days 1, 8 and 15, with Carboplatin area under the curve (AUC) = 5, on day 1 of each 28 days cycle; or
- Arm 2 - Paclitaxel (175 mg/m2) and Carboplatin (AUC= 5), both on day 1 of each 21 days cycle. Treatment was planned for upto a maximum of four cycles.

Patients who had symptomatic Brain and Bone metastases completed palliative Whole Brain / Bone Radiation, before being started on palliative chemotherapy, as per protocol.

RESULTS: In our study, an Overall Response rate of 20% (4/20 patients) in the experimental arm and 15% (3/20 patients) in the standard arm was observed, reflecting a trend, modestly in favour of the experimental weekly arm**.** An improved QOL was apparent in the weekly arm. The overall incidence of patients with a moderate to good QOL, was an overwhelming 75%, with 50% of these patients experiencing a very good QOL. Paradoxically, 20% of patients suffered a poor QOL, as well**.** The overall incidence of Gr 2/3 Neutropenia was observed to be 23%, with the weekly arm showing a significant reduction**.** The overall incidence of Gr 3/4 Anemia was noted to be 30% and 20% respectively, in our weekly and standard arms.

The overall incidence of Gr 2/3 Peripheral sensory neuropathy in our weekly arm was noted to be 25%. The overall incidence of Gr 2/3 Peripheral sensory neuropathy in our standard arm was noted to be an overwhelming 45%.

The overall incidence of Myalgia / Arthralgia in the weekly arm was observed to be 25%, and that of Myalgia / Arthralgia in the standard arm was observed to be as high as 50%**.**

CONCLUSION: Treating Advanced Stage-IV NSCLC patients with combination chemotherapy using a weekly Paclitaxel regimen along with standard dose Carboplatin, is not only feasible, but also better than the conventional Paclitaxel and Carboplatin given every 21 days.

Patients are also able to complete the planned number of Chemotherapy cycles, with a performance status reasonably well maintained and eligible for further maintenance therapy. And especially, the favourable Non-hematologic toxicity profile of this weekly combination, makes it the ideal treatment option for patients with advanced NSCLC, even in the elderly and in patients with a reduced performance status.

KEYWORDS :NSCLC, Paclitaxel, Carboplatin.

INTRODUCTION

Lung cancer is one of the most common malignancies occuring worldwide, with a high degree of mortality. Annually, approximately 15% new cancer cases, and 28% total cancer deaths globally, are attributable to lung cancer.[1] And, amongst Lung cancers, Non-small-cell lung cancer (NSCLC) forms the majority, the incidence being about 80–85%, while small-cell lung cancer has been on the decline over the last few decades. [2] The foremost cause of lung cancer, is Smoking, responsible for almost 80% of cases. Other less common risk factors include, exposure to Asbestos, Radon, Arsenic, Environmental Tobacco Smoke (ETS) and Non-Tobacco-related Polycyclic Aromatic Hydrocarbons.[3]

Prevalence of lung cancer in Non-smoking females is on the rise, and is estimated to represent about 19% compared with 9% of male Non-smokers, globally [3]. Younger women seem to be more susceptible to lung carcinogens [11]. Recently, a sizeable increase in the proportion of Asian NSCLC patients who are Never-Smokers has been demonstrated [12]. Hence, 'Non-Smoking-Associated Lung Cancer' is nowadays being recognized as a separate disease entity, where specific tumor characteristics at the molecular and genetic levels are being recognized.

NSCLC is usually diagnosed at an advanced stage in more than 40% of patients [7]. The 5-year survival for stage IV NSCLC is a meagre 1%. [10] The histology, Molecular Pathology, Age, PS, Comorbidities, and Patient's Preferences are hence taken into account, while treatment strategy is being planned. [1]

MATERIALS & METHODS

It is a two arm Prospective Randomized Controlled Trial. Twenty patients were randomized each to the control as well as the study (experimental) arm, fulfilling all the Inclusion criteriae.

INCLUSION CRITERIAE :

Age - 18 years or older & less than / equal to 65 years, Performance status - 0 to 2, by ECOG**,**Comorbidities - Hypertension, Bronchial Asthma, Tuberculosis, (All well under control) and IHD (ECHO Cardiogram showing normal LV function and EF more than 50%)**,**Immune status – Immunocompetent**,** Viral markers (HBsAg and HIV) - Negative / Non-reactive**,** No underlying Neuropathy**,** Normal Blood chemistry and Renal parameters and Consent - Voluntary willingness to participate in the trial**.** Histologically or Cytologically confirmed stage-IV NSCLC and Measurable disease by RECIST criteria.

EXCLUSION CRITERIAE :

Failure to fulfil any one of the aforesaid Inclusion criteria**,** Small cell Lung cancers**,** Previous chemotherapy**,** History of Radiation therapy in the preceding 6 months**,** History of hypersensitivity to either Paclitaxel or Carboplatin**,** Participation in previous clinical trials**,** Diabetes Mellitus (As there would be bias regarding Neuropathy) and Uncontrolled symptomatic associated Psychiatric illness

TREATMENT APPROACH :

Eligible patients were either assigned to:

- Arm1- Paclitaxel 75mg/m2 weekly on Days 1, 8 and 15, with Carboplatin area under the curve (AUC) = 5, on day 1 of each 28

days cycle; or
- Arm 2 - Paclitaxel (175 mg/m2) and Carboplatin (AUC= 5), both on day 1 of each 21 days cycle. Treatment was planned for upto a maximum of four cycles.

Considering the overall performance and nourishment status in the subgroup of patients in our institution, it was decided to cap the dosage of Carboplatin in both the standard and experimental arms, to 450mg.

Before administering Paclitaxel, it was ensured that Dexamethasone Ranitidine and chlorpheniramine maleate were given to prevent hypersensitivity and gastritis. And subsequently, patients who did not encounter a hypersensitivity reaction to Paclitaxel during the first cycle, had the dosage of the premedications lowered for the subsequent cycles.

Patients who had symptomatic Brain and Bone metastases completed palliative Whole Brain / Bone Radiation, before being started on palliative chemotherapy, as per protocol.

ASSESSMENT OF EFFICACY AND SAFETY :
Response assessments were performed every two cycles (ie, every 8 weeks for arm 1, every 6 weeks for arm 2) during the initial therapy phase of the study. Responses were confirmed with repeat assessments, 28 days after completing the planned final cycle of chemotherapy. Responses and toxicities were assesed and documented as per the guideline recommendations [28].

Blood Chemistry, LFTs and RFTs were checked every 2 weeks, and when needed corrective and supportive measures were also instituted. In patients above 60 years of age and those with a previous history of IHD, repeat ECHO Cardiogram was done before each cycle of chemotherapy and when needed, a Cardiologist opinion was also sought.Taxane-related adverse effects and thereby the Quality of Life was assessed 2 weeks after completion of each cycle, using the Functional Assessment of Cancer Therapy (FACT) Taxane subscale [68,69].

STATISTICAL ANALYSIS :
The primary end point was Response assesment [28] and Toxicity assesment, of either of the treatment arms during the course of treatment and after completion as well. CR, PR and Stable disease were considered in the Overall Response Rate (ORR). The individual responses are defined as follows :

COMPLETE RESPONSE (CR):
Disappearance of all target lesions (28). Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <1 cm.

PARTIAL RESPONSE (PR):
At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters [28].

PROGRESSIVE DISEASE (PD):
At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression [28].

STABLE DISEASE (SD):
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum-diameters while on study [28].

For the primary endpoint, the response rates were arrived at, taking into account CR, PR and SD for Overall response and the various grades of Haematological and Non-haematological toxicities charted. Both were derived using standard recommended guidelines.

The secondary end point was to determine the Optimal dosing schedule of the combination of Paclitaxel and Carboplatin, in treating Advanced Stage NSCLC patients. This was determined by a direct comparison of both the treatment arms, analysing both the response rates, as well as associated toxicities.The statistical significance of both endpoints was derived, using the multivariate regression method.

RESULTS:
The average age incidence observed in our study was 50 years and above**(table 1).**As expected, predominantly males were involved, the proportion being slightly more than twice than in females**(table 2).** Since Diabetes was excluded in our study, the incidence of associated co morbidities was found to be only 30%, with systemic hypertension being the commonest association**(table 3).**

In our study smokers and non-smokers were found to be distributed in an equal manner**(table 4).** It was observed that our subgroup of patients predominantly were of the Adenocarcinomatous variety. Incidence of Gr 2 and 3 tumours were noted to be much higher than Gr 1 tumours, in our study. In our study, an Overall Response rate of 20% (4/20 patients) in the experimental arm and 15% (3/20 patients) in the standard arm was observed, reflecting a trend, modestly in favour of the experimental weekly arm**(table 5).**

An improved QOL was apparent in the weekly arm. The overall incidence of patients with a moderate to good QOL, was an overwhelming 75%, with 50% of these patients experiencing a very good QOL. Paradoxically, 20% of patients suffered a poor QOL, as well**(table 6).** The overall incidence of Gr 2/3 Neutropenia was observed to be 23%, with the weekly arm showing a significant reduction**(table 7).** The overall incidence of Gr 3/4 Anemia was noted to be 30% and 20% respectively, in our weekly and standard arms.

The overall incidence of Gr 2/3 Peripheral sensory neuropathy in our weekly arm was noted to be 25%. The overall incidence of Gr 2/3 Peripheral sensory neuropathy in our standard arm was noted to be an overwhelming 45%.

The overall incidence of Myalgia / Arthralgia in the weekly arm was observed to be 25%, and that of Myalgia / Arthralgia in the standard arm was observed to be as high as 50%**(table 8).**The overall incidence of Fatigue in the weekly arm was noted to be only 40%, when compared to the standard arm, which was as much as 70%, in our study.

DISCUSSION
Literature review shows that the overall response rates and toxicities are comparable, in both the standard 3-weekly arm and the weekly arm, using the Paclitaxel and Carboplatin combination, whilst treating Advanced Stage-IV NSCLC [6,66].

Dose intensity of Paclitaxel in the weekly arm was said to be advantageous, because of the proposed Anti-angiogenic and pro-apoptotic properties of Paclitaxel, when given in this fashion [67]. Even though patient compliance was questionable in the weekly arm, severe toxicities were considerably lesser in this arm, thereby prompting patients to complete therapy.

Maintenance therapy with Pemetrexed, Docetaxel or Erlotinib was an option after completing 4 cycles of first-line therapy, depending on the patient's PS , response and associated toxicities [54, 55, 56, 57, 58, 59, 61]. Considering the generally poor PS and the nutritionally compromised status of majority of the patient population encountered in our institution, it was decided to cap the dosage of Carboplatin to 450mg, in both treatment arms.

The patients were assessed for subjective response or disease progression, 3-4 weeks after completion of each cycle of chemotherapy, and also in an objective manner, after completion of 2 cycles (Interim assessment). At the end of each cycle, QOL Assessment was also done, using the FACT-Taxane subscale tool [68,69]. Likewise, Arthralgia and Fatigue were also assessed and documented.

In our study, an Overall Response rate of 20% (4/20 patients) in the experimental arm and 15% (3/20 patients) in the standard arm was observed, reflecting a trend, modestly in favour of the experimental weekly arm. But, this was significantly lesser than that observed by Belani et al. [6], where the same chemotherapy combination, in the same design as in our study was compared.

Although, when compared to the combination of Cisplatin and Etoposide, which is the commonly employed regimen in our institution, the response rates noted in our study, were comparable. A head-on comparison between Cisplatin / Etoposide and Carboplatin / Paclitaxel, done by Belani et al. showed a trend in favour of the Carboplatin / Paclitaxel arm [66].

The overall incidence of Gr 2/3 Neutropenia in our weekly arm was observed to be 15%, with an equal distribution amongst the Squamous, Adeno and BAC varieties, which was similar to that shown in a phase 3 study [6]. Two patients, one with Squamous variety and the other with BAC, required higher antibiotics and G-CSF support to tide over the Neutropenic crises. And one more patient with BAC developed Gr 3 Neutropenia and severe fatigue while on therapy and succumbed after completing 3 cycles.

The overall incidence of Gr 3/4 Anemia in our weekly arm was noted to be 30%, which was much higher than that shown in a similar phase 3 study [6]. And almost 75% of the Squamous variety and 50% of the poorly-differentiated type, which was noted in our study amongst the involved 30%, required multiple units of Red cell transfusions, prompting a delay in therapy, of upto 2-3 weeks.

The overall incidence of Gr 3/4 Thrombocytopenia in our weekly arm was observed to be 25%, notably the Squamous variety, where as many as 50% of the patients required platelet transfusions, and 25% of which caused a treatment delay, as well, of upto 2 weeks. One patient with the Squamous variety especially had severe symptomatic Gr IV Thrombocytopenia, necessitating multiple sittings of multiple platelet transfusions and 25% reduction of the Carboplatin dose, after which the patient stabilised.

The overall incidence of Gr 2/3 Peripheral sensory neuropathy in our weekly arm was noted to be 25%, with the Squamous variety being predominantly involved (as many as 50% of the patients). This was very high compared to the incidence in a phase 3 trial (6). One patient each of the Squamous and Adenocarcinomatous variety developed severe Gr 3 PSN affecting their activities of daily living (ADL), like buttoning their shirts, gripping and lifting coffee cups, etc.

The overall incidence of Myalgia / Arthralgia in the weekly arm was observed to be 25%, of which 50% was noticed in the Squamous variety and 30% in the Adenocarcinomatous variety. One patient of Squamous and one of Adenocarcinoma variety required NSAIDs for prolonged periods of time. A close watch was kept on their Renal parameters, periodically.Interestingly, Fatigue was complained of, by many patients. The overall incidence of Fatigue in the weekly arm being, as much as 40%, with a trend towards increased incidence amongst the Adenocarcinomatous variety. Three patients of this histological subtype required Nutritional enhancement and Vitamin supplements as well.

The patients in the Standard 3-weekly arm fared slightly differently, in terms of both Response and Toxicity.

The overall response rate was observed to be, a modest 15%, in the standard arm and only 1/11 patients amongst the Adenocarcinomatous variety showing a CR, 2/9 patients amongst the Squamous variety acheiving some sort of response, one PR and the other, Stable disease. A vast majority of patients experienced progression of disease (as many as 85%).

Fifteen patients progressed upon completion of 4 cycles. One each from the Squamous and Adenocarcinomatous variety progressed while on therapy, prompting a change-over to Docetaxel and Gefitinib, respectively.

The overall incidence of Gr 2/3 Neutropenia in our standard arm was noted to be 30%, equally distributed amongst both the Squamous and Adenocarcinomatous varieties, which was indeed very high compared to the incidence noted in a large phase 3 study [6]. Two patients with Squamous variety and two more with Adenocarcinoma, required higher antibiotics and G-CSF support to tide over the Neutropenic crises.

The overall incidence of Gr 3/4 Anemia in our standard arm was noted to be 20%, with almost equal occurence in both the Squamous and Adenocarcinomatous varieties, which was also much higher compared to the incidence seen in a large phase 3 trial [6]. Only one patient of the Squamous type required multiple units of Red cell transfusions, prompting a delay in therapy, of upto 3 weeks.

The overall incidence of Gr 3/4 Thrombocytopenia in the standard arm was observed to be 25%, with an equal number of patients with the Squamous and Adenocarcinomatous varieties requiring platelet transfusions, and 25% of which caused a treatment delay, as well, of upto 2 weeks. The overall incidence of Gr 2/3 Peripheral sensory neuropathy in our standard arm was noted to be an overwhelming 45%, with an equal number of patients with the Squamous and Adenocarcinomatous varieties being affected. The incidence was much lesser in a phase 3 study conducted by a large group [6].

The overall incidence of Myalgia / Arthralgia in the standard arm was observed to be as high as 50%. The distribution was found to be almost equal in both the Squamous and Adenocarcinomatous varieties.

Two patients of Squamous and two of Adenocarcinoma variety required NSAIDs and Muscle-relaxants for prolonged periods of time. Their Renal parameters were closely monitored, regularly.The overall incidence of patients with a moderate to good QOL, in the standard arm was 55%, with 50% of these patients experiencing a good QOL. Paradoxically, almost 45% of patients suffered a poor QOL. This vast group of patients were counselled and given, Best Supportive Care.

Patients who had stable disease and who were in good PS were started on the same chemotherapy regime, for a further 2 cycles. Those who were in PS of 2 and more, were kept under observation, or if symptomatic, were started on Gefitinib.Patients who experienced disease progression and who were in good PS were started on 2nd line chemotherapy or Gefitinib. Patients in PS 3 were either given Gefitinib or best supportive care.
Patients with very poor Performance status (PS 4) were only offered best supportive care.

The overall toxicity profile with both the standard 3-weekly regimen and the experimental weekly arm in our study was found to be almost the same as noted in other trials using the same platinum doublet in treating Advanced NSCLC, though the overall response rates proved to be inferior in both the arms. Notably, the incidence of debilitating neuropathy was much lesser, when Paclitaxel was given in a weekly fashion. [6]Altogether, Paclitaxel when given in a weekly schedule along with standard dose Carboplatin can be

considered a very viable treatment option for front-line therapy of advanced NSCLC [6].

CONCLUSION:

Treating Advanced Stage-IV NSCLC patients with combination chemotherapy using a weekly Paclitaxel regimen along with standard dose Carboplatin, is not only feasible, but also better than the conventional Paclitaxel and Carboplatin given every 21 days, for the following reasons :

- Improved response rates
- Better symptom palliation
- Added advantage of Anti-angiogenesis
- Better patient compliance
- Improved QOL
- Significantly lesser Neurotoxicity
- Favourable Non-haematological toxicity profile
- Less frequent treatment delays

Patients are also able to complete the planned number of Chemotherapy cycles, with a performance status reasonably well maintained and eligible for further maintenance therapy.And especially, the favourable Non-hematologic toxicity profile of this weekly combination, makes it the ideal treatment option for patients with advanced NSCLC, even in the elderly and in patients with a reduced performance status.

Table 1: Shows Average Age Incidence

Age					
	Group	**N**	**Mean**	**Std. Deviation**	**P-value**
Age	**Standard**	20	51.80	8.218	**0.721**
	Weekly	20	50.85	8.481	

Table 2:Distribution of sex in our study

Sex					
			Sex		**Total**
			Male	**Female**	
Group	**Standard**	Count	15	**5**	**20**
		% within Group	75.0%	**25.0%**	**100.0%**
	Weekly	Count	13	**7**	**20**
		% within Group	65.0%	**35.0%**	**100.0%**
Total		Count	28	**12**	**4040**
		% within Group	70.0%	**30.0%**	**100.0%**

Table 3: Distribution Of Comorbids In Our Study.

			comorbids				**Total**
			BA	**CAD**	**None**	**SHT**	
Group	**Standard**	Count	2	3	9	6	20
		% within Group	10.0%	15.0%	45.0%	30.0%	100.0%
	Weekly	Count	0	0	19	1	20
		% within Group	.0%	.0%	95.0%	5.0%	100.0%
Total		Count	2	3	28	7	40
		% within Group	5.0%	7.5%	70.0%	17.5%	100.0%

Table 4: Distribution Of Smokers In Our Study.

			Smoking		**Total**
			No	**Yes**	
Group	**Standard**	Count	10	10	20
		% within Group	50.0%	50.0%	100.0%
	Weekly	Count	10	10	20
		% within Group	50.0%	50.0%	100.0%
Total		Count	20	20	40
		% within Group	50.0%	50.0%	100.0%

Table 5: Overall response in our study.

			OR		**Total**
			Yes	**No**	
Group	**Standard**	Count	3	17	20
		% within Group	15.0%	85.0%	100.0%
	Weekly	Count	4	16	20
		% within Group	20.0%	80.0%	100.0%
Total		Count	7	33	40
		% within Group	17.5%	82.5%	100.0%

Table 6: Quality Of Life

			QOL			**Total**
			Good	**Moderate**	**Poor**	
Group	**Standard**	Count	6	5	9	20
		% within Group	30.0%	25.0%	45.0%	100.0%
	Weekly	Count	10	5	5	20
		% within Group	50.0%	25.0%	25.0%	100.0%
Total		Count	16	10	14	40
		% within Group	40.0%	25.0%	35.0%	100.0%

Table 7: Distribution Of Smokers In Our Study

Neutropenia				
		Gr 2/3 Neutropenia		**Total**
		Yes	**No**	
Standard	Count	6	14	20
	% within Group	30.0%	70.0%	100.0%
Weekly	Count	3	17	20
	% within Group	15.0%	85.0%	100.0%
Total	Count	9	31	40
	% within Group	22.5%	77.5%	100.0%

Table 8 :distribution Of Non Hematological Toxicities

Toxicities		**Group**		**Total**
		Standard	**Weekly**	
NIL	Count	6	10	16
	% within Group	30.0%	50.0%	40.0%
Arthralgia, Fatigue	Count	1	1	2
	% within Group	5.0%	5.0%	5.0%
Fatigue	Count	4	6	10
	% within Group	20.0%	30.0%	20.0%
Gr 2/3 PSN	Count	0	1	1
	% within Group	.0%	5.0%	2.5%
Gr 2/3 PSN, Arthralgia, Fatigue	Count	9	4	13
	% within Group	45.0%	20.0%	32.5%
Total	Count	20	20	40

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