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ORIGINAL ARTICLE

Combining Two Different Chemotherapy Agents with Platinum Analogs as Induction and Consolidation Regimes in Nonsmall Cell Lung Carcinoma

Mohsin Khan[1], Shahid Ali Siddiqui[1]

[1]*Department of Radiotherapy, JNMC, AMU, Aligarh, Uttar Pradesh, India*

Background: There are limited data pertaining to the combined use of induction and consolidation chemotherapy with concurrent chemo-radiotherapy (RT) for treating nonsmall cell lung carcinoma (NSCLC). To find out an optimum/effective regime for treating NSCLC utilizing both induction and consolidation approach with concurrent chemo-RT is the primary aim of this study. **Materials and Methods:** We retrospectively analyzed 132 patients with NSCLC. Fifty-four patients treated with paclitaxel-carboplatin and 78 with gemcitabine-cisplatin combinations in induction and consolidation phases. Concurrent chemo-RT included 60–66 Gray (Gy) of RT with weekly cisplatin and was similar in both the arms. **Results:** After completion of the consolidation phase, we observed on overall response rate (ORR) of 42.7% in the paclitaxel-carboplatin arm and 42.3% in gemcitabine-cisplatin arm with 2 and 3 years' survival rates of 32% and 19% with paclitaxel-carboplatin and 38% and 24% with gemcitabine-cisplatin regimes. We also observed higher ORR for squamous cell histology treated with the gemcitabine-cisplatin combination. **Conclusion:** Although both paclitaxel-carboplatin and gemcitabine-cisplatin combinations are equally effective in treating NSCLC, gemcitabine-cisplatin provided slightly better response rates but with clinically more frequent and relevant toxicities.

Key words: Chemotherapy, lung cancer, radiotherapy

INTRODUCTION

In patients with unresectable locally advanced nonsmall cell lung carcinoma (NSCLC), a concurrent approach based on combined radiotherapy (RT) and chemotherapy is warranted. Concurrent chemo-RT improves 5 years survival by an additional 5% as compared to sequential chemotherapy followed by RT.[1-3] Although cisplatin is still considered the main drug for NSCLC, variety of other drugs are also available. Both induction and consolidation approaches are in clinical use, but still the optimal schema is debatable. Different practitioners or institutions have varied standards of protocols, with induction chemotherapy before concurrent chemo-RT preferred by some,[4] and others practicing consolidation chemotherapy after concurrent chemo-RT.[5] As far as recommended systemic treatment for stage 3 NSCLC is concerned, it comprises 2–4 cycles of chemotherapy.

To find out an effective/optimum regimen of induction and consolidation chemotherapy with concurrent chemotherapy in NSCLC is the main aim of the present study.

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Corresponding Author: Dr. Mohsin Khan, Department of Radiotherapy, JNMC, AMU, Aligarh, Uttar Pradesh, India. Tel: 08266891077; Fax: 05712721130. E-mail: mohsinkhan793@gmail.com

MATERIALS AND METHODS

Patients

From July 2012 to June 2015, 132 patients of lung cancer were retrospectively analyzed. Eligibility criteria included (a) previously untreated patients of lung cancer with unresectable and or inoperable (due to medical reasons) disease, (b) nonsmall cell histology, (c) nonmetastatic without pleural effusion.

Treatment

We mainly tried to analyze two important and widely used chemotherapy combinations of paclitaxel with carboplatin or gemcitabine with cisplatin in treating NSCLC. Therefore, we divided our patient group into two arms. Those in arm A received paclitaxel-carboplatin combination during induction and consolidation phases at a dose of paclitaxel 175 mg/m^2 intravenous (i.v.) with carboplatin area under curve 6 i.v. on

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day 1 every 21 days for 2–3 cycles each in induction and consolidation phases, respectively. While in arm B gemcitabine 1.2 g/m^2 i.v. day 1 and 8 with cisplatin 75 mg/m^2 i.v. day 1 every 21 days were administered for 2–3 cycles each during induction and consolidation phases.

Concurrent chemo-RT phase was similar on both arms with RT delivered to total doses of 60–66 Gray (Gy) in 30–33 fractions with 5 fractions per week, single fraction per day. RT was delivered with Cobalt 60 machine. Treatment planning was done on the conventional simulator, and majority of the patients were treated with parallel opposed anterior and posterior portals. Prechemotherapy tumor volumes were mainly taken into account for defining target volumes. Forty-four Gy in 22 fractions were delivered in phase 1 followed by boost to the target volume. Cisplatin at a dose of 40 mg week during RT was employed as concurrent chemotherapy.

Assessment

Blood cell counts, liver function tests, and renal function tests were performed three weekly during induction and consolidation phases and weekly during the concurrent chemo-RT phase. The majority of patients were restaged with contrast-enhanced computed tomography scan at the end of induction phase, chemo-RT phase, and 1 or 2 months after consolidation phase. Treatment response was assessed using Response Evaluation Criteria in Solid Tumors criteria. Toxicities were graded according to the National Cancer Institute-Common Toxicity Criteria (version 4.0).

Data analysis

Descriptive statistics were used to summarize characteristics of the study population. Primary endpoints were response rates and the secondary end point was survival. Survival was calculated using Kaplan–Meier method. Statistical analysis was performed using the Statistical Package for the Social Sciences, IBM SPSS Inc. Released 2008 (SPSS Statistics for Windows, version 17.0. Chicago: SPSS Inc).

RESULTS

A total of 132 patients with the diagnosis of NSCLC were retrospectively reviewed. O which 54 underwent treatment with paclitaxel-carboplatin (arm A) and 78 were treated with gemcitabine-cisplatin labeled as arm B.

Patient characteristics

Majority of patients were ≤60 years age both in arm A and B, 77.8% and 82.1%, respectively. Of which 81.5% and 74.4% were males, respectively, in each arm. However, regards stage grouping there were 7.7% with stage 2 treated under arm B while there were none in arm A. Of 54 patients, 26% had stage 3b in arm A, whereas 48.7% out of 78 had stage 3b status in arm B [Table 1].

Dose intensity

During the induction phase, the total doses of paclitaxel and carboplatin received by patients in arm A were 315 ± 35 mg and 450 ± 90 mg, respectively. For arm B, the doses were for gemcitabine 2000 ± 160 mg and for cisplatin 100 ± 20 mg. Mean numbers of cycles per patient received during induction phase were 2.5 ± 0.13 in arm A and 1.9 ± 0.14 in arm B. During concurrent chemo-RT phase the doses of cisplatin delivered were 40 mg in arm A and 40 mg in arm B with mean no. of cycles per patient equal to 5.8 ± 0.32 and 5.7 ± 0.22, respectively, in arms A and B. While during consolidation phase dose intensities in arm A were for paclitaxel 260 ± 20 mg with carboplatin 450 ± 100 mg and in arm B gemcitabine 1500 ± 500 mg with cisplatin 80 ± 15 mg [Table 2].

Survival analysis

After induction chemotherapy, complete responses (CR) were observed only in arm B (2.6%). After consolidation phase, 3.7% in arm A and 5.1% in arm B experienced CR with overall response rates (ORRs) of 42.7% in arm A and 42.3% in arm B,

Table 1: Patient characteristics

	Paclitaxel-carboplatin (arm A)	Gemcitabine-cisplatin (arm B)
Age (years)		
≤60	42	64
61-70	12	12
≥71	0	2
Sex		
Males	44	58
Females	10	20
Performance status		
0	14	28
1	34	44
2	6	6
Histology		
Squamous	22	30
Adenocarcnoma	32	46
Large cell	0	2
Stage		
1	0	0
2	0	6
3a	40	34
3b	14	38

Table 2: Dose intensity (mean±standard deviation)

	Induction chemotherapy		Concurrent chemo-RT		Consolidation chemotherapy	
	Paclitaxel-carboplatin	Gemcitabine-cisplatin	Paclitaxel-carboplatin	Gemcitabine-cisplatin	Paclitaxel-carboplatin	Gemcitabine-cisplatin
Total number of cycles	135	153	Cisplatin-315	Cisplatin-450	172	231
Mean number of cycles per patient	2.5±0.13	1.9±0.14	5.8±0.32	5.7±0.22	2.5±0.18	2.5±0.18
Dose intensity (mg)	Paclitaxel-315±35 Carboplatin-450±90	Gemcitabine-2000±160 Cisplatin-100±20	Cisplatin-40	Cisplatin-40	Paclitaxel-260±20 Carboplatin-450±100	Gemcitabine-1500±500 Cisplatin-80±15

RT=Radiotherapy

respectively [Table 3]. On close examination, we observed more ORR in arm B for squamous cell histology (ORR - 73.3%) as compared to that observed in arm A (ORR - 41%) [Table 4]. Last survival analysis was performed on June 2015 with a median follow-up of 21 months. The survival rates at 1 year, 2 year, and 3 year were 67% and 71%, 32% and 38%, and 19% and 24%, respectively, for arm A and arm B.

Toxicity

We mainly reported clinically significant >Grade 2 (Gr 2) toxicities as worst toxicity experienced after the entire treatment in each arm. Patients in arm B experienced more >Gr 2 hematological toxicities with 23% experiencing >Gr 2 thrombocytopenia in arm B as opposed to 10% in arm A. Moreover, patients in arm B frequently required granulocyte-colony stimulating factor support. Similarly, we observed high rates of gastrointestinal toxicities in arm B. More patients in arm B developed >Gr 2 esophagitis requiring parenteral nutrition support as compared to those in the paclitaxel-carboplatin arm [Table 5].

Table 3: Response analysis

	After induction chemotherapy		After concurrent chemo-RT		After consolidation chemotherapy	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
CR	0	2	2	3	2	4
PR	3	8	15	21	21	29
Stable disease	45	60	31	39	22	25
Progressive disease	2	1	1	3	4	8
Not available for analysis	4	7	5	12	5	12
ORR (%)	5.6	12.9	31.5	30.8	42.7	42.3

n=Number of patients; ORR=Overall response rate; CR=Complete response; PR=Partial response

Table 4: Response analysis based on histology

	CR/PR/ORR (%)	
	Paclitaxel-carboplatin	Gemcitabine-cisplatin
Squamous cell carcinoma	0/9/41	3/19/73.3
Adenocarcinoma	2/12/43.8	1/10/24

ORR=Overall response rate; CR=Complete response; PR=Partial response

Table 5: Greater than Grade 2 toxicity experienced after the entire treatment

	Paclitaxel-carboplatin	Gemcitabine-cisplatin
Neutropenia	12	23
Thrombocytopenia	5	17
Anemia	3	10
Nausea	5	17
Vomiting	3	11
Diarrhea	2	3
Esophagitis	9	20
Dyspnea	5	6

DISCUSSION

NSCLC is a biologically and clinically heterogeneous disease. Although local control is important, is still not sufficient enough to significantly improve outcomes. A good proportion of patients with locally advanced NSCLC has systemic disease at diagnosis, thereby leading to poor long-term survival rates with local modalities like RT alone or surgery. Strategies to improve outcomes in this subset of patients have mainly resulted in usage of more effective systemic treatments in the form of induction or consolidation treatments.

Although neither of the two strategies used alone, i.e., induction chemotherapy followed by concurrent chemo-RT or concurrent chemo-RT followed by consolidation chemotherapy, has shown any significant difference in various trials,[6] there is limited data on these two strategies being used together. In a setup like ours, where there is a long waiting list for RT, patients are usually prescribed 2–3 cycles of chemotherapy pending RT. Moreover, patients are referred to us by local/government practitioners, after being given 1–2 cycles of chemotherapy, for RT. Usually,

combinations of paclitaxel-carboplatin or gemcitabine-cisplatin are mainly in use.

Through this study, we observed ORRs of 42.7% and 42.3%, respectively, in paclitaxel-carboplatin and gemcitabine-cisplatin arms after completion of treatment. Two and 3 years' survival rates of 32% and 19% in paclitaxel-carboplatin arm and corresponding rates of 38% and 24% in gemcitabine-cisplatin arm were observed.

Senan *et al*.[7] while comparing the toxicity of involved field chemo-RT with either induction or consolidation chemotherapy reported 1 year survival rates of 63.2% and 65.5% with induction and consolidation arms, respectively, with median overall survival for all eligible patients being 28 months. In a recent trial by Fournel *et al*.,[8] the authors reported ORR of 58% and 56%, respectively, in induction and consolidation arms with 2 year and 4 year survival rates of 42% and 21% in induction arm, and 40% and 30% in consolidation arm.

Although we also obtained similar results in our study, none of the studies mentioned above segregated their results based on the type of histology. We interestingly recorded a better ORR in the gemcitabine-cisplatin arm for patients with squamous cell NSCLC as compared to those treated with the paclitaxel-carboplatin combination (73.3% vs. 41%). In contrast, there was a trend to better ORR with the paclitaxel-carboplatin combination in patients with adenocarcinoma histology (43.8% vs. 24%). Scagliotti *et al*.[9] in a phase three randomized trial found significantly better improvement in survival in patients with squamous cell histology treated with the cisplatin-gemcitabine combination (10.8 months) versus those treated with cisplatin-pemetrexed (9.4 months). They hypothesized overexpression of thymidylate synthetase and S-phase kinase-associated protein (Skp2) in squamous cell NSCLC as a possible explanation for reduced sensitivity to pemetrexed.

Although we observed modest improvement in survival with gemcitabine-cisplatin as compared to paclitaxel-carboplatin arm at 3 years, the results might have been influenced by various factors mainly the inclusion of six stage 2 patients in gemcitabine-cisplatin arm while there were none in paclitaxel-carboplatin arm. Moreover, the inclusion of proportionately more patients with good performance status (0 or 1) in gemcitabine-cisplatin arm. However, patients treated with gemcitabine-cisplatin required more supportive care interventions, i.e., parenteral nutrition, hematopoietic growth factors, and blood transfusions.

CONCLUSION

To conclude both paclitaxel-carboplatin and gemcitabine-cisplatin combinations can be used as induction and consolidation therapy in NSCLC patients. Although the survival rates are slightly better in the gemcitabine-cisplatin arm, this comes at clinically more frequent and relevant toxicities with the gemcitabine-cisplatin combination. The retrospective, nonrandomized nature of this trial should be taken into account while interpreting the results with the potential for selection bias that must also be acknowledged.

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Conflicts of interest

There are no conflicts of interest.

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