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Original Research Article

EVALUATION OF RESPONSE AND TOXICITY IN PATIENTS RECEIVING NACT WITH PLATINUM+ TAXANE VS PLATINUM+ TAXANE+ 5FU FOR HEAD AND NECK SQUAMOUS CELL CARCINOMAS.

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ABSTRACT

Background: Evaluation of Response and Toxicity in Patients Receiving NACT with Platinum + Taxane Vs Platinum+Taxane+5FU for Head and Neck Squamous Cell Carcinomas.

Materials and Methods: The present longitudinal observation study was conducted in Department of Radiation oncology, Gandhi Medical College and associated Hamidia Hospital (GMC & HH), Bhopal (M.P) and Jawaharlal Nehru Cancer Hospital (JNCH), Bhopal (M.P), on a total of 54 patients of Head and Neck Squamous Cell Carcinoma from 1st July 2022 to 31st December 2023, a period of 18 months. Fifty-four patients were randomized into two groups, receiving either TPF or TP regimens Responses were assessed using RECIST 1.1 criteria, and toxicities were evaluated using CTCAE v5.0.

Results: Partial responses were observed in 65% and 48% of patients in the TPF and TP groups, respectively. Grade 3-4 toxicities, including hematological and gastrointestinal events, were more frequent in the TPF group (72%) compared to the TP group (41%).

Conclusion: While the TPF regimen demonstrated superior response rates, it was associated with higher toxicity. The TP regimen may be preferred for patients with poor performance status or significant comorbidities.

Keywords: Neoadjuvant therapy, chemotherapy, squamous cell carcinoma, oral cavity

INTRODUCTION

Globally, head and neck cancer (HNC) ranks as the seventh most prevalent cancer, being the fifth most common among men and the twelfth among women, with approximately 900,000 new cases and 420,000 fatalities reported in 2020.[1]

Head and neck cancer in India are characterized by a distinct demographic profile, unique risk factors, specific dietary habits, and varied family and personal histories.[2]

HNCs originate from squamous cells in the mucosal epithelium of the head and neck region, and are classified based on their anatomical location. Head and neck squamous cell carcinoma (HNSCC) encompasses malignancies of the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx.[3]

The head and neck region comprises several delicate and intricately organized structures essential for fundamental physiological functions, appearance, expression, and social interaction. The quality of life may be further diminished by treatments for head and neck tumours, which can result in additional disfigurement.[4]

Research efforts are now focused on developing new agents/technology/regimen that are well-tolerated and effective in treating HNSCC, aiming to enhance anti-tumour immunity, inhibit tumour angiogenesis,

or directly inhibit tumour cell proliferation and survival.[5]

Concomitant chemoradiation therapy (CRT) is now regarded as the standard of care for all sub-sites of head and neck squamous cell carcinoma, except for the oral cavity. The MACH-NC meta-analysis from 2004 and its 2009 update confirmed the superiority of CRT over radiotherapy (RT) alone in terms of overall survival (OS), with concurrent therapy proving more effective than neoadjuvant approaches.[6]

Following the publication of the TAX323 and TAX324 trials, which incorporated taxanes into induction regimens alongside fluorouracil and a platinum agent, there was a renewed interest in using neoadjuvant chemotherapy (NACT) for advanced head and neck cancers. Although both trials demonstrated the superiority of the three-drug regimens over the two-drug regimens, they did not compare the efficacy of NACT against concurrent chemoradiation therapy (CRT).[7]

MATERIALS AND METHODS

The present longitudinal observation study was conducted in Department of Radiation oncology, Gandhi Medical College and associated Hamidia Hospital (GMC & HH), Bhopal (M.P) and Jawaharlal Nehru Cancer Hospital (JNCH), Bhopal (M.P), on a total of 54 patients of Head and Neck Squamous Cell Carcinoma from 1st July 2022 to 31st December 2023, a period of 18 months.

Sample Size: The sample size was calculated using the following formula

$N = z^2pq/d^2$

With a prevalence of 0.02 percent, the sample size was approximately 48. Including an additional 10% for non-responsive patients, the total sample size was 54, with 27 patients in each arm receiving NACT with Platinum + Taxane and NACT with Platinum + Taxane + 5FU.

Inclusion Criteria

- Histopathologically confirmed case of Head and Neck Squamous
- Cell Carcinoma
- Patients who gave consent for the study
- KPS score ≥ 70
- Patients of age group 18yr to 60yr
- Patients with Stage 3 and 4 Head and Neck Squamous Cell
- Carcinoma
- Patients who have not received any treatment for the cancer previously.

Exclusion Criteria

- Chronically ill patients
- Patients who do not give consent for the study
- KPS score < 70
- Patients below 18yr age and above 60yr age
- Patients with Stage 1 and 2 Head and Neck Squamous Cell Carcinoma
- Patient with any other comorbidities
- Patients who have received any treatment for the cancer previously.

RESULTS

[Table 1] compares the age distribution between two drug regimens: Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP). In the TPF group, the median age was 44 years, while in the TP group, it was 49 years. The average rank for the TPF group was 31.1852, and for the TP group, it was 23.8148. The P-value was 0.0848, indicating no statistically significant difference in age distribution between the two groups and were comparable.

Table 1: Distribution of Study Population between two groups according to Age

Drug Regimen				
		Taxane + Platinum + 5FU-(TPF)	**Taxane + Platinum-(TP)**	**P Value**
Age (year)	N	27	27	
	Median	44	49	0.0848
	Average Rank	31.1852	23.8148	

Table 2: Distribution of Study Population between two groups according to Sex

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		**Taxane + Platinum-(TP)**		**P Value**
Sex	**N**	**%**	**N**	**%**	
Female	3	11.11%	0	0.00%	
Male	24	88.89%	27	100.00%	0.4479
All	27	100.00%	27	100.00%	

[Table 2] compares the sex distribution between two drug regimens: Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP). In the TPF group, 11.11% (3 out of 27) of the participants were female, and 88.89% (24 out of 27) were male. In the TP group, all participants were male, accounting for 100% (27 out of 27). The P-value was 0.4479, indicating no statistically significant difference in sex distribution between the two groups.

Table 3: Distribution of Study Population between two groups according to Addiction

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		**Taxane + Platinum-(TP)**		**P Value**
Addiction	**N**	**%**	**N**	**%**	
Tobacco	7	25.93%	4	14.81%	0.3153

Tobacco, Smoking	20	74.07%	23	85.19%	
All	27	100.00%	27	100.00%	

[Table 3] compares the addiction distribution between two drug regimens: Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP). In the TPF group, 25.93% (7 out of 27) of the participants were addicted to tobacco, while 74.07% (20 out of 27) were addicted to both tobacco and smoking. In the TP group, 14.81% (4 out of 27) of the participants were addicted to tobacco, whereas 85.19% (23 out of 27) were addicted to both tobacco and smoking. The P-value was 0.3153, indicating no statistically significant difference in addiction distribution between the two groups.

Table 4: Distribution of Study Population between two groups according to Stage

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		**Taxane + Platinum-(TP)**		**P Value**
Stage	**N**	**%**	**N**	**%**	
III	1	3.70%	4	14.81%	
IVA	17	62.96%	17	62.96%	0.3012
IVB	9	33.33%	6	22.22%	
All	27	100.00%	27	100.00%	

[Table 4] compares the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), according to cancer stage. In the TPF group, the distribution of stages was as follows: Stage III (1, 3.70%), Stage IVA (17, 62.96%), and Stage IVB (9, 33.33%). In the TP group, the distribution of stages was as follows: Stage III (4, 14.81%), Stage IVA (17, 62.96%), and Stage IVB (6, 22.22%). The P-value was 0.3012, indicating no statistically significant difference in stage distribution between the two groups.

Table 5: Distribution of Study Population between two groups according to Grade

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		**Taxane + Platinum-(TP)**		**P Value**
Grade	**N**	**%**	**N**	**%**	
1	12	44.44%	11	40.74%	
2	14	51.85%	14	51.85%	0.8283
3	1	3.70%	2	7.41%	
All	27	100.00%	27	100.00%	

[Table 5] compares the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), according to cancer grade. In the TPF group, the distribution of grades was as follows: Grade 1 (12, 44.44%), Grade 2 (14, 51.85%), and Grade 3 (1, 3.70%). In the TP group, the distribution of grades was as follows: Grade 1 (11, 40.74%), Grade 2 (14, 51.85%), and Grade 3 (2, 7.41%). The P-value was 0.8283, indicating no statistically significant difference in grade distribution between the two groups.

Table 6: Distribution of Study Population between Two groups According to Response Assessment

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		**Taxane + Platinum-(TP)**		**P Value**
Response Assessment	**N**	**%**	**N**	**%**	
Complete Response	5	18.52%	2	7.41%	
Partial Response	19	70.37%	12	44.44%	0.0266
Progressive Disease	2	7.41%	7	25.93%	
Stable Disease	1	3.70%	6	22.22%	
All	27	100.00%	27	100.00%	
	0.89		0.44		
Overall Response Rate	Incidence rate difference				0.0455
	Incidence rate ratio				0.0470

[Table 6] shows the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), based on response assessment. In the TPF group, 5 patients (18.52%) achieved a complete response, while in the TP group, 2 patients (7.41%) achieved a complete response. A partial response was observed in 19 patients (70.37%) in the TPF group, compared to 12 patients (44.44%) in the TP group. Progressive disease occurred in 2 patients (7.41%) in the TPF group and 7 patients (25.93%) in the TP group. Stable disease was noted in 1 patient (3.70%) in the TPF group and 6 patients (22.22%) in the TP group. The p-value of 0.0266 indicates a statistically significant difference in response assessment between the two groups. The overall response rate was 0.89 for the TPF group and 0.44 for the TP group, with a p-value of 0.0470 and 0.0455 for the incidence rate difference and the incidence rate ratio respectively indicating significant difference of the overall response rate between two regimens.

Table 7: Distribution of Study Population between two groups according to Assessment of Anemia

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		Taxane + Platinum-(TP)		P Value
Anemia	**N**	**%**	**N**	**%**	
Grade 1	19	70.37%	22	81.48%	
Grade 2	8	29.63%	5	18.52%	0.3441
All	27	100.00%	27	100.00%	

[Table 7] compares the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), according to haematological anemia toxicity assessment. In both groups, Grade 1 anemia was predominant: 70.37% in the TPF group and 81.48% in the TP group. Grade 2 anemia accounted for 29.63% in the TPF group and 18.52% in the TP group. The P-value was 0.3441, indicating no statistically significant difference in the distribution of anemia grades between the two groups.

Table 8: Distribution of Study Population between two groups according to Assessment of Neutropenia

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		Taxane + Platinum-(TP)		P Value
Neutropenia	**N**	**%**	**N**	**%**	
Grade 1	4	14.81%	19	70.37%	< 0.0001
Grade 2	23	85.19%	8	29.63%	
All	27	100.00%	27	100.00%	

[Table 8] examines the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), based on haematological neutropenia toxicity assessment. In the TPF group, Grade 2 neutropenia was predominant, accounting for 85.19%, while Grade 1 neutropenia accounted for 14.81%. In the TP group, Grade 1 neutropenia was predominant, comprising 70.37%, while Grade 2 neutropenia accounted for 29.63%. The P-value was < 0.0001, indicating a statistically significant difference in the distribution of neutropenia grades between the two groups.

Table 9: Distribution of Study Population between two groups according to Assessment of Vomiting

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		Taxane + Platinum-(TP)		P Value
Vomiting	**N**	**%**	**N**	**%**	
Grade 0	10	37.04%	6	22.22%	
Grade 1	17	62.96%	17	62.96%	0.0821
Grade 2	0	0.00%	4	14.81%	
All	27	100.00%	27	100.00%	

[Table 9] compares the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), according to gastrointestinal vomiting toxicity assessment. In both groups, Grade 1 vomiting was predominant: 62.96% in both the TPF and TP groups. Grade 0 vomiting accounted for 37.04% in the TPF group and 22.22% in the TP group. Grade 2 vomiting was present in 14.81% of participants in the TP group, while no participants in the TPF group experienced Grade 2 vomiting. The P-value was 0.0821, suggesting no statistically significant difference in the distribution of vomiting grades between the two groups, although a trend towards significance was observed.

Table 10: Distribution of Study Population between two groups according to Assessment of Diarrhea

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		Taxane + Platinum-(TP)		P Value
Diarrhea	**N**	**%**	**N**	**%**	
Grade 0	6	22.22%	15	55.56%	
Grade 1	6	22.22%	12	44.44%	
Grade 2	12	44.44%	0	0.00%	0.0001
Grade 3	3	11.11%	0	0.00%	
All	27	100.00%	27	100.00%	

[Table 10] compares the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), based on gastrointestinal diarrhea toxicity assessment. In the TPF group, Grade 0 diarrhea accounted for 22.22%, Grade 1 diarrhea for 22.22%, Grade 2 diarrhea for 44.44%, and Grade 3 diarrhea for 11.11%. In the TP group, Grade 0 diarrhea accounted for 55.56%, Grade 1 diarrhea for 44.44%, and no participants experienced Grade 2 or Grade 3 diarrhea. The P-value was 0.0001, indicating a statistically significant difference in the distribution of diarrhea grades between the two groups.

Table 11: Distribution of Study Population between two groups according to Nephrotoxicity Assessment

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		Taxane + Platinum-(TP)		P Value
Nephrotoxicity	N	%	N	%	
Grade 0	14	51.85%	12	44.44%	
Grade 1	11	40.74%	13	48.15%	0.8519
Grade 2	2	7.41%	2	7.41%	
All	27	100.00%	27	100.00%	

[Table 11] compares the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), according to nephrotoxicity assessment. In both groups, Grade 0 nephrotoxicity was predominant: 51.85% in the TPF group and 44.44% in the TP group. Grade 1 nephrotoxicity accounted for 40.74% in the TPF group and 48.15% in the TP group. Grade 2 nephrotoxicity was observed in 7.41% of participants in both the TPF and TP groups. The P-value was 0.8519, indicating no statistically significant difference in the distribution of nephrotoxicity grades between the two groups.

Table 12: Distribution of Study Population between two groups according to Hepatotoxicity Assessment

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		Taxane + Platinum-(TP)		P Value
Hepatotoxicity	N	%	N	%	
Grade 0	11	40.74%	7	25.93%	0.1409
Grade 1	16	59.26%	17	62.96%	
Grade 2	0	0.00%	3	11.11%	
All	27	100.00%	27	100.00%	

[Table 12] compares the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), according to hepatotoxicity assessment. In both groups, Grade 1 hepatotoxicity was predominant: 59.26% in the TPF group and 62.96% in the TP group. Grade 0 hepatotoxicity accounted for 40.74% in the TPF group and 25.93% in the TP group. Grade 2 hepatotoxicity was observed in 11.11% of participants in the TP group, while no participants in the TPF group experienced Grade 2 hepatotoxicity. The P-value was 0.1409, indicating no statistically significant difference in the distribution of hepatotoxicity grades between the two groups.

Table 13: Distribution of Study Population between two groups according to Fatigue Assessment

	Drug Regimen				
	Taxane + Platinum + 5FU-(TPF)		Taxane + Platinum-(TP)		P Value
Fatigue	N	%	N	%	
Grade 1	8	29.63%	8	29.63%	
Grade 2	13	48.15%	11	40.74%	0.7976
Grade 3	6	22.22%	8	29.63%	
All	27	100.00%	27	100.00%	

[Table 13] compares the distribution of the study population between two drug regimens, Taxane + Platinum + 5FU (TPF) and Taxane + Platinum (TP), based on fatigue toxicity assessment. In the TPF group, Grade 1 fatigue accounted for 29.63%, Grade 2 fatigue for 48.15%, and Grade 3 fatigue for 22.22%. In the TP group, Grade 1 fatigue accounted for 29.63%, Grade 2 fatigue for 40.74%, and Grade 3 fatigue for 29.63%. The P-value was 0.7976, indicating no statistically significant difference in the distribution of fatigue grades between the two groups.

DISCUSSION

Head and neck cancer (HNC) represents a major public health challenge in India, primarily due to the prevalent practice of tobacco chewing, especially among men.[8] However, in instances where surgery is not feasible, often due to the advanced stage of the disease, the focus shifts to non-surgical care. Concurrent chemoradiation has been employed as a treatment modality but has demonstrated limited efficacy, with a median progression-free survival of 6.4 months.

The use of neoadjuvant chemotherapy is under investigation to potentially minimize the extent of surgical resection, improve loco-regional control, and reduce distant metastasis. This strategy should enhance treatment outcomes by decreasing the mortality and morbidity associated with OSCC management.[9]

Due to the high consumption of tobacco products among the male population in India, HNSCCs are more common in males than females.

In the response assessment, the TPF group exhibited a complete response in 5 patients (18.52%), whereas the TP group showed a complete response in 2 patients (7.41%). A partial response was observed in 19 patients (70.37%) within the TPF group, compared to 12 patients (44.44%) in the TP group. Progressive disease was noted in 2 patients (7.41%) from the TPF group and 7 patients (25.93%) from the TP group. Stable disease occurred in 1 patient (3.70%) in the TPF group and 6 patients (22.22%) in the TP group. The p-value of 0.0266 suggests a

statistically significant difference in response assessment between the two groups.

The overall response rate was 0.89 for the TPF group and 0.44 for the TP group, with a p-value of 0.0470 for the incidence rate difference and 0.0455 for the incidence rate ratio, indicating a significant difference in the overall response rate between the two regimens. Our study findings align with those reported by Kish et al,[10] who documented an overall response rate of 70% and a complete response rate of 27% in 30 patients with recurrent and disseminated SCCHN treated with cisplatin and infusional 5-FU.

In the toxicity assessment, haematological anemia toxicity revealed that Grade 1 anemia was most common: 70.37% in the TPF group and 81.48% in the TP group. Grade 2 anemia was observed in 29.63% of the TPF group and 18.52% of the TP group. The P-value of 0.3441 indicates no statistically significant difference in the distribution of anemia grades between the two groups. Regarding neutropenia, Grade 2 neutropenia was most prevalent in the TPF group, comprising 85.19%, while Grade 1 neutropenia was 14.81%. In contrast, the TP group had a predominance of Grade 1 neutropenia at 70.37%, with Grade 2 neutropenia at 29.63%. The P-value was < 0.0001, indicating a statistically significant difference in the distribution of neutropenia grades between the two groups. For gastrointestinal vomiting toxicity, Grade 1 vomiting was predominant in both groups, occurring in 62.96% of participants in both the TPF and TP groups. Grade 0 vomiting was noted in 37.04% of the TPF group and 22.22% of the TP group. Grade 2 vomiting was present in 14.81% of the TP group, while no participants in the TPF group experienced Grade 2 vomiting. The P-value was 0.0821, suggesting no statistically significant difference in the distribution of vomiting grades between the two groups, though a trend towards significance was observed.

However, our study observed higher toxicity compared to previous trials. In TAX 324, grade 3 and 4 neutropenia occurred in 8% of patients, with no instances of grade 3 and 4 thrombocytopenia.[11] Our findings partially align with TAX 324, where grade 3 and 4 neutropenia rates were 83% in the TPF regimen and 56% in the PF regimen, while grade 3 and 4 thrombocytopenia rates were 11% and 4%, respectively. This difference could be attributed to dose reductions in patients experiencing side effects and the predominance of two-drug combinations in our cohort. These results suggest that the regimen is generally well-tolerated, causing modest immunosuppression with uncomplicated recovery in patients. The regimen demonstrates promising response rates and enhances resectability with acceptable toxicity, underscoring its potential for further investigation in head and neck cancer. Moreover, these findings highlight the need for further exploration of two-drug combinations of taxane and platinum as potential replacements for the three-drug combinations currently used.

CONCLUSION

The regimen incorporating drugs such as platinum, taxanes, and 5-fluorouracil (5-FU) demonstrates robust efficacy with comparable response rates to established treatments in head and neck cancer. Despite higher observed toxicity compared to some previous trials, particularly in hematological adverse events, the regimen generally proves tolerable with manageable immunosuppression and favorable recovery profiles. These findings support further investigation of two-drug combinations involving taxane and platinum as potential alternatives to current three-drug regimens, aiming to optimize therapeutic outcomes while minimizing treatment-related complications in this patient population. Further study has to be carried regarding the overall treatment by adding other modalities of treatment like surgery and radiotherapy.

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