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Carboplatin and Paclitaxel as Induction Chemotherapy in Locally Advanced Head and Neck Cancer Patients

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Abstract: *Head and neck malignancies constitute about 3% of all newly diagnosed cancers in humans. Overall, 57.7% of global head and neck cancers occur in Asia, especially in India, for both sexes. Previously standard approach for locally advanced head and neck cancers was surgery followed by external beam radiation therapy(EBRT). Other approach was CRT i.e. concomitant chemotherapy and radiotherapy but systemic relapse was seen more by this approach due to a lack of systemic control. For this reason nowadays incorporation of induction chemotherapy is done in treatment of locally advanced head and neck cancers. Our study is a retrospective study done in 250 patients with locally advanced head and neck cancers. These patients were given carboplatin and paclitaxel as induction chemotherapy and the response of the patients and adverse effects of the drugs were noted.*

Keywords: *Induction chemotherapy, head and neck cancers, carboplatin, paclitaxel*

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I. Introduction

Head and neck cancers in India are emerging as major public health problem, which are lifestyle related, have a lengthy latent period and need dedicated infrastructure and human resource for treatment.

Head and neck malignancies account for 30% of all cancers in males. Over 200,000 cases of cancers occur each year in India. Nearly 80,000 oral cancers are diagnosed every year in our country. In India 60 to 80% of these patients present with advanced and inoperable diseases. Around 40,000 cases of pharyngeal cancers excluding nasopharyngeal cancers (31% of global cases) and nearly 29,000 cases of laryngeal cancers (18% of global cases) occur in India every year. In our state, Madhya pradesh , Bhopal region has the world's highest standardized incidence of both tongue(10.9) and oral cavity(9.6) in males. In India 60 to 80% of these patients present with advanced and inoperable diseases.[1]

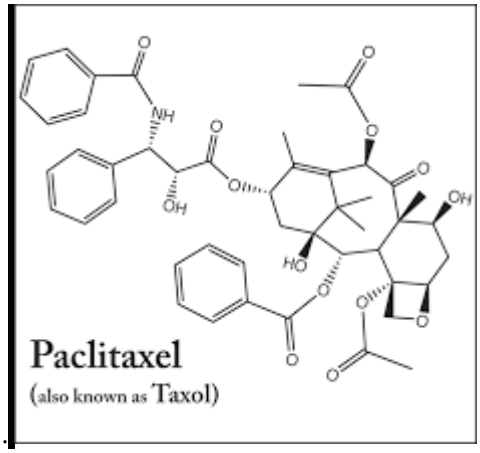
Oral squamous cell carcinoma is the most common type of tumor in the oral cavity.[2] The majority of the tumors are locally advanced and have relatively poor prognosis with 5 year survival of <50-60%.[3,4,5]

Advanced loco regional disease, defined as either non metastatic stage III or stage IV, is the most frequent clinical situation appearing in 60% of the diagnosed patients. For the loco regional disease, an acceptable option is a local treatment based on surgery and/or radiotherapy (RT). On the other hand, in the treatment of unresectable loco regionally advanced SCCHN (squamous cell carcinoma head and neck) the principal treatment in most institutions is the combined-modality treatment with chemo radiotherapy (CRT) if the patient is medically fit. During the last years, this last approach has become the standard treatment for most clinicians.[6] But retrospective studies have shown that in patients treated with concurrent or concomitant chemotherapy (chemotherapy given at the same time

as radiotherapy), there was an increase in systemic relapse due to a lack of systemic control. To this regard, a renewed interest has appeared for the use of induction chemotherapy (chemotherapy given before radiotherapy).

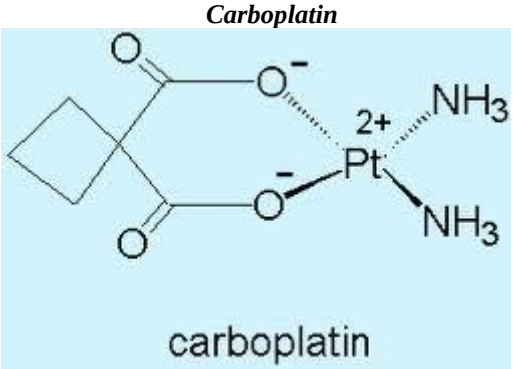
Our study is a retrospective study done in patients who received carboplatin and paclitaxel as induction chemotherapy.

Paclitaxel



Paclitaxel belong to the group anti-microtubule agents i.e. Taxanes, they have a broad anti-tumour activity and are derived from the bark of the Pacific Yew Tree Taxus Brevifolia. The Taxane rings of Paclitaxel are limited to an ester side chain attached to C13 position of the ring, which is essential for anti-microtubule and anti-tumour activity .Paclitaxel bind to microtubule, promotes microtubule assembly and resistance to depolymerization resulting in production of non-functional microtubules.

Carboplatin



Carboplatin belong to the group Platinum compounds. Carboplatin , produces predominantly interstrand DNA crosslinks.

AIMS AND OBJECTIVES

1.To evaluate the response of paclitaxel and carboplatin in combination as induction chemotherapy.
2.To evaluate the adverse effects / toxicities of induction chemotherapy.

II. Material And Methods

A retrospective analysis was conducted in department of radiotherapy, SSMC, Rewa, M.P. In this analysis 250 patients of locally advanced Head and Neck cancer were analysed .

Inclusion criteria

(a) Patients of either sex.
(b)Age less than or equal to 60 years.
(c) Patients who had not undergone surgical treatment.
(d) Patients with positive histopathology report(squamous/adenocarcinoma) .
(e) patients who received chemotherapy paclitaxel and carboplatin in combination.
(f) stage III to IV disease.

Exclusion Criteria

(a)patients of previous surgery
(b)patients of carcinoma in situ, stage I and II disease
(c)patients who received chemotherapy other than paclitaxel and carboplatin(ex.cisp+5fu,doce+cisp+5fu)

(d) age>60 years

Parameters of Study

(1)Response :-The response will be described as either –

(a)Complete response – No evidence of the pretreatment tumor and symptoms and no recurrence within one month.

(b)Partial response - More than 50% of regression of loco –regional disease.

(c)Stable disease- Less than 50% regression or no regression at all

(d) Progresive disease - Increase in the size of growth during treatment.

(2)Adverse Effects:-Toxicities like myelosuppression, nausea, vomiting and alopecia were evaluated. Common toxicities were graded on the basis of WHO toxicity criteria.

III. Observations & Results

The observations are recorded from the files of registered patients.

Total no. of males was 201 while 49 were females.

Maximum no. of patients were in their 5^{th} decade(50-60 years)-60% patients.

Patients from rural areas were approx. 60%(150) while urban area people were 40%(100).

The most common site of malignancy was oral cavity(49.6%) followed by oropharynx (16.4%) and least common site was nasopharynx(6%) [Table 1]

Table 1 : Distribution of patients according to site of primary disease

Site	No.of patients	Percentages
Neck	22	8.8%
Oral cavity	124	49.6%
Nasopharynx	6	2.4%
Oropharynx	41	16.4%
Hypopharynx	17	6.8%
Larynx	34	13.6%
Nasal cavity,PNS	6	2.4%
Total	250	100%

Maximum no. of patients presented with stage III carcinoma(57.6%) followed by stage IVA disease(29.2%). Only 1 patient presented with stage IV C(Table 2)

Table 2: Distribution of patients according to stage

Stage	No.of patients	Percentages
III	144	57.6%
IVA	73	29.2%
IVB	32	12.8%
IVC	1	0.4%
Total	250	100%

Table 3: Distribution of patients according to response

Response	No.of patients	Percentages
Complete response	84	33.6%
Partial response	101	40.4%
Stable disease	25	10%
Progressive disease	40	16%
Total	250	100%

Of the 250 patients studied, 101(40.4%) showed partial response, 84 patients (33.6%) showed complete response, 25 patients (10%) persisted with stable disease and 40 patients showed progressive disease.

Table4: Adverse effects observed during Induction Chemotherapy

Side effects observed	No. of patients	Percentage(%)
Haematological toxicity	240	96
Neurosensory toxicity	90	36
G.I. tract toxicity	235	94
Alopecia	132	52.8

Maximum no. of patients(96%) showed haematological toxicity (anaemia, neutropenia and thrombocytopenia). Approx. 94% patients(235 patients) showed gastrointestinal toxicity (nausea, vomiting and diarrhea).Hair loss was seen in 52.8% of the total patients while neurosensory toxicity (peripheral sensory neuropathy) was seen in 90 patients which is 36% of the total patients.There were no other side effects noted.

IV. Discussion And Conclusion

Both induction chemotherapy and chemoradiotherapy provide clinical benefit in the treatment of locally advanced head and neck cancer. Induction chemotherapy can significantly reduce local disease prior to definitive radiation and/or surgery, potentially permitting preservation of organ function and appearance. Induction therapy is also effective in controlling distant disease.[7,8,9] With the use of chemotherapeutic agents as radiation sensitizers, chemoradiotherapy increases locoregional treatment intensity and disease control but ostensibly is not as effective as induction therapy in managing distant disease.[10,11,12,13,14]

The rationale underlying the use of an induction treatment plan is based on two hypotheses. One involves the better delivery of the drug in untreated, well-vascularized tumors and the second involves the eradication of the micrometastatic disease with systematically active doses of chemotherapy. In addition, the patient who is treatment-naïve is possibly more tolerant of the adverse effects of the chemotherapy treatment than the patient who has been irradiated.

The use of both induction chemotherapy and chemoradiotherapy in a sequential approach may provide optimal benefit for patients with locally advanced head and neck cancer.[15,16]

Induction chemotherapy with paclitaxel and carboplatin followed by chemoradiotherapy has been evaluated in trials conduced at the University of Chicago [17], the Sarah Cannon Cancer Center [18], and the Vanderbilt-Ingram Cancer Center [19]. Toxicities, particularly during chemoradiotherapy, were high, but overall survival rates appear promising. At Brown University, an outpatient weekly induction regimen of paclitaxel, carboplatin, and ifosfamide (IfexR; Bristol-Myers Squibb) followed by chemoradiotherapy produced very high response rates, though longer follow-up is needed to determine survival.[20]

Patil et al. published a retrospective study of 123 patients with technically unresectable locally advanced oral cavity cancers. Unresectibility in these cases was defined as disease reaching up to the zygoma and/or soft tissue swelling up to the zygoma, extensive soft tissue involvement reaching up to the hyoid cartilage, extensive skin infiltration, and the involvement of the infratemporal fossa. The patients were given NACT with TPF or TP and assessed for resectibility. The response rate with the three drug and two drug regimens was 32.00% and 27.37%, respectively. Resectability was achieved in 17 patients with 3 drug regimen (68.00%) and 36 patients with 2 drug regimen (37.89%). The estimated median overall survival(OS) was 12.7 months.

The estimated median survival was not reached for patients undergoing post chemotherapy resection. This was statistically significant compared to patients treated with nonsurgical modalities post chemotherapy. The estimated median OS in these patients was 8 months ($P = 0.0001$). They demonstrated the effectiveness of NACT in down-staging tumors and enabling radical surgery with comparable 2 years survival to primary surgery.[21]

In the phase III trial reported by Vermorken et al, (TAX 323)[22] presented at ASCO 2004, 358 patients with unresectable disease were treated with docetaxel, cisplatin and 5-Fu (DPF) or cisplatin and 5- FU (PF), followed by radiotherapy. This study was updated and recently published with a median follow up of 32.5 months. The DPF regimen resulted in a significantly higher disease free survival(11.0 months vs. 8.2 months) and OS i.e. overall survival (18.8 months vs. 14.5 months). This study showed the superiority of DPF in terms of not only survival, but also quality of life.

Another randomized phase III trial conducted by Calais et al,[23] presented at ASCO 2006 showed significant improvement in the response rate with the addition of a taxane along with 5-fluorouracil and cisplatin. Patients with locally advanced cancer of the larynx or hypopharynx were treated with cisplatin and 5-Fu with or without docetaxel, followed by radiotherapy alone for responders or total laryngectomy with neck dissection and postoperative radiotherapy for non responders. The overall response rate was significantly higher with DPF (82% vs. 60%) and more patients with DPF were able to avoid undergoing laryngectomy compared with patients receiving PF (73% vs. 63%).

In a phase III study conducted by Hitt et al,[24] 383 patients were randomized to receive three cycles of paclitaxel and cisplatin and 5-FU (TPF) in one arm, or cisplatin and 5-FU (PF) in the other arm, followed by cisplatinum based CRT. Resectable and unresectable patients were included (66% resectable vs. 33% unresectable). The primary objective was objective response. CR was observed in 33% in the TPF arm compared with 14% in the PF arm ($p < 0.001$).

In the present study, we found complete response(CR) in 33.6% of the patients. This is in accordance with the studies done by Patil et al[21] and Hitt et al[24].

The toxicities seen with induction chemotherapy (haematological, G.I. toxicity, alopecia, peripheral neuropathy) were of mostly grade I which were easily manageable. Thus, carboplatin and paclitaxel are well tolerated, safe and efficient agents for induction chemotherapy in locally advanced head and neck cancer patients.

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