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Neo-adjuvant Chemotherapy with Cisplatin & Vinorelbine Followed by Radical Radiotherapy in Locally Advanced Head & Neck Cancers-An Experience From Regional Cancer Center, Raipur, India.

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Abstract:
Background: *Head and neck cancer are very common in India, and most of the patients present with loco-regionally advanced disease. Combination of radical surgery and radiotherapy with or without chemotherapy is the standard management. However therapeutic results are poor with this modality. Therefore neoadjuvant chemotherapy and locoregional management by radiotherapy and/or surgery have emerged as a feasible alternative.*
Methods: *30 patients with locally advanced head and neck cancer, from August 2009 to September 2010, treated with three cycle of neoadjuvant chemotherapy (NACT) using Cisplatin (80 mg/m^2 D1) and Vinorelbine (25 mg/m^2 D1) followed by radical radiotherapy, consisted of total dose up to 60-70 Gy by conventional fractionation schedule.*
Results: *The objective response after NACT was observed in 90% (27/30) patients, with 1 patient had complete response. After completion of radiotherapy 53.4% patients achieved complete response and 43.3% patients achieved partial response. At 6 month follow up 40% patients were disease free. Most common hematological toxicities during NACT were anemia (66.7%) and neutropenia (60%), while mucosities (46.7%) and dysphagia (30%) were most common side effects observed during radiotherapy.*
Conclusion: *The present study has shown that NACT with cisplatin and vinorelbine followed by radical radiotherapy is feasible and well tolerated by patients with locally advanced head and neck cancer. All acute toxicities with grade III & IV were managed conservatively and well. Further large randomized study is needed to judge disease free survival and overall survival.*
Keywords: *Cisplatin, Head & neck cancer, Neo-adjuvant Chemotherapy (NACT), Radiotherapy, Vinorelbine.*

I. Introduction

The incidence of head and neck cancer still continues to increase worldwide with approximately half million cases per year. Nearly 58% of the global head and neck cancer occurs only in Asia and constitute approximately 5% of all cancer worldwide (1). In India due to increased use of smoking and chewing tobaccos the head and neck cancer are very common and account for almost 30% of all cancers, moreover most of the patients present with locally or locoregionally advanced disease (2).

The most important prognostic factors for the management of the head and neck cancer is depends on the primary site, histological grade and its stage at the time of diagnosis. For early stage disease, radical radiotherapy or curative surgery are both equally effective with excellent disease control and long term survival (3, 4). While in locally advanced disease is still difficult to treat, in general resectable locorgionally advanced disease are treated with combined surgery and radiotherapy with or without chemotherapy. In more advanced tumors, as a result of their location, the radical surgery can cause varying degree of functional and cosmetic deformity that is often exacerbated by postoperative adjuvant radiotherapy. However therapeutic results are poor with this modality due to propensity for local recurrence and distant metastatic spread (5, 6).

Therefore treatment of head and neck cancer requires effective systemic treatment such as chemotherapy in addition to the standard surgical and radiation treatment. The value of adding chemotherapy to definitive surgery and/or radiotherapy in the treatment of locally advanced head and neck cancer has been evaluated extensively over the past of several decades (7, 8).

Concurrent chemoradiotherapy has now become an integral part of standard treatment of patients with locally advanced head and neck cancer. Combination of classical chemotherapeutic agents and radiotherapy have increased response rates, but the survival rates have not increased significantly, furthermore chemoradiotherapy is associated with a higher incidence of severe (grade III/IV) acute adverse events compared with radiotherapy alone (9, 10).

The chemotherapy regimens combining cisplatin with a variety of other drugs used before surgery and / or radiotherapy have shown improved overall response rates in head and neck malignancies. The increased responsiveness to chemotherapy of previously untreated patients with head and neck cancer is probably due to the presence of intact blood supply of undisturbed tumor by surgery or radiotherapy (11).

Two large landmark trials the TAX323 and TAX324 had highlighted the role of NACT in unresectable and locally advanced head and neck cancer (12, 13).

The rationally for use of an NACT is based on a possible strategy to shrink or down stage locally advanced disease, and also the eradication of micro-metastatic disease with consistently active doses of chemotherapy that may not be adequately treated by local therapy or lower dose chemotherapy as part of chemoradiotherapy, therefore ultimately improving treatment outcomes and increase organ preservation rates (14, 15). Previous studies of phase II clinical trial of NACT using combination of cisplatin and vinorelbine have demonstrated its antitumor activity in patients with recurrent or metastatic carcinoma of the head and neck (16, 17). The aim of present study is to evaluate the feasibility and outcome of tow drug NACT regimen with cisplatin and vinorelbine followed by radical radiotherapy in patients with locally advanced head and neck cancer. The primary objective of this study is assessment of disease free survival and secondary end points included assessment of toxicities and organ preservation rate.

II. Material and Methods

The present study was conducted on patients reporting to Department of Radiotherapy, Regional cancer center, Raipur (CG) India, from August 2009 to September 2010. For inclusion into the study, the patient must have fulfilled the following criteria's.

Inclusion Criteria were:

a) Patients must have histologically confirmed squamous cell carcinoma of head and neck.
b) Patients must have no prior exposure to chemotherapy, radiotherapy and surgery.
c) Age: >18 year and <=70 year.
d) Karnofsky performance status: >=70.
e) Normal values of renal and liver function test.
f) Patients must not have severe medical illness like chronic renal failure, CCF, and IHD.

After confirmation of squamous cell carcinoma of head and neck with histopathology report, complete head and neck examination has done to evaluate tumor extent (both primary and regional lymph node) by both the radiation oncologist and ENT specialist. Disease was assessed clinically by indirect/direct laryngoscopy and by CT scan whenever necessary, and staged according to American Joint Committee on Cancer (AJCC) 2002 staging system. On entering the study a written and informed consent were taken from all the patients, and received NACT with following order.

1. Injection Granisetron 3 mg, Injection Dexamethasone 8 mg, Injection Ranitidine 50 mg were employed as antiemetic, intravenously with 500 ml of normal saline before starting of chemotherapy, and oral Granisetron 1 mg twice daily for 5 days.
2. After prehydration, injection Cisplatin 80 mg/m^2 of body surface area given in 500 ml of normal saline, and then for diuresis injection Mannitol (20%) given rapidly on D1.
3. After that 1000 ml of normal saline added 20 mEq of potassium chloride and 8 mEq of magnesium sulfate given intravenously.
4. Injection vinorelbine 25 mg/m^2 of body surface area given intravenously on D1.

Patient was encouraged to take oral fluid as much as possible on day of chemotherapy and thereafter.

Same chemotherapy schedule was repeated every 21 days for three cycles. Complete blood count and renal function test were done before each cycle of chemotherapy. Patients must have Hemoglobin >=10 gm%, TLC >=3000/cu.mm, Platelet count >=1, 00,000 /cu.mm, Serum urea <= 40 mg%, Serum creatinine <=1.5 mg%

before the next course could be administered. If these values are not found, courses were delayed until these values are reached.

After completion of three cycles of chemotherapy, patients were given a rest period of three weeks for hematological recovery. Then every patient was treated with external beam radiotherapy using cobalt –60 [Theratron 780 E] unit at source to skin distance/ source to axis distance (SSD/SAD) of 80 cm. Proper patients positioning and immobilization done during both planning and treatment.

The treatment portal and field arrangements varies with the primary site of lesion and lymph node involvement. All patient was treated five days/week to a total dose ranging from 6000 cGy to 7000 cGy in 30 to 35 fractions with 200 cGy/ fraction/day in 6 to 7 weeks. Whenever necessary shrinking field technique was used and then spinal cord was excluded after 4400 cGy.

Evaluation and follow-up: Throughout the course of NACT and radiotherapy patients were monitored for tumor response and acute toxicity. Patients were examined after completion of chemotherapy and radical radiotherapy, and follow-up at monthly interval for the first 6 months then at 3 month interval for the rest period. Whenever indicated imaging technique such as CT scan were part of the routine follow-up. Response terminologies are shown in table-1.

Table-1 Response was registered in terms of

Response type	**Description**
C.R.(Complete response)	No clinical evidence of disease/complete regression of disease at primary site and regional lymph node.
P.R. (Partial response)	>= 50% Regression of tumor size and regional lymph node.
NR (No Response)	<= 25% Regression of the tumor size on either direction.
PD (Progressive Disease)	>25% increase in size of tumor or appearance of secondary.

III. Results

Present study provide follow-up of patients of locally advanced head and neck carcinoma treated with three cycle of NACT followed by radical radiotherapy alone. Our goal was to optimize local and distant control for longer survival and organ preservation, for this purpose we used cisplatin and vinorelbine as NACT regimen.

From August 2009 to September 2010, total 30 patients evaluated in this study belonged to the age ranging from 23 to 68 years, with the median age of 53 years. Majority of the patients belonged to low socioeconomic status and are habitual to smoking and chewing tobaccos.

The most common site of the primary disease was the hypopharynx 43.4% (n=13), followed by oropharynx 33.3% (n=10) and larynx 23.3% (n=7). After complete head and neck examination it is revealed that 16.7% (n=5) patients were stage II, 56.7% (n=17) patients were stage III and 26.6 % (n=8) patients were stage IVA disease. Background characteristics of study subjects are shown in Table-2.

Table-2 Background of study subjects

Patients and disease characteristics		Total no of cases	Total %
Age	Range 23-68 years (Median 53 years)	30	100%
Sex	Male	24	80%
	Female	6	20%
Primary site	Oropharynx	10	33.3%
	Hypopharynx	13	43.4%
	Larynx	7	23.3%
AJCC Staging	Stage II	5	16.6%
	Stage III	17	56.7%
	Stage IV	8	26.7%
Histological differentiation	Well differentiated	15	50%
	Moderately differentiated	10	33.3%
	Poorly differentiated	4	13.4%
	Undifferentiated	1	3.3%

Clinical response: When response evaluation was done in all patients after completion of NACT, the overall response rate was observed in 27 (90%) patients. The 26 (86.7%) patients have partial response, with 1 (3.3%) patient has complete response, 2(6.7%) patients has stable disease or no response and 1 (3.3%) patient has progressive disease despite NACT.

After 3 weeks of completion of NACT all patients underwent for radical radiotherapy. When response was observed after completion of radiotherapy, the complete response rate was achieved in 16(53.4%) patients with partial response in 13(43.3%) patients and 1 (3.3%) patients has progressive disease despite treatment. All patients were kept on close monthly follow-up. After 6 month follow-up 27 patients were available for evaluation.

However at 6 month follow-up 12(40%) patients were disease free, 14(46.7%) patients has locoregional disease and 1(3.3%) patient has distant metastasis in addition to locoregional disease. Responses after NACT and Radiotherapy are shown in table-3.

Table-3 Response after NACT and Radiotherapy

After 3 weeks of NACT	**Total no of cases**	**Percentage of cases**
CR (Complete response)	1	3.3%
PR (Partial Response)	26	86.7%
NR (No Response)	2	6.7%
PD (Progressive Disease)	1	3.3%
After 4-6 weeks of Radiotherapy	**Total no of cases**	**Percentage of cases**
CR (Complete response)	16	53.4%
PR (Partial Response)	13	43.3%
NR (No Response)	nil	nil
PD (Progressive Disease)	1	3.3%
After 6 months of radiotherapy	**Total no of cases**	**Percentage of cases**
CR (Complete response)	12	40%
PR (Partial Response)	14	46.7%
NR (No Response)	nil	nil
PD (Progressive Disease)	1	3.3%

Adverse Events: All patients were monitored for acute toxicity during NACT and radiotherapy. The most frequently reported adverse events of NACT included nausea & vomiting, anemia, neutropenia, thrombocytopenia, and mucosities. Most of these toxicities were mild (grade I & II) and mange with supportive care without interruption of treatment. None of the patients experienced any anaphylactic reactions during NACT. The grade III & IV hematological toxicities of NACT were managed by injection GCSF (granulocyte colony stimulating factor), packed cell transfusion, or platelet transfusion as indicated.

The main toxicities of radiation alone were dysphagia, mucosities, and skin reactions. Grade III & IV toxicities of mucosities and dysphagia were the most troubling toxicities require hospitalization of patients for parental nutrition and supportive treatment. The acute adverse events observed during NACT & Radiotherapy, including hematological & non-hematological toxicities, are summarized in Table-4.

Table-4 Anticipated side effect of treatment

Toxicity of Chemotherapy	Severity				Total patients	Total %
	Grade I	Grade II	Grade III	Grade IV		
Nausea &Vomiting	36.6% (n=11)	46.7% (n=14)	6.7% (n=2)	nil	27	90%
Anemia	33.4% (n=10)	30% (n=9)	3.3% (n=1)	nil	20	66.7%
Neutropenia	26.7% (n=8)	16.7% (n=5)	13.3% (n=4)	3.3% (n=1)	18	60%
Thrombocytopenia	20% (n=6)	13.3% (n=4)	6.7% (n=2)	nil	12	40%
Mucosities	23.3% (n=7)	10% (n=3)	nil	nil	10	33.3%
Toxicity of Radiotherapy	Severity				Total patients	Total %
	Grade I	Grade II	Grade III	Grade IV		
Mucosities	23.3% (n=7)	13.3% (n=4)	6.7% (n=2)	3.3% (n=1)	14	46.7%
Dysphagia	16.7% (n=5)	10% (n=3)	3.3% (n=1)	nil	9	30%
Anemia	13.3% (n=4)	6.7% (n=2)	nil	nil	6	20%
Neutropenia	9%(n=3)	3.3% (n=1)	nil	nil	4	13.3%
Thrombocytopenia	13.3% (n=4)	3.3% (n=1)	nil	nil	5	16.7%
Skin reactions	70% (n=21)	23.3% (n=7)	6.7% (n=2)	nil	30	100%

IV. Discussion

Cases of persistent or recurrent primary and distant metastatic disease despite surgical resection and postoperative radiotherapy with its functional deficits, or primary radiotherapy to the maximally tolerated doses remain the major pattern of treatment failure of locally advanced head and neck cancer (18, 19).

Theoretically a main cause of failure of radiation to advanced diseases is due to presence of hypoxic malignant cells at or near the center of the tumor and their decrease radio-sensitivity. NACT improves intratumor blood circulation by down stage the tumor and thereby reduces the percentage of malignant hypoxic cells making them more radio-sensitive (20).

The indications for NACT are not well defined in clinical practice. The rationally for use of NACT is based on two hypothesis, one involves the better drug delivery in untreated, well vascularized tumors and the second involves the obliteration of micro-metastatic disease with corresponding active doses of chemotherapy (21). In our study, overall response was observed in 90% patients after completion of NACT. After 4-6 weeks of radiotherapy 16 (53.4%) patients achieved complete response, with 13 (43.3%) patients partial response, and 1 (3.3%) patient has progressive disease despite treatment. When response were evaluated after 6 months follow-up 40% patients were disease free and 46.7% patients had locoregional disease.

Most of the hematological toxicities during NACT were mild (grade I & II), except with 4 cases of grade III and 1 case of grade IV neutropenia, those were managed by injection GCSF (granulocyte colony stimulating factor). The most relevant adverse events of radiotherapy were mucosities; dysphagia and skin reactions, with 2 cases of grade III and 1 case of grade IV mucosities require hospitalization of patients for parental nutrition and supportive treatment.

Our findings are very close to study done by Orecchia R at el, treated 25 patients with locally advanced head and neck cancer with 4 cycles of vinorelbine (20 mg D1 & D3), cisplatin (60 mg/m^2 D1) and 5-fluorouracil (200mg/m^2 continuous infusion) followed by bifractionated radiotherapy (bid RT) up to 74.4 Gy in 62 fractions of 1.2 Gy twice daily. Response to chemotherapy was observed in 19(76%) patients including 3 complete responses and 16 partial responses. Evaluation after the completion of bid RT, 13 patients had complete responses, 7 patient's partial responses, 2 stable disease and 3 tumor progressions (22).

Although we recognize that our study has certain drawbacks like, it was not randomized, the study group was heterogeneous in respect to primary tumors, and the patient's number was small to achieve a statistically significant result. Our intention was to report our experience with NACT regimen using cisplatin and vinorelbine followed by radiotherapy in locally advanced head and neck cancer.

Even though the length of follow-up in our study was short the responses and well tolerated by the patients have shown encouraging results. However more multi-institutional trials are required to arrive at a definite conclusion or protocol with neoadjuvant chemotherapy that may make a difference in locally advanced head and neck cancer.

V. Conclusion

In conclusion, the results of our study have demonstrate that NACT using cisplatin and vinorelbine followed by radiotherapy in patients with locally advanced carcinoma of head and neck was well tolerated and gives acceptable toxicities. Despite initial promising results, long term disease free survival and overall survival times remain poor. However a large randomized study is needed to judge the efficacy of NACT regimen and at the same time whether combining it with chemoradiotherapy, or conventional radiotherapy, or higher radiation doses by hyper fractionated schedule will produce better result or not.

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