Original Article

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A comparative evaluation of effect of concomitant Vinorelbine with radiotherapy versus conventional radiotherapy in management of head and neck cancers- An experience from Central India Regional cancer centre

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Abstract:

Introduction: The worldwide incidence of head and neck cancers exceeds half a million cases and ranked 5th most common malignancies and varies widely throughout the world, about two thirds of them arising in developing countries. Squamous cell carcinoma and its variant represent more than 90% of all head and neck cancers. Vinorelbine is a unique semi synthetic vinca alcaloid and is a cell-cycle- dependent antimitotic agent blocking progression in the G2/M cell phase, which is the most sensitive phase of the cell cycle to irradiation. **Materials and Methods:** The present study was conducted on patients reporting to Department of Radiotherapy, Pt J.N.M. Medical College and Dr. B.R.A.M. Hospital Raipur (C.G.), India from September 2005 to June 2006. All patients taken in to study were randomized in to trial arm and control arm. In trial arm patients were monitored during vinorelbine infusion for any infusion reaction and reviewed at once a week during the course of chemo-radiotherapy for documenting acute toxicity. In control arm patients were monitored weekly during the course of radiotherapy. **Results:** Patients evaluated in this study belonged to the age from 30 to 70 years with the median age of 50 year. In both arms 44(73.3%) patients were male and 16(26.7%) patients were female out of 60 patients. When response were evaluated after 6 months of follow-up in both arms it was found that in trial arm 18(60%) patient had loco regional control and 5(16.7%) had persisting disease as compared to 12(40%) and 9(30%) patient respectively in control arm. It has been observed that earlier stage disease is better response. **Conclusion:** Treatment response was significant better among patients with early stages. The chemotherapy regimen used in this study gives acceptable results and toxicities. Even though the length of follow up in our study was short the responses have shown encouraging results.

Key words: Head and neck cancer, Vinorelbine, Radiotherapy, Chemotherapy, Raipur, Chhattisgarh

Introduction:

The worldwide incidence of head and neck cancers exceeds half a million cases and ranked 5th most common malignancies and varies widely throughout the world, about two thirds of them arising in developing countries such as India and Sri Lanka [1].

Cancer registry of last 6 year of the Regional cancer centre, Raipur (Chhattisgarh) revealed collectively head and neck cancer accounts for 18 to 20 % of all new cancer.

Squamous cell carcinoma and its variant represent more than 90% of all head and neck cancers. The complex process of head and neck carcinogenesis involves dynamic interactions among many factors. The primary risk factors for development of Squamous cell carcinoma of the head and neck are the use of tobacco and alcohol [2].

Other important etiologic factors are viruses, genetic predisposition, occupation, radiation exposure, and dietary deficiencies [3].

Unlike many other malignancies, head and neck cancer is predominantly a local and regional disease. Even patient with clinically advanced stages are rarely found to have distant metastasis at the time of initial diagnosis. But the majority of head and neck cancer patients present with locally advanced stage **[4].**

The longer survival for patients with locally advanced head and neck cancer treated with radiation alone is limited. In addition radiation therapy by itself fails to control the locoregional disease, despite

improvements in radiation therapy techniques and equipments [5].

The high risk of loco regional failure and probability of distant metastasis are responsible for the poor prognosis of the locally advanced head and neck cancer. To improve treatment out comes for locoregionally advanced head and neck cancers, clinical trials using different techniques and protocols have been investigated with controversial results [6].

Concurrent chemo-radiotherapy has become a standard modality for patients with high risk resectable and unresectable locally advanced head and neck cancer [7].

The simultaneous administration of chemotherapy and radiotherapy is theoretically aimed at improving both systemic and locoregional tumor control [8].

The addition of various chemotherapy agents to radiotherapy has also been extensively investigated. Single agent cisplatin is accepted as standard reference regimen for chemo-radiation of locally advanced head and neck cancer, but can be associated with considerable acute and late toxicity [9].

Vinorelbine is a unique semi synthetic vinca alcaloid and is a cell-cycle- dependent antimitotic agent blocking progression in the G2/M cell phase, which is the most sensitive phase of the cell cycle to irradiation [10].

Present study is undertaken to evaluate the feasibility, safety profile and outcome of vinorelbine as concomitant chemo-radiation in patient with locally advanced head and neck cancers.

Material and Methods

The present study was conducted on patients reporting to Department of Radiotherapy, Pt J.N.M. Medical College and Dr. B.R.A.M. Hospital Raipur (C.G.), India from September 2005 to June 2006. After confirmation of head and neck cancer with histopathology report a complete head and neck examination has done to evaluate tumour extent by physical examination and appropriate imaging. Dental evaluation for any decayed, missing, filled teeth had done. Then disease was staged according to American Joint Committee on Cancer (AJCC) 2002 staging system. Before starting the study, a written and informed consent were taken from all the patients.

All patients taken in to study were randomized in to trial arm and control arm. 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, 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. The spinal cord was excluded after 4200 cGy.

Vinorelbine at dose of 20 mg / m^2 was administered as 15 minute intravenous infusion 2hrs before radiotherapy on D_1, D_8, D_{22} and D_{29} to patients in trial arm. Patient in control arm received conventional external beam radiotherapy only.

In trial arm patients were monitored during vinorelbine infusion for any infusion reaction and reviewed at once a week during the course of chemo-radiotherapy for documenting acute toxicity. In control arm patients were monitored weekly during the course of radiotherapy.

Response to chemo-radiation and radiation alone was evaluated after completion of treatment and then patients were followed up at 3 monthly intervals for the first 2 years and 6 monthly intervals thereafter. In both arms toxicities were assessed on weekly basis during treatment and on monthly basis after treatment.

Response was registered in terms of:-

Response type	**Description**
C.R. (Complete response)	No clinical evidence of disease/complete regression of disease.
P.R. (Partial response)	Partial regression in tumour size on clinical examination. (either 50% or 75%)
NR (No Response)	Stable disease/no effect of chemoradiotherapy/ radiotherapy.
PD (Progressive Disease)	Increase in size of tumour or appearance of secondaries.

Results:

Patients evaluated in this study belonged to the age ranging from 30 to 70 years with the median age of 50 year. In both arms 44(73.3%) patients were male and 16(26.7%) patients were female out of 60 patients. Majority of the patients belonged to low

socioeconomic status. Most of the patients were habitual to tobacco chewing and/or smoking with or without alcohol consumption. All patients were diagnosed as squamous cell carcinoma. After complete head and neck examination it is revealed that 44(73.3%) patients were stage III and 16(26.7%) patients were stage IVA. In both arms primary site of tumour included oral cavity 48.3 %(n=29), oropharynx 16.7 %(n=10), hypopharynx 20% (n=12) and larynx15% (n=9). No patient had received prior systemic chemotherapy or radiotherapy. **[Table-1, 2]**

Table -1 Background characteristic of study subject

Age	**No of Cases**					
	Trial – Arm		**Control –Arm**		**Total**	
	No.	**%**	**No.**	**%**	**No.**	**%**
30-40	8	26.6%	3	10%	11	18.3%
41-50	10	33.4%	7	23.3%	17	28.3%
51-60	5	16.6%	13	43.3%	18	30%
61-70	7	23.4%	7	23.4%	14	23.4%
Sex						
Male	19	63.3%	25	83.3%	44	73.3%
Female	11	36.7%	5	16.7%	16	26.7%
Socioeconomic status						
Lower	17	56.6%	18	60%	35	58.3%
Lower – middle	10	33.4%	10	33.4%	20	33.4%
Upper-middle	3	10%	2	6.6%	5	8.3%
Total	30	100%	30	100%	60	100%

Table - 2 Addiction associated, Site and Staging of Head and Neck Cancers

Addiction	**Duration in year**	**Trial arm**		**Control arm**		**Total**	
		No.	**%**	**No.**	**%**	**No.**	**%**
Tobacco chewing	10-20	8	26.7%	3	10%	11	18.3%
	21-30	5	16.7%	6	20%	11	18.3%
	31-40	5	16.7%	5	16.7%	10	16.6%
Tobacco smoking	10-20	-	-	-	-	-	-
	21-30	4	13.3%	3	10%	7	11.7%
	31-40	2	6.7%	5	16.7%	7	11.7%
Tobacco (smoking + chewing) + Alcohol	10-20	1	3.3%	1	3.3%	2	3.4%
	21-30	1	3.3%	3	10%	4	6.7%
	31-40	4	13.3%	4	13.3%	8	13.3%
	Total	30	100%	30	100%	60	100%
Site of tumors							
Oral cavity		16	53.3%	13	43.3%	29	48.3%
Oropharynx		5	16.7%	5	16.7%	10	16.7%
Hypopharynx		5	16.7%	7	23.3%	12	20%
Larynx		4	13.3%	5	16.7%	9	15%
AJCC staging							
Stage III		23	76.7%	21	70%	44	73.3%
Stage IV A		7	23.3%	9	30%	16	26.7%

Clinical Response/ Outcome Analysis:

After 50 Gy of external beam radiotherapy (EBRT) and completion of treatment the number of patients who achieved complete response are much more in trial arm than control arm, also residual disease in trial arm is

less than control arm. When response to concomitant vinorelbine and radiotherapy was observed after 1 month of completion of treatment as compared to radiotherapy alone, in trial arm 22 (73.3%) patients were disease free, 8 (26.7%) patients had persisting residual disease, where as in control arm only 14 (46.6%) patients were disease free and 16 (53.4%) patients were residual disease. Patients in both arms were kept on close monthly follow up. In trial arm 23 out of 30 and in control arm 21 out of 30 patients regularly came for monthly follow up till sixth month. When response were evaluated in both arms it was found that in trial arm 18(60%) patient had loco regional control and 5(16.7%) had persisting disease as compared to 12(40%) and 9(30%) patient respectively in control arm. **[Table-3]**

It has been observed that earlier stage disease is better response. In both arms stage III patients show better response than stage IVA, and also in both stages trial arm patients have significant better than control arm. **[Table-4]**

Table 3: Responses after treatment at different time interval

Response after receiving	**No of Cases**					
	Trial – Arm		**Control –Arm**		**Total**	
	No.	**%**	**No.**	**%**	**No.**	**%**
50 Gy of EBRT						
PR 50%*	10	33.3%	20	66.7%	30	50%
PR 75%**	17	56.7%	5	16.7%	22	3.7%
CR#	2	6.7%	1	3.3%	3	5%
NR##	1	3.3%	4	13.3%	5	8.3%
Total	30	100%	30	100%	60	100%
Completion of EBRT						
PR 50%	4	13.3%	10	33.3%	14	23.3%
PR 75%	8	26.7%	13	43.3%	21	35%
CR	18	60%	6	20%	24	40%
NR	-	-	1	3.4%	1	1.7%
Total	38	100%	30	100%	60	100%
1 month of completion of treatment						
CR (no evidence of disease)	22	73.3%	14	46.6%	36	60%
PR (residual disease)	8	26.7%	16	53.4%	24	40%
Total	30	100%	30	100%	60	100%
3 month of completion of treatment						
CR (no evidence of disease)	21	70%	14	46.7%	35	58.4%
PR (residual disease)	7	13.4%	12	40%	19	31.7%
6 month of completion of treatment						
CR (no evidence of disease)	18	60%	12	40%	30	50%
PR(residual disease)	5	16.7%	9	30%	14	23.4%

*P.R. (50%) – Partial response, ½ reduction size on clinical examination.
** P.R. (75%) - Partial response, 2/3rd reduction size on clinical examination.
# C.R. - Complete response, complete regression of disease.
N.R. - No response, Stable disease.

Table 4: Responses according to stage of tumors

Stage	Percentage of response			
	Trial – Arm		Control –Arm	
	No.	%	No.	%
Stage III	19/23	82.6 %	12/21	57.2%
Stage IV A	3/7	42.8%	2/9	22.3%

Acute Toxicity

All patients were assessed for acute toxicity of chemo-radiation and radiation alone during and after treatment according to RTOG toxicity criteria's. Toxicities during treatment are detailed in Table 5. The most frequently reported adverse events included mucosities and dysphagia. Most of these toxicities were mild (grade I and grade II) and manage with supportive treatment without interruption of treatment. None of the patients experienced any anaphylactic reaction with vinorelbine. In trial arm 3(10%) patients had grade III and 2(6.7%) patients had grade IV mucosities were the most troubling toxicities require hospitalization of the patients and delay or interruption of the treatment. Other toxicities founded in both arms included anemia, leucopenia, nausea/vomiting and skin reactions. **[Table-5]**

Table 5: Acute toxicity of chemoradiotherapy and radiotherapy.

Acute Toxicity Of Chemo-Radiotherapy	Patient in trial arm				Total no of patient	(%)
	Grade I	Grade II	Grade III	Grade IV		
Mucosities	10	6	3	2	21	70%
Dysphagia	10	5	3	0	18	60%
Anemia	6	2	0	0	8	26.7%
Leucopenia	4	2	0	0	6	20%
Nausea/Vomiting	10	2	0	0	12	40%
Acute Toxicity Of Radiotherapy	**Patients in control arm**				**Total no of patient**	**(%)**
	Grade I	**Grade II**	Grade III	**Grade IV**		
Mucosities	10	5	0	0	15	50%
Dysphagia	6	4	0	0	10	33.4%
Anemia	3	2	0	0	5	16.7%
Leucopenia	2	1	0	0	3	10%
NV	5	1	0	0	6	20%
Skin Reactions: - Is expressed in terms of hyperpigmentation / hypopigmentation (H), dry desquamation (DD) and wet desquamation (WD). It revealed H=20, DD=8, WD=2 in trial arm and H=19, DD=10, WD=1 in control arm.						

Discussion

Early detection and treatment by multiple modalities is important for better prognosis in head and neck cancer. In India due to the lack of awareness and lack of early detection programs around 80% of the cases are diagnosed in advanced stages, where uncontrolled locoregional disease is the cause of morbidity. Thus locoregional control is paramount importance to survival [11].

In current study, no significant deference between trial arm and control arm patients with respect to parameters such as age, sex, socioeconomic status, tobacco chewing, smoking habit, alcohol consumption and disease stage.

Present study has shown better response of concomitant use of vinorelbine with radiation as compared to radiation alone in locally advanced head and neck cancer. It is clearly evident that number of patients who achieved complete response is much

more in trial arm than control arm after completion of treatment.

When response were evaluated after 6 month follow up, it was found that in trial arm 18(60%) patients had loco-regional control with no distant metastasis and 5(16.7%) patients had persisting disease as compared to 12(40%) patients had cmplete response and 9(30%) patients had partial response in control arm.

As expected the oral mucosities, dysphagia and hematological toxicities were higher in patient treated with chemo radiation (Trial arm) than that seen in patients treated with radiation alone (Control arm). Skin reactions including hyper-pigmentations /hypo-pigmentation, dry desquamation and wet desquamation were observed in equally same proportions in both arms.

A study has been published by Sarkar S.K., Patra NB conducted a trial of vinorelbine and radiation therapy in patients with locally advanced head and neck (stage II and III) cancer. In this study 16 patients received weekly vinorelbine 6 mg/m^2 with external beam radiotherapy by telecobalt machine, total dose given was 66 Gy in 33 fractions over 6 ½ weeks. 13 (81%) out of 16 patients achieved complete response and rest achieved partial response .All patients had mild toxicities included mucosities, dysphagia, skin reaction and nausea/vomiting except 2 patients had grade II dysphagia requiring liquid nutrition and 1 patient had grade IV oral mucosities requiring break in therapy. In current study complete response was 22(73.3%), when comparing results 13(81%) study carried out by Sarkar SK, this might have been due to inclusion of stage II disease **[12]**.

In a study by G. Sudershan and S. Mahadev, the initial response rate was 28/30 (93%) and at the end of 20 months 25(83%) out of 30 cases were alive with no evidence of disease. One had a partial response and one case did not response. Mucosities grade III in 6 cases and grade IV in 1 case. Grade IV dysphagia in1case **[13].**

Another study by Wilkowski, Ralf, 15 patients with locally advanced squamous cell carcinoma of head and neck were treated with vinorelbine and mitomycin C and simultaneous accelerated radiotherapy. Grade 3-4 acute mucosal toxicity was observed in 9/15 patients [14].

The complete response in the above studies ranges from 60% to 83%, studies carried out by G. Sudershan S. Mahadev have shown 83% complete response as compared to 81% complete response study carried out by Sarkar S.K. and Patra NB. This might have been due to difference between doses of vinorelbine and different stages of disease. G. Sudershan and S. Mahadev have been used vinorelbine 10mg/m^2/week while Sarkar SK and Patra N.B. have used vinorelbine 6mg/m^2/week.

All patients had grade I oral mucosities except for 1 of them who had grade II mucosities observed in study carried out by Sarkar SK while grade II mucosities in 6^{th} patients observed in study carried out by G. Sudershan [11-14].

When comparing with the present study the most frequent reported adverse effects include mucosities and dysphagia by more than 50% of patients. Most of these complaints were mild, except with 3 cases of grade III mucosities and 2 cases of grade IV mucosities. 2 patients had neutropenia who was managed by injection GCSF (granulocyte colony stimulating factors) without interruption in treatment.

The chemotherapy regimen used in this study had a predictable study profile and gives acceptable results and toxicities are within tolerable limits. Although our study limited by small number of patients and the length of follow up was short the comparable responses have shown encouraging results. However longer follow up and investigational evaluation will be required to define the relapse free interval and overall survival. The protocols having combination of vinorelbine with other chemotherapeutic agents also needs to be investigated.

Conclusion

Treatment response was significant better among patients with early stages. The chemotherapy regimen used in this study gives acceptable results and toxicities. Even though the length of follow up in our study was short and number of patients was less the responses have shown encouraging results. However longer follow up and investigational evaluation will be required to define the relapse free interval, late toxicities and overall survival.

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