A B S T R A C T

**Aim:** Head and neck cancer is one of the most commonly occurring malignancies in the world. In India, the most commonly occurring head and neck cancers are those of the oral cavity and the pharynx. The majority of these cancers present with stage III/IV disease. Surgery and radiation therapy are the main treatment modalities. Concomitant chemoradiation is being investigated with the goal of improved local control that translates into improved survival. In this background, we have started this prospective randomized trial to ascertain the dose, schedule and sequence of therapy and to note whether Vinorelbin as radiosensitizer is equally effective as Cisplatin, comparing compliance, local control and toxicity. 

**Patients and Methods:** Forty patients of advanced head and neck cancer were randomized into two arms. Arm A received weekly injection Cisplatin 40mg/m$^2$ along with radiation. Arm B received weekly injection of Vinorelbin 6mg/m$^2$ along with radiation. Radiotherapy was delivered at a dose of 6,600–7,000 Gy in conventional fractionation in a telecobalt machine.

**Results:** The complete response (CR) rate was higher in arm B (90%) than in arm A (70%). Major toxicities included neutropenia, anemia, mucositis and nausea.

**Conclusion:** Concomitant chemoradiation with Vinorelbin produced more CR than chemoradiation with Cisplatin in advanced head and neck cancer. Toxicities were more in the Cisplatin arm, but they were manageable. Although a majority of the study was performed using Cisplatin as the radiosensitizer, Vinorelbin can be recommended as radiosensitizer in advanced head and neck malignancy.

**Key words:** Cisplatin, concomitant chemoradiotherapy, radiosensitizer, vinorelbin

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PATIENTS AND METHODS

This study was carried out in the radiotherapy department of I.P.G.M.E.R, Kolkata, from September 2004 to July 2005. Forty patients of head and neck cancer were randomized into two arms, with 20 patients in each arm.

Patients of head and neck carcinoma having stage II–IV disease with squamous cell histology were included in this trial. These patients had no prior surgery, chemotherapy or radiotherapy. The performance status was >70% (according to Karnofsky’s scale). Hematological parameters were within the normal range, like hemoglobin >11 mg%, absolute neutrophil count >1,900, platelet count >1 lakh/mm³, serum bilirubin <1 mg%, liver enzymes within 1.5-times of the normal limit and serum creatinine <1.5 mg%. Patients were excluded from the study if they had already received some form of anticancer therapy, if there was presence of metastatic disease, if they had participated in a clinical trial in the last 30 days, if there was simultaneous participation in a clinical trial or if they had any uncontrollable systemic illness like diabetes, tuberculosis and hypertension.

Treatment protocol

Patients who fulfilled the above eligibility criteria were required to sign the informed consent form and were then randomized to assign either of the treatment arms.
Arm A: External beam radiotherapy (EBRT) along with weekly injection Cisplatin 40 mg/m² IV.
Arm B: EBRT along with weekly Vinorelbine 6 mg/m² IV.

The dose of EBRT was 66–70 Gy, with conventional fractionation, using a telecobalt machine with cord sparing after 4,400 cGy.

Response was assessed by local examination and indirect laryngoscopy 1 month after completion of radiotherapy. Regular follow-up was carried out at monthly intervals. Local control was recorded using the terminology complete response (CR), partial response (PR) and progressive disease (PD) (as per WHO definition).

Toxicity assessment was carried out weekly during treatment and thereafter monthly up to 3 months for acute toxicities using Radiation Therapy Oncology Group criteria. Subsequently, patients were being followed-up monthly up to 6 months and then at 3-monthly intervals for any sign of recurrence and treatment-related morbidity.

RESULTS

Patient characteristics

From September 2004 to July 2005, 41 patients were enrolled. One patient in arm B dropped out due to mucositis. Patient characteristics are listed in Table 1. The majority of the patients are in the range of 50–70 years. Patients were predominantly male (95%). They had a good performance status. The larynx and laryngopharynx were the dominant sites (47.5%). Histologically, all were squamous cell carcinoma, the majority of which was well-differentiated (62.5%). Stage III disease was predominant (67.5%). Patients were equally distributed among the two treatment arms.

Response to treatment

All the patients who completed the treatment were assessed in terms of CR, PR, stable disease and PD. Ninety percent of the patients in arm B achieved CR. This result is better than the weekly Cisplatin arm, which has 70% CR (as shown in Table 2).

When arm B was compared with arm A in terms of CR, it was not statistically significant.

| Table 1: Patient characteristics |
|---------------------------------|
| Arm A                          |
| Age   | 56.50 |
| Range | 56-70 |
| Gender |
| Male  | 19    |
| Female| 01    |
| Addiction |
| Smoker | 15   |
| Nonsmoker | 05  |
| Site |
| Laryngopharynx | 13 |
| Glottis   | 02   |
| Hard palate | 00  |
| Pyriform fossa | 03  |
| Tongue   | 01   |
| Tonsil   | 01   |
| Cheek    | 00   |
| Retromol trigone | 00  |
| Stage |
| II      | 00   |
| III     | 16   |
| IV      | 04   |
| Histology |
| Well differentiated | 05 |
| Mod differentiated | 14  |
| Poor differentiated | 01  |
Acute toxicity

All the toxicities were higher in the Cisplatin-containing arm. All the toxicities were higher in arm A when Cisplatin was used as a radiosensitizer compared with the Vinorelbine arm. Mucositis was almost similar in both arm B and arm A.

When arm B was compared with arm A, myelosuppression was higher in arm A (statistically significant, P-value 0.05). Skin reaction was also lower in the Vinorelbine arm when compared with the other arm. Nausea was significantly higher in arm A (RT+cisplatin) when compared with arm B [Table 3].

Late toxicity

As the follow-up is short, no definite comment of late toxicity is possible at this stage. All the patients are alive and no serious complication has occurred till date.

DISCUSSION

Therapeutic approach in head and neck cancer is widely discussed and is a debatable one also, with the optimum treatment modality, the intention of treatment and managing toxicities occupying the mind of the physician with the survival effect defining the effectiveness of treatment modality.

The management of primary cancer is considered separately for each anatomic site. If external beam radiation therapy is selected, it may be given with either conventional once-daily fractionation to 66–70 Gy in 2 Gy/fraction, 5 days a week in a continuous course or with an altered fractionation schedule. EBRT may also be delivered with intensity-modulated radiation therapy (IMRT)\(^{[14]}\) to reduce the dose to the normal tissues.\(^{[15]}\) The disadvantages of IMRT are that it is much more time consuming to plan and treat the patient, the dose distribution is often less homogeneous so that “hot spots” may increase the risk of late complication and the risk of marginal miss may be increased. Whether an altered fractionation schedule is better than a conventional one depends on the altered fractionation technique that is selected. Altered fractionation schedules shown to result in improved locoregional control rates are the University of Florida hyperfractionation technique and HD Anderson concomitant boost technique. The Randomized Radiation Therapy Oncology Group 90-03 found that acute toxicity is increased with altered fractionation whereas late toxicity is comparable with that of conventional fractionation.

Management of the neck is closely tied to management of the primary site. The rationality of combining chemotherapy with radiation in doses mentioned was:

1. to improve the locoregional control rate and increase the response in this fairly advanced disease
2. assessment of tolerability of patients with a concurrent approach, determining the dose to normal tissues tolerability to avoid toxic effects
3. decrease the distant metastasis rates by acting on systemic micrometastasis present at the diagnosis in more than 50% of the cases.

Calais \etal\(^{[16]}\) recently reported that disease-free survival and 3-year rate of locoregional control were significantly improved with concomitant chemotherapy, although patients in the combined radiation therapy–chemotherapy arm experienced higher rates of grade 3 or 4 mucositis, feeding tube placement and severe cervical fibrosis.

Although a majority of studies were performed by using Cisplatin as the radiosensitizing drug, some studies also support the use of Vinorelbine as a radiosensitizer.

After 1-year follow-up, CR is higher in the Vinorelbine plus radiation arm followed by the Cisplatin plus radiation arm, which needs further evaluation. Although toxicities like mucosal, hematologic and dermatologic were higher in they concomitant arm, they were manageable. All toxicities were significantly higher when Cisplatin was used as a radiosensitizer. Compliance was also greater with Vinorelbine as toxicities were less when compared with Cisplatin.

Our study had a limited number of patients and the duration of follow-up is also short. Further evaluation of treatment protocol with large number of patients and also with prolonged follow-up may have a positive impact on survival as the response rate is already showing improvement in a concomitant protocol.
REFERENCES

1. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy vs radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310-7.
2. Taylor SG 4th, Murthy AK, Vannetzel JM, Colin P, Dray M, Caldarelli DD, et al. Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation vs. concomitant treatment in advanced head and neck cancer. J Clin Oncol 1994;12:385-95.
3. Coughlin CT, Richmond RC. Biologic and clinical developments of cisplatin combined with radiation: Concepts, utility, projections for new trials, and the emergence of carboplatin. Semin Oncol 1989;16:31-43.
4. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.
5. Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy-results of a multicentric randomized German trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50:1161-71.
6. Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. Radiother Oncol 1989;16:83-101. completed.
7. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. N Eng J Med 1991;324:1685-90.
8. Potier P. The synthesis of Navelbine prototype of a new series of vinblastine derivatives. Semin Oncol 1989;16:2-4.
9. Mastbergen SC, Duivenvoorden I, Versteegh RT, Geldof AA. Cell cycle arrest and clonogenic tumor cell kill by divergent chemotherapeutic drugs Anticancer Res 2000;20:1833-8.
10. Sudarshan G, Mahadev S. Vinorelbine as radiosensitizer in head and neck and oesophageal cancer: A plot study. Journal of Clinical Oncology, 2004 Asco Annual meeting proceedings (post meeting edition) (July 15 supplement), 2004;22:5562.
11. Gremman RA, Erjala KO, Pulkkiner JO, Kulmaal JA, Alalen KA, Granma SE. Vinorelbine and concomitant irradiation in head and neck squamous cell cancer 2002 ASCO Annual Meeting Head and Neck Cancer: No: 257-7.
12. Gasparini G, Pozza F, Recher G, Panizzoni GA, Cristoferi V, Squaquara R, et al. Simultaneous cis-platinum and radiotherapy in inoperable or locally advanced squamous cell carcinoma of the head and neck. Oncology 1991;48:270-6.
13. Glaser MG, Leslie MD, O'Reilly SM, Ceesman AD, Newlands ES. Weekly cisplatinum concomitant with radical radiotherapy in the treatment of advanced head and neck cancer. Clin Oncol (IR Coll Radiol) 1993;5:286-9.
14. Chao CK, Ozyigit G, Tran BN. Pattern of failure in patients receiving definitive and post operative IMRT for head and neck cancer. Int J Radiat Oncol Biol Phys 2003;15:312.
15. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Enslie JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92-8.
16. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiotherapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 1999;91:2081-6.

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