HYPERFRACTIONATED ACCELERATED CONCOMITANT BOOST WITH WEEKLY CISPLATIN IN STAGE III AND STAGE IVA CANCERS OF OROPHARYNX AND HYPOPHARYNX

P. Anandhi¹, N. Rathithilagam²

¹Assistant Professor, Department of Radiotherapy, Government Arignar Anna Memorial Cancer Hospital and Research Institute, Karapettai, Kancheepuram.

²Assistant Professor, Department of Radiotherapy, Government Arignar Anna Memorial Cancer Hospital and Research Institute, Karapettai, Kancheepuram.

ABSTRACT

BACKGROUND

Head and neck cancer is now the fourth most common malignant disease worldwide and constitute one-third of all new cases registered in our Institute in a calendar year. More than 95% of head and neck cancers are squamous cell carcinomas. Most of the patients present in stage III and IV. At present, 40% - 60% of the patients are at risk of dying because of loco-regional recurrence compared with 20% - 30% who will die from metastases.

MATERIALS AND METHODS

Aim of this study is to describe the rates of loco-regional response on completion of treatment, to determine the feasibility of treatment delivery, patient tolerance and acute toxicities, and also to determine the effects of zinc sulfate supplementation on radiation-induced mucositis. Patient assessment, inclusion criteria, treatment factors and toxicity criteria were defined in this study.

RESULTS

30 patients met the eligibility criteria of the protocol and were recruited. The duration of Radiation therapy was ≤ 46 days in 27 patients (90%) and was 47 - 51 days in three patients (10%). Overall response to therapy was recorded in all patients (100%). This included a complete response in 25 patients (83.3%) and partial response in five patients (16.7%). A significant observation was the association between the grade of squamous cell carcinomas. Complete response was seen with 80.8% of Grade II and 100% of Grade III carcinomas (P). Five (16.7%) patients showed Grade I skin toxicity, 15 patients (50%) showed Grade II and 10 patients (33.3%) Grade III skin toxicity. Loss of body weight was kept to less than 10% in 20 patients.

CONCLUSION

This data shows that accelerated hyper-fractionated concomitant boost radiotherapy with weekly cisplatin can be administered with acceptable morbidity in patients with good performance status and achieves high rate of loco-regional control and survival.

KEYWORDS

Head and Neck Cancer, Treatment, Toxicity, Hyper-Fractionated Concomitant Boost.

HOW TO CITE THIS ARTICLE: Anandhi P, Rathithilagam N. Hyperfractionated accelerated concomitant boost with weekly cisplatin in stage III and stage IVa cancers of oropharynx and hypopharynx. J. Evolution Med. Dent. Sci. 2017;6(7):527-531, DOI: 10.14260/Jemds/2017/112

BACKGROUND

Head and neck cancer is now the fourth most common malignant disease worldwide and constitute one-third of all new cases registered in our Institute in a calendar year.¹ More than 95% of head and neck cancers are squamous cell carcinomas, only less than 5% accounts for other histology.² The oropharynx cancers more often afflict men and usually diagnosed in 6th and 7th decade of life. The squamous cell carcinoma is the commonest and highly radio-sensitive and preferred therapy mode, because of organ function properties. Most of the patients present in stage III and IV.³

Both oropharynx and hypopharynx have smoking and alcohol as an aetiological factor; 20% - 25% of hypopharynx

cancers and 46% of oropharynx cancers are positive for human papilloma virus, those of the lower hypopharynx are associated with nutritional deficiencies of iron and possible vitamin C.⁴ Plummer-Vinson Syndrome is also one of the precursors for post-cricoid carcinoma, mostly in females.

Local control is a major issue in treating patients with advanced head and neck cancer. At present, 40% - 60% of the patients are at risk of dying because of loco-regional recurrence compared with 20% - 30% who will die from metastases.

It is estimated that approximately 60% of the patients receiving standard Radiation Therapy [RT] and more than 90% of them receiving experimental modalities (i.e. combined chemotherapy and RT, altered fractionation) will develop severe oropharyngeal mucositis. Because most of the patients with stage III and IV are surviving with intensified radiation therapy with chemotherapy, an increasing need for oral care has resulted.

Epidemiology

In our Institution, we register around 2500 - 2800 new cancer patients annually. Of this patient load 30% are head

Financial or Other, Competing Interest: None.

Submission 30-12-2016, Peer Review 10-01-2017,

Acceptance 16-01-2017, Published 23-01-2017.

Corresponding Author:

Dr. P. Anandhi,

Assistant Professor,

Government Arignar Anna Memorial Cancer Hospital and Research Institute, Karapettai, Kancheepuram.

E-mail: makkvellore@gmail.com

DOI: 10.14260/Jemds/2017/112

and neck cancers, nearly 15% - 20% being cancers of the Oropharynx, Larynx and Hypopharynx.

65% - 80% of the Head and Neck cancers present in the locally advanced stage (Stage III - IVB) at our Institution tumours in each site in the head and neck region (Oropharynx, hypopharynx, larynx and oral cavity) have the same squamous tissue and biologic features, but their clinical presentation and responses to therapy differ according to site.⁵

MATERIALS AND METHODS

Objectives

1. To describe the rates of loco-regional response on completion of treatment.
2. To determine the feasibility of treatment delivery, patient tolerance and acute toxicities.
3. To determine the effects of zinc sulfate supplementation on radiation-induced mucositis.

Patient Selection

Conditions for Patient Eligibility

1. Age < 70 years.
2. Patients with histological proof (From the primary lesion and/or lymph nodes) of squamous cell carcinoma of the oropharynx and hypopharynx.
3. Patients with Stage III or IVA disease (M0) (AJCC - UICC 2002).
4. Patients with a life expectancy of at least 6 months and a Zubrod/ECOG performance status of 0 - 1.
5. No distant metastatic disease.
6. Patients with adequate bone marrow function defined as an absolute peripheral granulocyte count (AGC) of ≥ 2000 cells/mm³, platelet count of $\geq 100,000$ cells/mm³, adequate hepatic function with bilirubin ≤ 1.5 mg%, serum creatinine ≤ 1.5 mg%, creatinine clearance ≥ 50 mL/min, SGOT or SGPT $\leq 2 \times$ the upper limit of normal and normal serum calcium (without intervention).
7. Creatinine clearance > 50 mL/min determined by 24-hr collection or nomogram.
8. Informed consent form signed prior to study entry.

Pre-Treatment Evaluation

1. Complete history and physical examination.
2. Indirect and direct laryngoscopy.
3. Biopsy of primary tumour and/or fine needle aspirate/biopsy of metastatic lymph node.
4. Location, type and size of all measurable lesions within 2 weeks prior to treatment be recorded and diagrammed prior to treatment.
5. Laboratory studies (Within 30 days prior to study entry)
 - a. CBC with differential and platelet count
 - b. Serum sodium, potassium, glucose, calcium, serum creatinine, total protein, albumin, alkaline phosphatase, total bilirubin, SGPT or SGOT and LDH.
 - c. Creatinine clearance.
 - d. Optional: Prothrombin Time (PT), Partial Thromboplastin Time (PTT).
6. Radiographic Studies
 - a. Appropriate radiographic study of tumour: CT Scan.
 - b. Chest x-ray or thoracic CT scan (within 8 weeks of study enrolment).
 - c. Abdominal CT if abnormal LFT's are noted.
 - d. Optional: Panendoscopy.

7. Dental evaluation with management.
8. Feeding tubes (Either Dobhoff, Percutaneous Endoscopic Gastrostomy [PEG] or Percutaneous Fluoroscopic Gastrostomy [PFG]) before treatment began. If not, nasogastric intubation.

Radiation Therapy

Dose Fractionation

1. Radiotherapy administered according to the concomitant boost regimen. The initial target volume encompassing primary tumour and neck nodes draining above both clavicles should receive 1.8 Gy per fraction (Fx), five fractions a week to 50.4 Gy in 28 fractions over 5.5 weeks (Days 1 - 38). After 27 Gy, starting at 4th week of treatment from 16th Fraction, (22 - 38 days) the boost target volume covering gross tumour and clinically/radiologically involved nodes receives boost irradiation of 1.5 Gy/Fx /13 Fx as second daily fraction (At least 6 h interval) for a total of 19.5 Gy.⁶
2. The primary treatment fields reduced off the spinal cord at 40.2 Gy (at 20th Fx).
3. Clinically/radiologically involved nodes receive a minimum dose of 69.9 Gy, 41 fractions in 5.5 weeks. All treatment times were documented on the treatment record.

Physical Factors

Megavoltage equipment, Cobalt-60 unit used to provide appropriate photon energies. 2. Treatment distances at 80 cm SSD.

Localisation Requirements

1. Simulation films of the field and the calculation form.
2. Portals were simulated.

Target Volume

The primary tumour and known or suspected lymph node disease were treated with either lateral-opposed fields (or several beam-directed fields with a margin). All fields start with a 2 - 3 cm margin around gross primary and nodal disease. A reduction off the spinal cord to limit its dose to ≤ 45 Gy mandatory. These reduced fields have a 1 - 1.5 cm margin around gross disease.⁷

Dose Constraint, Anticipated Side Effects and Toxicities

Maximum dose to the spinal cord was 45 Gy.

Concurrent Chemotherapy

Cisplatin (Cis-Diaminedichloroplatinum, CDDP)

Administration: Intravenous.

Cisplatin Dose Schedule

Patients received Cisplatin (40 mg/m²) administered intravenously on days 1, 8, 15 and 22.

Toxicity Reporting

The revised NCI Common Toxicity Criteria (CTC) Version 2.0 was used to score toxicity.

Patient Assessments

Acute Reactions

Local reaction of skin and mucous membranes was scored at least weekly during radiotherapy and post therapy until clearance.

Tumour Clearance

Response of tumour documented weekly during therapy and at each follow-up inspection and palpation. The local reaction of mucous membranes was assessed by clinical and indirect laryngoscopy examination.

Follow-Up and Data Analysis

Patients were inpatients and underwent weekly examination during treatment. Following the treatment, first follow-up for evaluation occurred around 6 weeks after completion.

In addition to tumour and clinical status, acute toxicity was graded. Systemic and acute radiation effects were scored using the National Cancer Institute Common Toxicity Criteria version 2.0.

The primary end-point of the study was the loco-regional response at 6 weeks. Additional end point includes acute toxicity rate. Apart from describing the distribution of different variables; chi-square test, cross-tabulation and percentage analysis was applied to the data available to determine the significance and relationship between the variables.⁸

RESULTS

Study Population and Compliance to Treatment

30 patients met the eligibility criteria of the protocol and were recruited. Table 1 lists pre-treatment patient and tumour characteristics. Some significant observations noted were that dysphagia and odynophagia were common troublesome symptoms in patients with oropharynx. In hypopharyngeal cancers the troublesome symptoms were swelling, pain and dysphagia ($p < 0.01$).

The fractionation regimen was according to protocol specification in all patients (100%). The duration of Radiation therapy was ≤ 46 days in 27 patients (90%) and was 47 - 51 days in three patients (10%).

All the patients received four cycles of Cisplatin. All patients received therapy as per protocol or acceptable variations for both radiation and chemotherapy.

Variables	No. of Patients	%
Sex		
Male	28	93.3
Female	2	6.7
Age (Years)		
Median	55 Years	
Range	40 - 65 Years	
ECOG Scale		
ECOG1	30	100
Habits		
Smoking	6	20
Tobacco	2	6.6
Smoking + Alcohol + Tobacco	3	10
Smoking + Alcohol	16	53.3

Table 1. Distribution of Patient and Tumour Characteristics

Site		
Hypopharynx	14	46.7
Oropharynx	16	53.3

Table 2. Distribution of Patients according to Tumour Site

Interpretation - Pre-dominant site being Oropharynx

Stage Grouping Chart

Oropharynx			Hypopharynx			
Tonsil	Soft Palate	Post 1/3 rd Tongue	Pyriform Fossa		Pharyngeal Wall	Post-Cricoids
			Right	Left		
3 (10%)	3 (10%)	10 (33.3%)	6 (20%)	3 (10%)	3 (10%)	2 (6.6)

Table 3. Distribution of Patients according to Tumour Subsite

Interpretation - Predominant subsite being post. 1/3 tongue.

Grade		
Moderately Differentiated	26	86.7
Poorly Differentiated	4	13.3

Table 4. Patients Distribution by Tumour Grade

Interpretation - Predominant grade being moderately differentiated.

Tumour Response

Overall response to therapy was recorded in all patients (100%). This included a complete response in 25 patients (83.3%) and partial response in five patients (16.7%). Of the five patients with residual disease (partial response), three patients (10%) had residual disease at the primary site, one (3.3%) patient at the nodal site and one (3.3%) patient had residual at the primary and nodal site.

A significant observation was the association between the grade of squamous cell carcinomas. Complete response was seen with 80.8% of Grade II, and 100% of Grade III carcinomas (P). Site-wise 78.6% of hypopharyngeal cancers and 87.5% of oropharyngeal cancers showed complete

response (P); 100% of T2 tumours, 100% of T3 tumours and 61.5% of T4a tumours showed complete response (P). Nodal response demonstrate 100% complete response among patients with N0, N1 and N2a lesions, while N2b lesions showed 33.3% and N2c lesions 25% complete response respectively (P).⁹

Acute Toxicity

Five (16.7%) patients showed Grade I skin toxicity, 15 patients (50%) showed Grade II and 10 patients (33.3%) Grade III skin toxicity. Loss of body weight was kept to less than 10% in 20 patients. Most of the patients had Grade I and Grade II nausea. Grade I and Grade II leucopaenia was seen in 19 (63.33%) patients and 11 (36.7%) patients respectively.⁹

Mucositis

Mucositis developed in almost all patients in the study. Grade III and Grade IV.

DISCUSSION

The findings that a number of modified radiation fractionation and concurrent chemoradiation regimens are more effective than conventionally fractionated radiation therapy in the treatment of advanced HNSCC generated interest to test the combination of altered fractionation regimens with chemotherapy.

RTOG 90-03 was a large randomised trial comparing Standard Fractionation (SFX) against Hyper-Fractionation (HFX), Accelerated Fractionation with Split-course (AFX-S),

and Accelerated Fractionation by Concomitant Boost (AFX-CB) in the management of patients with advanced HNSCC. Between September 1991 and August 1997, 1113 patients were enrolled. Loco-regional control was higher with the HFX and AFX-CB ($p = 0.045$ and 0.05) than SFX. The disease free survival showed a trend in favour of AFX-CB and HFX ($p = 0.054$ and 0.067), but there was no difference in overall survival. Accelerated concomitant boost was associated with a higher transient Grade III late toxicity. However, there was no difference in the incidence of persistent Grade III or Grade IV late toxicity among the arms at one year or longer followup.^{10,11}

In comparison with chemoradiation treatment strategies attempted in this Institution, this treatment protocol compares favourably of 61.6%. Another study that evaluated hyper-fractionated radiation therapy and concurrent Cisplatin-5FU chemotherapy (2 cycles, week 1 and 5) recorded a complete response of 73.1% and acute Grade III toxicity of 62%.^{12,13}

This study was based on the German trial. All the patients completed the treatment, both radiation therapy and chemotherapy as specified or with very minor variations. The acute toxicity of the treatment was rather severe as expected. Comparing the acute toxicity with trials conducted by several Institutions, however, is rather difficult because of inconsistency in recording and reporting as clearly pointed out by Trotti and Bentzen.

CONCLUSION

The strategies used during the past decades to improve the outcome for patients with loco-regionally advanced Head and Neck cancers include altered fractionation and combined radio-chemotherapy. This data shows that accelerated hyper-fractionated concomitant boost radiotherapy with weekly cisplatin can be administered with acceptable morbidity in patients with good performance status and achieves high rate of loco-regional control and survival. The compliance to therapy is high and the loco-regional response achieved compared favourably with ACB alone or other concurrent chemoradiation regimens using standard or altered fractionation regimens tested by the Institute. It also compares well with the available literature.

Further clinical trials using larger subset of patients are necessary before embarking on this promising regimen.

REFERENCES

- [1] Rodgers LW, Stringer SP, Mendenhall WN, et al. Management of squamous cell carcinoma of the floor of mouth. *Head Neck* 1993;15(1):16-9.
- [2] Weber RS, Gidley P, Morrison WH, et al. Treatment selection for carcinoma of the base of tongue. *American Journal of Surgery* 1990;160:415-9.
- [3] El Badawi SA, Fletcher GH, Oswald MJ, et al. Squamous cell carcinoma of the pyriform sinus. *Laryngoscope* 1982;92(4):357-64.
- [4] Yuen A, Medina JE, Goepfert H, et al. Management of stage T3 and T4 glottic carcinomas. *American Journal of Surgery* 1984;148(4):467-72.
- [5] Ang KK. Altered fractionation trials in head and neck cancer. *Seminars in Radiation Oncology* 1998;8(4):230-6.

- [6] Robbins MEC, Hopewell JW. Radiation-related renal damage. In: Bach PH, Lock EA, eds. Nephrotoxicity in the experimental and clinical situation. part 2: Martinus Nijhoff Publishers 1987:817-46.
- [7] Rooney M, Kish J, Jacobs J, et al. Improved complete response rate and survival in advanced head and neck cancer after three-course induction therapy with 120-hour 5-FU infusion and cisplatin. *Cancer* 1985;55(5):1123-1128.
- [8] Popkin JD, Hong WK, Bromer RH, et al. Induction bleomycin infusion in head and neck cancer. *Am J of Clin Oncol* 1984;7(3):199-204.
- [9] VALCSG: Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *New England Journal of Medicine* 1991;324(24):1685-90.
- [10] Taylor SG, Appelbaum E, Showel JL, et al. A randomized trial of adjuvant chemotherapy in head and neck cancer. *J of Clin Oncol* 1985;3(5):672-9.
- [11] Glickman AS, Slotman G, Clark J, et al. Concurrent cis-platinum and radiation with or without surgery for advanced head and neck cancer. *Int J of Radiat Oncol Biology Phys* 1994;30(5):1043-50.
- [12] Ertekin MV, Koc M, Karslioglu I, et al. Zinc sulfate in the prevention of radiation-induced oropharyngeal mucositis: a prospective, placebo-controlled, randomized study. *Int J Radiat Oncol Biol Phys* 2004;58(1):167-74.
- [13] Lin LC, Que J, Lin LK, et al. Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head-and-neck cancers: a double-blind, randomized study. *Int J Radiat Oncol Biol Phys* 2006;65(3):745-50.