Research Article

Concurrent chemoradiation with paclitaxel in locally advanced head and neck cancer: A feasibility study from tertiary cancer care center

Anjan Bera, Chandrima Banerjee, Shatarupa Dutta, Linkon Biswas

Department of Radiotherapy, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal, India

Correspondence to: Chandrima Banerjee, E-mail: chandrimab14@gmail.com

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ABSTRACT

Background: In India, the majority of the head and neck squamous cell carcinoma (SCC) of head and neck (60–80%) presented in locally or locoregionally advanced stage but non-metastatic disease as compared to 40% in developed nations. Uncontrolled local and/or locoregional disease causes most fatalities and predominant failure pattern is local and/or locoregional. Concurrent chemoradiation (CRT) is now standard of care. However, regarding either the optimal scheduling of chemotherapy regimen or radiotherapy (RT) dose fractionation scheme, no consensus exists. Paclitaxel is also active agents against squamous cell carcinoma of head and neck. Weekly paclitaxel appeared to be equivalent to weekly cisplatin with concurrent radiation in the treatment of locally advanced SCC of head and neck cancer (HNC). Concurrent chemoradiotherapy with paclitaxel in locally advanced head and neck malignancy is recommended in NCCN Guideline. **Objectives:** The aim of our study is feasibility and efficacy of CRT with paclitaxel for the treatment locally advanced HNC in our institute, Nil Ratan Sircar Medical College and Hospital, Kolkata. **Material and Methods:** Between January 2014 and December 2018 ninety eight (98) previously untreated patients with locally advanced histologically confirmed carcinoma oral cavity, oropharynx, and hypopharynx treated with CRT. Chemotherapy consisted of paclitaxel at a dose 40 mg/m^2 over 1 h given once weekly from 1st week of RT, up to 4–6 cycles. RT consisted of 66 Gy/33#/61/2 weeks, 2 Gy/fraction, delivered by two parallel opposed lateral face and neck and low anterior neck portal, in cobalt 60 machines. Toxicity was graded using Common Terminology Criteria for Adverse Events v3. To assess response to therapy contrast-enhanced computed tomography (CECT) head and neck and/or magnetic resonance imaging head and neck; CECT chest or whole-body fluorodeoxyglucose and positron emission tomography computed tomography scan were done. **Results:** Overall complete response (CR) rate seen in 68% and partial response seen in 32% patients. Two-year disease-free survival, progression free survival, and overall survival were 59%, 72% and 85%, respectively. Grade II acute skin reaction seen in 45% patients and Grade III acute skin reaction seen in 55% patients. Similarly, Grades II and III mucosal reaction is seen in 48% and 52% patients. All patients experience Grade II dysphagia and managed conservatively. **Conclusions:** CRT with paclitaxel in locally advanced HNC is safe and confers high CR rate with acceptable toxicity. However, more randomized study with large number of patients is needed to come to conclusions regarding its efficacy.

KEY WORDS: Paclitaxel; Head and Neck Cancer; Radiotherapy; Efficacy

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INTRODUCTION

Worldwide non-communicable disease (NCD) responsible for 63% death in the year 2008, and in India NCD accounts for 53% deaths. Among NCD, cancer one of the leading causes of death in India and accounts for 6% mortality in the year 2008.[1] In Asia, especially in India, for both sexes,

57.5% of global head and neck occurs and in India, head and neck cancer (HNC) is a major form of cancer, accounting for 30% of all cancer[2] and its higher prevalence strongly reflects exposure to certain environmental agents, particularly to tobacco and alcohol.[1-5] The majority of the head and neck squamous cell carcinoma (SCC) of head and neck (60–80%) presented in locally or locoregionally advanced stage but non-metastatic disease as compared to 40% in developed nations.[2,5] SCC of tongue base presents a more difficult problem than other HNC because of its anatomic location, there is a tendency to late diagnosis, and a frequent association with nodal metastasis. Uncontrolled local and/or locoregional disease causes most fatalities, and predominant failure pattern is local and/or locoregional.[5] Historically, the standard nonsurgical therapy for locally advanced disease was radiotherapy (RT) alone. Although, compared to conventional RT, modification of fractionation with hyper fractionation and altered fractionation resulted in 7–10% improvement in locoregional control and 8% absolute improvement in 5-year survival, the local control rate and disease-free survival rate were still lower, in between 50%–70% and 30%–40%, respectively.[5] Hence, there was need for improvement of disease control, survival and combination of chemotherapy and RT have been tried. As chemotherapeutic agents may provide additive cytotoxicity and radio sensitize malignant cells, this concurrent chemoradiotherapy is most commonly used and biologically attractive strategy. Because of existence of interaction between radiation and chemotherapy drugs at the molecular cellular, microenvironmental, and metabolic level, resulting in anti-tumor effect greater than that would be expected on the basis of additive action.[5] The goal of combining chemotherapeutic drugs with RT is to increase patients' survival by improving locoregional control, decrease or eliminates distant metastasis, or both while preserving organ function and integrity. The superiority of combined RT and chemotherapy to RT alone seen in most of the randomized trials.[6-9] In a meta-analysis of chemotherapy in Head and Neck Cancer (MACH-NC) by Pignon *et al*.,[7] demonstrated that, concurrent chemoradiation (CRT) is more efficacious than RT alone in advanced HNC and there was an improvement in 13.5% locoregional control, 6.5% improvement in 5 years overall survival (OS), and 19% reduction in risk of death with CRT over RT alone. CRT is now standard of care for treatment of locally advanced head and cancer.[10] In SCC of other sites including cervix and esophagus, the superiority of concurrent CRT compared to RT alone has been proven in multiple trials.[10-14] However, regarding either the optimal scheduling of chemotherapy regimen or RT dose fractionation scheme, no consensus exists. Single-agent high dose cisplatin, given every 3 weeks at a dose of 100 mg/m^2 on days 1, 22, and 43 of RT, is frequently used concurrent chemoradiotherapy regimen, but it is associated with significant compliance problem. Carboplatin, a second-generation platinum compound, tends to have less nephrotoxic or neurotoxic effects compared to cisplatin but with slightly increased hematologic toxicity. Because of less toxicity it is incorporated in the CRT schedule for the treatment of head and cancer, esophageal cancer, lung cancer for its potential efficacy as radiosensitizer.[15] Paclitaxel is also active agents against squamous cell carcinoma of head and neck. The combination of cellular arrest in G2M phase of cell cycle which is most radiosensitive phase of cell cycle, drug-induced apoptosis, and drug-induced reoxygenation of surviving hypoxic cells underlies paclitaxel's radiosensitizing ability.[16,17] In a single small Phase III trial from India, weekly paclitaxel appeared to be equivalent to weekly cisplatin with concurrent radiation in the treatment of locally advanced SCC of HNC.[16] Although concurrent chemoradiotherapy with paclitaxel in locally advanced head and neck malignancy recommended in NCCN Guideline, we have limited experience regarding use of this CRT regimen we have limited clinical knowledge regarding safety and feasibility of its clinical use in recommended dose. After getting formal permission from our ethical committee, we wanted to study whether this combination of RT and chemotherapy regimen in recommended dose can be delivered safely in our hospital or not.

MATERIALS AND METHODS

Treatment protocol is depicted in Figure 1. Between January 2014 and December 2018 98 previously untreated patients with locally advanced unresectable, histologically confirmed carcinoma oral cavity, oropharynx, and hypopharynx with ECOG ≤2 treated with CRT in our hospital (Nil Ratan Sircar Medical College and Hospital, Kolkata) included for analysis. After confirming diagnosis by biopsy, all patients underwent complete blood count, complete metabolic profile, endoscopy, contrast-enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI) of head and neck, CECT of chest, ultrasonography of whole abdomen, bone scan when indicated, whole body fluorodeoxyglucose (FDG), positron emission tomography (PET), and computed tomography (CT) scan to assess extent of locoregional disease and to rule

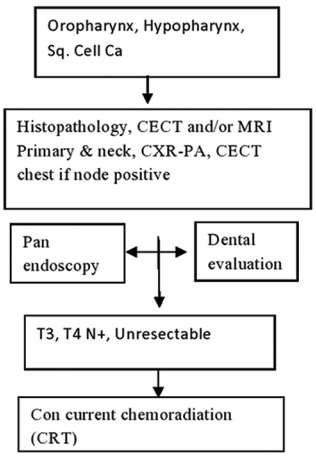

Figure 1: Treatment algorithm for locally advanced unresectable carcinoma of hypopharynx and oropharynx

out distant metastasis. All patients asked to quit smoking and drinking alcohol during RT because smoking, drinking alcohol during radiation associated with poor treatment outcomes. All patients advised for pre radiotherapy dental prophylaxis in the form of extraction of tooth which are unrestorable, filling and scaling for tooth which are restorable. Concurrent chemotherapy consisted of paclitaxel at a dose 40 mg/m^2 over 1 h given once weekly from 1st week of RT. We have use filgrastim routinely for secondary neutropenia prophylaxis. Chemotherapy administered every week up to 4–6 cycles. RT consisted of 66 Gy/33#/6 1/2 weeks, 2 Gy/fraction, delivered by two parallel opposed lateral face and neck and low anterior neck portal, in cobalt 60 machine. During CRT, patients were reviewed weekly by physical examination along with routine blood investigation. All patients asked to take adequate nutrition to maintain health and body weight. Toxicity was graded using Common Terminology Criteria for Adverse Events v3. To assess response to therapy CECT head and neck and/or MRI head and neck; CECT chest or whole-body FDG, PET, and CT scan were done. After getting formal permission from our ethical committee, we wanted to study whether this combination of RT and chemotherapy regimen in recommended dose can be delivered safely in our hospital or not.

RESULTS

Between January 2014 and December 2018, 98 previously untreated patients with locally advanced histologically confirmed carcinoma oral cavity, oropharynx, and hypopharynx treated with CRT included for analysis. Baseline patient's disease and demographic characteristics are depicted in Table 1. Six months after completion of CRT, response assessment was done. Overall complete response (CR) rate seen in 68% and partial response seen in 32% patients [Table 2]. Response rate according primary site of malignancy was comparable and statistically not significant. Two-year disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) were 59%, 72%, and 85%, respectively. Grade II acute skin reaction seen in 45% patients Grade III acute skin reaction seen in 55% patients. All patients managed with gentian violet paint and oral anti-inflammatory agents. Similarly, Grades II and III mucosal reaction is seen in 48% and 52% patients, respectively, and all patients managed conservatively [Table 3]. All patients experienced Grade II dysphagia and managed conservatively. Among late toxicity, Grades II and III xerostomia, Grade II fibrosis, and Grade II dysphagia were seen in 60%, 22%, and 29%, respectively.

Table 1: Patient's baseline characteristic

Characteristics	Number of patients (*n*=98) (%)
ECOG PS score	
1	63 (64)
2	35 (37)
Age (year)	
Range	33–69
Median	54
Sex	
Male	75 (77)
Female	23 (23)
Stage	
III	73 (74)
IV	25 (26)
Primary site of tumor	
Oral cavity	15 (15)
Oropharynx	60 (61)
Hypopharynx	23 (22)

Table 2: Site wise response to CRT

Primary site of tumor	Complete response (%)	Partial response (%)
Oral cavity	10 (67)	5 (33)
Oropharynx	42 (70)	18 (30)
Hypopharynx	15 (65)	8 (35)
Overall	67 (68)	31 (32)

CRT: Concurrent chemoradiation

Table 3: Adverse events (*n*=98)

Adverse events		Grade	*n* (%)
Acute toxicity	Skin reaction	II	44 (45%)
		III	54 (55%)
	Mucosal reaction	II	47 (48%)
		III	51 (52%)
Late toxicity	Xerostomia	II	33 (34%)
		III	25 (26%)
	Dysphagia	II	28 (29%)
	Fibrosis	II	21 (22%)

DISCUSSION

In our study, the overall CR rate is seen in 68% and partial response seen in 32% patients. Two year DFS, PFS, and OS were 59%, 72%, and 85%, respectively. Response rate according primary site of malignancy was comparable and statistically not significant. Grade II and Grade III acute skin reaction is seen in 45% and 55% patients, respectively. Similarly, Grades II and III mucosal reaction is seen in 48% and 52% patients, respectively, and all patients managed conservatively. All patients experienced Grade II dysphagia and managed conservatively.

The median age of patients in our study was 54 years. According to available literature, the most common age for the development of HNC is 4th–7th decades in India.[1-4] Thus, the median age of our study corresponds to the existing data.

In the present study, 77% patients were male; indicating that HNC carcinoma is more prevalent in males than in females and its higher prevalence strongly reflects higher rate of exposure to tobacco and alcohol.[1-5] In the era of modern RT planning, delivery technique and CRT, the outcome oropharyngeal cancer has improved a lot. Current standard treatment for AJCC Stage III and non-metastatic Stage IV oropharyngeal carcinoma is CRT[10] and this is based on the results of MACH-NC study which demonstrated 6.2% absolute improvement in OS.[7] In Phase III randomized study from India, by Jain *et al*.,[16] low dose weekly paclitaxel concurrent regimen appears to be equivalent to weekly cisplatin concurrent radiation in the treatment of locally advanced HNCs. In multiple randomized trials, for the treatment locally advanced oropharyngeal or hypopharyngeal SCC, CRT was associated with high level of locoregional control and superior results to maximally intensive RT alone.[17,18,19] In our study, locoregional control ranging from 65% to 70% across primary sites and comparable to above-mentioned study [Table 4]. This improvement result was maybe due to additive cytotoxicity, and radio sensitizes malignant cells because of the interaction between radiation and chemotherapy drugs at the molecular cellular, microenvironmental, and metabolic level, resulting in anti-tumor effect greater than that would be expected on the basis of additive action. The mechanism of chemotherapy-induced radiation sensitization is depicted in Table 5.[20-26] The efficacy of CRT may be reflected by improvement of locoregional control, but this improved locoregional control may also be due to at least in part, increased incidence of HPV positive disease compared to older series because HPV associated malignancy usually carries better prognosis than HPV negative malignancy. We have excluded patients >70 years of age because, with advancing age, those with modest performance status, a steadily decreasing benefit of chemotherapy seen and this was explained by the accelerated repopulation because of toxicity related treatment break.[19,27] Acute skin and mucosal toxicity are increased with the use of CRT compared to RT alone and most significant problem encountered in CRT and may lead to treatment breaks. RT delivery time significantly prolonged in 30% of combined modality patients because of toxicity in EORTC trial but not in any of the RT alone patients. In case treatment breaks and prolongation of overall treatment time, because accelerated repopulation of tumor, may adversely affect success of CRT in HNC.[28-30] Typically, in CRT, both late and acute toxicity are greater than those from RT alone. Acute toxicities include nausea, vomiting, fatigue, xerostomia, mucositis, odynophagia, dysphagia, and hematological toxicities. All toxicities are usually self-limiting except xerostomia and dysphagia, and these two may be continued as late toxicity. Post CRT late toxicities can also be quite significant and include xerostomia, odynophagia, dysphagia, fibrosis, trismus, osteoradionecrosis, dental caries, and 56% patients treated with CRT had at least one Grade 3–4 late toxicity compared to 30% treated with RT alone.[10] In our study, incidence of acute skin reaction and mucosal reaction slightly higher than those reported in literature, and this may be explained by the fact that all patients treated with conventional RT technique in cobalt 60 machines. All toxicity was managed conservatively, and none of this toxicity was dose-limiting.

Table 4: CR and PR in selected contemporary series of CRT using paclitaxel

Series	CR (%)	PR (%)
Jain *et al*.[15]	73	37
Essa *et al*.[25]	85.7	14.3
Kanotra *et al*.[26]	72.7	23.3
Present study	68	32

CRT: Concurrent chemoradiation, CR: Complete response, PR: Partial response

Table 5: Mechanism of chemotherapy-induced radiation sensitization

Class of compound	Mechanism of radiation sensitization
Platinum-based compounds	DNA synthesis inhibition, inhibition of transcription elongation by DNA interstrand cross-link, radiation-induced DNA damage repair inhibition
Taxenes	Cellular arrest in G2M phase of cell cycle, induction of apoptosis, reoxygenation of tumor cells

Limitations of our study are non-randomized, single-arm, retrospective in nature.

CONCLUSIONS

CRT with paclitaxel in locally advanced HNC is safe and confers a high CR rate with acceptable toxicity. However, more randomized study with more number of patients is needed to come to conclusions regarding its efficacy.

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