ORIGINAL ARTICLE

IS THERE ANY ROLE OF INDUCTION CHEMOTHERAPY IN UNRESECTABLE LOCALLY ADVANCED HEAD AND NECK CANCERS: AN INSTITUTIONAL DATA

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ABSTRACT

Background: Head and neck cancers are very common in India due to habit of betel quid and areca nut chewing along with bidi smoking and alcoholism, with more than half of the patients presenting in locally advanced stage. Chemo-radiotherapy with or without induction chemotherapy is the mainstay of treatment for these patients. We have performed a prospective study to determine the effectiveness of induction chemotherapy followed by concurrent chemo-radiotherapy.

Methodology: A total of 20 patients with unresectable locally advanced head and neck cancers were enrolled in the study. Treatment included two cycles of induction chemotherapy with Paclitaxel (135mg/m^2, day1) and Cisplatin (40mg/m^2 onday1, 2) at an interval of 21days followed by Cisplatin 40mg/m^2 weekly along with conventional radiotherapy (70Gy/35#/7weeks). The tumor response and acute toxicities were evaluated.

Results: Of the 20 patients, only 8 patients completed the planned treatment schedule. Of the 8 patients, radiological complete response was observed in 5 patients. The partial response was seen in 2 patients. One patient had progressive disease. Few grade 1 and 2 toxicities including skin toxicity, diarrhea, anemia, acute kidney injuryand peripheral sensory neuropathy were observed. Only 4 patients had grade 3 toxicities of acute mucositis, vomiting and neutropenia.

Conclusion: Sequential therapy incorporating induction chemotherapy and chemo-radiotherapy appears to be an inferior approach. Further investigations are required to select a better regimen in patients with unresectable locally advanced head and neck cancer.

Keywords: Head and neck cancer, Induction Chemotherapy, Chemo-radiotherapy, Paclitaxel, Cisplatin.

INTRODUCTION

Head and neck cancer (HNC) is the 6th most common cancer worldwide. Each year there are approximately 650,000 new incident cases worldwide.[1,2]Of these, 200,000 cases occur each year in India. In India it accounts for 30% of all cancers in males. In females they constitute 11 to 16% of all sites of cancers. Among them, tongue and mouth in males contribute to more than one-third of the total cancers and among females mouth cancer is the leading cause.[3] Nearly two-thirds of oral cancers are located in the buccogingival sulcus, where the betel quid is kept for long periods in the oral cavity. The consumption of tobacco in various forms such as smoking bidi, betel quid (paan) along with alcohol are the major 'preventable' risk factors. Both tobacco and alcohol are dose-dependent[4]and synergistic risk factors. Numerous research studies have proved that most of the head and neck cancers are squamous cell carcinomas in origin.[5]

60 to 80% of patients present with advanced disease in India, as compared to 40% in developed countries, consistent with which, the overall survival is also reduced.[6] A MACH-NC meta-analysis demonstrated that use of Radiotherapy and concurrent Chemotherapy (CRT) resulted in 19% reduction in the risk of death and overall 6.5% improvement in 5-year survival compared to treatment with Radiotherapy alone (p value <0.0001).[7] This benefit is attributable to 13.5% improvement in loco-regional control.

Concurrent Chemo-radiation has become a standard modality for loco-regionally advanced HNC.[8] Cisplatin is a potent radiosensitizer and the drug most commonly used for chemo-radiotherapy in HNC. To further improve survival rates, there is increasing interest in the use of induction chemotherapy which may improve local control, and reduce the rate of

distant metastases that may not be adequately treated by local therapy or by lower-dose chemotherapy as part of chemo-radiotherapy.

Phase III clinical trials evaluating induction chemotherapy showed better control of distant disease [9,10]suggesting the possibility of a sequential approach in which IC may eradicate occult metastatic foci and that subsequent concomitant CRT may suppress loco-regional disease in head and neck cancer.[11,12]The Veterans Affairs' laryngeal cancer trial, which demonstrated functional organ preservation in up to 64% of patients at 2 years, was the first in a series of studies to demonstrate the utility of induction chemotherapy for controlling distant failure in locally advanced disease, improving survival rates, and allowing for organ preservation.[13]

We have performed a prospective study to determine the effectiveness of two drug regimen (Paclitaxel and Cisplatin) administered as induction chemotherapy followed by concurrent chemo-radiotherapy in patients with unresectable locally advanced head and neck cancer.

METHODOLOGY

The aim of this study was to assess the response and acute toxicity of induction chemotherapy followed by chemo-radiotherapy in locally advanced Head and Neck Cancer. All eligible patients coming to Sri Aurobindo Institute of Medical sciences between october 2013 to april 2015, who are willing to be a part of this study were included. Institutional ethics committee clearance was obtained. The patients between age 18 – 65 years with Karnofsky Performance Status (KPS) more than 70% with histologically proven squamous cell carcinoma of stage III or IV head and neck cancer who were ineligible for curative surgery were included in the study. AJCC 7th edition, 2010 was used to stage the patients. The patients with metastatic or recurrent disease or second primary malignancy or those who have received prior chemotherapy or radiotherapy were excluded from the study. 20 patients were found eligible and were included in the study. Pretreatment evaluation was done. An informed consent was taken from the patients explaining them the whole procedure.

Treatment included two cycles of induction chemotherapy with Paclitaxel (135mg/m^2, day1) and Cisplatin (40mg/m^2 onday1, 2) at an interval of 21days followed by Cisplatin 40mg/m^2 weekly along with radiotherapy (70Gy/35#/7weeks at 2Gy/# with 5#/week) using Intensity Modulated Radiation Therapy (IMRT) technique. Prior to all chemotherapy cycles, blood counts, renal parameters and electrolytes were assessed and chemotherapy was administered only if they were within acceptable limits (Hb >10gm%, TLC >3500/mm^3, ANC > 1500/mm^3, Platelets >1.5lakhs/mm^3 and urea < 40mg/dl, creatinine <1.2 mg/dl, Na^+>130mg/dl, K^+>3.5mg/dl and <5mg/dl).

Paclitaxel (135mg/m^2) was given intravenously in 500mL fluid as a 3-hour infusion. Adequate hydration with added potassium and magnesium pre and post cisplatin was administered with adequate anti emetics including ondansetron, ranitidine and dexamethasone was given as intravenously. Antihistamine diphenhydramine was added in pre-medication with Paclitaxel. The urine output was monitored at regular intervals. To prevent delayed emesis, oral ondansetron and dexamethasone was given.

During the course of radiotherapy,6 cyclesof cisplatin were administered on weekly basis at a dose of 40mg/m^2 each. Hydration, electrolyte balance, emesis and urine output were taken care of. 10% weight loss since inception of treatment was considered as an indication for Ryles tube insertion. For radiotherapy, patients were treated in supine position and immobilization was done using thermoplastic mask for head, neck and shoulders. Computed Tomography (CT) scan images were taken from above the calvarium to the carina with 3mm slice thickness. Intravenous contrast was given during CT simulation to help delineate lymph nodal groups. Target volumes and organs at risk were contoured as per the institutional protocol. Danish Head and Neck Cancer Group (DAHANCA) guidelines were followed in delineation of the neck nodal levels. Pre-treatment MRI and PET-CT scan images were fused with planning CT scan for target delineation, whenever available. The dose constraints to organs at risk were defined as per the institutional protocol. Dose volume histograms were used to evaluate the treatment plan. All patients were irradiated with megavoltage beams on Varian Clinac DMX Linear Accelerator with conventional fractionation (200 cGy per fraction, one fraction per day, 5 fractions per week) to a total dose of 70Gy/35#/7weeks using IMRT technique. Boosts were delivered as and when indicated.

During treatment all patients were assessed weekly and one month after completion of treatment. Tumor response was evaluated by clinical examination and CT scan according to Response Evaluation Criteria In Solid Tumors (RECIST version 1.1). Complete Response (CR) was defined as disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm. At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters was labeled as Partial Response (PR).

Toxicities were evaluated by history, physical examination and laboratory tests. The grading system was based on the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria. The

systemic toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

RESULTS

The patient and tumor characteristics are shown in the following table. Total 20 patients were enrolled in the study. Median age was 50 years (range 32-71 years). Oral cavity (50%) and Oropharynx (20%) were the most common primary tumor sites. There were 14 patients with stage IV A disease. The performance status of most of the patients was 80% according to KPS Scale. The presence of Human Papillloma Virus (HPV) and p16 status were not evaluated.

Table 1: Patient characteristics of the study group (n=20)

Characteristics	Cases (%)
KPS	
70%	8 (40)
80%	12 (60)
Tumor Site	
Oral Cavity	10 (50)
Oropharynx	4 (20)
Larynx	3 (15)
Hypopharynx	3 (15)
TNM Stage	
III	2 (10)
IV A	14 (70)
IV B	4 (20)

Table 2: Grade wise treatment related toxicities of the study group.

Toxicity	Grade I	Grade II	Grade III	Grade IV
Acute Mucositis	2	4	2	-
Skin toxicity	6	2	-	-
Vomiting	2	3	1	-
Diarrhoea	2	3	-	-
Anaemia	4	2	-	-
Neutropenia	3	2	1	-
Acute Kidney Injury	2	1	-	-
Peripheral sensory neuropathy	3	1	-	-

All patients received the planned induction chemotherapy; following which chemo-radiotherapy was fully delivered in 8 patients. Two patients died during chemo-radiotherapy due to disease progression and two patients left treatment in middle of chemo-radiotherapy due to intolerable acute toxicity (grade III mucositis). Remaining 8 patients received induction chemotherapy only (3 patients had subjective response and discontinued treatment and 5 patients were lost to follow up after induction chemotherapy).

Evaluation after chemo-radiotherapy showed radiological complete response in 5 patients. The partial response was seen in 2 patients. One patient had progressive disease.

Skin toxicity, diarrhoea, anaemia, acute kidney injury and peripheral sensory neuropathy were mainly grades 1 and 2 . Grade 3 toxicities of acute mucositis (seen in 2 patientspeaked during 4th week of radiotherapy), vomiting and neutropenia (1 patient each) were observed. All haematological toxicities were taken care of with blood transfusions and granulocyte colony stimulating factor (GCSF) support. Acute kidney injury was managed with oral and intravenous hydration before and after chemotherapy. Mucositis was managed with oral local anaesthetic agents such as benzydamine, lignocaine, maintaining good oral hygiene with use of mouthwash and patients who were not able to take food orally were given Ryles tube feeding support.

DISCUSSION

Radiotherapy with concomitant cisplatin is currently the standard treatment in patients with unresectable locally advanced head and neck cancer.[14] An approach of using induction chemotherapy followed by definitive local therapy may have theoretical advantages including the potential to decrease the risk of distant failure and a rapid reduction in tumor bulk in responders.

There is an evidence of a phenomenon known as accelerated repopulation of tumor cells according to which treatment with any cytotoxic agent can trigger tumor clonogens to divide faster than before. If overall treatment time is too long as might happen when we include the induction chemotherapy along with chemo-radiotherapy, there might be paradoxical increase in tumor size during therapy or immediately afterwards because the surviving clonogens in the tumor have been triggered into rapid repopulation.

MACH-NC meta-analysis [7] included 87 phase III trials and 16,485 patients. It demonstrated 4.5% overall survival benefit at 5 years when chemotherapy was added to RT, with greater benefit for concurrent chemo-RT compared to induction chemotherapy followed by RT (6.5% OS benefit with concurrent chemo-RT).

A phase III study, TAX 324 trial [15] randomized 501 patients with unresectable stage III/IV head and neck cancer (33% were larynx or hypopharynx) to induction TPF chemotherapy (docetaxel, cisplatin, 5-FU) versus PF (cisplatin, 5-FU) every 3 weeks for 3 cycles. Patients then had concurrent weekly carboplatin and RT to 70Gy. TPF improved 3-year

overall survival (48->62%) and loco-regional control (62->70%), but not distant metastasis. TPF increased neutropenia (54->84%). Twenty-one percent of patients who got TPF induction were not able to receive subsequent concurrent chemo-RT.

Our centre has mainly economically poor patients who cannot afford docetaxel and infusional 5FU based regimen with G-CSF support. Also, a two-drug regimen with combined cisplatin and taxane is more convenient than a 5- fluorouracil infusion regimen which requires indwelling catheters and ambulatory pumps. Despite this there is a 60% lost to follow up after NACT and all of those patients probably would have relapsed as it is well established that NACT should be followed by RT.

In our study, complete response was achieved in 62.5% patients, partial response was seen in 25% patients and progressive disease was observed 12.5% patients. These results are quite similar with a study by investigators at Yale University who evaluated a sequential regimen of cisplatin, 5-FU and leucovorin (PFL) induction chemotherapy followed by concurrent Cisplatin and radiation therapy for organ preservation in patients with advanced head and neck cancer.[16] Complete responses were seen in 67% of patients, with an impressive 5-year progression-free survival rate of 60%.

The toxicity analysis of our study showed that paclitaxel may be used for induction chemotherapy. Haematological toxicity was not severe. Grade 3-4 neutropenia occurred in 12.5% of patients receiving induction chemotherapy. It was similar to a study by Barone et al [19] who carried out a phase II study to investigate an induction regimen with cisplatin and paclitaxel followed by radiotherapy concurrent with weekly cisplatin for locally advanced HNSCC and had grade 3-4 neutropenia in 14% of patients. Grade 3–4 anaemia was uncommon.

Grade 1-2 mucositis was 75%, grade 3 was 25% and no one had grade 4 mucositis. Our results were comparable to the study by Barone et al [19] who used similar regimen of induction chemotherapy and showed 77% and 23% mucositis in grade 1-2 and grade 3, respectively. The main side effect of paclitaxel in combination with cisplatin was peripheral neuropathy. In our study, the peripheral neuropathy grade 2-3 was 12.5% only which is comparable to that seen with combination of paclitaxel, cisplatin and 5-fluorouracil as induction chemotherapy (grade 2–3, 14%) in a study by Hitt et al.[17]

Grade 3 vomiting occurred in 12.5% patients and no one had grade 4 vomiting. It was similar to the study by Pergolizzi et al [18] who evaluated activity and toxicity of a sequential treatment in advanced, non-metastatic, unresectable HNSCC. In their study, 16.66% patients experienced grade 3-4 vomiting. However, diarrhoea was slightly increased in our study with grade 2 diarrhoea in 37.5% of patients. Even though it was slightly high, it was acceptable and manageable.

Another important toxicity of paclitaxel and cisplatin is renal impairment which was measured using serum creatinine levels. It was deranged in 37.5% of patients in which most of them had grade 1 renal toxicity. It was comparable to 35% renal toxicity observed in the study at Yale University evaluating sequential regimen of PFL induction chemotherapy followed by concurrent Cisplatin and radiation therapy in patients with advanced head and neck cancer.[16]

In clinical practice the question of whether the addition of induction chemotherapy to concurrent chemo-radiotherapy will improve survival over concurrent chemo-radiotherapy alone remains unfortunately unansweredas the recent MACH NC update and NCCN guidelines have made NACT as a category 3 recommendation. It also makes more sense in our population that definitive local therapy in the form of CT-RT be administered upfront so as to mitigate the phenomenon of accelerated repopulation.

However, a poor compliance was seen which may be explained by prolonged treatment time, or subjective response following induction chemotherapy, or low socio-economic group of patients and/or additional chemotherapy-related toxic effects.

CONCLUSION

Sequential therapy incorporating induction chemotherapy and chemo-radiotherapy is an inferior approach and needs to be investigated further to select better regimen in patients with unresectable locally advanced head and neck cancer.

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