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Comparison of response and acute toxicities of concurrent chemoradiation with weekly cisplatin vs. paclitaxel/ carboplatin in locally advanced squamous cell carcinoma of head & neck: Protocol of a short-term phase III trial

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Abstract

Concurrent chemoradiation therapy (CCRT) has become the treatment of choice for locally advanced squamous cell carcinoma of head & neck (SCCHN). Multiple chemoradiation treatment paradigms are existent, but unfortunately the optimum timing, dosing and choice of systemic agents are controversial. Even though the current most widely accepted standard chemotherapy for radiation sensitization remains cisplatin, the toxicities are significant. Carboplatin possesses radiation-sensitizing properties as a result of its ability for repairing sublethal damage, binding thiols and inducing chromosomal aberrations. Compared to cisplatin, it is less nephrotoxic, neurotoxic and ototoxic. Paclitaxel is also a potent radiosensitizer, as demonstrated in preclinical and clinical trials, due to its effect of inducing cell cycle arrest in G2/M phase. The combining of carboplatin and paclitaxel with radiation has demonstrated promising clinical activity in respect of efficacy and improved tolerability against newly diagnosed, recurrent and metastatic SCCHN. This study intends to explore the advantage of multiagent CCRT with taxane over single agent cisplatin for patients with locally advanced, non-metastatic SCCHN. Patients with stage-III & IVA/B SCCHN will be randomly enrolled to receive following treatments: CDDP arm-Cisplatin (30mg/m^2) weekly plus radiotherapy (RT) (66-70 Gy, 1.8-2 Gy/ fraction); PC arm-weekly paclitaxel (40mg/m^2) and carboplatin (AUC-2) plus RT (66-70 Gy, 1.8-2 Gy/ fraction). Patients will be followed-up weekly and six weeks after completion of treatment, and treatment response will be evaluated with RECIST criteria. Toxicities will be assessed by RTOG Acute Radiation Morbidity Criteria. Chi-squared test, Fisher's exact test and t-test will be employed to compare between two treatment arms.

Ethics and dissemination: The study is registered at German Clinical Trials Register (DRKS00012877) and "National Institute of Cancer Research & Hospital Ethics Committee", Bangladesh (Ethical Clearance Certificate Reference: NICRH/Ethics/2015/185). Results will be disseminated through peer-reviewed international journals and major international conferences.

Trial registration number: DRKS00012877. http://www.drks.de/DRKS00012877

Abbreviations: AUC: Area Under the Curve; CCRT: Concurrent Chemoradiation Therapy; CT: Computed Tomography; ECOG: Eastern Cooperative Oncology Group; Gy: Gray; LRC: Loco Regional Control; OS: Overall Survival; PFS: Progression Free Survival; RECIST: Response Evaluation Criteria for Solid Tumor; RT: Radiotherapy; RTOG: Radiation Therapy Oncology Group; SCCHN: Squamous Cell Carcinoma of Head and Neck; SPSS: Statistical Package for Social Sciences

Article Summary

Article focus

1. Our hypothesis is that taxane containing regimen is superior to cisplatin only regimen in combination with radiation therapy for locally advanced SCCHN.

Key messages

1. For SCCHN, different chemotherapy regimens can be used with Radiation therapy where Cisplatin and Paclitaxel/Carboplatin both are acceptable options.
2. This randomized prospective trial will answer whether the integration of taxane into CCRT regimen will benefit patients of this group.

Strengths and limitations of this study

1. This is a short-term intervention and follow-up allowing the assessment of treatment response and acute toxicity.
2. Long-term outcome like late toxicity and survival will not be assessed in this short period of study.
3. The study will be conducted with all types of SCCHN in general.

Background

For many tumors, concurrent chemoradiotherapy (CCRT) has a central role in the treatment of locoregional disease. The use of CCRT in head & neck cancer is important because locoregional control is pivotal here. This is the fifth most common cancer worldwide, with an estimated annual global incidence of 529,451 cases [1]. 90-95% head

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& neck cancer diagnosis are squamous cell carcinomas (SCCHN) [2]; hence it is this type of disease should be focused on.

For practical purposes, SCCHN is divided into three clinical stages: early, locoregional/locally advanced, and metastatic or recurrent. Treatment approaches can vary depending on the disease stage. Most patients in the less developed regions in the world are diagnosed at locally advanced stage. In the past, survival at 5 years for locally advanced disease was reported to be only 40% [3] (10–30% for patients with stage IVA and IVB tumors) [4], and locoregional failure was the predominant cause of recurrence. More than 50% of patients who die from SCCHN have locoregional disease as the only site of failure, and almost 90% of patients with distant failure also have persistent locoregional disease [5-7]. Therefore, it is clear that the efficacy of any curative approach is measured by its ability to achieve local control.

Historically, locally advanced tumors were treated with surgery (with or without adjuvant radiotherapy) or radiotherapy alone. Only a minority of patients with locally advanced disease can undergo adequate surgical resection, and the outcomes were poor with respect to survival and organ preservation [4]. Radiotherapy alone is not sufficient to successfully treat most SCCHN at intermediate or advanced stages.

Currently, three different treatment options are available for locally advanced head & neck squamous cell cancers. All of these three treatment options are multimodality treatment approaches sequential or concurrent. The first and foremost approach involves definitive surgery; which is followed by adjuvant CCRT or RT alone, which ensures accurate pathologic staging and precise identification and documentation of high-risk features that guides the adjuvant treatment. Although this approach may fail to preserve valuable organ like larynx, it ensures treatment guided by histopathological diagnosis [8,9].

The alternate approach includes definitive concurrent chemoradiotherapy (CCRT) with salvage surgery as an optional backup treatment plan. This treatment approach lacks the pathologic information, a setback which is balanced by improved organ preservation. This benefit is already established for laryngeal cancer but is increasingly recognized for other anatomic locations; however, this approach remains controversial for oral cavity tumors [2].

The third approach uses of neoadjuvant chemotherapy followed by definitive surgery or radiation with curative intent. Major advantages include rapid reduction in tumor bulk in responders and the potential to decrease the risk of distant failure. Oftentimes response to induction predicts responsiveness to following definitive chemoradiotherapy. However, this can result in prolonged treatment time and additional chemotherapy-related toxic effects from systemic doses. This sequential approach also increases the total cost of treatment. This approach remains controversial for valid reasons, and is currently under investigation in several large, multicenter, randomized trials in order to determine significant benefit over CCRT [2,10].

Nonetheless, sensitizing effects are not tumor specific and affect adjacent normal tissues within the radiation field [2]. CCRT trials have consistently reported an increased incidence of acute grade 3 and 4 toxic effects, with mucositis and dermatitis being the most prominent [2]. This creates concern about chronic toxic effects, including consequential late effects, which evolve from persistent severe acute toxic effects. Interestingly, multiple studies have confirmed that, compared with radiation alone, the long-term side effects of CCRT, such as on swallowing function or speech, are not increased [3,11-13]. Owing to the prominent incidence of acute toxic effects, treatment should preferentially be performed at experienced centers, in which improved overall outcomes are observed [14].

Various chemotherapeutic agents including cisplatin, 5-fluorouracil, bleomycin, hydroxyurea, paclitaxel, docetaxel, carboplatin, mitomycin C, methotrexate, pemetrexed [15] and tirapazamine, and targeted therapies including cetuximab, gefitinib [16] and bevacizumab [17] have been tested as single agents in combination with radiotherapy [2,18-22]. Further research has suggested that combination chemotherapy regimens offer the potential to improve response rates further and possibly improve survival [23-25]. Multiagent based CCRT are investigated with 5-FU/cisplatin, paclitaxel/cisplatin, cetuximab/cisplatin, tirapazamine/cisplatin, paclitaxel/carboplatin, 5-FU/carboplatin and 5-FU/hydroxyurea [2].

Cisplatin is a potent radiosensitizer and the drug most commonly used for CCRT in head & neck cancer. A meta-analysis examining various chemoradiotherapy regimens indicated that platinum containing regimens might provide a survival advantage compared with non-cisplatin containing regimens [14]. Currently, the most widely used standard regimen is 100 mg/m^2 cisplatin every 3 weeks, combined with ~70 Gy radiation delivered in 1.8–2.0 Gy daily fractions. This regimen causes severe toxic effects, such as nephro-, oto- and neurotoxic effects, nausea and vomiting, as well as severe mucositis, which make the treatment suitable only for patients with normal creatinine clearance and a good performance status. Furthermore, locoregional failure rates are 35–65%, depending on tumor location, stage, and resectability [11-13]. To limit toxic effects, alternative administration schedules are also being used, but equivalent efficacy has not been established. For example, with once-weekly 30 mg/m^2 cisplatin regimen, no nephrotoxic effects were reported, but mucositis and neutropenia were prominent [26].

Carboplatin is a second-generation platinum agent that is structurally and functionally similar to cisplatin [27,28]. However, the radiosensitizing properties of carboplatin are not as well established as those of cisplatin [2]. One Head & neck cancer trial comparing cisplatin with carboplatin demonstrated similar efficacy and survival [29]. Carboplatin is frequently used in combination with other radiosensitizers, such as paclitaxel. The side effects of carboplatin are more favorable than those seen with cisplatin-based CCRT because few nephrotoxic or neurotoxic effects arise [2,18]. Nevertheless, hematologic toxic effects are slightly increased, and grade 3/4 toxic effects are seen in 40% of patients [2,18]. Single-agent carboplatin based CCRT has a favorable toxicity profile for patients with SCCHN, and this regimen is usually used in combination with paclitaxel.

Taxanes are potent radiosensitizers, and studies have examined single-agent paclitaxel based CCRT in locally advanced SCCHN [30,31]. Paclitaxel is tolerated with radiotherapy when administered at weekly doses of up to 40 mg/m^2 in SCCHN [32]. Mucositis and leukopenia are reported, but these toxic effects are generally predictable and manageable [2].

The radiation-sensitizing properties of both paclitaxel and carboplatin, as well as their documented activity in SCCHN have, therefore, motivated us to design a phase III trial. This project aims to assess short-term toxicity and efficacy of low-dose, multiagent chemotherapy with paclitaxel/carboplatin and single agent cisplatin given weekly in concurrently with, daily external beam radiotherapy.

Hypothesis of the trial: Our hypothesis is that taxane containing regimen is superior to cisplatin only regimen in combination with radiation therapy for locally advanced SCCHN.

Methods/Design

Study population

The diagnosis of locally advanced stage III, IVA or IVB SCCHN will be confirmed by a radiation oncologist prior to the initiation of the treatment. Histopathological confirmation will be done for all patients. Physical examination, panendoscopy, CT scan of neck & face as well as chest radiograph and ultrasound of abdomen will be done to determine the extent of disease and to exclude distant metastases. The patients will be staged according to the tumour-node-metastasis (TNM) classification. Pretherapy dental evaluation will be required prior to the start of chemoradiation. Patients will be selected randomly from National Institute of Cancer Research & Hospital, who will meet the eligibility criteria of the study.

Inclusion criteria

- SCCHN proved by histopathology
- AJCC stage-III, IVA and IVB
- Age: 18 to 75
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Biochemical tests values: WBC $\geq 3.5\times10^9$/L, Neutrophils $\geq 1.5\times10^9$/L, Platelets $\geq 100\times10^9$/L, haemoglobin ≥9 gm/dl, Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin ≤1.5×the upper limit of normal range, Creatinine concentration ≤120 umol/L, and creatinine clearance ≥50 ml/min
- No serious diseases of important organs
- Written informed consent signed prior to enrollment.

Exclusion criteria

- Prior chemotherapy or head & neck irradiation
- Pregnant or lactating woman
- Serious diseases of important organs
- Other malignancies
- Active uncontrolled infection
- Joined in other clinical trial

Operational definition

There will be two arms. In each arm 50 patients will be enrolled randomly.

CDDP Arm: Concurrent chemoradiotherapy regimens with CDDP (cisplatin 30mg/m² weekly with premedications and adequate hydration; radiotherapy- 6600-7000 cGy in single daily 1.8-2 Gy/fraction, 5 days a week on linear accelerator with 4 or 6 MV photon beams).

PC Arm: Concurrent chemoradiotherapy regimens with PC (paclitaxel 40mg/m² over 1 hour followed by carboplatin AUC-2 over 30 min with premedications, weekly; radiotherapy- 6600-7000 cGy in single daily 1.8-2 Gy/fraction, 5 days a week on linear accelerator with 4 or 6 MV photon beams).

Primary outcome measure

Primary endpoint of this study is treatment response. Treatment response will be measured 6 weeks after completion of treatment according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 as complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD) using the data of panendoscopic evaluation and CT scans of neck & face obtained 6 weeks after therapy. Pathologic confirmation will be required for patients suspected to have clinical evidence of residual disease at the primary site 6 weeks after therapy.

Secondary outcome measure

Secondary endpoint of this study is treatment related acute toxicities. Acute toxicities will be reported weekly during treatment and 6 weeks after completion of treatment. Acute toxicities of the two regimens will be evaluated by determining the frequency of severe (≥ grade 3) toxicities based on RTOG Acute Radiation Morbidity Criteria using the information of history and physical examinations, ECOG performance status, and blood tests like CBC, electrolyte, creatinine, ALT etc.

Randomization

All the locally advanced head & neck cancer patients from National Institute of Cancer Research & Hospital, Dhaka, Bangladesh will be assigned serial numbers. Then random number table will be used to choose each single patient until desired sample size is allocated to each group.

Blinding

The study is double blinded. Both patients and treating physician will be blinded about treatment groups.

Sample size calculation

Based on the data from recent relevant trials, standardized difference was calculated Using Altman's normogram and verified by Quick formula.

Ethical implications

- Institutional permission to collect data was obtained before conducting the study.
- Participants will be volunteered.
- All patients will be included in the study after informing about the nature of the study. They will be explained about the aim, objective, procedure, risk and benefit of the procedure in easily understandable language.
- Informed written consents will be obtained from the patients.
- All patients will be coded by a serial number which can be referenced to the chart number only.
- All participants will be free to take part or refuse to be a part of the study.
- The study will not interfere with patient management or deal with moral or social issue.
- The study protocol was submitted to the ethical review committee of the institution and an ethical clearance certificate was obtained.
- The study protocol was submitted to WHO Primary Registry German Clinical Trials Register for trial registration and was officially registered.

Statistical analysis

Data will be expressed by adding error bars which will show +/- standard deviation. Differences in patient demographics between CDDP and PC treated patients will be analyzed with chi-squared tests or two-sided student's t-tests. Fisher's exact test or chi-squared test will be used to compare treatment arms with respect to toxicity rates and response. Statistical co-relation will be done by SPSS (Statistical Package for the Social Sciences) software. A value of $P < 0.05$ will be considered statistically significant with confidence interval of 95%.

Discussion

Head & neck cancer is a worldwide health problem. More than 90% of these cancers are of squamous cell histology [33]. The majority of patients present with locoregionally advanced disease [33] and are managed with combined modality approaches. Newer treatment strategies that incorporate a combination of systemic agents and radiation (CCRT) are being widely investigated in this setting with the goal of improving both locoregional and distant disease control.

Recent trials have shown that CCRT offers a significant advantage over surgery followed by radiotherapy [18] or radiotherapy alone [34-38], and induction chemotherapy followed by CCRT has shown no demonstrable benefit over CCRT for patients with locally advanced SCCHN [10]. Despite a substantial number of clinical trials performed to justify the safety and efficacy of several CCRT regimens, important questions on the optimal treatment paradigm remain. While the most commonly used chemotherapeutic agent in combination with RT has been cisplatin, multi-agent regimen, paclitaxel/carboplatin, has evolved with encouraging result in terms of efficacy and tolerability. [2,18,33].

Patients with head & neck cancer, most of the time, present with non-metastatic state. Advanced stage without distant disease (locally advanced) is curable in 50% cases with the introduction of an aggressive treatment protocol [2]. Concurrent chemoradiation is, although, based on the most robust evidence, unfortunately, is hampered by severe toxicity, and patients must be selected carefully before treatment [39]. The experience of the staff (physicians and nurses), and in particular its familiarity with toxicity management, as well as the structural facilities, play an important role in the final outcome [39]. Poor performance status and coexisting illness are other causes which restrain concomitant chemoradiation. Thus the optimal CCRT regimens remain questioned related to safety, efficacy and cost effectiveness. Hence a lot of patients experience locoregional or distant progression of their diseases and die within 5 years of diagnosis. Continued development with participation in clinical trials is, therefore, an immense need for further improvement on the treatment of patients with locally advanced SCCHN.

To the best of our knowledge, no clinical trial has hitherto been conducted in Bangladesh to directly compare the CCRT protocols over another. For this reason we are taking an attempt to analyze the safety and efficacy of the two effective CCRT regimens, weekly cisplatin and weekly paclitaxel/carboplatin. This project may provide a precise idea regarding the ideal CCRT protocol for locally advanced SCCHN patients. On completion of this short-term study, a large study may be embarked on to determine long-term outcome including long-term toxicity, overall survival, and progression free survival.

Declarations

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Authors' contributions

Md Shuayb is the principal investigator (PI) of this trial, and developed the study concept, designed the protocol and wrote the manuscript. Md Shah Jalalur Rahman Shahi reviewed the manuscript. Md Shuayb is responsible for acquisition of clinical information from the patients, follow up of the patients, data interpretation and statistical analysis. Both authors read and approved the final manuscript.

Consent for publication

Informed written consent will be obtained from all patients for publication of this study and any accompanying images (with appropriate anonymity). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval and consent to participate

The study protocol was approved by the Chairman of "National Institute of Cancer Research & Hospital Ethics Committee" on 22nd July, 2015 and an Ethical Clearance Certificate was obtained (Reference number of the Ethical Clearance Certificate: NICRH/Ethics/2015/185). Later the study protocol was submitted to German Clinical Trials Register for trial registration and was officially registered on 16th August, 2017 (Trial Registration number: DRKS00012877). URL of registry: http://www.drks.de/DRKS00012877 Enrollment of the first participant to the trial is yet to begin. All patients will be included in the study after informing about the aim, objective, procedure, risk and benefit of the procedure in easily understandable language and informed written consents for the participation will be obtained individually from all. Participants' privacy and confidentiality will be maintained strictly.

Availability of data

The study results will be published through peer-reviewed international journals and major international conferences.

Competing interests

The authors declare that they have no competing interests.

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