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Research Protocol

Oncology Section

Adverse Event Profile and Compliance of Docetaxel with Radiation in Cisplatin-Ineligible Patients of Locally Advanced Head and Neck Squamous Cell Carcinoma: A Research Protocol

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ABSTRACT

Introduction: Concomitant chemoradiation with cisplatin is standard treatment for non-metastatic head and neck cancers, but often limited by toxicities, especially deranged renal function and hearing complications. This leads to limited cycles of cisplatin due to challenges in administration and is not suitable for patients with poor renal function and hearing issues.

Need of the study: Not enough data is available for patients who are not suitable for cisplatin administration along with radiation either due to sensitivity to cisplatin or the adverse effects mentioned earlier. Docetaxel has been recently observed to benefit such patients in overall response outcome including Disease Free Survival (DFS) and Overall Survival (OS) when administered concurrently with radiation. Improved clinical response with minimal toxicity to normal tissue is seen with docetaxel, as it is a phase-specific agent. Therefore, this would be a good alternative to Cisplatin in patients with deranged kidney function and sensorineural hearing loss.

Aim: To estimate the adverse event profile and compliance of docetaxel with radiation.

Methodology: This prospective observational study will be conducted in the department of Medical Oncology and Radiation Oncology at Sidharth Gupta Memorial Cancer Hospital, Datta Meghe Institute of Medical Sciences, Sawangi (M), Wardha, Maharashtra, India, starting from May 2024 to May 2025. Patients with pathologically confirmed non-metastatic Head and Neck Squamous Cell Carcinoma (HNSCC), who are planned for Concurrent Chemoradiation (CCRT) but not suitable for cisplatin, will receive concurrent weekly docetaxel at a dose of 15 mg/sqm. Radiotherapy (RT) will be delivered according to the institutional protocol, daily dose of 200 cGy for five days a week will be given.

Continuous monitoring during treatment will include weekly clinical evaluations, regular blood tests (haemoglobin, blood counts, renal functions), and grading of adverse events (CTCAE v5 criteria). Treatment response will be assessed via clinical evaluation and CECT scans (RECIST v1.1). Statistical analysis will be performed using Statistical Package for Social Sciences (SPSS) version 26.0 and will involve analysis of categorical variables with Chi-square and Fisher-exact tests, and continuous variables with unpaired t-tests and Analysis of Variance (ANOVA). Time to event analysis will be done using the Kaplan-Meier method with p-value <0.05 considered significant.

Keywords: Carcinoma, Creatinine clearance, Head and neck neoplasm, Radio sensitizer

INTRODUCTION

Head and Neck Carcinoma (HNC) ranks as the fifth most prevalent human malignancy globally [1]. The standard approach for treating HNC involves a combination of surgery, RT, and Chemotherapy (CT) or alone. The selection of therapy depends on the tumour types and staging and is aimed at organ function preservation, when feasible. Several factors affect the tumour radio-sensitivity and the treatment outcome. In non-distant metastatic oral malignancies, most randomised trials show the superiority of CCRT to conventional RT alone, the integration of radio-sensitisers represents a significant advancement in enhancing the efficacy of RT as a standalone treatment. Radiosensitisers play an important role by arresting the cell cycle in the G2/M phase. This increases the cytotoxic effects of radiation, making the treatment more potent and targeted [2].

Common radiosensitisers like cisplatin and taxanes not only boost radiosensitivity but also possess intrinsic cytotoxic effects. Cisplatin, though widely used, is associated with significant toxicities, particularly kidney dysfunction and hearing issues. This often renders patients ineligible for cisplatin-based treatment, prompting exploration of alternatives like carboplatin or cetuximab [3,4]. Docetaxel, a taxane, emerges as a promising option due to its unique mechanisms of action, enhancing tubulin polymerisation and cell cycle synchronisation, leading to heightened radiosensitivity. Studies demonstrate its efficacy in squamous cell carcinoma, suggesting its potential as a substitute for cisplatin in patients with renal or hearing impairments [5,6]. Here, the authors in this study are trying to estimate the adverse event profile of docetaxel in combination with radiation.

Carboplatin, frequently used in routine clinical practice, becomes a viable alternative when cisplatin is either not tolerated or contraindicated. However, the effectiveness of carboplatin in combination with RT has shown limited impact on overall outcomes, as seen in the MACH-NC meta-analysis [7]. This emphasises the need for a better understanding of the effectiveness of carboplatin in conjunction with RT, especially in comparison to other radiosensitisation options, prompting further exploration of treatment strategies for improved patient outcome. Cetuximab may be a viable consideration for pharyngeal and laryngeal cancers in cases where cisplatin is not suitable and radical chemoradiotherapy is required, logistical feasibility remains a challenge for the majority of patients due to cost considerations [8].

Taxanes have shown promising response rates in both locally advanced and metastatic head and neck cancer in initial trials [9]. Among these, docetaxel distinguishes itself with unique mechanisms of action. Docetaxel as a radiosensitiser has been established in-vitro, and its impact is likely linked to its ability to synchronise cell cycles. This synchronisation effect leads to cell cycle arrest specifically in the G2/M phase [10].

As the authors mentioned earlier, the G2/M phase is more sensitive to the effects of radiation when compared to those in the G1/S phase. This enhances the susceptibility of cancer cells to the cytotoxic effects of radiation, thereby augmenting the overall efficacy of RT in the presence of docetaxel [11].

Studies conducted in laboratory settings have demonstrated that docetaxel serves as a strong radiation sensitiser for cell lines of squamous cell carcinoma. Human studies focused on lung cancer and HNSCC have validated the notable response rates in the context of radiation [12,13]. Due to its phase-specific nature, the frequent administration of docetaxel holds promise for enhanced response rates while minimising toxicity to normal tissues. Therefore, this is another alternative to cisplatin in patients with poor renal function and defective hearing. Here, in this study, the authors are trying to estimate the adverse event profile of docetaxel in combination with radiation.

The aim of the study to estimate the adverse event profile and compliance of docetaxel with radiation in cisplatin-ineligible patients.

- **Primary objective:** To estimate the rate of grade 3 or above adverse events via CTCAE v5 criteria
- **Secondary objectives:**
    - To estimate the rate of any grade adverse event
    - To estimate the compliance of patients with
        - Radiation- 90% completion rate
        - Concurrent CT (Docetaxel)- 5 or more cycles
    - To evaluate the percentage of Interruptions during the course of treatment
    - To evaluate the number of Hospital admissions during the course of treatment
    - To assess one year OS
    - To assess one year DFS

REVIEW OF LITERATURE

Numerous clinical studies and meta-analysis highlight the superiority of concomitant chemoradiation over RT alone in treating locally advanced head and neck cancers (MACH-NC) [7,14-16]. Cisplatin is commonly used but often causes significant toxicities such as nephrotoxicity and hearing loss [17]. Alternatives like carboplatin, cetuximab, or taxanes (e.g., docetaxel) are considered in such cases. However, there is limited research on the use of docetaxel as a radiosensitiser in patients unsuitable for cisplatin due to its toxicities or hypersensitivity. This study is planned with an aim to evaluate the adverse event profile of docetaxel combined with radiation in this patient population.

A study was done by Raphael CJ et al., to investigate the viability, adverse reactions, and treatment response associated with the concurrent administration of docetaxel alongside RT in patients with non-distant metastatic locally advanced HNSCC. Additionally, the research is planned to study the level of compliance and tolerance to the weekly docetaxel regimen when used in conjunction with RT. The adverse events noted were Grade-III mucositis in 57% of patients and Grade-III dermatitis in 23%, Grade-II weight loss in 23% and Grade-III dysphagia in 38% of patients. There were no other significant toxicities. The initial follow-up revealed an overall locoregional response rate of 85%, comprising a Partial Response (PR) in 15% and a Complete Response (CR) in 70% of cases. Concurrent administration of docetaxel proves to be a viable and appropriate substitute for cisplatin and 5-fluorouracil CT, demonstrating favourable patient compliance [18].

A study done by Liao J-F et al., compares the efficacy and adverse event profile of concurrent docetaxel given weekly versus three weekly cisplatin along with radiation in locoregionally advanced nasopharyngeal carcinoma [19]. The study involved 962 patients, with 448 forming a matched cohort. In both cohorts, three year nodal recurrence-free survival was significantly improved with docetaxel. There were no significant differences seen in OS, local recurrence-free survival, and distant metastasis-free survival. The docetaxel group had higher rates of mucositis, radiodermatitis, and leukopenia, while the cisplatin group exhibited more renal injury, vomiting, and Alanine Transaminase (ALT) elevation. The study concludes that weekly docetaxel has good efficacy and is well-tolerated along with radiation in locoregionally advanced nasopharyngeal carcinoma, offering a survival benefit, especially for patients with low pre-treatment Ebstein Barr Virus (EBV) De-oxyribonucleic Acid (DNA) levels.

Several studies showed that RT can be combined with weekly Docetaxel (doses between 10mg/sqm and 20mg/sqm) with minimal toxicity [5,7,12].

A similar study conducted at Tata Memorial Hospital, Mumbai by Patil VM et al., recruited 356 patients (176 in RT and 180 in docetaxel-RT arm), the 2-year DFS was 30.3% in the RT arm and 42% in the docetaxel-RT arm, with significantly improved outcomes in the latter (Hazard ratio=0.673, p=0.002) [20]. Median OS was 15.3 months in RT and 25.5 months in docetaxel-RT, showing a significant advantage for docetaxel-RT (Log-rank p=0.035). The 2-year OS was 41.7% in RT and 50.8% in docetaxel-RT, further supporting the survival benefit with docetaxel (Hazard ratio=0.747, p=0.035). Adverse events were higher in the docetaxel-RT arm (81.6% vs. 58%), with increased Grade-III mucositis, odynophagia, and dysphagia. However, quality of life scores did not worsen with docetaxel addition. They concluded that concurrent chemoradiotherapy with docetaxel is a good alternative in terms of improved DFS and OS in cisplatin-ineligible locoregionally advanced HNCs and represents a new standard of care [20].

Docetaxel with radiation has been in a single-centre trial. Hence, it is important to see the reproducibility of the results. This provides us an opportunity to conduct an observational study to estimate the adverse event profile and compliance with Docetaxel with Radiation in cisplatin-ineligible patients.

MATERIALS AND METHODS

This prospective observational study will be conducted on pathologically proven locally advanced non-metastatic HNC patients not suitable for concurrent cisplatin use at the department of Medical Oncology and Radiation Oncology at Sidharth Gupta Memorial Cancer Hospital, Datta Meghe Institute of Medical Sciences, Sawangi (M), Wardha, Maharashtra, India, for a duration of one year. The study has been started in May 2024 and is currently under progress. It is expected to end in May 2025. The Jawaharlal Nehru Medical College, Sawangi research project has got approval from the institutional ethics panel. The citation is DMIMS(DU)/IEC/2022/296. And informed consent will be taken from all the participants. The CTRI Approval number: CTRI/2024/05/066839 was taken.

Inclusion criteria:

- Histopathologically proven squamous cell carcinoma of head and neck cancer patients
- Patient must be the candidate for CCRT with at least one of the following:
    - Radical setting: Stage III-IV head and neck cancer
    - Adjuvant setting: Stage III-IV head and neck cancer postoperative with one of the below-mentioned features on pathology specimen

i. Extracapsular extension
ii. Margin positive

- Age group-18 to 70 years.
- Unsuitable for cisplatin due to at least any one of the following reasons:
  - Creatinine clearance <50 ml/min;
  - Hearing loss or tinnitus grade≥3;
  - Allergy to agents that contain platinum.
- Eastern Cooperative Oncology Group (ECOG) ≤2 [21];
- Complete blood count: absolute neutrophil count>1500/dL, WBC>4000/dL, platelets >100000/dL, haemoglobin>10 mg/dL;
- Kidney function test: Creatinine clearance > 30 ml/min;
- Hepatic function test: serum bilirubin<1.0;
- Ejection fraction >55% for fitness of treatment;
- Patients willing to give consent and participate in the study.

Exclusion criteria: Patients with history of previous malignancy or previous irradiation, or distant metastasis, presence of immunodeficiency syndromes or uncontrolled hypertension, diabetes mellitus, hypothyroidism or any other chronic disease despite medication or pregnancy will be excluded from the study.

Sample size: Due to the time constraint of this study, all patients who will come to the department within the allotted time frame will be enrolled. Samples will be collected via convenience sampling method.

Planned Procedure

A detailed history and examination will be performed in all patients of non-distant metastatic advanced HNC. Diagnostic investigations will include the use of flexible nasopharyngoscopy/laryngoscopy, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans for staging and determining the extent of the disease, and obtaining tissue samples through biopsy or fine needle aspiration for histopathological confirmation.

Additionally, baseline assessments such as blood tests, chest X-ray, soft-tissue neck imaging, audiometry, and cardiac evaluations will be conducted. The treatment protocol will integrate advanced RT techniques as per institutional protocol. This will involve the delivery of dose 66-70 Gy/33-35#, administered at a rate of 200 cGy per fraction, with treatments scheduled five times per week. Concurrently, a weekly infusion of Docetaxel at 15mg/sqm will be administered prior to RT.

Continuous monitoring during the treatment course will include weekly clinical evaluations, regular blood tests (haemoglobin, blood counts, and renal functions), and the systematic grading of adverse events according to CTCAE v5 criteria [22]. Response to the treatment will be assessed through a combination of clinical evaluation and CECT scans, by RECIST version 1.1 criteria [23].

The follow-up protocol will include weekly clinical assessment of the adverse events, compliance, dose and cycles of concurrent CT. Also, will be assessing the interruptions of treatment due to adverse events and admission in the hospital because of side-effects. Response assessment radiologically will be done at six weeks post-treatment, followed by subsequent evaluations every three months in the first year to assess the DFS and one year OS. These assessments will include clinical examinations and investigations to assess the response and potential late radiation toxicities.

Primary outcome:

- Incidence and severity of adverse events, measured according to CTCAE v5.0.

Secondary outcome:

- Rate of completion of the prescribed docetaxel and radiation therapy regimen.
- Overall Response Rate (ORR), evaluated using RECIST v1.1 criteria.
- DFS.
- OS.

STATISTICAL ANALYSIS

All the data will be entered in the Microsoft Excel sheet. The statistical software SPSS version 26.0 will be used for the analysis. Categorical variables will be expressed as percentages or proportions and will be analysed using the Chi-square test and Fisher exact test. Continuous variables will be expressed as mean±standard deviation and will be analysed using an unpaired t-test or Analysis of Variance (ANOVA). Time to event analysis, OS, and DFS will be analysed by the Kaplan Meier method. An alpha level of 5% will be taken, i.e., if any p-value is less than 0.05 it will be considered significant.

REFERENCES

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
[2] Vermorken JB. Treatment intensification in locoregionally advanced head and neck squamous cell carcinoma: What are the options and for whom? In: Vermorken JB, Budach V, Leemans CR, Machiels JP, Nicolai P, O'Sullivan B, editors. Critical Issues in Head and Neck Oncology. Cham: Springer International Publishing; 2023. p. 129-64.
[3] Sun L, Candelieri-Surette D, Anglin-Foote T, Lynch JA, Maxwell KN, D'Avella C, et al. Cetuximab-based vs carboplatin-based chemoradiotherapy for patients with head and neck cancer. JAMA Otolaryngol-- Head Neck Surg. 2022;148(11):1022-28.
[4] Akerley W, Glantz M, Choy H. Preliminary results of a phase I study of weekly paclitaxel infusion in patients with non-small cell lung cancer. Semin Oncol. 1996;23(5 Suppl 12):14-18.
[5] Mason KA, Kishi K, Hunter N, Buchmiller L, Akimoto T, Komaki R, et al. Effect of docetaxel on the therapeutic ratio of fractionated radiotherapy in vivo. Clin Cancer Res Off J Am Assoc Cancer Res. 1999;5(12):4191-98.
[6] Moos PJ, Fitzpatrick FA. Taxanes propagate apoptosis via two cell populations with distinctive cytological and molecular traits. Cell Growth Differ Mol Biol J Am Assoc Cancer Res. 1998;9(8):687-97.
[7] Pignon-JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2009;92(1):04-14.
[8] Bauml JM, Vinnakota R, Park YHA, Bates SE, Fojo T, Aggarwal C, et al. Cisplatin versus Cetuximab with definitive concurrent radiotherapy for head and neck squamous cell carcinoma: An analysis of veteran's health data. Cancer. 2019;125(3):406-15.
[9] Schrijvers D, Vermorken JB. Role of taxoids in head and neck cancer. The Oncologist. 2000;5(3):199-208.
[10] Hihara J, Yoshida K, Hamai Y, Emi M, Yamaguchi Y, Wadasaki K. Phase I study of docetaxel (TXT) and 5-fluorouracil (5-FU) with concurrent radiotherapy in patients with advanced esophageal cancer. Anticancer Res. 2007;27(4C):2597-603.
[11] Karasawa K, Matsumoto F, Ito S, Oba S, Furuya T, Hirowatari H, et al. Hyperfractionated radiotherapy with concurrent docetaxel for advanced head and neck cancer: A phase II study. Anticancer Res. 2012;32(9):4013-18.
[12] Mauer AM, Masters GA, Haraf DJ, Hoffman PC, Watson SM, Golomb HM, et al. Phase I study of docetaxel with concomitant thoracic radiation therapy. J Clin Oncol Off J Am Soc Clin Oncol. 1998;16(1):159-64.
[13] Tishler RB, Norris CM, Colevas AD, Lamb CC, Karp D, Busse PM, et al. A Phase I/II trial of concurrent docetaxel and radiation after induction chemotherapy in patients with poor prognosis squamous cell carcinoma of the head and neck. Cancer. 2002;95(7):1472-81.
[14] Adelstein DJ, Li Y, Adams GL, Wagner H, Kish JA, Ensley 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 Off J Am Soc Clin Oncol. 2003;21(1):92-98.
[15] Hitt R, Grau JJ, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol Off J Eur Soc Med Oncol. 2014;25(1):216-25.
[16] Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: A comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(7):845-52.
[17] Seiwert TY, Salama JK, Vokes EE. The chemoradiation paradigm in head and neck cancer. Nat Clin Pract Oncol. 2007;4(3):156-71.

[18] Jomon Raphael C, Rajesh I, Rajesh B, Selvamani B, John S. Feasibility and response of concurrent weekly Docetaxel with radical radiotherapy in locally advanced head and neck squamous cell carcinoma. J Clin Diagn Res. 2015;9(3):XC01-04.
[19] Liao JF, Zhang Q, Du XJ, Lan M, Liu S, Xia YF, et al. Concurrent chemoradiotherapy with weekly docetaxel versus cisplatin in the treatment of locoregionally advanced nasopharyngeal carcinoma: A propensity score-matched analysis. Cancer Commun. 2019;39:40. Doi: 10.1186/s40880-019-0380-x.
[20] Patil VM, Noronha V, Menon-N, Singh A, Ghosh-Laskar S, Budrukkar A, et al. Results of phase III randomized trial for use of docetaxel as a radiosensitizer in patients with head and neck cancer, unsuitable for Cisplatin-Based Chemoradiation. J Clin Oncol Off J Am Soc Clin Oncol. 2023;41(13):2350-61.
[21] ECOG Performance Status Scale [Internet]. ECOG-ACRIN Cancer Research Group. [cited 2024 May 27]. Available from: https://ecog-acrin.org/resources/ecog-performance-status/.
[22] Common Terminology Criteria for Adverse Events (CTCAE). 2017; Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
[23] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

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