THE COMPARISON BETWEEN WEEKLY BLEOMYCIN WITH THREE-WEEKLY CISPLATIN AND 5-FU DELIVERED CONCURRENTLY WITH RADIOTHERAPY IN HEAD AND NECK CANCER

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ABSTRACT

BACKGROUND

Head and neck cancer is most common in South-East Asia. In India, it is a leading cause of cancer related mortality and morbidity. Affected males were more than females, it is mainly to the consumption of the tobacco. Surgery and radiotherapy with or without chemotherapy are the most frequently used therapeutic modalities. Concurrent chemoradiation improves overall survival, disease free survival and locoregional control and has become the standard treatment for squamous cell carcinoma of head and neck.

The main objective of the study is to determine the response, acute toxicity and compliance of treatment with concurrent chemoradiation using cisplatin and 5-FU versus bleomycin in squamous cell carcinoma of head and neck.

MATERIALS AND METHODS

The present study was done in the Department of Radiotherapy, MNJ Institute of Oncology and RCC. The patients were randomly selected from 2013 to 2015 and were allotted to ARM-A - cisplatin and 5-FU; and ARM-B - bleomycin. ARM-A were treated with cisplatin 100 mg/m² in divided dose IV infusion, 5-FU 750 mg/m² IV infusion for 3 days once in every 3 weeks for 3 cycles; and ARM-B were treated with bleomycin 15 mg IV push once per week for 6 weeks, both ARMs received radiotherapy concurrently.

RESULTS

Arm-A: Complete response 22 patients (61%), partial response 12 (33%), no response 2 (6%). Arm-B: Complete response 21 (60%), partial response 13 (37%), no response 1 (3%) respectively. When compared to Arm-A mode of administration of bleomycin is easy and convenient to the patients as hydration is not required. Tumours confined to oral cavity have shown good response though mucosal toxicity is more.

CONCLUSION

Concurrent weekly bleomycin is recommended in squamous cell carcinoma of oral cavity to achieve meaningful regression and probably survival benefit.

KEYWORDS

Acute Toxicity, Compliance, Concurrent Chemoradiotherapy, Head and Neck Cancer, Mucositis, Squamous Cell Carcinoma.

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BACKGROUND

The head and neck cancers form the 7th most common cancer worldwide. Its frequency is high in South East Asian countries and is linked mainly to the chewing and smoking tobacco and alcohol intake. In India head and neck cancers are leading causes of cancer morbidity and mortality affecting both males (25%-30%) and females (15%).⁽¹⁾

Surgery and radiotherapy (RT) with or without chemotherapy (CT) are the most frequently used therapeutic modalities in head and neck cancers. In early stage (I-II), surgery or radiotherapy has shown good comparable results. For advance stage (III-IV) with large primary tumours, the primary curative modalities are surgery, radiotherapy

and chemotherapy. Most of the time chemotherapy is used in neoadjuvant setting.

The principle objective of combining radiotherapy and chemotherapy (CCRT) is to increase local tumour control, decrease the distant metastasis and improve the survival. To improve upon response rates and survival in head and neck cancer, various researchers have advocated various regimens with different drugs. Drugs most commonly used in concurrent chemotherapy include cisplatin, carboplatin, 5-fluorouracil, paclitaxel, hydroxyurea and bleomycin.

For squamous cell carcinoma of head and neck (SCCHN), 100 mg/m² dose of cisplatin administered once every 3 weeks concurrently with radiotherapy is the commonly recommended treatment regimen. Its high emetic potential, neurotoxicity, and ototoxicity demand further efforts to be made towards improving its therapeutic and toxicity profiles. 40 mg/m² dose of cisplatin administered once per week has been widely used in concurrent CRT for cervical cancer as it is effective and has a relatively low toxicity.^(2,3,4,5) A randomised phase III trial that evaluated the weekly administration of 40 mg/m² cisplatin plus RT versus RT alone for the treatment of Nasopharyngeal cancer also demonstrated favourable outcomes in patients with an advanced T-stage treated by CCRT.^(6,7)

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Several studies have compared the weekly and 3-weekly cisplatin CCRT regimens in patients with SCCHN and the results have been inconclusive.^{8,9,10} However, no randomised controlled trials have compared the efficacy and toxicity profiles of bleomycin versus cisplatin and 5-FU concurrently with radiotherapy in SCCHN.

Concurrent chemoradiotherapy (CCRT) improves overall survival (OS), disease-free survival (DFS) and local regional control and has become the standard treatment for squamous cell carcinoma in head and neck (SCCHN).^{11,12,13} The main objective of this study is to determine the response, acute toxicity and the compliance of treatment with concurrent chemoradiation using cisplatin and 5-FU versus bleomycin in head and neck cancer.

MATERIALS AND METHODS

Present study was done in the Department of Radiotherapy in MNJ Institute of Oncology and Regional Cancer Centre. The patients were randomly selected from year 2013 to 2015 and were allotted two arms. ARM-A - 36 patients (cisplatin + 5-FU + RT), ARM-B - 35 patients (bleomycin + RT), based on inclusion and exclusion criteria.

Prior to the onset of therapy, the patients were thoroughly informed about all aspects of the study and regulatory requirement that needs to be met for informed consent.

Patients were selected according to the following Inclusion Criteria:

- Patients of both sexes between 18 – 70 years
- T1-T2 with positive neck nodes and T3-T4 cases
- Histologically proven squamous cell carcinoma of head and neck (SCCHN)
- No prior radiotherapy or chemotherapy
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of
 - 0-2
- Complete blood count, HB at least 10 g%
 - WBC more than 3000 cells/dL.
 - Platelets >100000 cells/dL.
- Routine Blood biochemistry panel - Renal and Liver functions
- Radiological
 - Chest -X-ray PA view.
 - OPG of the mandible.
 - CT scans of head and neck when required.
 - Ultrasonogram of the abdomen.

Exclusion Criteria

- Poor performance status (PS) >2.
- Systemic diseases (comorbidity conditions- HTN/DM/COPD/Renal/Liver).
- Oral submucosal fibrosis.
- Pregnancy.
- Evidence of distant metastasis.

Methods

All study participants underwent an extensive pre-treatment evaluation, which included-

- Complete history, clinical examination and staging of the disease.
- Complete dental examination and extraction of the decayed and loose teeth under antibiotic coverage. The patients who were randomised ARM-A were treated with cisplatin 100 mg/m² in divided dose IV infusion for 2 days

and 5-FU 750 mg/m² IV infusion for 3 days once in every 3 weeks for 3 cycles concurrently with radiotherapy.

The patients who were randomised ARM-B were treated with bleomycin 15 mg IV push once per week for 6 weeks concurrently with radiotherapy. Radiotherapy was administered using 6 MV photon beam with a conventional fractionation. Dose of 2Gy/fraction/day and 5 days per week. Phase-I – 44 Gy/22# 5# per week -for primary tumour and lymph-node drainage areas, Phase-II – 22 Gy/11# 5# per week- boost dose sparing the spinal cord all patients were irradiated with a total dose of 66 Gy/33# over 6.5 weeks.

Data Collection and Statistical Analysis

The collected data was analysed using standard statistical software package (SSSP version 20.0). The response, acute toxicity and compliance of treatment were analysed in both ARMs. Both ARMs were compared using chi-square test to check whether they were balanced in terms of patients and disease-related characteristics like age, sex, performance status and tumour site, stage, histology.

RESULTS

Fifty patients were taken into the study; they were divided in to two arms (ARM-A - 36 and ARM-B - 35). Maximum incidence of age is 3rd to 6th decade, male to female ratio 7:3 in both ARMs. Host and tumour characteristics is shown in Table-1. Response relation to Primary site of the tumour, stage, and histological grade in both ARMs are shown in Table-2; and overall toxicity, acute non-haematological and haematological toxicity are shown in Table-3.

The intensity of reaction is increased at the end of the 3rd, 4th and 5th week, mucosal toxicity varied from grade II to grade III. The intensity was so severe that radiation therapy was interrupted and the patients were managed with best supportive care. Arm-A: Complete response 22 patients (61%), partial response 12 (33%), no response 2 (6%). Arm-B: Complete response 21 (60%), partial response 13 (37%), no response 1 (3%) respectively.

Characteristics of Host and Tumour	ARM-A (Cisplatin-100 mg/m ² and 5-FU-750 mg/m ²) 3-weekly Number =36	ARM-B (Bleomycin-15 mg) weekly Number =35
Gender		
Male	26 (72%)	25 (71%)
Female	10 (28%)	10 (19%)
Age (years) mean age	28-60 44	30-60 45
Primary Site		
Oral cavity	18 (50%)	17 (49%)
Oropharynx	9 (25%)	7 (20%)
Hypopharynx	6 (17%)	7 (20%)
Supraglottis	3 (8%)	4 (11%)
Stage		
Stage-II	4 (11%)	3 (9%)
Stage-III	18 (50%)	15 (44%)
Stage-IV	14 (39%)	17 (47%)
Tumour Size		
T2	4 (11%)	4 (11%)
T3	20 (56%)	21 (60%)
T4	12 (33%)	10 (29%)
Nodal Status		
N1	3 (8%)	2 (6%)
N2	23 (64%)	23 (66%)
N3	10 (28%)	10 (28%)

Table 1. Host and Tumour Characteristics

Characteristics	ARM-A N=36 CR PR NR			ARM-B N=35 CR PR NR		
Tumour size						
T2	4 (11%)	-	-	4 (11%)	-	-
T3	15 (42%)	5 (14%)	-	15 (43%)	8 (23%)	-
T4	3 (8%)	7 (19%)	2 (6%)	2 (6%)	5 (14%)	1(3%)
Nodal status						
N1	2 (6%)	-	-	1(3%)	-	-
N2	17(47%)	8 (22%)	-	16 (46%)	9 (26%)	-
N3	3 (8%)	4 (11%)	2 (6%)	4 (11%)	4 (11%)	1 (3%)
Grade						
Well	4 (11%)	1(3%)	-	5 (14%)	1(3%)	-
Moderate	14 (39%)	9 (25%)	1 (3%)	14 (40%)	8 (23%)	-
Poor	4 (11%)	2 (5%)	1 (3%)	2 (6%)	4 (11%)	1 (3%)
Primary site						
Oral Cavity	13 (36%)	4 (11%)	1 (3%)	17 (48%)	-	-
Oropharynx	4 (11%)	2 (6%)	1 (3%)	4 (11%)	3 (9%)	-
Hypopharynx	7 (19%)	1 (3%)	-	6 (17%)	-	1 (3%)
Supraglottis	3 (8%)	-	-	3 (9%)	1(3%)	-

Table 2. Response relation to Tumour Size, Nodal Status, Grade and Anatomical Site

Note; N=Number, CR=Complete Response, PR=Partial Response, NR=No Response

CCRT- Toxicity	ARM-A Cisplatin + 5-FU N=36	ARM-B Bleomycin N=35
Overall toxicity		
Grade-2	8 (22%)	4 (11%)
Grade-3	26 (72%)	28 (80%)
Grade-4	2 (6%)	3 (9%)
Non-haematological toxicity		
Mucositis		
<Grade-3	21 (58%)	10 (29%)
>Grade-3	15 (42%)	25 (71%)
Pharyngitis		
<Grade-3	21 (58%)	17 (49%)
>Grade-3	15 (42%)	18 (51%)
Stomatitis		
<Grade-3	17 (47%)	18 (51%)
>Grade-3	19 (53%)	17 (49%)
Laryngeal oedema		
<Grade-3	6 (17%)	27 (77%)
>Grade-3	30 (83%)	8 (23%)
Dermatitis		
<Grade-3	22 (89%)	14 (40%)
>Grade-3	4 (11%)	21 (60%)
Nausea/vomiting		
<Grade-3	4 (11%)	30 (86%)
>Grade-3	22 (89%)	5 (14%)
Haematological toxicity		
Anaemia		
<Grade-3	23 (64%)	30 (86%)
>Grade-3	13 (36%)	5 (14%)
Leukopenia		
<Grade-3	4 (11%)	30 (86%)
>Grade-3	22 (89%)	5 (14%)
Neutropenia		
<Grade-3	23 (64%)	35 (100%)
>Grade-3	13 (36%)	0
Thrombocytopenia		
<Grade-3	22 (89%)	35 (100%)
>Grade-3	4 (11%)	0

Table 3. Acute Toxicity Profiles

Figure 1. Study Design

DISCUSSION

Radiotherapy with or without chemotherapy is the most frequently used therapeutic modality in head and neck cancer.

Concurrent chemoradiotherapy (CCRT) improves overall survival (OS), disease-free survival (DFS) and locoregional control and has become the standard treatment for squamous cell carcinoma of head and neck.^{6,9,10,11,12,13}

Several single- and multi-institutional trials have reported both survival and locoregional control benefits from more aggressive concurrent radiation and multi-agent chemotherapy regimens.^{14-17} Concurrent administration of 100 mg/m² cisplatin once every three weeks and RT is recommended as the standard regimen of adjuvant CCRT for SCCHN because two large scale randomised trials used this regimen.^{18,19} Majority of the studies used cisplatin 100 mg/m² and 5-FU 750 mg/m² D1-D4 every 3 weeks for 3 courses during radiation. This gain was due to increased locoregional control rate; however, concurrent chemoradiotherapy was associated with statistically significant increases in acute toxicity especially severe mucositis, sometimes unacceptable systemic toxicity, particularly haematological toxicity such as febrile neutropenia and sepsis.^{20,21}

Northern California Oncology Group (NCOG) and European Organization for the Research and Treatment of Cancer (EORTC) tested concurrent RT with single agent chemotherapy bleomycin versus radiotherapy alone.^{22,23} Fractionation was similar in the two studies, but patients in the EORTC trial received 15 mg of bleomycin twice weekly during the first 5 weeks of RT for a total dose of 150 mg

whereas the NCOG patients received bleomycin 5 mg twice weekly for a total dose of 70 mg. Acute mucosal and skin toxicity was worse in the RT/bleomycin ARM in both trials, but the outcomes were quite different in both trials. Toxicity significantly prolonged the RT delivery time in 30% of the combined modalities in patients in the EORTC trial, but not in any of the RT alone patients. This prolongation of treatment time in such a large proportion of patient may have negated any benefit accrued from the use of concurrent therapy. There were no differences in overall treatment time between the two treatment ARMs in the NCOG trials.

The EORTC trial showed no improvement in DFS or OS but in NCOG RT/bleomycin ARM led to a statistically significant doubling of the locoregional control and DFS, as well as a near significant improvement in OS from 24% to 43%, because lower doses may improve the therapeutic ratio more effectively than higher dose.

In our studies, we have given bleomycin 15 mg weekly to a total dose of 90 mg. When compared to ARM-A (cisplatin +5-FU +RT) mode of administration of bleomycin is easy and convenient for patients as hydration is not required. Tumours confined to oral cavity have shown good response to ARM-B(bleomycin +RT) though mucosal toxicity is more; in contrary tumours confined to Oropharynx, hypopharynx and supraglottis have shown good response to ARM-A. The intensity of reactions increased at the end of 3rd, 4th, 5th, week, mucosal toxicity varied from grade II to grade III, patients were able to continue radiotherapy without interruption with supportive therapy.

Chemotherapy timing should be tailored in such a way that the drug acts as a radiosensitiser. However, as the

chemoradiation increased mucosal toxicity compared to radiotherapy alone, it may cause treatment interruption leading to increased duration of treatment of more than 6 to 7 weeks. This gap may cause tumour repopulation leading to development of resistant strains.

Hence, concurrent chemoradiation should be planned very carefully and radiotherapy technique should be perfect.

CONCLUSION

Our study is comparable to all other positive randomised trials with concurrent chemoradiation in squamous cell carcinoma of head and neck. The CCRT regimen is tolerable with appropriate supportive care. Locoregional and distant metastasis control are likely. We do not have overall survival in our study as the study period is short. Hence, concurrent weekly bleomycin is recommended in squamous cell carcinoma of oral cavity (OSCC) to achieve meaningful regression and probably survival benefit.

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