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Retrospective Analysis between Three Weekly and Weekly Cisplatin Concurrently with Radiotherapy for Patient with Post-Operative High Risk Squamous Cell Carcinoma of Oral Cavity

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ABSTRACT

Background: The aim of this study is to compare the outcomes of postoperative adjuvant concomitant chemo radiotherapy using two different schedules of cisplatin received by patients with high risk squamous cell carcinoma(SCC) of oral cavity.

Methods: A retrospective study of 44 patients with high risk oral SCC were analyzed from January 2017 to December 2019. Patients were divided into two treatment groups receiving either 100mg/m^2 every 3weeks (arm A) or 40mg/m^2 cisplatin once in a week (arm B). All the patients were irradiated 60Gy.

Results: out of the 44 eligible patients, 22 were assigned to arm A and 22 to arm B. Both groups received same mean doses of radiation and cisplatin. 68.2% in arm A and 52.7% in arm B (p value=0.0026received ≥ 200mg/m^2 of total cisplatin with statistical difference. The overall toxicity was greater in arm B (p =0.621) and the grade 3 toxicity is slightly higher in arm B, but statistically not significant.

Conclusions: Three weekly high dose cisplatin showed high compliance and similar acute toxicity compared to weekly low dose cisplatin and is feasible for administration in outpatient settings with low rate of hospitalization. Advance post op case of oral cavity needs both chemotherapy and radiotherapy for better survival and outcome. It needs larger study to demonstrate which chemotherapy schedule is slandered of care.

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KEYWORDS: oral cavity cancer, concurrent chemo radiotherapy, acute toxicity, compliance.

BACKGROUND

Surgery followed by postop adjuvant radiotherapy is the primary therapeutic option for locally advanced squamous cell carcinoma of oral cavity. There is an high risk of treatment failure in patients with high risk features such as extra capsular spreading (ECS) of involved lymph nodes, a positive surgical margins and lymph node staging ≥N2. In high risk postoperative squamous cell carcinoma of head and neck (SCCHN), concurrent chemo radiotherapy (CCRT) has become the standard treatment improving overall survival(OS), disease free survival (DFS) and locoregional control (LRC) in the randomized phase III trials by Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC)[(1,2)].

Commonly used regimen for CCRT in SCCHN is 100mg/m^2 cisplatin given once in 3 weeks concurrently with radiation. Because of its high emetic potential, neurotoxicity and ototoxicity, several other chemotherapy regimens and different schedules of cisplatin tried in this settings for improved compliance and less toxicity. Most widely used such regimens is cisplatin 35-40mg/m^2 given weekly in adjuvant and radical treatment.

Several randomized trials evaluated the weekly cisplatin 40mg/m^2 doses in cervical and nasopharyngeal cancers as CCRT treatment demonstrated favorable outcomes and relatively low toxicity. In Studies comparing weekly and three weekly cisplatin CCRT in SCCHN, there has been an inconclusive results obtained [(3-5)].

Our study aims to evaluate the efficacy and acute toxicity in postoperative adjuvant CCRT using weekly versus three weekly cisplatin in locally advanced oral SCC with high risk features for therapeutic failure. Preliminary results aimed to compare compliance, acute toxicity between two cisplatin groups and end points of this study will include OS,LRC ,and DFS.

METHODS

Study design

Our study is a retrospective study to compare three weekly high dose and weekly low dose cisplatin in postoperative adjuvant CCRT treatment of patients with locally advanced oral SCC and high risk pathological factors.

Patient selection

Baseline investigations, tests and examination were done before starting the treatment. Eligible patients were between 18 and 70 years old with karnofsky performance scale (KPS) >70 and Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 with adequate hematological, liver and renal function. Histologically proven cases of oral squamous cell carcinoma, pathologic documentation of ECS of involved lymph nodes,positive surgical margin, lymph node staging ≥N2 were included . Patients were staged according to the 2017 American Joint Committee on Cancer (AJCC 8th edition).

Patients with suspected distant metastasis proven by imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT) or 2-deoxy -2(F-18)fluoro-D-glucose positron emission tomography (FDG-PET) were excluded. Patients with comorbid conditions such as cardiac diseases, uncontrolled hypertension and diabetes mellitus and previous history of treatment such as chemotherapy and radiation were excluded from the study.

Treatment

All the patients underwent an complete evaluation of medical history, physical examination, complete blood count, blood chemistry, CT or MRI of head and neck, chest radiograph and dental evaluations done by dentist. Composite resection of the primary tumor with flap reconstruction and neck dissections were performed as surgical procedure.

Patients in three weekly high dose cisplatin regimen were treated with cisplatin at 100mg/m^2 once in every 3 weeks (arm A) and those in low dose cisplatin regimen were treated with cisplatin at 40mg/m^2 once in a week (arm B). Radiotherapy was administered using 6MV photon beams at a conventional fractionation dose of 2 Gy/fraction /day and 5 days per week. Patients were treated in outpatient basis with dose of 60

Assessment and outcomes

Follow up visits were analysed till March 2022. OS time was calculated as the period between the date of start of treatment and date of death. Locoregional recurrence free survival (LRRFS) time was calculated as the period between the start of treatment and date of local relapse, regional failure or death. Toxicity was assessed according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

RESULTS

Table 1: The demographic and ontological characteristics

Patient characteristics	Arm A Cisplatin 100mg/m^2 N=22	Arm B Cisplatin 40 mg/m^2 N=22
Gender		
Male	**20(90.9%)**	**20(90.9%)**
female	**2(9.1%)**	**2(9.1%)**
Age (years old)		
Mean (range)	**43.3 (30-61)**	**45.5 (30-59)**
PT		
PT1/2	**10(45.5%)**	**6(27.3%)**
PT3/4	**12(55.5%)**	**16(72.7%)**
N		
PN2	**14(44.6%)**	**13(69.2%)**
PN3	**8(36.4%)**	**7(31.8%)**
Stage		
Stage III	**4(29.2%)**	**1(4.5%)**
Stage IV	**18(81.8%)**	**21(95.5%)**
differentiation		
Well	**14(63.6%)**	**11(50%)**
moderate	**7(31.8%)**	**9(40.9%)**
Poor	**1(4.5%)**	**2(9.1%)**

Primary site		
Buccal	**11(50%)**	**15(68.2%)**
Tongue	**8(36.4%)**	**6(27.3%)**
Gum	**1(4.5%)**	**1(4.5%)**
Others	**2(9.1%)**	**0**
ECS		
Yes	**8(36.4%)**	**8(36.4%)**
No	**14(63.6%)**	**14(63.6%)**
Margin		
Positive	**0**	**0**
Negative	**22(100%)**	**22(100%)**
Tumor size(mm)		
Mean (range)	**29.92 (15-62)**	**28.34 (14-60)**
Cisplatin≥200mg/m2		
Yes	**15(68.2%)**	**5(22.7%)**
No	**7(31.8%)**	**17(77.3%)**
RT after surgery (>8 weeks)		
Yes	**7(31.8%)**	**5(22.7%)**
No	**15(68.2%)**	**17(77.3%)**
RT dose (cGy)		
Mean (range)	**5763.63 (3400-7000)**	**5363.63 (1800-6600)**
RT duration(weeks)		
Mean (range)	**6.25(3.5-8.5)**	**6.6(1.5-8.6)**
RT duration >8weeks		
Yes	**1(4.5%)**	**2(9.1%)**
No	**21(95.5%)**	**20(90.9%)**

Table 2: Acute toxicity profile

CCRT toxicity	**Arm A Cisplatin 100mg/m^2 N=22**	**Arm B Cisplatin 40mg/m^2 N=22**
Overall toxicity		
Grade 1	**16(72.8%)**	**13(59.1%)**
Grade 2	**3(13.6%)**	**5(22.7%)**
Grade 3	**3(13.6%)**	**4(18.2%)**
Grade 4	**0**	**0**
Non hematologic		
Mucositis		
< Grade 3	**22(100%)**	**22(100%)**
≥ Grade 3	**0**	**0**
Dermatitis		
<Grade 3	**22(100%)**	**22(100%)**
≥Grade 3	**0**	**0**
Nausea /vomiting		
<Grade 3	**19(86.4%)**	**21(95.5%)**
≥Grade 3	**3(13.6%%)**	**1(4.5%)**
Hematologic		
Anemia		

<Grade 3	**22(100%)**	**21(95.5%)**
≥Grade 3	**0**	**1(4.5%)**
Leukopenia		
<Grade 3	**22(100%)**	**21(95.5%)**
≥Grade 3	**0**	**1(4.5%)**
Neutropenia		
<Grade 3	**22(100%)**	**21(95.5%)**
≥Grade 3	**0**	**1(4.5%)**
Thrombocytopenia		
<Grade 3	**22(100%)**	**22(100%)**
≥Grade 3	**0**	**0**

DISCUSSION

The 5 year rates for buccal and tongue carcinoma with local control rate 85%, disease free survival rate 70% and distant metastasis around 8-15%. 3 year OS and recurrence free survival were 47% and 50% respectively.

Cisplatin 100mg/m^2 3 weekly regimen is the standard regimen recommended for adjuvant CCRT for SCCHN, which is used in 2 large scale randomized trials. Alternatives such as weekly cisplatin can be given, may show similar efficacy and less toxicity. More frequent administration could provide radiosensitizing chemotherapy as a large proportion of the administered RT dose and also smaller doses may lead to less chemotherapy induced morbidity without compromising efficacy. Studies and reviews support this hypothesis that cisplatin radiosensitization can be improved with frequent small doses [6, 7]. Daily administration of cisplatin led to improvement in tumor control by 35% than radiation alone and weekly cisplatin improved RT by 6%. Many trials showed that daily cisplatin administration improved tumor control with less toxicity compared to weekly high doses, which will be of our future interest for further studies. Minimum cumulative dose of cisplatin 200mg/m^2 during RT is required. In RTOG 9501 study, 61% of patients received all 3 planned cycles, 23% received 2 cycles, 13% received 1 cycle and 2% received no chemotherapy. In the EORTC 22931 study, compliance to chemotherapy also decreased according to the number of courses delivered as the first,second and third cycles were administered to 88%,66% and 49% of patients respectively. Weekly cisplatin 40mg/m^2 is thought to be more easily administered than cisplatin given 100mg/m^2 three weekly.

In our study ,no difference were found between two groups in terms of RT compliance. In the mean cisplatin dose received, patients in arm A received cumulative dose of 200mg/m^2 more than those in arm B. Inadequate dose of cisplatin could led to worst long term treatment results although several studies support the use of weekly low dose cisplatin. In a retrospective study by Ho et al., the dose intensity of cisplatin was compared for one weekly and two different 3 weekly regimens. Both mean cisplatin dose and cumulative dose were not significantly different between weekly and lower dose 3 weekly group. No patients in higher dose 3 weekly group received the full 3 cycles of cisplatin.

Ho et al., reported similar toxicities between the weekly and 3 weekly groups. 3 weekly cisplatin group suffered more grade 3 radiation dermatitis (56% vs 26%), but this difference was not significant. Uygun et al,. Reported that grade 3-4 toxicities were observed in 53.3% of 3 weekly cisplatin and 40% in weekly cisplatin, but this difference also insignificant. Geeta et al. suggested 3 weekly cisplatin is less toxic than weekly treatment, as weekly schedule resulted in higher rate of severe mucositis. In our study no difference in between 2 groups in terms of severe mucositis. Overall toxicities was also greater in arm B ,as more grade 3 toxicities was seen in arm B. Grade 3 hematological toxicity is seen only in arm B. one possible reason for this high toxicity could be the lower adherence of patients to this treatment protocol. Forced hydration with normal saline infusion over 2 hours before and after cisplatin is the only mandatory thing in arm A. Hydration and post chemotherapy care of patients may also account for some difference in toxicity.

We do plan to follow all these patients and report additional details regarding their treatment results, such as OS, LRC, and DFS when the data become available.

CONCLUSION

Three weekly high dose cisplatin showed high compliance and similar acute toxicity compared to weekly low dose cisplatin and is feasible for administration in outpatient settings with low rate of hospitalization. Advance post op case of oral cavity needs both chemotherapy and radiotherapy for better survival and outcome. It needs larger study to demonstrate which chemotherapy schedule is slandered of care.

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