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# EVALUATION OF TOXICITY AND COMPLIANCE OF CISPLATIN GIVEN WEEKLY VS THREE WEEKLY CONCURRENTLY WITH RADIOTHERAPY IN HEAD AND NECK CANCER

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## ABSTRACT

**BACKGROUND:** Concurrent Chemoradiotherapy with cisplatin is widely accepted modality of treatment for head and neck cancer.

**AIM:** To compare three weekly cisplatin and weekly cisplatin given concurrently along with external beam radiotherapy in locally advanced Head and Neck cancers(LAHNC) for toxicity and response.

**MATERIALS AND METHODS:** 50 patients of LAHNC were taken for this prospective study. In Arm A 25 patients received 6 cycles of weekly cisplatin 30mg/m2along with radiotherapy and in arm B 2 cycles of Cisplatin 100mg/m2 given 3 weekly along with radiotherapy. Treatment response was seen at the end of treatment as per RECIST v1.01 criteria. All chemotherapy toxicities were graded as per common toxicity criteria v4.0 and all radiation toxicities were graded as per RTOG toxicity criteria. Student unpaired t test was used for statistical analysis.

**OBSERVATIONS AND RESULTS:** In our study no significant difference was seen in terms of all measured toxicities but hematological toxicities were higher in group B. Regarding acute mucositis and dermatitis, most of them were grade 1 and 2 and were taken care of on outpatient care basis. With regards to response to treatment in our study CR was seen in 56% of patients in group A and 54.5% of patients in group B while 3 (12%) patients had stable disease and 6 (24%) patients had partial response in group A while 1 (4.55%) patient in group B had stable disease and 7 (31.82%) patients had partial response with no significant difference between both groups.

**CONCLUSION:** Weekly cisplatin chemotherapy can provide good alternative to 3 weekly cisplatin chemotherapy with lesser toxicity.

**KEYWORDS :** Head And Neck Cancer, Radiotherapy, Concurrent Chemotherapy

## INTRODUCTION

World-wide, the head and neck cancers are the sixth most common cancer. It is the most common cancer in developing countries. In India it is the most common cancer of males and the fifth most common in females. Cigarette-smoking and alcohol consumption are the main reasons for HNSCC in the Western population, whereas the use of smokeless tobacco and areca nut is the most common cause of HNSCC in Southeast Asia[1].

In India, nearly two-thirds of patients present with advanced stages. The mean age of patients at presentation of head and neck cancers is the fifth and early sixth decades in Asian populations compared with the seventh and eighth decades in the North American population. [1-3]

Loco regionally advanced head and neck cancers(LAHNC) i.e Stage III & IV comprise > 60% of these tumours for which cure rates have been < 30 %, with notably high morbidity for surgical as well as non surgical treatment and therefore prognosis remained poor in this group of patients and this has remained unchanged over the past 30 yrs. [4]

In meta analysis reported in 2000, comparison of local treatment with or without chemotherapy yielded an absolute benefit of 4% in overall survival (OS) at 2 and 5 yrs. in favour of chemotherapy. When analysing the data for concomitant chemo-radiotherapy, survival benefit was 8% at 5 yrs. An update of this analysis focusing on chemo-radiotherapy (with additional 24 trials) show a 4.5% overall survival (OS) for all and 6.5% (p value < 0.0001) for patients who received concurrent chemo-radiotherapy. [5]

The advent of concurrent chemo radiation has significantly contributed to the curability of head and neck cancers including the loco regionally advanced stages. Radiation with concurrent single agent cisplatin has been established as standard of care in the management of patients with unresectable head and neck cancers. Previously 3 weekly cisplatin regimen with concurrent radiotherapy was consid ered to be the standard treatment in patients with unresectable HNSCC but it was also seen that it was associ ated with significant increase in toxicities. Therefore, it was thought that splitting this dose as weekly cisplatin might decrease toxicities maintaining the dose intensity and also avoids the problem of inadequate inpatient beds and delay in administration of chemotherapy.

In this background, this prospective, institutional study was undertaken to compare the two different chemotherapy schedules given concurrently with radiotherapy.

## MATERIALS AND METHODS:

This Prospective study was conducted on 50 histologically proven squamous cell carcinoma LAHNC(AJCC Stage III and IV)inoperable patients coming to this hospital between age of 18 to 55 years who were previously untreated .All patients were randomized into two arms of 25 patients each. In Arm A patients received Inj cisplatin 30mg/m2 weekly on day 1,8,15,22,29,36 given concurrently along with standard rad iotherapy and in Arm B patients will receive inj. cisplatin 100mg/m2 on a three weekly basis on days 1,22 given concurrently along with standard radiotherapy. Patients received Radiotherapy to dose of 70 Gray(Gy) over 35 fractions(#) over 7 weeks with 5#/week @ 2Gy/# .The Theratron 780c tele-cobalt machine was used for radiotherapy of the patients after convention planning by radiation oncologist For assessment of toxicity all patients were monitored weekly during the course of CCRT for assessing the early toxicity of therapy.

## RESPONSE ASSESSMENT:

For assessment of response RECIST v1.01 was used. Com plete response (CR) was defined as the complete abs ence of disease 6 weeks. Partial response (PR) was defined as a reduction of disease by at least 50% in the sum of all measurable products of the longest perpendicular diameters of measurable tumor masses for at least 6 weeks,with no

growth of other lesions or appearance of new lesions. Stable diseases (SD)was defined as reduction in lesion by less than 50%, or increase by less than 25%. Progressive disease(PD) was defined as an increase by at least 25% of tumor lesions or appearance of new lesions.

### EVALUATION OF TOXICITY

Toxicities were evaluated by history, physical examination and laboratory tests. The grading system was based on the radiation therapy oncology group (RTOG) acute radiation morbidity scoring criteria.and CTCAE v.4.

### STATISTICAL ANALYSIS

For Statistical Analysis student unpaired T test was applied and P value was calculated between two arms.The statistics was calculated using mini tab version 17.0.

### OBSERVATIONS AND RESULTS:

According to staging in group A, stage III patients were 8 (32%), with stage IV A were 15 (60%) and with stage IV B were 2(8%). In group B, stage III patients were 7 (28%), stage IV A patients were 15 (60%) and stage IV B were 3 (12%). Table 1 Shows the site wise distribution of patients in both the arms.

**Table 1: Distribution of Patients According to site of disease.**

| Site | Weekly Group | | 3 Weekly Group | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Larynx | 6 | 24.0 | 5 | 20.0 |
| Oral cavity | 13 | 52.0 | 10 | 40.0 |
| Pharynx | 6 | 24.00 | 10 | 40.0 |
| Total | 25 | 100.0 | 25 | 100.0 |

### TOXICITY EVALUATION:

Details given Table 2 showing different toxicities observed

| Toxicity | Weekly Group | | 3 Weekly Group | | P Value |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| **Anemia** | | | | | |
| Grade I | 8 | 32.0 | 8 | 36.36 | 0.75 |
| Grade II | 8 | 32.0 | 9 | 40.91 | 0.526 |
| Grade III | 4 | 16.0 | 4 | 18.18 | 0.84 |
| **Leucopenia** | | | | | |
| Grade I | 7 | 28.0 | 8 | 36.36 | 0.54 |
| Grade II | 8 | 32.00 | 7 | 31.82 | 0.989 |
| Grade III | 2 | 8.00 | 3 | 13.64 | 0.53 |
| **Renal Toxicity** | | | | | |
| Grade I | 12 | 48.00 | 10 | 45.45 | 0.86 |
| Grade II | 6 | 24.00 | 5 | 22.73 | 0.92 |
| Grade III | 2 | 8.00 | 2 | 9.09 | 0.89 |
| **Vomiting** | | | | | |
| Grade I | 5 | 20.00 | 10 | 45.45 | 0.056 |
| Grade II | 12 | 48.00 | 9 | 40.91 | 0.62 |
| Grade III | 3 | 12.00 | 1 | 4.55 | 0.34 |
| **Dermatitis** | | | | | |
| Grade I | 14 | 56.00 | 13 | 59.09 | 0.83 |
| Grade II | 10 | 40.00 | 9 | 40.91 | 0.94 |
| Grade III | 1 | 4.00 | 0 | 0.00 | 0.30 |
| Mucositis | 0 | 0.00 | 0 | 0.00 | |
| Grade I | 14 | 56.00 | 10 | 45.45 | 0.46 |
| Grade II | 9 | 36.00 | 10 | 45.45 | 0.51 |
| Grade III | 2 | 8.00 | 2 | 9.09 | 0.89 |

### RESPONSE EVALUATION:

Complete response was achieved in 14 (56%) patients in group A and 12 (54.55%) patients in group B, while Progressive disease was seen in 2 (8%) patients in group A and 2 (9.09%) patients in group B.

In group A, 3 (12%) patients had stable disease and 6 (24%) patients had partial response while 1 (4.55%) patient in group B had stable disease and 7 (31.82%) patients had partial response with no significant difference between both groups.

### DISCUSSION:

Historically cisplatin 100 mg/m2 once in every 3 weeks along with radiotherapy was recommended as standard regimen for adjuvant treatment in HNSCC. However it was seen that schedules that deliver cisplatin in smaller doses on a more frequent basis may be preferable to high dose bolus administration as more frequent administration could provide radio sensitizing chemotherapy and small individual doses of cisplatin may lead to less chemotherapy induced morbidity without compromising efficacy. In our study the baseline characteristics of patients were similar and no significant difference was seen between group A and group B with respect to age, sex, performance status, grade and stage.

According to AJCC staging in our study majority of patients had stage IVA disease, constituting 60% in both groups which was similar to what was seen in study by Ahmed El-Azony[6] in which 45% of patients had stage IVA disease in both groups.

With regards to response to treatment in our study CR was seen in 56% of patients in group A and 54.5% of patients in group B while 3 (12%) patients had stable disease and 6 (24%) patients had partial response in group A while 1 (4.55%) patient in group B had stable disease and 7 (31.82%) patients had partial response with no significant difference between both groups. In similar study by Ahmed El- Azony, [6] CR was achieved in 10 (50%) in 3 weekly group and 9 (45%) patients in weekly group, while PR was achieved in 7(35%) patients in both groups. 3 (15%) patients in group A had no response of whom 2 patients had SD and 1 patient had PD while 4 (20%) patients in group B had no response of whom 3 (15%) had SD and 1 (5%) patient had PD. Similar to our study no statistically significant difference was seen in both arms and comparison between two modalities resulted in statistically similar response rates and adverse event profile.

In our study no significant difference was seen in terms of all measured toxicities but hematological toxicities were higher in group B. Regarding acute mucositis and dermatitis, most of them were grade 1 and 2 and were taken care of on outpatient care basis. No significant difference was seen between acute toxicities in two groups. No grade IV toxicities were seen in either groups..Uygun et al, [7] showed that grade 3-4 toxic events were 53.3% in 3 weekly and 40% in weekly cisplatin and no statistical difference was seen similar to our study. Similiarly in a study by Kose et al[8] showed no difference in terms of grade 3-4 mucositis.Geeta et al.[9] showed that 3 weekly was less toxic as compared to weekly cisplatin. Less grade III toxicity of skin and mucous membrane was seen in 3 weekly (40% vs 33%) which was probably attributed to delivery of chemotherapy in divided doses.

In our study there was no significant difference regarding hematologic toxicity, nephrotoxicity and vomiting between both groups due to proper hydration and other symptomatic care measures taken along with regular weekly check up.Ugyun et al,[7] reported similar vomiting in both groups. Grade 3-4 nephrotoxicity was 16.6% in 3 weekly and 5% in weekly cisplatin group. Difference being statistically insignificant. In 3 weekly group neutropenia was mildly higher. .In study by Ho et al,[10] no significant difference was seen between two groups with regard to grade III neutropenia, there was similar renal toxicity in both groups and no grade 3-

4 renal toxicity was seen.

Geeta et al[9] reported higher grade III hematological toxicity in weekly group. Grade III anaemia was 12.5% in weekly and 4% in 3 weekly group. Grade III neutropenia was also higher in weekly group. Grade I thrombocytopenia was 8% in 3 weekly and 6% in weekly group.

In our study, in group A, 8 (32%) patients had grade I, 8 (32%) patients had grade II and 4 (16%) patients had grade III anemia. In group B, 8 (36.36%) patients had grade I, 9 (40.91) patients had grade II and 4 (18.18) patients had grade III anemia with no significant statistical difference and regarding thrombocytopenia, in group A, 4 (16%) patients had grade I, 5 (20%) patients had grade II, 3 (12%) patients had grade III thrombocytopenia. In Group B, 4 (18.18%) patients had grade I, 2 (9.09%) patients had grade II, 4 (18.18%) patients had grade III thrombocytopenia. No significant statistical difference was seen between both groups in terms of anemia and thrombocytopenia and both were taken care of with blood transfusions wherever needed. No grade IV anemia or thrombocytopenia was seen.

In our study, in group A, 22 out of 25 patients completed treatment without any breaks whereas in group B, out of 22 patients 20 patients completed treatment without any breaks and due to severe dermatitis and mucositis along with hematological toxicity. Jemal A [11]in his study showed that significant number of patients could not receive the third cisplatin dose of 100 mg/m2. In our study in group B, 3 patients did not complete full course of treatment and therefore were excluded from the study.

Compliance is another significant problem with the standard cisplatin 100mg/m2 concurrent chemo-radiotherapy regimen.in our study in which the compliance was 100% in group A and 88% in group B which was similar to the study done previously by EORTC and RTOG

## CONCLUSIONS

In our study comparison of both regimens given concurrently with radiotherapy showed statistically similar response rates and adverse event profile. In terms of tumor response and toxicity both the regimens had equal results due to more potent medications available to manage them. However better compliance was seen in weekly cisplatin group as compared to 3 weekly due to toxicities. Thus use weekly cisplatin can be used nowadays due to less tolerability of 3 weekly regimen in some settings because of which less patients achieve cumulative dose beyond 200 mg/m2, lowering chemotherapy dose intensity .

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