

Comparative Study of Weekly and Three Weekly Chemoradiation Regimen in Advanced Head and Neck Cancer at Silchar Medical College

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Abstract: Majority of head and neck cancer cases present in an advanced stage and at sites where resection is not easy or it is impossible. For such cases, definitive chemoradiation is the solution. Cisplatin-based chemoradiation is the most common modality in chemoradiation in head and neck cancer world. There is a debate regarding the schedule of regimen whether weekly or three weekly regimens. With this in mind, we aim to compare the response, compliance, and toxicities of weekly low-dose cisplatin regimen and three weekly high-dose cisplatin regimen in our study. **Materials & Methods:** 41 patients were eligible for the prospective study in the department of ENT, Silchar Medical College. 24 in arm A (weekly based regimen) and 17 in arm B (three weekly based regimen) were studied for response to chemoradiation, compliance of treatment and their toxicities. The patients were divided into two arms; Arm A i.e. Cisplatin 30mg/kg body weight in one day given weekly for 6 cycles and Arm B i.e. Cisplatin 100mg/kg body weight in two days given three weekly for 3 cycles. Radiations were delivered in a fraction of 2Gy per day for 5 days per week for 6-7 weeks amounting to a total range of 60-70 Gy in both arms. **Results & Observations:** 70.73% of total patients showed a complete response. 75% of weekly regimen and 64.7% of three weekly regimens showed a complete response. 79.2%, 64.7% of cases of weekly and three weekly regimens respectively completed their treatment. Mucositis was the most common toxicity in both arms involving all the patients. Grade III toxicities are more in arm B (64.7%) than in arm A (41.6%). Anemia, leucopenia, and vomiting are more in arm B than in arm A. Leucopenia in arm B is more esp. grade III and it's statistically significant. **Conclusion:** Toxicities are more in three weekly regimens than weekly regimen. Response and compliance are more in weekly regimen than three weekly regimens. Hence it can be concluded that weekly low-dose cisplatin regimen is superior to three weekly high-dose cisplatin regimen.

Keywords: Chemotherapy in Head and Neck cancer, Cisplatin, weekly regimen, three weekly regimens, chemotherapy toxicity

1. Introduction

With the advent of chemotherapy, a new regimen of the combined modality of chemotherapy and radiation has arisen in the last two decades as a definitive treatment for unresectable or difficult to resect head and neck cancer cases. It certainly has improved the survival rates but with the high rate of complications which is the limiting factor for most patients. Cisplatin-based chemotherapy or chemoradiation regimen is the most commonly used in head and neck cancer but there is a debate about the schedule of treatment. A weekly regimen of low dose and three weekly regimens of high-dose are the two most sought-after regimens in practice in head and neck cancer. In our endeavor to contribute to the ongoing research, we have studied the effectiveness, complications, and compliance of weekly and three weekly cisplatin-based chemoradiation regimen in our head and neck cancer patients of the department.

2. Materials and Methods

This is a randomized prospective study conducted at the Department of ENT, Silchar Medical College between the period of August 2015 to July 2017. Forty-one eligible patients with locally advanced carcinoma of oropharynx, hypopharynx, and larynx were taken into the study. The study was approved by the institutional ethical committee.

Inclusion criteria: Locally advanced stage (TNM stage III-IV excluding metastasis), histologically proven as

squamous cell carcinoma, Karnofsky scores more than 70 and normal hematological and biochemical parameters.

Exclusion criteria: Prior history of chemotherapy, radiotherapy, metastasis.

The patients were divided into two arms; Arm A i.e. Cisplatin 30mg/kg body weight in one day given weekly for 6 cycles and Arm B i.e. Cisplatin 100mg/kg body weight in two days given three weekly for 3 cycles. Radiations are given in fractions of 2Gy per day for 5 days weekly for 6-7 weeks amounting to the total range of 60-70Gy. Clinical examination, endoscopy, and CT scan are done after one month to evaluate the response of chemoradiation. Toxicities are evaluated using RTOG scale.

Patients were followed up monthly.

Out of 41 patients, 24 patients were in arm A and 17 in arm B.

3. Results & Observations

From the table no. 1, it was observed that the median age is 60 years, prevalence of male gender was much higher, most common site is oropharynx (39%), most common histological grading is moderately differentiated (44%) and most common stage is stage III (31%)

Table 1: Showing Patient Characteristics in the Study

| | Total | Arm A | Arm B |
|---------------------------|----------|----------|----------|
| Age (Median) | 60 | 58 | 60 |
| SEX | | | |
| Male | 34 | 19 | 15 |
| Female | 7 | 5 | 2 |
| Male: Female | 4.85:1 | 3.8:1 | 7.5:1 |
| SITE | | | |
| Oropharynx | 16 (39%) | 10 (42%) | 6 (35%) |
| Hypopharynx | 13 (32%) | 6 (25%) | 7 (41%) |
| Larynx | 12 (29%) | 8 (33%) | 4 (24%) |
| Histological Grading | | | |
| Well differentiated | 9 (22%) | 6 (25%) | 3 (18%) |
| Moderately differentiated | 18 (44%) | 14 (58%) | 8 (47%) |
| Poorly differentiated | 14 (34%) | 4 (17%) | 6 (35%) |
| STAGING | | | |
| III | 31 (76%) | 19 (79%) | 12 (71%) |
| IV | 10 (24%) | 5 (21%) | 5 (29%) |

Response assessment

Out of the 41 patients, 70.73 % patients showed complete response and 29.26% partial response. 75% in weekly regimen showed a complete response, 64.7% in three weekly

regimens showed a complete response. It was statistically not significant. ($p=0.475$, $X^2=0.509$).

Table 2: Showing Response Rate of Both Arms

| Response | Total | ARM A | ARM B |
|------------------|-------|----------|------------|
| Total Response | 29 | 18 (75%) | 11 (64.7%) |
| Partial Response | 12 | 6(25%) | 6 (35.3%) |

Toxicities assessment

All the patients receiving either regimen suffered from chemotherapeutic toxicities more or less. Using the RTOG scale for acute toxicities, 64.7 % cases of three weekly regimens showed grade III toxicity while only 41.6% of weekly regimen showed grade III toxicity.

Anemia, Leucopenia, and Vomiting are more in arm B than arm A. Statistically only the incidence of leucopenia is significantly more in arm B than A ($p=0.011$, $X^2=6.46$). Grade III leucopenia, grade II vomiting was significantly more in arm B. The incidence of Dermatitis and Dysphagia are almost equal in both arms with not much difference in grading also.

Table 3: Showing Toxicities of Both Arms

| Toxicities | GRADE I | | GRADE II | | GRADE III | | GRADE IV | |
|------------|---------|--------|-----------|--------|-----------|--------|----------|-------|
| | Arm A | Arm B | Arm A | Arm B | Arm A | Arm B | Arm A | Arm B |
| Dermatitis | 8(33%) | 6(35%) | 2(8%) | 1(6%) | 0 | 0 | 0 | 0 |
| Mucositis | 11(46%) | 7(41%) | 9(37%) | 8(47%) | 4(17%) | 2(12%) | 0 | 0 |
| Dysphagia | 6(25%) | 4(23%) | 4(16.67%) | 4(24%) | 3(12%) | 2(12%) | 0 | 0 |
| Vomiting | 8(33%) | 6(35%) | 4(21%) | 7(41%) | 1(4%) | 3(18%) | 0 | 0 |
| Anemia | 8(33%) | 5(29%) | 4(17%) | 6(35%) | 2(8%) | 2(12%) | 0 | 0 |
| Leucopenia | 4(17%) | 6(35%) | 2(8%) | 3(18%) | 0 | 2(12%) | 0 | 0 |

Compliance assessment

19 out of 24 cases (79.2%) of arm A completed their weekly 6 cycles while 11 out of 17 cases (64.7%) of arm B completed their three weekly 3 cycles. Though in terms of percentage it seems compliance is more in arm A, statistically it is not significant. It has been observed that there were interruptions in both arms but were not significant. Two patients (8%) refused completion of radiation in arm A and one patient in arm B (6%). Interruptions in radiation were not analyzed properly.

4. Discussion

There is no definite protocol till date regarding the definitive chemoradiation treatment of locally advanced squamous cell carcinoma of head and neck region. Several trials with several chemotherapeutic agents and radiation with different schedules have been going on in the head and neck cancer world amongst whom monotherapy cisplatin 100mg/m² three weekly regimens was the most frequent and accepted chemotherapy regimen in the world. It is being considered as the standard. However, with good response rate, they come with the good amount of toxicities esp. of higher grades. In the pursuit of fewer toxicities with good response rate, low-dose cisplatin given weekly for 6 cycles regimen has been proposed and tried.

In our study, we found that the complete response rates of the tumor in weekly and three weekly were 75% and 64.7% respectively. In *Rawat et al.* study, there was not much

difference between the weekly and three weekly chemotherapy regimen. In *Tapan Kumar Sahoo et al.* study, they found 73.33% and 85.71% in weekly and three weekly cisplatin chemotherapy regimen respectively which shows a better response in three weekly regimens. Also in *Mitra et al.* study, they found the three weekly better than weekly chemotherapy in terms of response. According to *Homma et al.* study, there were 98.1% complete response on weekly Cisplatin 40mg/ kg body weight in stage II-IV HNSCC.

It was observed that mucositis was the most common toxic symptom of cisplatin-based chemoradiation whether it is weekly or three weekly regimen. In our studies, grade III mucositis was 17% and 12 % in weekly and three weekly regimens respectively. This was supported by the *Geeta SN study et al.* But in studies, *Tapan Kumar Sahoo et al., Mitra et al., Azony et al.*, grade III mucositis is more in three weekly than weekly chemotherapy regimen.

Vomiting in our studies was 54.16% in the weekly regimen and 76.47% in three weekly regimens respectively. The difference in this study was statistically significant. ($p=0.005$, $X^2=7.62$). Our study corroborated with the studies of *Rawat et al.* and *Azony et al.* where the incidence was more in three weekly. Grade III vomiting is more in our study.

Hematological toxicity like anemia and leucopenia are the most important toxicity of chemotherapeutic agents. They are the limiting factors for stoppage of treatment. In our

study, both anemia and leucopenia were much higher in three weekly cisplatin regimen than weekly regimen. We found 35% and 65% leucopenia in weekly and three weekly respectively with the incidence of grade III and II leucopenia more in three weekly regimens. 76% and 58% of total cases of three weekly and weekly cisplatin regimen suffered from anemia respectively. Increase in Leucopenia was statistically significant in our study but not anemia. We got grade III leucopenia only in three weekly regimens i.e., 12%. In regards to anemia, according to *Rawat S et al.*, 55.2% cases in three weekly arm and 26.7% cases in weekly arm were with neutropenia. According to *Mitra D et al.*, 33% of cases in the weekly arm and 43% cases in three weekly arms were

with grade III neutropenia. According to *Tapan Kumar Sahoo et al.*, they found 6.67% grade III anemia in weekly chemotherapy regimen, which is similar to our finding i.e. 8%.

When the overall analysis was done, it was observed that grade III toxicity was higher in three weekly regimens than weekly regimen i.e., 66% vs 41%.

All the patients were alive except for one patient with stage IV oropharyngeal cancer of arm A (weekly regimen) who after completing chemoradiation died suddenly.

Table 4: Showing Comparison Of Different Studies

| Serial no. | Study | No. of cases | weekly & 3 weekly dose | treatment response | treatment compliance | anemia | leukopenia | mucositis | vomiting |
|------------|-------------------------|--------------|------------------------|--------------------------------------|--------------------------|--|---|--|-------------------------------|
| 1 | Our study | 41 | 30vs100 | 66% in weekly vs 53% three weekly | ↑ in weekly (71% vs 47%) | ↑ in 3 weekly (88% vs 83%) Gr. II, III more in 3 weekly | ↑ in 3 weekly (65% vs 25%) gr II, III more in 3 weekly | almost similar in both regimen | ↑ in 3 weekly (94.1 vs 54.1%) |
| 2 | Tapan Kumar Sahoo et al | 30 | 30vs100 | 73% in weekly vs 85.71% three weekly | ↑ in weekly (67% vs 47%) | ↑ in weekly (73% vs 67%) Gr. II more in weekly | ↑ in weekly (87% vs 73%) | All the patients were affected. Gr. III & IV more in 3 weekly | ↑ in 3 weekly (94.1 vs 54.1%) |
| 3 | Geeta SN et al | 83 | 40vs100 | - | ↑ in 3 weekly | ↑ in weekly | ↑ in weekly | ↑ in weekly | - |
| 4 | Azony et al | 40 | 30vs100 | - | - | - | ↑ in 3 weekly | similar | ↑ in 3 weekly |
| 5 | Mitra et al | 90 | 30vs100 | 76% in 3 weekly vs 67% in weekly | - | ↑ in 3 weekly | ↑ in 3 weekly | Similar but grade III mucositis ↑ in weekly | ↑ in weekly |

5. Conclusion

From our study, it can be concluded that response rates are better in weekly regimen than three weekly regimens but this cannot be a decisive factor for preference to weekly regimen till the overall survival of cases of both regimens is analyzed. On the other hand looking at the toxicities profile and compliance, weekly regimen seems superior to three weekly regimens. Further studies by increasing the number of cases, and prolong follow-up will certainly establish which regimen is exactly superior.

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