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CONCURRENT PACLITAXEL AND RADIATION THERAPY IN CISPLATIN CONTRAINDICATED LOCALLY ADVANCED HEAD AND NECK CANCER – A PROSPECTIVE STUDY

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ABSTRACT

Concurrent chemoradiation with Cisplatin is the standard of care in locally advanced head and neck cancer. The present study was done with Paclitaxel, a potent radiosensitiser in Cisplatin contraindicated patients. Fifty patients of non-metastatic locally advanced squamous cell carcinoma in whom cisplatin was contraindicated were divided into two arms. Arm 1 received weekly Paclitaxel 40mg/m2 along with External Beam Radiotherapy. Arm 2 received Ext RT only. In the combined arm 60% showed complete response (CR) whereas 20% had partial response (PR) with a total response of 80%. In the RT only arm 40% had CR and 20% had PR with total response of 60%. Grade II/III mucositis the major toxicity was seen in 88% cases in combined against 36% in the single arm. Concurrent Paclitaxel + RT showed excellent results with increased toxicity.

KEYWORD

Head and Neck cancer, Concurrent Chemoradiotherapy, Paclitaxel

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Squamous cell cancer of the head neck is the commonest solid cancer among adult males in India[1]. Standard local therapy – Radiation or Surgery alone yields poor results in locally advanced head and neck cancer[2]. Chemotherapy alone is also not satisfactory but it enhances the effects of RT and is routinely used as part of combined modality treatment in patients with Stage II or IV disease[3]. Concurrent Chemoradiation with Cisplatin is the standard care now. There is no standard drug for concurrent chemoradiation in patients with contraindications to Cisplatin.

Radiation potentiation is an additional desirable benefit of some anti-cancer drugs. They increase cell kill by reducing the clonogenic cell numbers both inside and outside the radiation field. Some drugs directly sensitise the tumour cells to radiation further increasing cell kill. Paclitaxel is a potent radiosensitiser that has major anti-neoplastic activity. It has excellent radio sensitisation property by cell blockage in G2/M phase. Concurrent chemoradiation with Paclitaxel results in greater response[4].

The present study was undertaken to see the effects of concurrent Paclitaxel chemoradiation in cisplatin contraindicated locally advanced head and neck cancer on locoregional control and acute toxicities.

MATERIALS AND METHODS

The prospective comparative study was done in the Department of Radiotherapy, Medical College, Kolkata from July 2000 to June 2001. Fifty previously untreated Stage III/IV squamous cell cancer of head and neck with ECOG performance 0-3, no distant metastasis and in whom Cisplatin was contraindicated were selected and randomised into two arms. Study arm of concomitant Paclitaxel chemoradiation (25 patients) and control arm of only radiation (25 patients). Patients with severe comorbid medical illness were excluded.

External Beam Radiotherapy was delivered using Telecobalt machine to primary and draining lymph nodes to a total dose of 70 Gray in 35 fractions over 7 weeks, with field shrinkage and sparing of spinal cord after 44 Gray. Study arm (Arm 1) received Paclitaxel 40mg/m^2 one hourly infusion one hour before radiation weekly IV on days - $D_1 D_8 D_{15} D_{22} D_{29} D_{36}$. Arm 2 received only radiation. During treatment patients were monitored for haematologic toxicities and radiation reactions weekly. After treatment completion follow up was done after 2 weeks and thereafter monthly for a median follow up of six months.

RESULTS AND ANALYSIS

The patients in both the arms were comparable in terms of sex, staging & disease sites. All the fifty patients completed their treatment as planned and were evaluable.

In the Arm 1 (Paclitaxel + RT) 15 patients achieved complete response (60%) and 5 patients (20%) had a partial response for a total response of 80%. On a median follow up of 6 months 5 patients progressed out of which one died. In the Arm 2 (RT only) 10 patients had complete response (40%) while 5 patients (20%) had partial response giving a total response of 60%. As many as 10 patients (40%) on radiation only showed no response and progressed.

TABLE 1: TREATMENT RESPONSE

RESPONSE	**Arm 1** (n=25) Paclitaxel+ RT	**Arm 2** (n=25) RT only
Complete Response (CR)	15 (60%)	10 (40%)
Partial Response (PR)	5 (20%)	5 (20%)
Total Response CR + PR	20 (80%)	15 (60%)
No Response	5 (20%)	10 (40%)

Mucositis was the most commonly encountered toxicity in both the arms. Mucositis was more severe in the combined arm where 88% of the patients developed Grade II or Grade III mucositis by the end of 6 weeks. Mucositis was observed from 2nd weeks onwards. Grade II dermatitis developed in 5 patients of Arm I. No patient had Grade III Neutropenia. In the RT only arm only 36% of the patients developed Grade II or III mucositis. No patient required discontinuation of treatment in either arms.

TABLE 2: TOXICITIES – MUCOSITIS

Weeks	ARM 1			ARM 2		
	Grade I	Grade II	Grade III	Grade I	Grade II	Grade III
2nd week	5 (20%)	0	0	0	0	0
3rd week	15 (60%)	5 (20%)	0	5(20%)	0	0
4th week	18(72%)	7 (28%)	0	10(40%)	0	0
5th week	7 (28%)	13(52%)	5(20%)	13(52%)	5(20%)	0
6th & 7th week	3 (12%)	15(60%)	7(28%)	15(60%)	7(28%)	2(8%)

DISCUSSION

Locally advanced head and neck cancer is treated by concurrent cisplatin based chemoradiation which is now the standard of care. Problem arises in patients with contra indication for cisplatin. There is no standard concurrent drug for these group of patients. Paclitaxel based concurrent chemoradiation is an attempt to achieve higher response than radiation alone with acceptable toxicities in those patients. Paclitaxel has been used in low dose because of clinical data of its powerful antitumor and radio sensitization effect.

Essa et al[5] studied 41 patients, 21 with concurrent Paclitaxel 30mg/m^2 weekly and 20 patients with concurrent Cisplatin 30 mg/m^2 with RT to a dose of 66-70 Gray in conventional fractionation. CR was seen in 57.1% in group in I & 50% of group II while PR was seen in 28.6% in group I & 25% in group II. Objective Overall response was 85.7% in group I versus 75% in Group II with no statistical significance. Treatment toxicities were comparable in both groups. The authors concluded that concurrent chemoradiotherapy with weekly paclitaxel was feasible when cisplatin was contraindicated.

Citrin D et al[6] studied 35 patients with locally advanced squamous cell carcinoma of head & neck who received 120 h infusion of Paclitaxel on Day 1,21 & 42 along with conventional fractionated radiotherapy. Initial 16 patients received 105 mg/m^2 and the later 19 patients received 120 mg/m^2/cycle. At a median follow up of 56.5 months median time to local recurrence was not reached. The authors concluded that concurrent chemoradiotherapy with a 120h infusion of paclitaxel provided long term local control and survival in patients with squamous cell carcinoma of head and neck cancer with acceptable toxicities.

Agarwala SS et al[7] conducted a phase II trial in inoperable locally advanced SCCHN with Carboplatin 100mg/m^2 and paclitaxel 40mg/m^2 weekly during external beam radiation (180 cGy per fraction) for 6-7 weeks. 40 of the 50 assessable patients (80%) had an objective response with a complete response of 52%. The authors concluded that treatment with concurrent carboplatin, paclitaxel and radiation was safe and offered curative potential for poor prognosis patients with locally advanced head and neck cancer.

Sunwoo J B et al[8] carried out a study with 33 patients with concurrent paclitaxel 120-hour infusion 3 weekly and radiation. 16 patients received 105mg/m^2 and 17 patients received 120mg/m^2. Radiation was delivered at 1.8 Gy/day to a total dose of 70.2 to 72 Gy. At 3 months 76% complete response was obtained at primary site. At 36 months locoregional control was 55.75, overall survival was 57.8% and disease-free survival was 51.1%. The authors concluded that paclitaxel administered as a 120-hr continuous infusion in combination with radiotherapy is a feasible and promising treatment for patients with advanced HNSCC.

Our study is in agreement with the other studies. 80% of our patients on concurrent weekly paclitaxel chemoradiotherapy achieved overall response as compared to 60% with radiation only arm. As expected, toxicity especially mucosal toxicity was much higher in the combined arm with 88% having Grade II/III toxicity in contrast to 36% Grade II/III toxicity in RT only arm. Toxicities were manageable and acceptable.

CONCLUSION

Treatment of locally advanced squamous cell carcinoma of head and neck cancer with concomitant weekly paclitaxel and external beam radiotherapy is feasible in cisplatin contraindicated patients and shows excellent results when compared to radiotherapy alone with acceptable toxicity.

Further study with more patients and longer follow-up is warranted.

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