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The Comparative Evaluation of Radiotherapy with Concurrent Weekly Cisplatin and Irinotecan versus Concurrent Weekly Cisplatin in Locally Advanced Carcinoma Esophagus

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Abstract: *Esophageal cancer is a disease of mid to late adulthood with a male predilection.It is associated with poor outcome. The 5 year survival rates ranges from 20% to 30%. The treatment depends on disease staging, patient's general condition and individual preferences. Surgery alone as a treatment modality is associated with poor survival rates. This lead to the integration of adjuvant and neoadjuvant chemoradiation in the treatment of esophageal carcinoma as they are associated with better survival rates. The present study is a prospective study conducted at cancer hospital NSCB Medical College Jabalpur and was done to evaluate the effect of radiotherapy with concurrent weekly Cisplatin and Irinotecan versus concurrent weekly cisplatin in locally advanced carcinoma esophagus. After follow up for 1 month, complete response in group A was 41.7% and in group B was 7%.. From our study we concluded that the weekly Cisplatin with Irinotecan and concurrent radiation is feasible and well tolerated.*

Keywords: *Cisplatin, concurrent radiation, complete response, Irinotecan, locally advanced esophageal carcinoma, treatment toxicities*

I. Introduction

Esophageal cancer is the eighth most common malignancy worldwide. It is unique among gastrointestinal tract malignancies because it embodies 2 major histopathological varieties- esophageal squamous cell carcinoma (ESCC) and adenocarcinoma(EAC). Squamous cell carcinoma arises from the epithelial lining and adenocarcinoma arise from glandular elements particularly in the lower third and is often associated with a metaplastic condition called Barrets esophagus[1]. ESCC comprises 60–70% of all cases of esophageal cancer worldwide, while EAC accounts for a further 20–30% (melanomas, leiomyosarcomas, carcinoids and lymphomas are less common types).[2] The incidence of the two main types of esophageal cancer varies greatly between different geographical areas.[3] In general, ESCC is more common in the developing world, and EAC is more common in the developed world.

The most common causes of the squamous-cell type are: tobacco, alcohol, very hot drinks, and a poor diet. The most common causes of the adenocarcinoma type are smoking tobacco, obesity, and acid reflux.[4]. Unfavorable dietary patterns seem to involve exposure to nitrosamines through processed and barbecued meats, pickled vegetablesand a low intake of fresh foods.[5] Chewing betel nut (areca) is an important risk factor in Asia.[6]Physical trauma may increase the risk. This may include the drinking of very hot drinks.[6]Corrosive injury to the esophagus by accidentally or intentionally swallowing caustic substances is a risk factor for squamous cell carcinoma.[1]Tylosis with esophageal cancer is a rare familial disease that has been linked to a mutation in the RHBDF2 gene: it involves thickening of the skin of the palms and soles and a high lifetime risk of squamous cell carcinoma.[1][7]Achalasia appears to be a risk factor for both main types of esophageal cancer, at least in men, due to stagnation of trapped food and drink.[8]Plummer–Vinson syndrome is also a risk factor.[1]

Disease is diagnosed by endoscopic biopsy. Treatment was based on tumor staging, site of tumor and patients general condition and individual preferences. Small localized squamous cell carcinoma may be treated with surgery alone. In other cases surgery is combined with chemotherapy with or without radiotherapy.Radiation therapy is successful in relieving dysphagia in approximately 50% of patients. In patients with advanced esophageal cancer, the preoperative combination of chemotherapy and radiotherapy has shown good results. Nearly three forth of patients present with locally advanced disease. Surgery was considered to be the treatment in olden days but it is associated with poor survival rates. This lead to the integration of adjuvant and neoadjuvant chemoradiation in the treatment of esophageal carcinoma as they are associated with better survival rates.Multi agent therapy with Cisplatin, 5 Flurouracil are themost frequently used chemotherapeutical agents used in the treatment of esophageal cancer. Otheragents used are Cisplatin, Carboplatin, Taxanes and

Anti Epidermal Growth Factor Inhibitors [9].A Phase 2 clinical trial was conducted atMemorial Sloan Kattering Cancer Centre New Yorkby David H Illison, Bruce Minsky, David Kelsento evaluate response to chemoradiotherapy in patients with locally advanced esophageal cancer with total 5040cGy radiation given as 180cGy fractions combined with Irinotecan 65mg/m^2 and Cisplatin 30mg/$m^{2.}$ In this study 38% responded completely, minimal toxicities were reported with no grade 3 or 4 esophagitis or diarrhea. On the other hand, only10 % showed complete response when radiation was combined with Cisplatin 30 mg/m^2 alone.

II. Materials And Methods

The present study is a prospective study and was carried out at cancer hospital under NSCB Medical College Jabalpur during the period of year September 2008 and August 2009. A total of 47 patients were enrolled in the study. 24 patients were enrolled in the study arm and 23 were enrolled in the control arm randomly. Patient and tumor characterstics, response to treatment and its associated toxicities were observed in the two groups and analysed.The study subjects werehistopathologically proven locally advanced Squamous cell carcinoma esophagus,Karnofsky performance status ≥ 60, ECOG performance status ≤ 1.Informed consent was obtained from all subjects.Those patients with Haematological, cardiac, renal or liver function abnormalities, distant metastasis i.e. stage IVB , prior Radiotherapy, prior Chemotherapy other synchronous malignancies, prior surgery were excluded.

Patients will be planned for External Beam Radiotherapy given with Co 60 teletherapy unit. Total dose of 5040cGy by AP- PA portals in supine position at 80 cm SAD as 5 fractions per week and each fraction was 180 cGydose.

2.1**: Concurrent Chemotherapy protocol schedule** :

2.1.1**: Arm A (Study Group):** Inj. Cisplatin 30mg/m^2 IV weekly followed byIrinotecan on days 1,8,22 and 29 of radiotherapy with a gap between second and third cycles of chemotherapy was given.

2.1.2:**Arm B (Control Group):**Inj. Cisplatin 30mg/m^2 IV started on day 1 of radiation repeated weekly for 5 weeks.

Patients were reviewed weekly and as and when required. Patient response in terms of symptomatic relief of dysphagia, chemo and radiotherapy induced toxicities were assessed. Response to treatment were evaluated using the following definitions- Complete response- no evidence of pretreatment tumor and symptoms, no recurrence in 1 month; Partial response- more than 50%regressiion of locoregional disease; No response- less than 50%regressiion of locoregional disease or progression or no regression at all; Progression- increase in size of the tumor during treatment.

III. Results

After follow up for 1 month, complete response in group A was 41.7% and in group B was 7%. Complete response in group A was statistically significant when compared to group B ($p < 0.05$). After follow up for 1 month, 58.3% of group A patients had evidence of persistence of disease compared with 91.3 % in group B. During the follow up period of 2-11 months 3 out of 10 complete responders in group A had locoregional relapse compared to 1 out of 2 in group B. In group A ,3 patients developed distant metastasis compared to 7 in group B

Treatment was well tolerated in both arms. No grade 3 / 4diarrhoea was noted. 7 patients in arm A and 3 in arm B developed grade 1 to 2 diarrhoea. . 10 patients developed radiation esophagitis- 6 in arm A and 4 in arm B.1 patient in arm A developed grade 3 pulmonary toxicity which might be related to acute radiation induced pneumonitis and was relieved with prednisone and antibiotics. Hematological toxicity was also minimal- 2 patients (8.3%) experienced grade 3 neutropenia and 1 patient (4.2%) experienced grade 3 thrombocytopenia in group A.

During the follow up period of 2-11 months 38% of patients in group A was disease free as compared to 9% in group A. Locoregional relapse rate in complete responders were 20% in group A as compared to 50% in group B. Disease free survival rate was also higher for group A.

IV. Figures And Tables

Patients baseline characterstics: Table 1

Characterstic	Number(Percentage)	
	Group A	Group B
Total patients	24	23
Males	14(58.3%)	15 (65.2%)
Females	10(41.7%)	8(34.8%)
Mean age(in years)	54.5± 10.9	56.3 ± 9.05

Patient's response characteristics– Table 2

Primary response	Group A	Group B
Complete response	10	2
	41.7%	8.6%
No response	1	6
	4.2%	26.1%
Partial response	13	15
	54.1%	65.2%

Patient toxicity characterstics- Table 3

Toxicity	Grade	N(percentage)	
		Group A	Group B
Nausea/vomiting	0	13(54.2%)	13(56.5%)
	1	6(25.0%)	7(30.4%)
	2	4(16.7%)	3(13%)
	3	1(4.2%)	0
Diarrhea	0	17(70.8%)	20(87.0%)
	1	5(20.8%)	2(8.7%)
	2	2(8.4%)	1(4.3%)
Myelosuppression	Present	9(37.5%)	7(30.4%)
	Absent	15(62.5%)	16(69.6%)
Acute skin reaction	0	0	0
	1	8(33.3%)	6(26.1%)
	2	12(50.0%)	13(56.5%)
	3	3(12.5%)	2(8.7%)
	4	1(4.2%)	2(8.7%)

V. Conclusion

After follow up for 1 month, complete response in group A was 41.7% and in group B was 7%..From our study we concluded that the weekly Cisplatin withIrinotecan and concurrent radiation is feasible and well tolerated. High degree of palliation of dysphagia was achieved with minimal side effects.Though the study regimen was costlier than the control regimen it was economical when compared with other regimens. A similar study was conducted atMemorial Sloan Kattering Cancer Centre New Yorkby David H Illison, Bruce Minsky, David Kelsen in which 38% responded completely, minimal toxicities were reported. Our study also brings out similar results. This suggests that weekly Cisplatin with Irinotecan and concurrent radiation definitively provides add on benefit for patients with locally advanced esophageal cancer.

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