ORIGINAL ARTICLE

Comparative Evaluation of Sequential with Concurrent Chemo-Radiotherapy in Locally Advanced Squamous Cell Carcinoma of Esophagus

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Abstract

To compare the results of sequential with concurrent chemo radiotherapy in locally advanced squamous cell carcinoma of esophagus in terms of loco regional control, toxicity profile and overall survival,65 patients were enrolled between Jan 2008 and Dec. 2010, of which 37 were male and 28 female. Patients had histologically confirmed squamous cell carcinoma with locally advanced disease with no prior treatment in the form of chemotherapy, radiotherapy or surgery. Patients were divided into two groups and were comparable in terms of patient characteristics. In Group-I, 35 were given sequentially paclitaxel 175mg/m2, cisplatin 75mg/m2 on day 1 of every 21 days for 3 cycles followed by external beam Radiotherapy followed by 3 more cycles of same chemotherapy. In Group-II, 30 patients were given two cycles of Induction chemotherapy same drugs and dosage as in Group-I and was followed by EBRT concurrent with paclitaxel 30mg/m2 given on day 1 of every week during radiation therapy treatment. The overall objective response rate at the end of treatment was superior 93.33% in Group-II as compared to 74.28% in Group-I. Thrombocytopenia was 73.33% and 17.14% in Group-II and Group-I respectively. Similarly, mucosites was higher 56.66% in Group-II as compared to 22.85% in Group-I. At 2 years of follow up, there was no statistically significant difference seen in overall and disease free survival.

Key Words

Esophageal Cancer, Chemotherapy, Radiotherapy, Sequential, Concurrent

Introduction

Esophageal cancer is one of the killer cancers, accounting 4% of all cancers world-wide (1). It is reported that 5.5% of all death related cancers are due to esophageal cancer (2). Squamous cell carcinoma is the most prevalent histological form accounting for over 90% of cases in developing countries (3).The efficacy of conventional treatment with surgery and radiation for cancer of the esophagus is limited, as less than 10% of patients survive for five years (4). Esophagectomy is a complex surgery associated with high morbidity 40% and mortality of 5-10% (5,6). External beam radiotherapy (EBRT) and concurrent chemotherapy has proven to be more efficacious than EBRT alone as a definitive therapy for localized squamous cell carcinoma of esophagus (7). Eastern co-operative oncology group (ECOG) trial of 135 patients showed that chemotherapy plus radiation therapy provided a better 2 year survival rate than did radiotherapy alone (8). In an attempt to improve the outcome,chemotherapy has been integrated in the primary management of this disease. However the sequence of chemotherapy and radiation for optimum benefits is yet to be established. The present study was undertaken to evaluate and compare the feasibility, efficacy and toxicities of sequential chemotherapy with concurrent chemo-radiation in squamous cell carcinoma of esophagus.

Material and Methods

A total of 65 patients with histologically confirmed

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squamous cell carcinoma of esophagus were enrolled in the study. Pre treatment evaluation included history, physical examination, CBC, KFT, LFT, chest x-ray, ultrasoundabdomen and pelvis,CECT chest and abdomen, bone scan (where ever indicated),barium swallow esophagus and upper GI endoscopy. Patients who had T2-T3 N0-1M0 and ECOG performance status of 0-2 were included in the study. Patients with surgery, Prior chemotherapy or Radiotherapy were excluded from the study. Patients were divided into two groups by simple randomization. Group-I(35 Patients) received sequential chemotherapy in the form of Ing.Paclitaxel175mg/m2 i/v infusion over 24hours and Cisplatin 75mg/m2 i/v infusion over 3 hours. Cycle was repeated after 3weeks. Three such cycles were followed by external beam radiation followed by three more cycles of chemotherapy of same drug and dosage. Group-II(30 Patients) received two cycles of induction chemotherapy with the same drug and dosage as in Group-I. It was followed by EBRT concurrent with Inj. Paclitaxel of 30mg/m2 given on day 1 of every week, during the radiation therapy treatment.

Radiation therapy in both the groups was delivered by Co-60 unit. A dose of 40-45 Gy was delivered by anterio-posterior portals in 4 weeks at the rate of 2 Gy per fraction which was followed by a supplementary dose of 20-25 Gy in 2 weeks by 3 field technique (2posterior oblique and 1 anterior). All the patients were assessed weekly and at the completion of treatment for the toxicities and response. Further, follow-up of patients was continued for 2 years after treatment.

Statistical Analysis

The statistical analysis was performed using chi-square test. This non-parameteric test was applied to determine the response, toxicity profile and the treatment outcome for the two groups. The reported p value ($p < 0.05$) is considered significant.

Results

Between January, 2008 to December, 2010, 65 patients were enrolled in the study of which 35 in sequential Group-I and 30 in the concurrent Group-II. The patients comprised of 37 male and 28 females. The median age was 55 (56± 9.5 years) in Group-I and 59 (58± 7.9 years) in Group-II. The demographies of the two groups are shown in table 1. There were no significant differences in age, sex, presentation, performance status, site of lesion between two groups. The treatment related toxicity profile is shown in table 2. There were no significant differences in gastrointestinal and neurological toxicities.However there were significant differences seen in haematological toxicities such as thrombocytopenia was 17.14% and 73.33% in Group-I and Group-II respectively. Neutropenia was 77.14% and 30.0% in Group-I and Group-II respectively. There was no significant difference seen in overall survival between the two groups as shown in table-3. Disease free survival at 2 years was 34.28% in Group-I, slightly higher thanGroup-II (30.0%). Distant metastasis was 5.7% and 10.0% in Group-I and Group-II respectively.

Discussion

The meaningful improvement in the treatment of carcinoma esophagus continuous to be an elusive and a challenging target. The prognosis of esophageal cancer is very poor. About 50% of patients have advanced disease at the time of diagnosis, though some patients undergo curative surgical treatment. The disease recurs and metastizes in 65% of cases at 5 years (9). Radiation therapy administered concurrently with chemotherapy is the standard treatment in patients with nonresectable oesophageal cancer (10). The most accepted chemotherapy for oesophageal cancer is Cisplatin combined with 5-flurouracil. The response rate to this combination vary between 20% and 50% and is associated with toxicities like esophagitis and neutropenias in significant numberof patients (11,12).In the present study, Paclitaxel-Cisplatin combination of chemotherapy was used. Paclitaxel has become a new promising chemotherapeutic agent in the treatment of esophageal cancer (13,14,15). The demographic profile and clinical presentation were comparable (*Table 1*).Though the treatment in both the groups was well tolerated, there was statistically significant difference inhematological toxicities (*Table 2*).Thrombocytopenia was 17.14% and 73.33% in Group-I and Group-II respectively.In Group-II, 22 patients developed pancytopenia of which grade-III toxicity was seen in 6 patients (20%) and grade-IV in 2 patients (6.7%). Leucopenia was observed in 74.28% and 73.33% of cases in Group-I and in Group-II respectively of which 46.6% of patients had grade III-IV toxicity in both the groups. Similarly neutropenia was seen in 77.14% and 30.0% in Group-I and Group-IIrespectively, of these grade-III toxicity was seen in 57.1% in Group-Iand 30% in Group-IIand10% developed grade-IV toxicity. These toxicities were manageable and patients with grade-IV toxicity (10%) needed hospitalization and G-CSF support. There was no treatment related deaths in current study. Haematological toxicities observed in the current study were almost similar and are better than reported by other clinicians (16,17,18). However C-Clin *et al* (19) has reported less haematological toxicities than our study. Gastrointestinal toxicities in the form of nausea, vomiting, diarrhoea were comparable and not significant in both the groups.

Table1. Patient Characteristics

Variable	GROUP 1 (n = 35)	GROUP II (n = 30)	P-value
GENDER			
Male	20	17	0.969
Female	15	13	
Age (in years)			
Median	55	59	0.519
Range	35 – 71	45 -70	
Presentation			
Dysphagia			
Grade I	23	11	
Grade II	11	15	0.051
Grade III	01	04	
Performance status			
ECOG			
0	02	06	
1	22	20	0.091
2	11	04	
Site of lesion			
Upper	02	03	
Middle	28	24	0.73
Lower	05	03	

Table 2.Toxicity Profile

Variable	Group I(n= 35)	Group II(n= 30)	P- Value
Haematological			
Leucopenia	26 (74.28%)	22(73.33%)	0.931
Neutropenia	27 (77.14%)	09 (30%)	< 0.001
Thrombocytopenia	06 (17.14%)	22 (73.33%)	< 0.001
Gastrointestinal			
Nausea/vomting	06 (17.14%)	07 (23.33%)	0.534
Diarrhea	17 (48.57%)	16 (53.33%)	0.702
Mucosites	08 (22.85%)	17 (56.66%)	0.005
Neurological			
Perip. Neuropathy	04 (11.42%)	13 (43.33%)	0.004

Table 3.Treatment response at 2 years

Variable	Group I (n=35)	Group II (n= 30)	P – Value
Overall Survival	26 (74.28%)	22 (73.33%)	0.931
Disease Free	12 (34.28%)	09(30%)	0.731\
Persistent disease	10(28.57%)	10(33.33%)	0.678
Distant Metastasis	02(5.71%)	03(10%)	0.655
Regional Metastasis	02 (5.71%)	---	0.495
Lost to Follow-up	06 (17.14%)	06 (20%)	0.767
Died	03(8.57%)	02 (6.6%)	1.00

However,mucosites was seen more in Group-II (56.66%) in comparison toGroup-I (22.85 %). It seems mucosites in Group-II may be related more to radiations than to chemotherapy. Non-haematological complications like peripheral neuropathy though statistically insignificant was seen more in Group-II(43.33%) than in Group-I (11.42%). Response at the completion of treatment was evaluated clinically, barium swallow and on endoscopy with biopsy.

Overall response in both the groups, though statistically insignificant, was superior inGroup-II (93.33%)than in Group-I (74.28%). At 2 years of follow-up, overall survival was 74.28% in Group-Iand 73.33% in Group-IIrespectively, of which disease free survival was 34.28% in Group-I and 30% in Group-II (table-3). Distant metastasis was slightly more in Group-II(10%) verses (5.7%) on Group-I. Our results in terms of response are similar as reported by Urba SG *et al.* (20).

Conclusion

The use of concurrent Paclitaxel based chemo-radiotherapy in patients with advanced squamous cell carcinoma of oesophagus has shown a good response rate (93.3%), however there is no difference observed in sequential versus concurrent chemo-radiotherapy in overall survival.Though concurrent chemo-radiation is a valuable treatment option for advanced esophageal cancer, but the subject needs to be studied further with larger population size.

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