Original Article

Comparative evaluation of gemcitabine concurrent with radiotherapy against cisplatin concurrent with radiotherapy in locally advanced squamous cell carcinoma of esophagus

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ABSTRACT

Background: Several trials using sequential and concurrent chemoradiation have established the role of concurrent chemoradiation in treatment of locally advanced esophageal carcinoma with encouraging but unsatisfactory results. We investigated the efficacy and toxicity of gemcitabine concurrent with radiotherapy against cisplatin concurrent with radiotherapy in locally advanced unresectable squamous cell carcinoma of the esophagus. **Materials and Methods:** Eighty patients were randomly allocated to two arms during the study. Arm 1 received cisplatin 40 mg/m^2 weekly concurrent with external beam radiotherapy to a total dose of 65 Gy while Arm 2 received gemcitabine 200 mg/m^2 weekly concurrent with external beam radiotherapy up to a total dose of 65 Gy. **Results:** Median follow-up was 11 months and 14.5 months in Arm 1 and Arm 2, respectively. Complete response was achieved in 20% of patients in Arm 1 and 32.5% of patients in Arm 2, with manageable acute toxicities in both arms. The progression-free survival in Arm 1 was 5.7 ± 4.7 months and 12.4 ± 6.8 months in Arm 2. The 2-year overall survival was longer in Arm 2. **Conclusion:** This study demonstrated that both cisplatin and gemcitabine concurrent with radiotherapy in locally advanced squamous cell carcinoma of the esophagus is safe and feasible with better response and progression-free survival with gemcitabine.

Key words: Carcinoma esophagus, comparison, concurrent chemoradiation, gemcitabine against cisplatin, locally advanced

INTRODUCTION

Esophageal carcinoma is the eighth most common cancer in the world[1] and is a highly virulent tumor with exceedingly dismal prognosis. Esophageal cancer belt extends across Asia from Southern shore of the Caspian Sea in Iran, through Soviet, Central Asia, and Mongolia to Northern China and Kashmir valley borders this belt on Southern side. In Kashmir valley, carcinoma of esophagus is the most common cancer[2] in adults and has a high incidence.[3] Treatment outcome of esophageal carcinoma is still not satisfactory. The majority of patients present with locally advanced disease irrespective of the histological type.[4]

Surgery is considered a standard treatment for operable esophageal carcinoma, but the majority of patients present with locally advanced disease, so multimodality therapy is essential. Whyte and Orringer reported a 5-year survival rate

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Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.177126

Cite this article as: Maqbool LM, Fatima K, Afroz F, Rasool MT, Hussain I, Andleeb A, *et al.* Comparative evaluation of gemcitabine concurrent with radiotherapy against cisplatin concurrent with radiotherapy in locally advanced squamous cell carcinoma of esophagus. Clin Cancer Investig J 2016;5:137-40.

with surgery alone in 27%[5] of patients, with local failure rate after surgery alone being still very high. The need to improve patient outcomes has led to the development of alternative primary treatments or adjuvant therapy in conjunction with surgery. Radiotherapy decreases the risk of local failure, but the 5-year survival in patients treated with conventional doses of radiotherapy is 0–10%.[6,7] Use of radiosensitizing doses of chemotherapy with radiotherapy has been demonstrated to further increase both local control and survival. Recent studies revealed that combined chemoradiation in locally advanced carcinoma of esophagus may result in improved survival. In randomized trials, definitive chemoradiation therapy has been demonstrated as a curative approach in locally advanced or unresectable squamous cell carcinoma.[8]

Huilgol *et al.*[9] concluded that concurrent weekly gemcitabine is toxic, but the toxicities are manageable, and the response is encouraging. Gemcitabine is one of the newer cytotoxic drugs in this setting and has shown the potential to augment the effects of radiation. It has shown antitumor activity in a number of solid tumors. Previous studies have focused on the use of this drug together with radiation therapy in esophageal carcinoma. However, to our knowledge, there have been no such studies comparing cisplatin versus gemcitabine concurrent with radiation as definitive treatment.

MATERIALS AND METHODS

The study was conducted from May 2010 to September 2012. We recruited a total of 80 patients. Patients were randomized into two arms with 40 patients in each group. In all patients, complete history was taken and physical examination was done, and all patients were evaluated at baseline by complete blood count, serum chemistry, X-ray chest, electrocardiogram, esophagogastroscopy with biopsy, barium esophagogram, and contrast enhanced computed tomography (CT) scan of the neck, chest, and abdomen. Informed consent was taken from all patients. Patients with locally advanced squamous cell carcinoma who were deemed unresectable by a multidisciplinary board of our hospital including thoracic surgeons, oncosurgeons, medical and radiation oncologists, radiologists, and pathologists. Patients with an Eastern Cooperative Oncology Group performance score 1 or 2 were included.

In Arm 1, cisplatin 40 mg/m^2 intravenous infusion over 1 h on the days 1, 8, 15, 22, 29, and 36 was given after proper hydration and use of antiemetics as per standard guidelines. In Arm 2, gemcitabine 200 mg/m^2 intravenous infusion over ½ h on the days 1, 8, 15, 22, 29, and 36 was given after antiemetics.

Radiotherapy in both the arms was delivered at Theratron 780E telecobalt unit using gamma rays as linear accelerator with newer technologies was not available at our center. All patients were planned on a simulation CT scanner (Siemens Somatom Sensation 26). An initial dose of 40 Gy in 20 fractions was delivered by two parallel opposite anterior and posterior portals with conventional fractionation over 4 weeks followed by a boost radiation of 25 Gy in 10 fractions over 2 weeks by spinal cord sparing three-field technique (one anterior and two posterior oblique) to the primary tumor to a total dose of 65 Gy in thirty fractions over 6 weeks.

Patients were assessed for toxicities weekly and at 1 month after completion of treatment. Toxicity was reported as per Radiation Therapy Oncology Group Common Toxicity Criteria version 3. Response assessment was done as per the WHO criteria. All patients were followed up with repeat esophagoscopy and a contrast enhanced CT scan of the neck, chest, and abdomen, 6 weeks after treatment completion. Positron emission tomography scan and endoluminal ultrasound were not available at our institute.

RESULTS

Initially, a total of 90 patients with previously untreated locally advanced squamous cell carcinoma esophagus were enrolled in the study. Of these, 10 were excluded because of the following reasons: four patients deteriorated before starting treatment, four patients withdrew consent and refused to continue after the 1st week of treatment, one patient was detected to have second malignancy (carcinoma lung), and one patient had adenocarcinoma when histology was reviewed. Therefore, a total of 80 patients received treatment of which 40 patients received cisplatin with concurrent chemoradiotherapy while 40 patients received gemcitabine with concurrent chemoradiotherapy.

Both arms were comparable with respect to age, sex, performance status, and grade of dysphagia [Table 1]. The median age in both arms was 57 years. The most common histological grade was moderately differentiated squamous cell carcinoma in both arms.

In cisplatin arm, Grade 1 hematological adverse effect with leukopenia and thrombocytopenia was seen in 5% and 0%, respectively [Table 2] while as in gemcitabine arm, 30% of patients developed both Grade 1 leukopenia and thrombocytopenia. Anemia was found more commonly in the cisplatin group. In cisplatin arm, 25% patients developed Grade 1 nephrotoxicity and no patient in the gemcitabine developed any nephrotoxicity. Hepatotoxicity (Grade 1) was found in 10% in the cisplatin group. Grade 2 esophagitis

was found in both arms—25% and 30% in Arms 1 and 2, respectively [Table 2].

Median follow-up in Arm 1 was 11.0 ± 5.5 months whereas in Arm 2, it was14.6 ± 7.1 months. There was a significant improvement in dysphagia in both the arms but was more favorable in gemcitabine arm. Complete response was achieved in 20% in Arm 1 and 32.5% in Arm 2 [Table 3]. The progression-free survival was 5.7 ± 4.7 months and 12.4 ± 6.8 months in Arm 1 and Arm 2, respectively. At last follow–up, 4 (10%) patients in Arm 1 and 15 (37.55%) patients in Arm 2 were surviving [Figure 1].

DISCUSSION

Chemoradiotherapy has been extensively studied over the past few decades in an attempt to decrease locoregional recurrences and improve the survival rate in locally advanced esophageal cancer. The goals of chemotherapy concurrent with radiotherapy are to achieve higher local control rates and simultaneously decrease the systemic metastasis. We compared the efficacy and toxicity of gemcitabine concurrent with radiotherapy against cisplatin concurrent with radiotherapy in locally advanced squamous cell carcinoma esophagus. This study indicates that the treatment in both the arms was well-tolerated with statistically significant hematological toxicity, but they were of low grade and easily manageable. The efficacy of gemcitabine, at a dose of 200 mg/m^2, suggests its potent radiosensitization effect, which is further supported from pharmacokinetic data from Eisbruch *et al*. which shows that at a dose as low as 50 mg/m^2 per week is able to achieve adequate intracellular concentrations of the active drug metabolite, dFdCTP.[10] The most important finding emerging from that study was that the combination of radiotherapy and gemcitabine, even at doses 5% of those administered when the drug is used as a cytotoxic agent, produced a high response rate of 66–89% among the different cohorts. In our study, we found only Grade 1 hematological toxicity in gemcitabine group which is acceptable. Bhandari *et al*.[11] compared the results of sequential chemotherapy followed by radiotherapy with cisplatin concurrent with radiotherapy in locally advanced squamous cell carcinoma esophagus and their results were comparable to our findings. Response rates were higher with gemcitabine than cisplatin. In head and neck cancers, gemcitabine has been studied as a radiosensitizer with promising results with complete response rates as high as 60%.[12] Mostafa *et al*.[13] compared the results of gemcitabine versus cisplatin concurrent with radiotherapy in locally advanced squamous cell carcinoma of head and neck. They achieved complete response in 40% in the gemcitabine arm and 30% in the cisplatin arm and a progression-free survival of 11 months in gemcitabine arm and 9 months in the cisplatin arm with manageable toxicity. With a median follow-up of 14.6 ± 7.7 months in the gemcitabine group and 11.0 ± 5.5 months in the cisplatin group, we achieved a progression-free survival of 12.4 ± 6.8 months and 5.7 ± 4.7, respectively. Gemcitabine concurrent with radiotherapy has been tried in squamous cell carcinoma at other sites of the body like in urinary

Table 1: Demographic profile of the studied subjects

Parameter	Cisplatin + RT *n* (%)	Gemcitabine + RT *n* (%)
Age (year)		
≤40	2 (5.0)	0 (0.0)
41-50	4 (10.0)	4 (10.0)
51-60	19 (47.5)	24 (60.0)
>60	15 (37.5)	12 (30.0)
Mean	57	58
Gender		
Male	29 (72.5)	23 (57.5)
Female	11 (27.5)	17 (42.5)
Level of lesion		
Cervical	5 (12.5)	1 (2.5)
Lower 3rd	10 (25.0)	15 (37.5)
Middle 3rd	16 (40.0)	10 (25.0)
Upper 3rd	9 (22.5)	14 (35.0)
ECOG performance score		
0	4 (11.4)	8 (20.0)
1	30 (74.3)	26 (65.7)
2	6 (14.3)	6 (14.3)
Dysphagia		
Grade 1	4 (8.6)	5 (11.4)
Grade 2	19 (48.6)	17 (42.9)
Grade 3	17 (42.9)	18 (45.7)

RT: Radiation therapy, ECOG: Eastern Cooperative Oncology Group

Table 2: Toxicity comparison of two groups

	Arm 1 (%)	Arm 2 (%)
Leukopenia	Grade 1 (5)	Grade 1 (30)
Thrombocytopenia	0	Grade 1 (30)
Anemia	Grade 1 (25)	Grade 1 (15)
Hepatotoxicity	Grade 1 (10)	0
Nephrotoxicity	Grade 1 (30)	0
Esophagitis	Grade 2 (20)	Grade 2 (30)
Stricture	Grade 1 (5)	Grade 1 (5)

Table 3: Overall outcome in studied patients

	Cisplatin + RT *n* (%)	Gemcitabine + RT *n* (%)
Response		
Complete	8 (20.0)	13 (32.5)
Partial	15 (37.5)	22 (55.0)
Stable disease	12 (30.0)	3 (7.5)
Progression	5 (12.5)	2 (5.0)
Locoregional recurrence	6 (15)	4 (10)
Distant metastasis	7 (17.9)	10 (28.6)
Progression free survival (months)	5.7±4.7	12.4±6.8
Survival assessment		
Survived	4 (10.0)	15 (37.5)
Died	30 (75.0)	18 (45.0)
Lost to follow-up	6 (15.0)	7 (17.5)

RT: Radiation therapy

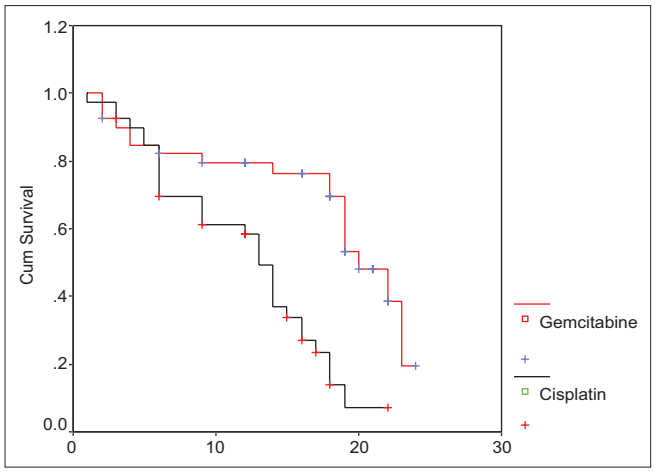

Figure 1: Survival status (months) in studied subjects

bladder carcinoma,[14] carcinoma cervix, and carcinoma vulva with encouraging results.

Esophageal carcinoma has overall a poor prognosis with an overall 5-year survival of 37%.[15] Due to short median follow-up, we cannot comment on the 5-year survival rates.

Most combined schedules of chemoradiation are associated with a high, sometimes unacceptable, systemic toxicity, particularly hematological toxicity. The most important theoretical advantage of using "low" dose gemcitabine is maintaining a high response rate and radiosensitization with low systemic toxicity. In our study, we also reported low hematological toxicity with an acceptable response and progression-free survival.

CONCLUSION

Esophageal cancer has an overall poor prognosis. Most patients are not surgical candidates. Long-term results of chemoradiotherapy alone are still unsatisfactory. High relapse rate along with higher mortality and morbidity rates has initiated a whole spectrum of more aggressive treatment including chemoradiotherapy. This study demonstrated that chemoradiotherapy in locally advanced squamous cell carcinoma esophagus is safe and feasible. Gemcitabine is a novel agent in the treatment of locally advanced squamous cell carcinoma esophagus with manageable toxicity and good response rates and progression-free survival. Hence, gemcitabine concurrent with radiotherapy should be tried in larger randomized trials to further assess treatment outcomes.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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