ORIGINAL ARTICLE

Response to Induction Chemotherapy with Cisplatin and 5-Flurouracil in Locally Advanced Squamous Cell Carcinoma of Esophagus

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ABSTRACT

Background: Esophageal cancer is considered a serious malignancy because of its extremely aggressive nature and poor survival rates. Its treatment depends on stage, for locally advanced disease treatment is still evolving and long term survival rates are very poor.

Aim: To evaluate the response of induction chemotherapy in patients of locally advanced squamous cell carcinoma of esophagus.

Methodology: Fifty consecutive Patients meeting inclusion criteria were enrolled for the study from Oncology Department Jinnah Hospital Lahore. Selected patients received chemotherapy with Cisplatin 75mg/m^2 on day 1 and 5-flurouracil 750mg/m^2/day continuous infusion from day1 to day5, repeated every three weeks for a total of 4 cycles. Response assessment was done after completion of planned therapy and it was documented as either complete response (CR) or Partial response (PR) or Stable Disease (SD) or Progressive Disease (PD) according to Standard Method of "Response Evaluation Criteria in Solid Tumors (RECIST 1.1)" with CT scan.

Results: The mean age of the study population was 58.02±9.24 years. 68% of patients were male. Nine patients (18%) had clinical stage II (T3, N0-1, M0) disease, while majority 31(62%) had clinical stage III (T3, N1-2, M0) disease, and stage IVA (T4, N0-2, M0)was present in 10(20%) patients. Most common primary tumor lesion was T3 (80%), and nodal involvement was present in 33(66%) of the patients. Over all response rate was 38% (p=0.009) with only two patient (4%) achieving CR and 17(34%) patients had partial response (p<0.005).Another nineteen (38%) patients showed stable disease, thus making the clinical benefit rate (CR+PR+SD) of 76% (p<0.005).

Conclusion: Induction chemotherapy has fair response rates in patients with locally advanced squamous cell carcinoma of esophagus.

Keywords: Squamous cell carcinoma, chemotherapy, malignancy,

INTRODUCTION

Esophageal cancer is a lethal disease. Both of the common histological types of esophageal cancer that is squamous cell carcinoma (SCC) and adenocarcinoma are considered as a serious malignancy because of their extremely aggressive nature and poor survival rates. Esophageal carcinoma affects more than 450000 people worldwide and the incidence is rapidly increasing[1]. It occurs most commonly during the sixth and seventh decades of life and is generally more common in men than in women[2]. Currently, it is the eighth most common incident cancer in the world and is the sixth leading cause of cancer death worldwide. The overall 5-year mortality for esophageal cancer is nearly 85%[3].

Squamous cell carcinoma is the predominant histologic type of esophageal cancer worldwide[4]. It is responsible for 90% of all esophageal cancers in developing countries. Treatment of esophageal cancer depends on stage. For early stage disease endoscopic resection or surgery is the recommended treatment and for metastatic disease, only palliative chemotherapy or symptomatic and supportive care is recommended[5]. Treatment options for locally advanced disease are still evolving and these patients should undergo multidisciplinary evaluation and tri-modality treatment should be considered[6]. Longterm survival rates are still poor[7]. To improve long term outcome, eliminate micro-metastases and for early relief of dysphagia clinical trials with induction / neo adjuvant chemotherapy in squamous cell carcinoma of esophagus have been done and these have shown encouraging results, with partial response rate ranging from 42 to 48% and complete response rate of up to 7% with Cisplatin and 5-flurouracil have been reported[8,9].

The potential benefits of neo adjuvant systemic chemotherapy includes down-staging of the primary tumor, elimination of any distant micro Mets, and better patient nutrition due to improvement in swallowing function, thus increasing the likelihood of tolerability as well as curative surgery,

MATERIAL AND METHODS

This was a quasi-experimental, single arm trial, carried at Department of Oncology, Jinnah Hospital, and Lahore. 50 patients with Squamous cell carcinoma of esophagus were recruited during Sep, 2014 to Dec, 2015 after approval from Institutional review board. Informed consent was taken from the patients before commencement of treatment. Eligible patients included those with histologically confirmed Squamous cell carcinoma, locally advanced tumor- clinical stage II (T3, N0-1, M0) disease, stage III (T3, N1-2, M0) or IVA (T4, N0-2, M0), age 20-70 years, both male and female. The primary end point was overall response rate (ORR). Complete pre-treatment

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evaluation was done. Fifty patients meeting inclusion criteria, i.e., patients, with histopathologically proven squamous cell carcinoma of esophagus, with normal cardiac function assessed with ECG, renal function with serum creatinine (<1.5mg/dl) and liver function with serum transaminases level <100 u/l and having good performance Status (ECOG PS ≤2)were enrolled for the study from Oncology Department Jinnah Hospital Lahore. Patient who already received any treatment (chemotherapy, radiotherapy), or having recurrent disease were not enrolled. Those who experienced severe toxicity or did not complete the planned therapy were excluded from the study. Selected patients received chemotherapy with Cisplatin 75mg/m^2 on day 1 and 5-flurouracil 750mg/m^2/day continuous infusion from day1 to day 5, repeated every three weeks for a total of 4 cycles. Response assessment was done after completion of planned therapy and it was documented as either complete response (CR) or Partial response (PR) or Stable Disease (SD) or Progressive Disease (PD) according to Standard Method of "Response Evaluation Criteria in Solid Tumors (RECIST 1.1)" with contrast CT scan imaging. Data was entered and analyzed in SPSS version 17. Size of primary tumor at the time of enrollment, number of lymph nodes involved, sites of metastases, grades of toxicity, response was calculated by taking mean and standard deviation and Pearson's Chi-square test was applied to determine the significance.

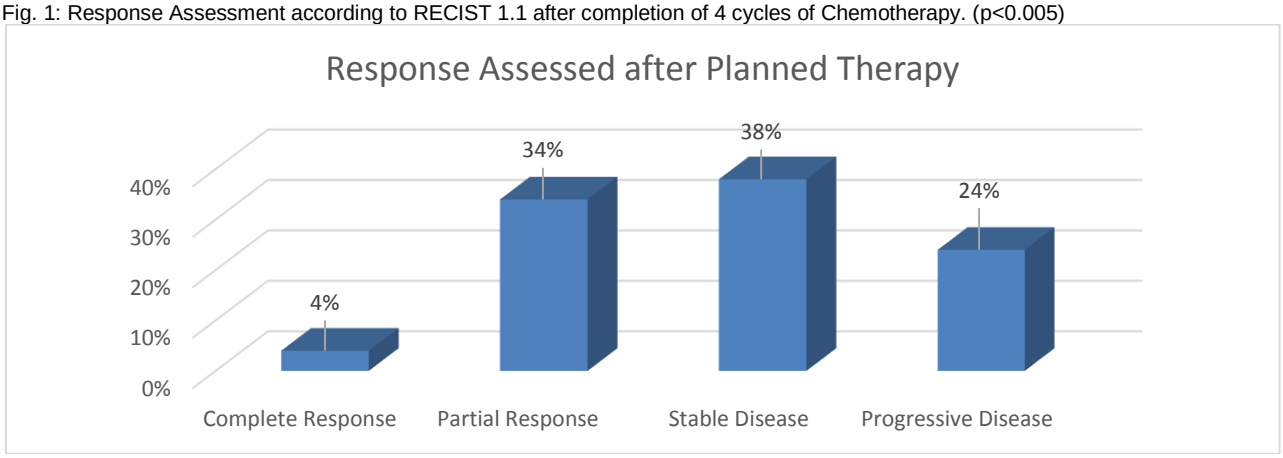
RESULTS

The mean age of the study population was 58.02±9.24 years. Youngest patient was 35 years old and oldest was 70 years old. 68% of patients were male and 32% were females. Nine patients (18%) had clinical stage II (T3, N0-1, M0) disease, while majority 31(62%) had clinical stage III (T3, N1-2, M0) disease, and stage IVA (T4, N0-2, M0) was present in 10(20%) patients. Most common primary tumor lesion was T3 (80%), and nodal involvement was present in 33(66%) of the patients. Over all response rate was 38% (p=0.009) with only two patient (4%) achieving CR and 17(34%) patients had partial response (p<0.005). Another nineteen (38%) patients showed stable disease, thus making the clinical benefit rate (CR+PR+SD) of 76% (p<0.005). Remaining 12(24%) patients had progressive disease while on therapy. Patients with low burden of disease i.e. without nodal involvement and/or having T3 lesion showed significantly better overall response with both CR were having T3N0 disease, while out of total 17 patients having PR, eleven patients (64.7%) had T3, N1 disease (P=0.03).

Table 1: Demographic data

	Count	%age
Gender		
Male	34	68%
Female	16	32%
Age		
Mean ± SD	58.02 ± 9.24 years	
Range	35 years – 71 years	
Clinical stage		
II	9	18%
III	31	62%
IV	10	20%
Grade of squamous cell carcinoma		
Grade 1	13	26%
Grade 2	22	44%
Grade 3	15	33%
ECOG performance status		
0	10	20%
1	24	48%
2	16	32%

Fig. 1: Response Assessment according to RECIST 1.1 after completion of 4 cycles of Chemotherapy. (p<0.005)



DISCUSSION

Use of induction / neo-adjuvant chemotherapy is supposed to have some advantages like possible improvement of baseline dysphasia, the down staging of tumor, increased resection rates and clearing of micrometastasis in regional lymph nodes and distant organs. Neo-adjuvant chemotherapy with cisplatin and 5-flurouracil has also reported to have induced immunological reaction in the cancer micro environment resulting in better outcomes.

In our study total 50 patients were enrolled with majority (68%) of male patients as this disease is more common in males with male to female incidence ratio of 4:1. All of the patients in this study had a fair ECOG performance status of 1 or 2. The mean age of study population was 58 years which was lower than the

internationally reported age of 67 years, which is may be due to overall lower life expectancy in Pakistan which is only 65 years as compare to 78 to 80 years in developed countries. The overall response rate of 38% is significantly (p=0.009) more than our expected target of 10% but it is somewhat lower than reported clinical response rates of 40 to 50%. This could have been due to less number of chemotherapy cycle (only 4) as compare to other studies where more than four cycles were given of these two drugs or a third drug was also added. In this study only two patient could achieve complete clinical response which is comparable to the results of previous studies done in recent times, with reported CR rates of 0%–10%[10,11]. A study[12] from Asian institute of oncology, Mumbai, India by I Ambulkar et al also showed radiological and endoscopic CR in (20%), PR in (53.3%), (16.6%) had SD and (10%) had PD in locally advanced cases of esophageal cancer treated with neo-adjuvant chemotherapy with cisplatin, 5-flurouracil and taxanes.No such data is available from Pakistan for comparison. There were four major prospective randomized trials comparing induction/ neoadjuvant chemo followed by surgery versus surgery alone in patients who were deemed operable and resectable with locally advanced esophageal cancers. Median survival of these patients was reported to be 18–28 months and 2-year OS rate of 43%[13].

Subset analysis in this study showed somewhat better results in stage II and III patients than stage IVA patients. Both the complete response was observed in stage II disease and Partial response was seen in 44.4% of stage II patients, 41.9% of stage III. Stable disease was seen in 22.2% of stage II patients, 54.8% of stage III. Most of the patients with stage IVA disease had progressive disease on assessment after planned therapy, showing the poor prognosis in stage IV disease, as well as lack of response to this regimen in case of high disease burden. Although the no complete response observed in stage III disease, but it raises the need to give more cycles of chemotherapy or adding third drug to achieve better response in these patients, as it would have been needed to get substantial response in view of increased disease burden.

As far as primary tumor size was concerned, all patients with T4 lesions had poor response to therapy, and observed progression of disease while on therapy. Thirty Three patients (66%) had lymph node positive disease, 12(36.3%) of these patients showed partial response 13(39.3%) showed stable disease. 8 of LN +ve patients mostly having T4 lesion observed progressive disease. Difference in this result was statistically not significant, but it was comparable to the reported literature where better responses were observed in the lymph node negative disease[14].

Similar results were obtained in male and female patients and between performance status 1 and 2 patients, 11(45.8%) of the patients with ECOG performance status of 1 showed partial response whereas 6 (37.5%) of the patients with ECOG PS of 2 showed partial response. No significant difference was noted in responses when data was stratified according to different age groups.

The strength of our study was that we explore an alternative therapy to deal with specific population of patients in whom no therapies were offered during the waiting period to receive definitive therapy i.e. surgery or radiotherapy and it showed significant benefit in terms of response rates. The down side of our study was that this study was done in a single center, with smaller sample size and in a non- randomized fashion.

CONCLUSION

Induction chemotherapy has fair response rates in patients with locally advanced squamous cell carcinoma of esophagus particularly with low disease burden and it may be considered in situations where either upfront surgery is not possible or in resource constraint circumstances where standard treatment facilities like radiotherapy and skilled oncological surgeons are sparse and not available readily. Further studies are needed to in randomized fashion with larger sample size to explore the definitive role of neo adjuvant chemotherapy in operable squamous cell carcinoma of esophagus.

REFERENCES

1. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381:400–412
2. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol. 2013;19(34):5598–606.doi: 10.3748/wjg.v19.i34.5598.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012 Jan-Feb. 62(1):10-29.
4. Cook MB. Non-acid reflux: the missing link between gastric atrophy and esophageal squamous cell carcinoma? Am J Gastroenterol.2011;106:1930–1932.
5. NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric Junction Cancers. v2.2013.
6. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011 Jul. 12(7):681-92.
7. Dubecz A, Gall I, Solymosi N, Schweigert M, Peters JH, Feith M, et al. Temporal trends in long-term survival and cure rates in esophageal cancer: a SEER database analysis. J Thorac Oncol. 2012; 7(2):443–7.
8. Campbell NP, Villaflor VM. Neo adjuvant treatment of esophageal cancer. World J Gastroenterol 2010; 16: 3793.
9. Ilson DH. Esophageal cancer chemotherapy: recent advances. Gastrointest Cancer Res 2008; 2:85–92.
10. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med.2003;349:2241–2252.
11. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062-5067.
12. Ambulkar IB. Taxane based neoadjuvant chemotherapy in locally advanced esophageal cancer: A single centre experience J Clin Oncol (Meeting Abstracts) June 2007 vol. 25no. 18_suppl 15143
13. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 2007;8:226-234
14. Aroori S, et al. Neoadjuvant Chemotherapy in Squamous Cell Carcinoma of the Esophagus using Low Dose Continuous Infusion 5-Fluorouracil and Cisplatin: Results of a Prospective Study Indian Journal of Cancer, Vol. 41, No. 1, (January-March 2004) , pp. 3-7.