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Study of efficacy and toxicity profile of gemcitabine and erlotinib based chemotherapy regimen in locally advanced (inoperable) and metastatic carcinoma pancreas

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Abstract

Background: This study was undertaken to assess the efficacy and safety of Gemcitabine and erlotinib combination in first line in locally advanced and metastatic (LA/M) carcinoma pancreas patients in Indian population, due to paucity of data.
Aims and Objectives: The primary objective was to evaluate efficacy in terms of the objective response rate, progression free survival and overall survival. Safety data was also analyzed.
Materials and Methods: In this prospective study, LA/M carcinoma pancreas patients were given standard gemcitabine plus erlotinib till progression or significant toxicities.
Results: A total of 50 patients were evaluated. The median age of patients was 59.5 yrs, out of which 28 (56%) were males and 22 (44%) were females. A total of 266 cycles of treatment were administered with a median number of 6 cycles per patient. The CR was not achieved in any patient, PR in 25 (50%), SD in 13 (26%) and PD in 12 (24%) patients. Disease control rate (PR and SD) was seen in (76%) patients. The median PFS was 5.2 months. The median OS was 7.0 months. The main grade 3/4 side effects seen were Rash in 9 (18%), thrombocytopenia in 8 (16%) and Diarrhea in 9 (18%) patients. Overall survival of patients who developed grade 3/4 skin rashes was significantly longer (P = 0.013).
Conclusions: Gemcitabine and erlotinib based chemotherapy regimen has good efficacy with reasonable toxicity profile in Indian advanced carcinoma pancreas patients. To the best of our knowledge, this is the first such study conducted in India.

Keyword:carcinoma pancreas, gemcitabine, erlotinib

Introduction

Pancreatic adenocarcinoma remains an aggressive treatment-refractory cancer. Estimated 46,420 patients diagnosed and 39,590 deaths attributable to pancreatic cancer anticipated in 2014.[1]The incidence of pancreatic cancer in India is low (0.5- 2.4 per 100,000 men and 0.2-1.8 per 100,000 women).[2] Although pancreatic adenocarcinoma is only the 10th most

common cause of new cancer in the United States, it is the fourth most common cause of cancer-related death highlighting the disproportionate mortality associated with this diagnosis. Additionally, unlike most of the more frequent causes of cancer mortality (lung, colon, prostate and breast) whose death rates are declining, the death rate for pancreatic cancer is relatively stable. The most patients are diagnosed with advanced disease and have a median survival with treatment of about 6 months. Data from 2000-2007 in the Surveillance, Epidemiology and End Results (SEER) registry[3] indicate that at diagnosis the majority of pancreatic cancer is advanced (50.5% metastatic vs. 8% localized, 25.9% regional spread, and 15.5% unstaged).

Early trials of chemotherapy for advanced pancreatic cancer were based on 5-FU and later, on 5-FU combinations. Gemcitabine was compared to 5-FU/leucovorin in randomized trials in the 1990s and has shown modest reproducible activity against advanced pancreatic cancer. Two of the initial trials of gemcitabine reported response rates ranging from 6% to 11%.[4-6]The clinical benefit and modest survival advantage produced by gemcitabine led to its approval by the U.S. Food and Drug Administration in 1997 for advanced pancreatic adenocarcinoma. Since that time, few drugs given as single agents have been directly compared with gemcitabine, and to date, none of these has shown superiority. Addition of another cytotoxic agent to gemcitabine results in conflicting survival results. Currently, more aggressive doublet therapy should not be routinely advised to unselected patients.[7-13]

The molecular defects responsible for pancreatic carcinogenesis, chemoresistance, invasion, metastatic potential, and angiogenesis are gradually being elucidated. Recent efforts to improve on gemcitabine-based systemic therapy have focused on inhibition of several targets to include matrix metalloproteinases, RAS, EGFR[14], and vascular endothelial growth factor (VEGF). Thus far only inhibition of EGFR with erlotinib combined with gemcitabine has led to a positive result.

In 2007, Moore *et al*. demonstrated improvement in survival from (6.24 months vs. 5.91 months) when the combination of gemcitabine and erlotinib, a small molecule tyrosine kinase inhibitor that targets and blocks EGFR, was compared to gemcitabine alone[14]. Despite the relatively small magnitude of this survival benefit, this was the first agent that had significant benefit in combination with gemcitabine in a phase III trial.

After that only few studies on gemcitabine and Erlotinib based chemotherapy in advanced carcinoma pancreas have been reported from western countries. Moreover Indians are culturally and ethnically different from their western counterparts, so the course of disease and response to different chemotherapeutic regimens may be different in an Indian scenario. The purpose of the present study was to study the efficacy and toxicity profile of gemcitabine and erlotinib based chemotherapy regimen in locally advanced (inoperable) and metastatic carcinoma pancreas in view of paucity of literature from the Indian subcontinent.

Materials & methods

Study design: Present study was a Prospective studyin whichhistologically or cytologically proven patients of locally advanced (Inoperable) and Metastatic carcinoma Pancreas, who have attended medical OPD of our institute, have been enrolled. Primary objectives of the present study was to assess Overall response rate (Complete Response/Partial Response /Stable Disease/ Progressive Disease) and survival analysis (Progression free survival (PFS) and Overall Survival), while secondary objective was to assess toxicity profile of gemcitabine and erlotinib based chemotherapy regimen in locally advanced (inoperable) and metastatic carcinoma pancreas patients.

Patient selection criteria

Patients with histologically or cytologically proven locally advanced or metastatic adenocarcinoma of Pancreas, with Eastern Cooperative Oncology Group performance status

(PS) 0, 1 and 2 and adequate hepatic, renal and hematologic functions were taken. Patients were chemo-naive although prior radiotherapy for local disease was allowed provided disease progression had been documented, and treatment completed at least 4 weeks before random assignment.
The ethics review boards of the institution approved the protocol and all patients provided written, informed consent. Individual proforma was prepared for each patient and a common master chart was prepared to record data of all the patients.

Treatment administration

Chemotherapy and targeted therapy was administered on an in-patient basis at Rajiv Gandhi Cancer Hospital. Each treatment cycle lasted 3 weeks. Standard treatment was defined as six cycles, unless there was disease progression or unacceptable toxicity.
Anti-emetic medications with 5 HT3 antagonists and steroids were administered prior to chemotherapy. Inj. Gemcitabine was administered in a dose of 1000 mg/m2 as 30-minute intravenous infusion on D1 and D8. Erlotinib was given orally at 150 mg/d. To administer chemotherapy, patients will be required to maintain an adequate Bone marrow reserve and adequate Hepatic and Renal functions.

Assessments

Evaluations before each cycle of therapy included a complete history, physical examination, complete blood cell count, calculation of creatinine clearance, and measurement of blood chemistry values. The duration of any grade 3 or 4 toxicity was documented by retesting every other day. To administer chemotherapy, patients were required to maintain a WBC >4000/mm^3, ANC>1500/mm^3, platelet count > 100000/mm^3 and serum creatinine < 1.4mg%.
The National Cancer Institute Common Toxicity Criteria (v. 4.0) were used to grade side effect.
Supportive care was given in the form of hospitalization, i.v. fluid, analgesics, antibiotics, antifungal, steroids, Granulocyte Colony Stimulating Factor and Ryle's tube insertion. Whenever patient needed such supportive care/hospitalization it was specified in patient proforma.
Total dose & no. of cycles of chemotherapy received, Days of interruption in chemotherapy was also specified in the proforma to assess the tolerability and compliance of each patient.
Patients who had received at least one cycle of Chemotherapy and had follow-up measurements performed to assess change in tumor size were assessable for response. RECIST response criteria (version 1.1)[15] were used to define the antitumor effects with tumor size defined as the sum of the longest diameter of all target lesions. Responses were assessed just prior to fourth cycle of chemotherapy and 3 weeks after completion of 6 cycles by clinical tumor measurements and documentation of the tumor size of measurable and non-measurable disease, using CT abdomen/PET scans, whatever scan used in baseline evaluation and follow up for individual patient. All sites with measurable lesions were followed for response.

Statistical analysis
All analyses were performed with the statistical software SPSS version 21 (SPSS, Inc., Chicago, Ill., USA). For response & progression data, two-sided 95% confidence intervals (CIs) were calculated based on an exact binomial probability at an alpha level of 0.05. Progression free survival was estimated using the Kaplan Meier method. Data were analyzed using Chi Square test and Fisher's exact test, wherever appropriate. Statistical significance was defined as $P< 0.05$.

Results

Between February 2013 and June 2014, a total of 57 patients of advanced Ca Pancreas were then enrolled into the study according to inclusion and exclusion criteria. Four patients did not receive chemotherapy because of deterioration in general condition and hence advised BSC. Of the rest, three were lost to follow up without a radiologic response evaluation. Thus 50 patients were evaluated for response, survival analysis and toxicity assessment.

Demographic profile: (Table 1) the median age at presentation was 59.5 years (Range 38-72 years). Majority of cases i.e. 48% were in the 61-72 year age group. The study included 28 Males and 22 Females, with good ECOG performance status (n=27, 54% had ECOG PS 0-1 and n=23. 46% had ECOG PS 2). Most of the patients with performance status of 2 were beyond their fifth decade. The majority of patients at the time of presentation were metastatic (n=39, 78%). 32% of patients were smokers and 38% were diabetic.

Table 1: Patients characteristics

Patient characteristics	Number of patients (%)
Age	56.98±8.19*; Median 59.5 (38-72)
Sex - Male	28 (56)
Female	22 (44)
ECOG PS - 0	5 (10)
1	22 (44)
2	23 (46)
Stage at entry-Locally advanced	11 (22)
Metastatic	39 (78)
(Metastasis) No of sites	
1	10 (25.64)
2	14 (35.89)
>2	15 (38.46)
Smokers	16 (32)
Non Smokers	34 (68)
Diabetic	19 (38)
Non- diabetic	31 (62)
Site Head	22 (44)
Body	14 (28)
Tail	10 (20)
Diffuse	4 (8)

ECOG, Eastern Cooperative Oncology Group; PS, performance status
*Mean ± SD wherever applicable

A total of 266 cycles of treatment were administered with a median number of 6 cycles per patient (range 1-6 cycles) (table 2). The majority of patients (76%) in this study completed full six cycles of chemotherapy. The reasons for discontinuation of chemotherapy were progression of disease, intolerance to chemotherapy and Grade 3 and 4 toxicities. 19 patients (38%) in this study required the dose reduction at least in one cycle of chemotherapy due to toxicities. 26 (52%) of patients in this study required delay in at least one cycle chemotherapy due to Grade 3 and 4 hematologic toxicities or febrile neutropenia. The median duration of delay was 4 days (Range 2-7 days).

Table 2: Distribution of patients according to number of chemotherapy cycles received

No. of cycles of chemotherapy	Frequency	Percentage
1	1	2.0
2	2	4.0
3	5	10.0
4	2	4.0

5	2	4.0
6	38	76.0
Total	50	100.0

The main toxicities overall most common side effect seen was fatigue (80%) and majority of Grade III and IV side effects were of hematologic, gastrointestinal, dermatological complications and fatigue (Table 3). The grade III and IV hematological complications were noted in 28% (n=14) of patients and they are the most common toxicities that lead to treatment delay. These toxicities were thrombocytopenia, neutropenia, anemia and febrile neutropenia and were noted in 16%, 6%, 4% and 4% of patients respectively. Grade III and IV gastrointestinal (GI) complications were second most common toxicities noted in the present study. They comprise of Diarrhea (n= 9, 18%), stomatitis (n= 4, 8%) and Vomiting (n=2, 4%) (Figure 1). The majority of these grade 3 and 4 complications were seen at the mean duration of day 11 (Range 7-14) of chemotherapy.

Table 3: Distribution of patients according to adverse effects

Complications	All grades (%)	Grade ¾ (%)
Diarrhea	30 (60)	9 (18)
skin rashes	33 (66)	9 (18)
Thrombocytopenia	15 (30)	8 (16)
Fatigue	40 (80)	5 (10)
Stomatitis	9 (18)	4 (8)
Neutropenia	6 (12)	3 (6)
Leukopenia	12 (24)	3 (6)
Anemia	5 (10)	2 (4)
Febrile neutropenia	2 (4)	2 (4)
Vomiting	7 (14)	2 (4)
HFS	1 (2)	1 (2)
ILD like infiltrate	1 (2)	1 (2)

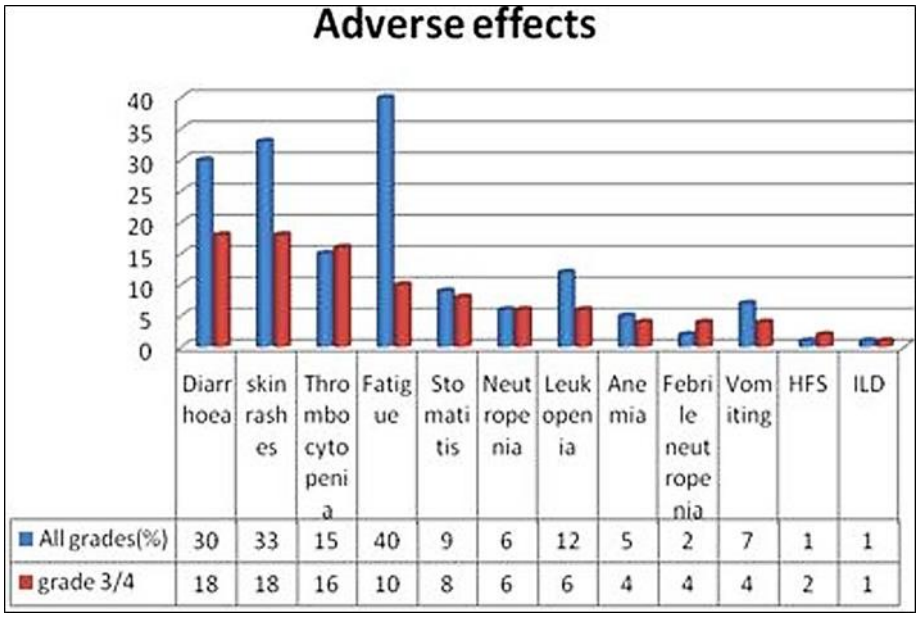

Fig 1: Adverse effects

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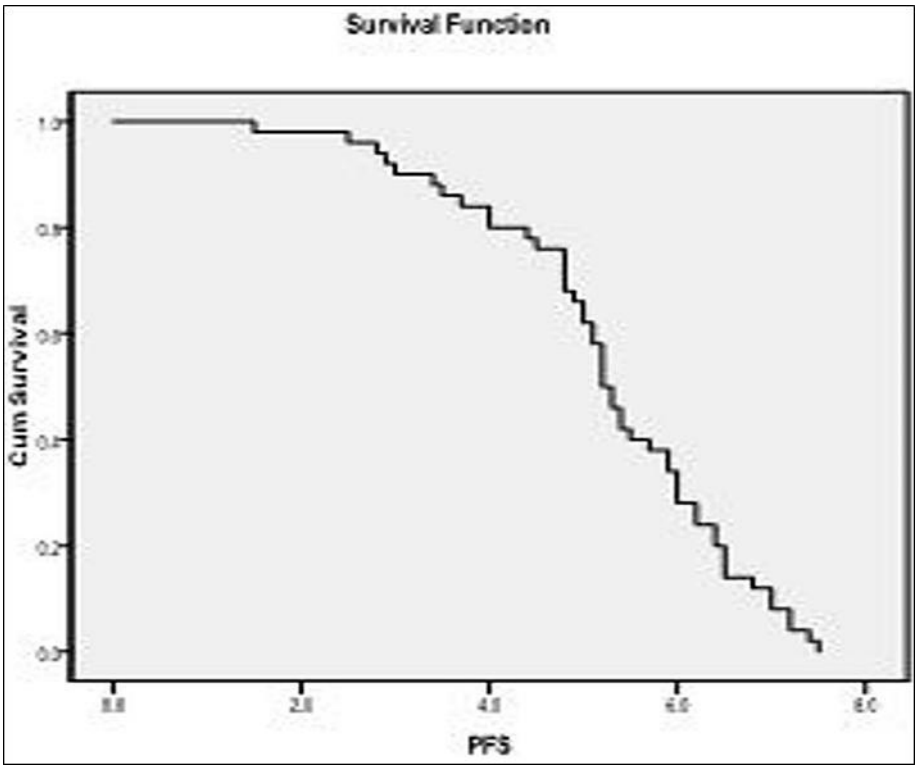

Fig 2: Kaplan-Meier distribution of Progression free survival

The grade 3/4 skin rashes were seen in 9 (18%) patients. Majority of skin rashes were of grade 3 and did not result in delay or discontinuation of chemotherapy except in 2 (4%) patients. There was no significant correlation between patients age (<65 vs. >65 years) and the development of rashes (P = 0.594). Similarly there was no significant correlation between ECOG status (0, 1 vs. 2) and the development of rashes (P = 0.914).

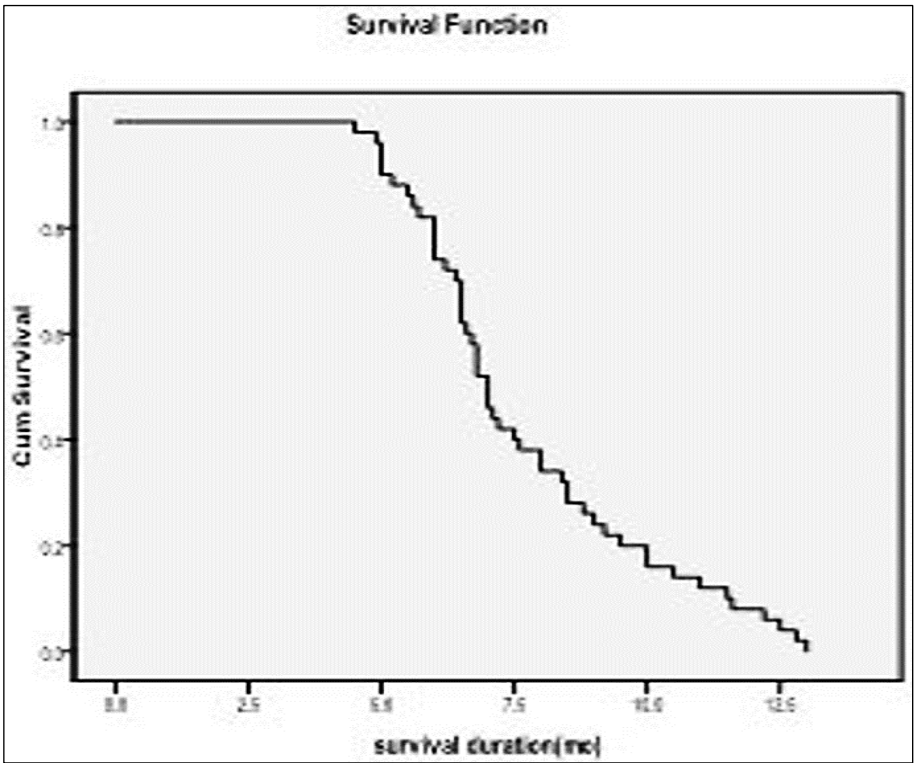

Fig 3: Kaplan-Meier distribution of overall survival

Table 4: Comparison of Efficacy results in Percentage

Response (%)	moore*et al.*[14] N=239	Beveridge*et al.*[16] N=55	park *et al.*[17] N=69	Present study N=50
DCR	57.5	47.3	48.8	76
CR	0	5.5	0	0
PR	8.6	20	18.8	50
PD	42.5	43.6	34.8	24
SD	48.9	21.8	30.4	26
TTP(months)	3.75	5.5	1.9	5.2
OS (months)	6.24	8.3	7.7	7
1 year survival	23	34.2	NR	8

Table 5: Comparison of toxicity profile- and Grade III and IV (In Percentage)

Authors	moore*et al.*[14] N=239		Beveridge*et al.*[16] N=55		park *et al.*[17] N=69		Present study N=50	
Side effects	All (%)	Grade 3/4 (%)	All (%)	Grade 3/4 (%)	All (%)	Grade 3/4 (%)	All (%)	Grade 3/4 (%)
Neutropenia	*NR*	*24*	*27.3*	*10.9*	*7*	*1*	12	6
Thrombocyto-penia	*NR*	*10*	*30.9*	*3.6*	*6*	*3*	30	16
Anemia	*NR*	*NR*	*52.7*	*5.5*	*19*	*9*	10	4
Fatigue	*89*	*15*	*67.3*	*14.5*	*NR*	*NR*	80	10
Diarrhea	*56*	*6*	*21.8*	*3.6*	*13*	*2*	60	18
Rashes	*72*	*6*	*32.7*	*3.6*	*22*	*4*	66	18

Abbreviation: NR= not reported.

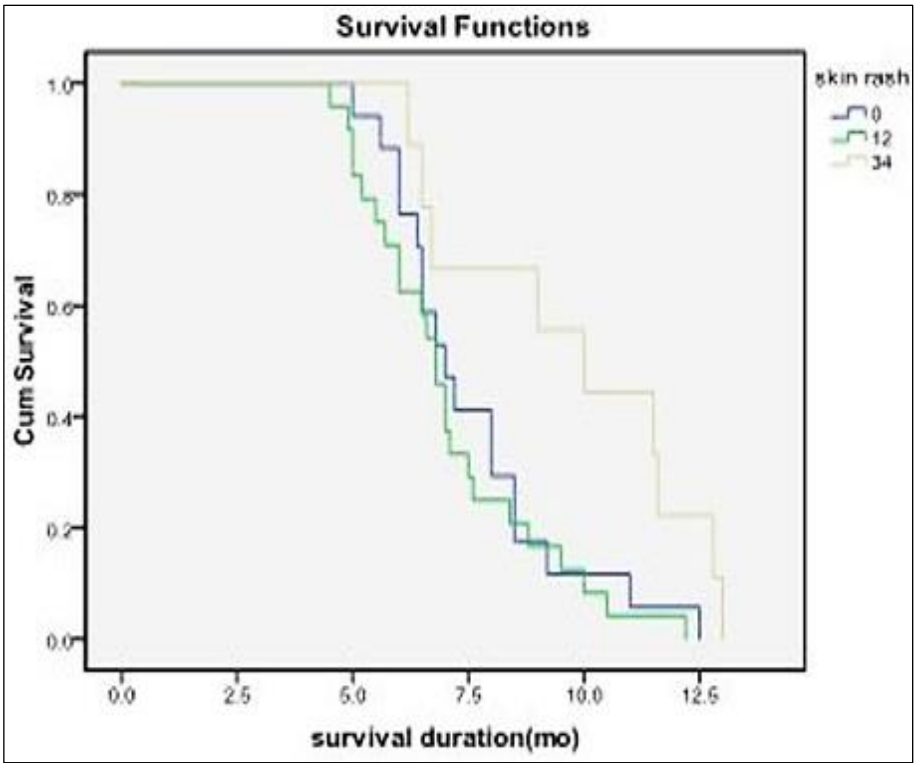

Fig 4: Kaplan-Meier distribution of overall survival in relation to skin rashes

Of the 50 enrolled patients, 50% (n=25) of patients had a partial response and 0% had complete response. A total of twelve (24%) patients progressed on chemotherapy and thirteen (26%) had stable disease. The disease control rate (responses and stable disease) was 76%.There was statistically significant correlation between Overall Response and ECOG PS ($p<0.0001$). Disease control rate was more in patients who developed grade 3/4 skin rashes

though statistically non-significant (P = 0.063).
The median duration of follow up these patients was 7 months. The median OS was 7.0 months (range 4.5 to 13, 95% CI, 6.6-7.39 months). The median time to tumor progression was 5.2 months (Range 1.5-7.5 months, 95% CI: 4.94-5.46 months) (figure 2,3).
Overall survival of patients who developed grade 3/4 skin rashes was significantly longer (P = 0.013; HR, 0.35; 95% CI, 0.153 to 0.800). The median survival rates for patients with grade 0, 1/2, and 3/4 rashes were 7.0, 6.8, and 10.0 months, respectively; and the 1-year survival rates were 2%, 2%, and 4% (P = 0.217) (Figure 4).

Discussion

The median age at presentation (59.5 years), male to female ratio (1.27:1) and distribution ofpatients with performance status of 0-1 (54%) and 2 (46%) was similar to reported literature.[14, 16] There was no statistically significant correlation seen between the age of the patient with the ECOG performance status (P=0.886).
The primary objectives of the present study were the overall response rate and progression free survival. In the present study, complete response was noted in 0% and partial response in 50% with overall response rates (ORR) of 50%. The study also revealed Stable disease in 26%, while 24% progressed on chemotherapy. DCR of the present study was 76%. The median time to tumor progression in this study was 5.2 months (Range 1.5-7.5 months). The response and outcome data were compared with other studies done by Moore *et al.* [14], Beveridge*et al.* [16] and park *et al.* [17]. These studies have shown DCR rates of 57.5%, 47.3% and 48.8% respectively. The median TTP in these studies were 3.75, 5.5 and 1.9 months respectively (Table 4). Overall DCR in the present study was better than other reported studies with more no. of patients achieving partial response and less no. of patients progressed on treatment. TTP was almost comparable to Beveridge*et al*. study[16] while TTP was less in the Moore *et al*.[14] and park *et al*.[17] studies. In this study, median OS was 7.0 months (range 4.5 to 13, 95% CI, 6.6-7.39 months). OS was almost comparable to park *et al*.[17] study while less in the moore*et al*.[14] study and more in Beveridge*et al*.[16] study.
The secondary aim of the study was to evaluate the toxicity profile. In the present study, overall most common side effect seen was fatigue (80%) and majority of Grade III and IV side effects were of hematologic, gastrointestinal, dermatological complications and fatigue.
The grade III and IV hematological complications were noted in 28% of patients and they are the most common toxicities that lead to treatment delay. Chemotherapy toxicity data was also compared with the other studies done by Moore *et al*.[14], Beveridge*et al*.[16] and park *et al*.[17] (Table 5). On comparison, it was found that among hematological toxicities thrombocytopenia was seen in more no. of patients in the present study while neutropenia and anemia were seen in less no. of patients. Gastrointestinal complications were seen in more no. of patients in the present study. However increased liver transaminases were noted in 11% of patients in the moore*et al*.[14] study, 1.8% patients in Beveridge*et al*.[16] study but were not seen in present study.
Moore *et al*.[14] have shown that DCR was more in patients with presence of a rash (P = .05). Similarly in the present study, disease control rate was more in patients who developed grade 3/4 skin rashes though statistically non-significant (P = 0.063). In moore*et al*.[14] study, median survival rates for patients with grade 0, 1/2, and 3/4 rashes were 5.3, 5.8, and 10.5 months, respectively; and the 1-year survival rates were 16%, 9%, and 43% (P = .001). In the present study, these values suggestive of similar trend though statistically non-significant.
In the reported literature, it was shown that skin rash is an important clinical predictable factor for chemotherapeutic response and associated with significantly better PFS and OS in the patients with the presence of skin rash over grade 2 compared to no skin rash. Similar finding of the present study can be emphasized with the value of statistically significant overall survival of patients who developed grade 3/4 skin rashes (P = 0.013; HR, 0.35).
Overall, the gemcitabine and Erlotinib combination chemotherapy regimen was very well

tolerated in the present study. And findings of clinical outcome and toxicity profile of patients receiving chemotherapy for advanced ca pancreas has been observed to be similar to that reported from the west. There is accumulating evidence now that gemcitabine and Erlotinib combination chemotherapy is safe and effective in advanced pancreatic cancer and the findings of the current study affirm that the same findings may also be extrapolated for an Indian population. The pitfall of the present study was that it includes small number of patients with short follow up.

Conclusion

On the basis of our experience, it can be concluded that the combination of Gemcitabine and Erlotinib is active and well tolerated in advanced carcinoma Pancreas. The convenience provided by the short infusion time of Gemcitabine further complement the tolerability of this regimen. The response rate of 50% and the promising progression free survival and Overall survival are strong arguments for clinically testing this combination and this treatment schedule further in carcinoma Pancreas. There are very few published studies regarding outcomes of chemotherapy in patients with advanced ca pancreas in India. To the best of our knowledge, there is no published literature of Indian patients regarding the use of Gemcitabine and Erlotinib based chemotherapy in advanced carcinoma pancreas. This is the first such study conducted in India.

Recommendation

To confirm the findings of present study, further large randomized controlled trials in Indian population, with longer follow up should be done.Furthermore,there should be further comparative studies, which should include chemotherapy regimen of present study and other regimen used in advanced carcinoma pancreas.

Conflict of interest: None.

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