Original Article

Is Combination Chemotherapy of Cisplatin and Gemcitabine in the First-line Treatment of Advanced Gallbladder Cancer the Right Choice? A Study in Indian Patients from the Gangetic Belt

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Abstract

Background: Owing to presentation at advanced stage, most of the time, gallbladder carcinoma is nonresectable. Nonsurgical palliative procedures such as stenting help in a limited number of patients. Although anecdotal Western data are present, combination chemotherapy data from Indian scenario are scanty. The present study was carried out with an aim to evaluate the response to first-line chemotherapy with cisplatin and gemcitabine in Indian patients with advanced gallbladder carcinoma. This observational study was conducted in the Departments of Oncology at the Army Command Hospital (Central Command), Lucknow, between April 2013 and May 2016. All patients presenting to this center with histologically proven advanced carcinoma of gallbladder were screened for eligibility for inclusion in the study. **Patients and Methods:** No prior approach for sample size calculation was followed owing to rarity of disease. Hence, all the patients falling in the sampling frame were included in the study. Power analysis was done *post hoc*. A total of 60 patients falling in sampling frame and completing 6 months of treatment protocol were enrolled in the study. **Statistical Analysis Used:** Chi-square test and independent samples *t*-test were used to compare and evaluate the data. $P < 0.05$ indicated a statistically significant association. **Results:** At 3 months, majority of the patients (28; 46.7%) had a progressive disease, and at 6 months, the number of patients having progressive disease increased to 36 (60%). Six-month mortality did not show a significant association with age, gender, stage, or mean duration of complaints. However, a significant association with a mean number of drug cycles and mean compliance rate was observed. **Conclusions:** Combination gemcitabine and cisplatin which is the standard first-line therapy in advanced gallbladder carcinoma patients showed limited response in the Indian patients, leading to invariable disease progression by 6 months.

Keywords: *Chemotherapy, cisplatin, gallbladder cancer, gemcitabine*

Introduction

Gallbladder carcinoma has an unusual geographic distribution. Higher prevalence has been reported from Bolivia, New Mexico, Israel, Chile, and Japan.[1] Ethnic groups from these parts of South America have an increased prevalence of cholelithiasis[2] which in turn has greater risk of developing a gallbladder carcinoma over a period of time.[2,3]

The incidence of gallbladder carcinoma in India ranges in males from 0.1 to 3.7/100000, while 0.3–8.9/100000 for females,[4] but the actual number is much more in the endemic zones of Western Bihar and Eastern Uttar Pradesh, where it is the third most common malignancy of the alimentary tract.[5,6]

Gallbladder carcinoma is a lethal malignancy with marked ethnic and geographical variations and gradually it is no longer a rare malignancy in India.[6] The basis for this variance in India likely resides in differences in environmental exposure, geographical elements, and intrinsic genetic predisposition to carcinogenesis, thereby ranking sixth among all gastrointestinal cancers.[7] Gallbladder cancer develops over 5–15 years starting initially with metaplasia which progresses to a dysplasia then a carcinoma *in situ* and finally an invasive cancer.[8] The mean overall survival rate for patients with advanced gallbladder cancer is only 6 months, with a poor 5-year survival rate of 5%.[1] This is attributed to the lack of muscular layer in the gallbladder, which usually acts as

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a protective barrier in other GI cancers.[2] The cancer therefore spreads silently and rapidly to the liver and the peritoneum before finally being detected in an advanced unresectable stage.[3] Mostly encountered in the sixth and seventh decades of life,[9] surgery, radiotherapy, and chemotherapy are the available treatment options, but these are only possible for early stages of the disease which is a rarely seen in India.[5,6] Advanced gallbladder cancer patients present with an obstructive jaundice requiring nonsurgical biliary drainage or stenting to relieve the obstruction, reduce the bilirubin, and temporarily palliate the symptoms before patient. External radiation therapy may provide some palliative benefit at the dose of 45 Gy. Palliative chemotherapy is the only option in such patients. Gemcitabine has shown a 36% response in 26 patients with metastatic or unresectable gallbladder carcinoma in a Phase-II trial.[10] Another clinical trial with gemcitabine had shown a response rate of 35.7% in patients of gallbladder carcinoma and 27.3% in patients of other biliary duct cancer.[11] Cisplatin along with gemcitabine was used in a small group of patients previously with better results.[12] In the absence of meaningful chemotherapeutic options in first line and limited data from the Western countries due to the disease being a rarity there,[13,14] the combination of cisplatin with gemcitabine was accepted as the most favorable option.[13-18] Despite showing a fair preliminary response, there are limited number of trials evaluating the response of combination chemotherapy and its long-term results. The data are also lacking with regard to the correlation between epidemiology, clinical profile of gallbladder cancer, and response to combination chemotherapy of gemcitabine and cisplatin.[19-21] A study of this type may educate us regarding the ideal patients who may benefit from this combination and the subset where other options need to be explored.

Aims and objectives

The present study was carried out with an aim to evaluate the response to first-line chemotherapy with cisplatin and gemcitabine in Indian patients with advanced gallbladder carcinoma. The aim was achieved with the help of the following objectives:

1. To evaluate the response to first-line chemotherapy with cisplatin and gemcitabine among patients with advanced gallbladder carcinoma using RECIST criteria
2. To record adverse/side effects if any, compliance, and acceptability of the combination.

Patients and Methods

We carried out this observational study in the Department of Oncology at the Army Command Hospital (Central Command), Lucknow, between April 2013 and May 2016 (3 years). The hospital is the largest defense tertiary hospital in the north-central part of India and receives patients from all over northern/central India and Nepal. All patients presenting to this center with histologically proven advanced carcinoma of gallbladder were screened for eligibility for inclusion in the study. The sampling frame was bound by the following inclusion and exclusion criteria.

Inclusion criteria

- Patients with histologically proven carcinoma of gallbladder
- Aged 18–70 years
- ECOG PS 0–2
- Serum bilirubin <2.5 mg% at least 1 week prior to starting chemotherapy
- Hemoglobin >10 g%, absolute neutrophil count >1500/cumm and platelets >100,00/cumm
- S. creatinine <1.5 mg %
- Creatinine clearance >40 ml
- Computed tomography/magnetic resonance imaging (CT/MRI) showing measurable disease as per RECIST criteria
- Negative for human immunodeficiency virus/hepatitis B virus/hepatitis C virus infections.

Exclusion criteria

- ECOG PS 3,4
- Hemogram/biochemistry/bilirubin not meeting the criteria for inclusion criteria
- Non-measurable disease (e.g., only ascites or only bone metastasis)
- Unwilling to participate.

Sample size/power analysis

All the patients falling in the sampling frame were included in the study. The power analysis was done *post hoc*.

Statistical analysis

Statistical analysis was done using Statistical Package for the Social Sciences version 15.0 (New Delhi, India) or above. Chi-square test and Independent samples *t*-test were used to compare and evaluate the data. $P < 0.05$ indicated a statistically significant association.

Methods

Informed consent from the patients was obtained. The demographic details, medical, and clinical history were noted. Patients were subjected to a clinical examination. Hematological/biochemical assessment was performed followed by histopathological (fine needle aspiration cytology/Biopsy), radiological (CT/MRI/magnetic resonance cholangiopancreatography), and immunohistochemical (CA19.9) evaluations. Type of initial management (percutaneous biliary drainage/Stenting), if any, was also noted.

All the eligible patients were administered standard chemotherapy (cisplatin 25/m^2 and gemcitabine 1000/m^2, both drugs on D1 and 8 in a 21 day cycle). Details of chemotherapy in terms of cycles planned and cycles administered were recorded. Radiological response was

evaluated and expressed in terms of RECIST criteria. Details of toxicity owing to drugs were recorded; compliance to drug and reason for withdrawal were also be noted.

Results

A total of 60 patients falling in sampling frame and completing 6 months of treatment protocol were enrolled in the study.

Age of patients ranged from 21 to 67 years is shown in Table 1.

Most of the patients were female (n = 56; 93.3%). Only 4 (6.7%) were male. Male-to-female ratio of patients was 0.07:1.

Jaundice/obstructive jaundice (n = 44; 73.3%) was the most common presenting complaint. Table 2 mentions presenting complaints in details.

Duration of complaints is shown in Table 3.

The presentation of most of the patients were Stage IV (n = 52; 86.7%). However, the remaining 8 (13.3%) were stage III cases.

Majority of patients (n = 36; 60%) completed full 6 cycles of treatment as described in Table 4.

At 3 months, 28 (46.7%) patients had a progressive disease. There were 14 (23.3%) patients showing a partial response and 4 (6.7%) had stable disease. A total of 10 (16.7%) patients expired during this period. Four (6.7%) patients were lost to follow-up/discontinued treatment. None of them had a complete response.

At 6 months, patients having a progressive disease increased to 36. In fact, all the patients alive and the remaining in the study had progressive disease. A total of 14 (23.3%) expired and 10 (16.7%) were lost to follow-up. Statistically, there was a significant difference in outcome at 3 and 6 months (P = 0.025) [Table 5].

38 (63.3%) patients had no adverse effect to treatment with combination cisplatin and gemcitabine. Different adverse effects are depicted in Table 6.

36 (60%) patients had full compliance. There were 6 (10%) patients who had 50%–75% compliance and the remaining 18 (30%) with prescribed treatment for <50% period. For up to 6 months of follow-up, the mean survival was 4.974 ± 0.342 months. Survival function was 0.748 [Figure 1].

Six-month mortality did not show a significant association with age, gender, stage, or mean duration of complaints. However, a significant association with a mean number of drug cycles and mean compliance rate was observed [Table 7].

Discussion

The combination of cisplatin and gemcitabine is being used as a viable first-line chemotherapy option for the treatment

Table 1: Age profile of patients enrolled in the study

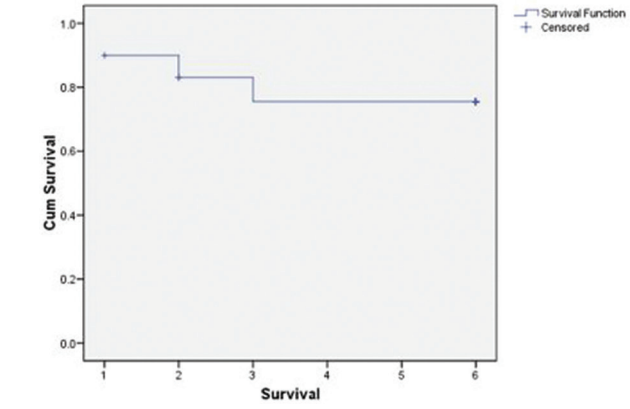
Age group (years)	Number of patients, *n* (%)
<40	2 (3.3)
41-50	28 (46.7)
51-60	16 (26.7)
61-70	14 (23.3)
Mean age±SD (range) (years)	52.13±10.44 (21-67)

Table 2: Profile of presenting complaints

Presenting complaint	Number of patients, *n* (%)
Jaundice/obstructive jaundice	44 (73.3)
Abdominal pain	34 (56.7)
Fever	22 (36.7)
Abdominal lump	16 (26.7)
Weight loss	14 (23.3)
Anorexia	12 (20.0)

Table 3: Distribution according to duration of complaints

Presenting complaint (months)	Number of patients, *n* (%)
<1	10 (16.7)
2-3	44 (73.3)
4-6	4 (6.7)
>6	2 (3.3)



Mean(a)			
		95% Confidence Interval	
Estimate	Std. Error	Lower	Upper
4.974	.342	4.304	5.643

a. Estimation is limited to the largest survival time if it is censored.

Survival function = 0.748

Figure 1: Survival up to 6 months

of unresectable gallbladder and biliary tract cancers of advanced stage.[13-18] However, there is an extreme dearth of such studies from India, particularly when the Gangetic belt of India is globally recognized as a hotspot for gallbladder cancer. The findings from our study indicate that gallbladder cancer was primarily a disease of middle and advanced age patients. The mean age of patients enrolled in the study was relatively lower (52.13 ± 10.44 years) as compared to a median age of 67 years reported in Western literature.[22] The Western data indicate a phenomenal rise in the incidence of gallbladder cancer with advancing age that shows a >50-fold rise between age 20 and 49 years to >75 years.[22] Relatively younger age of patients in the present study is in agreement with the findings of Dutta *et al*.[19] who reported the risk of gallbladder cancer to be increased in younger patients (<50 years) with gallstone disease. These findings in general suggest a definite epidemiological variance in gender profile of patients in Eastern and Western Hemispheres.

Table 4: Distribution according to number of cycles of treatment

Number of cycles	Number of patients, *n* (%)
1	8 (13.3)
2	10 (16.7)
3-5	6 (10.0)
6	36 (60.0)

Table 5: Distribution of cases according to treatment response at 3 and 6 months

Response	3 months, *n* (%)	6 months, *n* (%)
PD	28 (46.7)	36 (60.0)
SD	4 (6.7)	0
PR	14 (23.3)	0
CR	0	0
Mortality	10 (16.7)	14 (23.3)
Lost to follow up	4 (6.7)	10 (16.7)

χ^2=11.1 (df=4), *P*=0.025. PD: Progressive disease, SD: Stable disease, PR: Partial response, CR: Complete response

Table 6: Adverse Effects during chemotherapy protocol

Adverse effect	Number of patients, *n* (%)
Total number of cases with adverse effect	22 (36.7)
Vomiting	12 (20.0)
Fever	6 (10.0)
Decreased counts	06 (10.0)
Increased bilirubin	4 (6.7)
Anemia	4 (6.7)
Thrombocytopenia	4 (6.7)
Intolerability	2 (3.3)
Diarrhea	2 (3.3)

Gupta *et al*.[20] reported the male-to-female ratio to be 1:4.83, thus showing a female predominance as observed in our study. Jaundice/obstructive jaundice (73.3%), abdominal pain (56.7%), and fever (36.7%) were the major presenting complaints. Obstructive jaundice is one of the most common complications of gallbladder cancer in our region.[21] These presenting complaints are in agreement with the advanced stage of disease as included in the present study. Majority of the cases (86.7%) were stage IV patients and only 8 (13.3%) were stage III patients. Moreover, the findings also suggest the rapid progression of disease at advanced stage and transition from Stage III to IV.

Thirty-six (60%) patients could complete all the six planned cycles. Among adverse events, decreased TLC counts, thrombocytopenia, and intolerability were responsible for withdrawal of the patient from study which has been also reported in a number of studies albeit with a variable proportion.[13,23-25] The dropout rate was 16.7% in our study.

10 (16.7%) patients expired within 3 months of institution of the treatment regimen. Among the remaining 46 patients, 28 (60.9%) had a progressive disease while 14 (30.4%) had a partial response and 4 (8.7%) had stable disease. None of the patients achieved a complete response. At 6 months of treatment, 14 (23.3%) patients had expired and 10 (16.7%) withdrew from the study. Among the remaining 36 (60%) cases, all had clinical and radiologically proven progressive disease. Contrary to these results, Malik *et al*.[12] found gemcitabine and cisplatin combination to be highly efficacious and reported complete remission of disease in one patient and partial response to chemotherapy in 55% of patients. The findings in our study are similar to the observations of Doval *et al*.[26] who had reported a median

Table 7: Factors associated with mortality*

Factor	Expired (*n*=14)	Survived (*n*=36)	Statistical significance
Mean age±SD	51.86±9.94	51.17±11.84	*t*=0.136; *P*=0.690
Male gender, *n* (%)	0	2 (5.6%)	*P*=1.000†
Stage, *n* (%)			
III	0	4 (11.1)	*P*=1.000†
IV	14 (100)	32 (88.9)	
Mean duration of complaints±SD (months)	2.57±1.62	3.00±2.50	*t*=0.418; *P*=0.680
Mean no. of cycles±SD	1.86±0.90	6.00±0.00	*t*=20.24; *P*<0.001
Mean compliance rate±SD (%)	30.96±14.98	100.00±0.00	*t*=20.26; *P*<0.001

*10 cases that were lost to follow up were excluded from this assessment, †Fisher's exact test. SD: Standard deviation

time to progression of disease to be 18 weeks. As both these studies are more than a decade old, one can also infer that the disease biology has evolved to a more aggressive nature rendering the existing treatment to be inefficacious in the present population. In the present study, after excluding the cases who expired and those who withdrew from the trial, the median time to progression could be envisaged as 12 weeks. However, a number of studies have shown promising outcomes and a better outcome in their series of gallbladder and biliary tract carcinoma undergoing similar therapeutic regimen.[14,16] Thongprasert *et al*.,[15] who had results somewhat similar to our study, found that gemcitabine plus cisplatin combination was able to bring about a partial response in only 27.5% of patients, while stable disease was observed in 32.5% of patients. In another study, Kim *et al*.[27] who evaluated the outcome at 3 months also found results similar to those obtained in our study with a partial response in 34.5%, stable disease in 13.8%, and progressive disease in 44.8%. In contrast to findings of the present study where the median PFS was <6 months, Meyerhardt *et al*. (2008)[28] in their study reported it to be 6.3 months. However, in our study, 23.3% of patients expired within 6 months; Meyerhardt *et al*. (2007)[28] reported a mortality rate of 61% over a period of 1 year.

In our study, the median survival up to 6 months of follow-up was 4.974 months and survival function till 6 months of follow-up was 0.748. One of the limitations of our study was its shorter follow-up duration. Among other studies showing a better drug response, the survival rate as well as median duration of survival is qualitatively not higher. Malik *et al*. reported a median overall survival rate to be 42 weeks. 14 (23.3%) mortalities took place up to a follow-up of 6 months in our study, and hence the overall survival rate of 42 weeks cannot be denied. In another study,[26] showing response rates similar to our study, the median survival was recorded as 20 weeks and a 1-year survival rate of 18.6%. Thongprasert *et al*.[15] also showed overall median survival time to be 36 weeks. In a larger trial including 410 patients,[29] similar median survival was reported as 8.1 months and by this time a total of 327/410 (79.76%) deaths had taken place.[29] Iyer *et al*.[30] in their study reported the probability of 1-year survival to be 0.58. In our study, the probability of 6-month survival was 0.748.

Thus, despite disagreement over response pattern to treatment, the overall survival seemed to be similar to that reported in other studies. The reason for difference in response pattern could be difference in study designs, inclusion criteria, and age of patients. The different biology of the disease due to difference in epidemiology and topography may also be a cause which needs to be studied further.

Conclusions

Gallbladder cancer is an aggressive cancer of the biliary tract. The Gangetic river belt of India has a higher incidence of gallbladder cancer which is triggered due to gallstone disease especially in the female population. Majority present in the advance unresectable stage where chemotherapy is the only option. Combination of gemcitabine and cisplatin which is the standard first-line therapy in such patients showed limited response in the Indian patients, leading to invariable disease progression by 6 months. Newer biomarkers need to be explored for early diagnosis and novel treatment options need to be implemented to improve survival in the Indian population. Further studies especially in India with newer treatment options are required to attain better outcomes in advanced gallbladder cancer which responds suboptimally to combination chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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