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ORIGINAL ARTICLE

A phase II study of gemcitabine and oxaliplatin (Oxigem) in unresectable gall bladder cancer

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Abstract
Purpose There is a need for effective chemotherapy protocols for gall bladder cancer (GBC). Gemcitabine has antitumor activity in pancreatic cancer. Oxaliplatin is effective in GI cancers. Based on evidence of synergy between these two, we designed this study to evaluate efficacy of this combination in unresectable GBC.
Design Unresectable GBC was enrolled for single center phase II study. Drugs gemcitabine 900 mg/m^2 and oxaliplatin 80 mg/m^2 IV infusion (Oxigem) on days 1 and 8 every 3 weeks for a maximum of six cycles or unacceptable toxicity which ever was earlier.
Materials and methods Fifty patients were enrolled and analysis was restricted to 48 who were treated. Median age was 50 years and 31 patients were females.
Results CR 3 (6.2%), PR 7 (15%), SD 17 (35.4%), and PD 18. One had complete pathological response. Median OS and PFS were 7.5 and 3 months, respectively. OS in responders was 10.5 versus 4 months in non-responders ($p < 0.0000$). Eleven patients (23%) survived for a year or more. There was no toxic death and grade III/IV toxicity seen in 10 (22%) patients: diarrhea 3, vomiting 2, neutropenia and thrombocytopenia 5 patients.
Conclusion This combination of Oxigem effective in unresectable GBC. It may even induce complete pathological response. One-year survival was 20%. There is a need for controlled trial to assess efficacy of this combination.

Keywords Gall bladder cancer · Gemcitabine · Oxaliplatin

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Introduction

Among all the biliary tract cancer, which includes gall bladder, ampulla of Vater, and hepatic ducts malignancies, gall bladder cancer (GBC) is the most common. GBC common among the females in the northern part of India is an uncommon cancer in most parts of the world. Incidence varies by geographic region and racial ethnic group. Age-adjusted incidence of GBC among females in Delhi is 7.4 persons/1,00,000 population per year (4th most common cancer in females after breast, cervix, and

ovary) [1]. Chile and Bolivia (10–15 persons/1,00,000 population/year) are other high incidence areas [2]. Male-to-female ratio is 1:4. Unfortunately, only 10% of patients are suitable for surgery and most of the cases present in advanced and unresectable stage and are candidates for palliative treatment only. Such patients are taken for palliative treatment either by placing a stent to relieve the obstructive jaundice and/or chemotherapy, which do not have a proven role. Currently, there is no standard therapy for GBC, and majority of studies involve all biliary tract cancers. With various chemotherapeutic agents (with or without 5FU), response rates (RR) reported are 0–36% of cases [3–11]. Median survival for patients presenting with unresectable disease is 2–4 months, with 1-year survival <5% [12].

Gemcitabine and oxaliplatin as single agents or in combinations with other drugs have shown some activity in adenocarcinoma of pancreas, gall bladder, and biliary tracts [5–8, 13–15]. Our institute has earlier presented studies showing that oxaliplatin when used with 5 FU, and folinic acid or gemcitabine may result in disease stabilization or partial responses in GBC, but these are unfortunately short lasting [5, 6]. Most of the reported studies constitute small number of patients, have included patients of biliary tract cancers, and it is widely appreciated that efforts should be made to segregate these diseases.

Gemcitabine is among several new anticancer drugs under investigation in the treatment of biliary tract cancer. Objective responses of up to 36% have been reported in different series [4, 7–9]. Two early phase II trials using gemcitabine has shown 16–36% response rates and median survival of 6.5 months [15, 16]. Combination of gemcitabine and cisplatin has also been studied with resultant higher response rates. Two phase II studied have reported response rates of 28–38% and median survival of 4.6–8.4 months [8, 17]. Oxaliplatin is a third generation platinum compound with much less emetic and renal toxicity when compared with cisplatin. Combination of gemcitabine and oxaliplatin (Oxigem) may be a suitable alternative to gemcitabine and cisplatin. This combination has been used by others also in pancreatic and biliary tract cancer [18, 19]. The lacunae of available literature are the inclusion of all biliary tract cancers in a single trial. Except the study by Doval et al. [8] most of the reported literature have included either pancreas with biliary tract cancer or bile ducts with GBC, which have its own flaws as the tumor biology and natural history of different organs may be different. The present study that is reported here is probably one of the largest trial with GBC patients alone for use of this combination. We could not find randomized trial in literature limited to only advanced GBC addressing the issue of superiority of chemotherapy over other supportive treatment.

Patients and methods

Design and patients

This study was designed in 2003 and approval from institute's ethics committee was taken. All the patients were enrolled after informed consent. Study was carried out as per declaration of Helsinki and good clinical practice.

Inclusion criteria included patients who had biopsy or FNAC-proven unresectable or metastatic adenocarcinoma of gall bladder, age 18 years or more, adequate organ and bone marrow functions: Hb > 10 gm/dl, ANC > 1.5×10^9/L, platelets > 100×10^9/L, serum creatinine < 1.8 mg%, serum bilirubin $\leq$ 3 mg%, liver enzymes (SGOT and SGPT) within three times the normal limit (5 times in case of diffuse hepatic involvement), ECOG performance status of $\leq$2; prior adjuvant chemotherapy and/or radiotherapy if given was allowed provided completed 6 months before enrollment. Patients of ampulla of Vater and hepatic ducts (intra or extra) were excluded.

Treatment

It includes gemcitabine 900 mg/m^2 IV 30 min infusion on day 1 and 8, oxaliplatin 80 mg/m^2 2 h infusion in dextrose 5% on Day 1 and 8. Treatment was repeated every 3 weeks for a minimum of three cycles and maximum of six cycles. After three cycles, if there was progressive disease, further treatment was discontinued and patients were followed up for survival data. These patients were provided best supportive care.

Patients who experienced grade III or IV toxicity, had their treatment delayed till complete resolution of toxicity or return of toxicity to less than grade 2. Chemotherapy dose was reduced by 25% and rounded off in cases of grade IV neutropenia or thrombocytopenia. Patients whose treatment was delayed for more than 3 weeks were taken off protocol.

Response evaluation

RECIST criteria for assessment of CR, PR, NR, stable disease, and progressive disease were used for response assessment. Response assessment was done by CT scan after three cycles and six cycles. During follow-up, CT scan was done every 3 months and thereafter every 6 months till 3 years. It was planned that whenever possible patient with PR and CR will be taken up for surgical resection.

Toxicity

NCI CTC toxicity criteria (v3.0) were used for defining toxicity.

Trial design and statistical methods

This was a single center prospective open label phase II study. It was hypothesized that to achieve median OS of >6 months and response rates of >20%, minimum sample size of 38 will be required with α error of 0.05 and β error of 0.2. Fifty patients were included, out of which 48 were treated (2 patients did not come after initial evaluation visits and lost the follow up without treatment). The analysis was restricted to 48 patients who received at least one dose of chemotherapy. Primary end points were, to investigate response rates of this drug combination in advanced/inoperable adenocarcinoma of gall bladder, to study toxicity pattern of study drugs, and to measure overall survival. Secondary, end point was progression free survival. Analysis was done using SPSS 10.0 software. Overall survival was calculated from date of entry to date of death or censured at the date last known alive for all the 48 patients. Progression free survival was calculated from date of enrollment to documented tumor progression. Survival was calculated using Kaplan–Meier method.

Results

Fifty patients were included in the study from December 2003 to December 2006 and 48 were analyzed. Their baseline characteristics (Table 1) were as follows: median age 50 years (range 31–72), females 31 and males 17, the most common presenting symptom was pain seen in 24 patients (50%) and 11 patients (22%) had jaundice at the time of presentation. Leucocytosis was seen in eight patients. Hyperbilirubinemia was seen in 7 patients only as some of patients came after biliary decompression, 34 patients had raised SGOT/SGPT, and 42 patients had raised alkaline phosphatase. CT scan revealed gall bladder mass in 38 (80%) patients, gall stones in 14 (28%), and diffuse hepatic involvement in 12 (24%) patients. Prior radical cholecystectomy was performed in 5 (10.8%), 10 had simple cholecystectomy, and 5 patients had biliary decompression. All the patients were chemotherapy naïve. Overall, 46 (95%) patients had stage IV disease. The commonest histology was adenocarcinoma in 42 (87%) patients and 6 patients had poorly differentiated histology.

In these 48 patients, totals of 164 cycles of chemotherapy were given with a median of three cycles per patients. The reasons for discontinuing chemotherapy at various stages were: completed six cycles (13 patients), progressive disease in 18, toxicity in 3, economic reasons in 6, lost to follow-up or withdrawal of consent in 5, and early deaths in 3 patients. Grade III and IV toxicity seen were: diarrhea 3, vomiting 2, and myelosuppression (neutropenia and or thrombocytopenia) 5 patients. Grade I and II neuropathy was noted in two patients each. Table 2 summarizes grade II–IV toxicity.

Table 1 Baseline characteristics of patients ($N = 48$)

Parameter	Number (%)
Age	Median 50 years (range 31–72)
Males	17
Females	31
Abdominal pain at presentation	24 (50)
Bilirubin (mg/dl)	
Median (range)	0.8 (0.5–18.0)
Hyperbilirubinemia	07 (15)
Median units/LSGOT/SGPT	38/40
Elevated SGOT/SGPT	33 (72)
Median IU SAP (range)	235 (36–1,445)
Increased SAP	42 (88)
Low albumin (<3.5 gm%)	07 (15)
Leucocytosis	08 (17.5)
CT scan	
GB mass	38 (80)
Gall stones	14 (28)
Diffuse liver involvement	12 (24)
Histology	
Adenocarcinoma	39 (85)
Prior cholecystectomy (simple or radical)	15 (32)
Stage IV	46 (95)

Table 2 Grade II–IV toxicity after chemotherapy in 48 patients

Toxicity	Number (%)
Diarrhea	8 (17)
Mucositis	2 (4.3)
Myelosuppression	9 (19.2)
Neuropathy	4 (8.5)
Vomiting	7 (14.7)

Response

Three patients (6.2%) had CR, 7 (15%) had PR, 17 (35.4%) had SD, 18 (37.5%) had progressive disease. In remaining 3 (6.2%), response assessment could not be done because of early death. One patient was taken up for surgery and there was no evidence of disease in surgical specimen suggesting complete pathological response.

Survival

Survival data for whole groups were available including those who withdrew consent or lost the follow up. Median

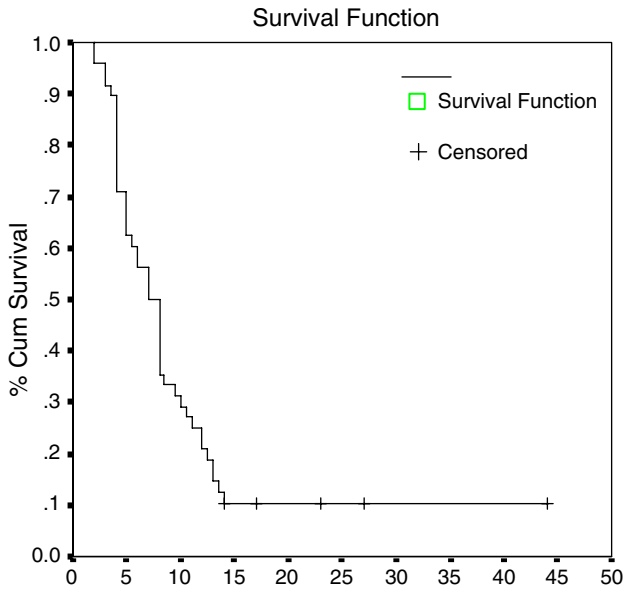

Fig. 1 Overall survival for whole group in months

follow-up of surviving patients was 23 months. Overall survival for whole group (Fig. 1) was 7.5 months (95% CI 5.6–8.4) (range 2–44 months) and progression free survival (Fig. 2) was 3 months (95% CI 2.2–3.8) (range 0–44 months). Response or stable disease after chemotherapy was an independent prognostic factor for survival. For the patients having SD or any response OS was 10.5 months (95% CI 6.5–12.5) compared to 4 months (95% CI 3.7–4.3) in non-responders ($p < 0.00001$) as shown in Fig. 3. Eleven patients (23%) survived for a year or more. Currently, five patients are surviving with follow-up of 14, 17, 23, 28 and 44 months.

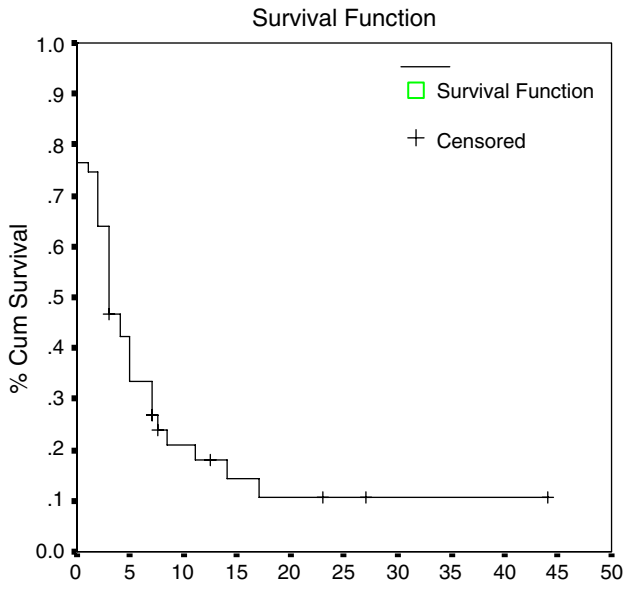

Fig. 2 PFS for whole group in months

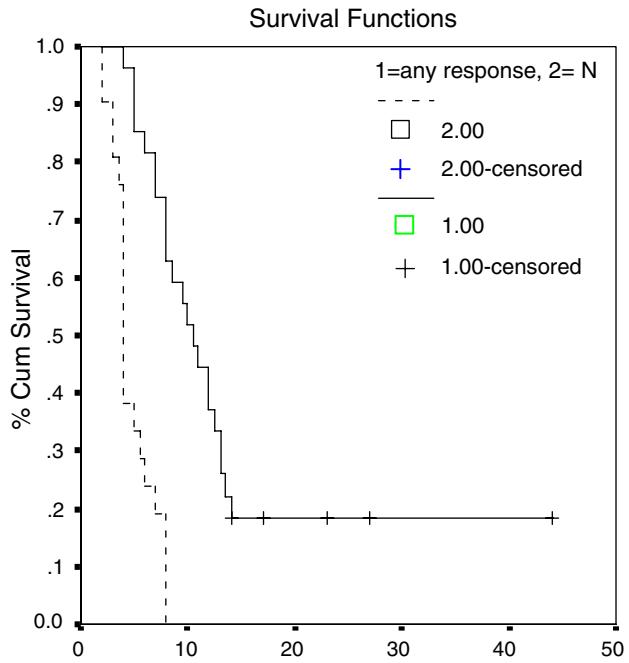

Fig. 3 OS in responders and non-responders

Discussion

Gall bladder cancer is the most common biliary malignancy. Age-adjusted incidence rates for GBC in females in Delhi is 7.4 per 1,00,000 population/year [1]. More than 75% cases present in advanced and unresectable stage and are candidates for palliative treatment only. Currently there is no standard chemotherapy protocol for GBC. Median survival for patients presenting with unresectable disease is 2–4 months, with 1-year survival <5% [12]. The three main drawbacks of the published literature in this field are: small number of patients, inclusion of bile duct, and ampulla of Vater cancers in the studies and lack of randomized control trials. 5FU with or without other agents has been the backbone of all GI tract cancers including GBC but now Gemcitabine is emerging as one of the commonly used drug either as a single agent or in combination. Response rates of 0–36% and a median survival of 8 months have been reported with gemcitabine in biliary tract cancers [3–11]. Oxaliplatin and 5FU or capecitabine-based combination has also been used with reported response rates of 24% and median survival of 10 months in these cancers [5]. Doval et al. [8] in a study using gemcitabine and DDP have reported 38% response rates and 4.8 months of median survival. Whereas combination of gemcitabine and cisplatin has been studied the most, there are few trials of gemcitabine and oxaliplatin. At the time we started this study, there was no report of use of this combination for GBC.

With the combination of gemcitabine and oxaliplatin (Oxigem) regimen, we have shown the confirmed response rates of about 22% and disease stabilization in another 32% when compared with 12–38% reported RR in other reports [7–9, 17, 20]. With gemcitabine and capecitabine, Riechelmnn et al. [21] have reported response rates of 29% and median OS of 12.7 months in patients with advanced biliary tract cancer. The response rates reported here appears some what lower than other gemcitabine-based studies but we would like to highlight here that most of other studies have included the heterogenous disease spectrum of bile duct cancers, which is likely to have better outcome [7–9, 17]. André et al. [22] have recently reported a phase II trial of biliary tract cancer. The objective response rates for GBC were 4.3% only (1/23) and OS and PFS for whole group were 8.8 months and 3.4 months, respectively. The major difference in this trial and others except the study reported by Doval et al. [8] is that all other trials have small number of gall bladder and majority of cholangiocarcinoma, and some have even included pancreatic cancer in the studies. Most of the responses reported with chemotherapy are radiological PR and some CR [5, 8, 15]. However, one of our patient with PR on CT scan was taken up for radical cholecystectomy and there was no evidence of cancer after extensive pathological review in surgical specimen. This signifies that whenever possible attempt should be made to do radical surgery and also it is possible that residual mass seen on CT scan may represent necrotic tissue only without viable tumor cells. The drug combination reported here is well tolerated. Grade III and IV toxicities observed in this study were 10 (22%). The overall survival of 7.5 months reported here is better than 4.7 and 4.6 months of OS reported by Hsu et al. [7, 8] and Doval et al. [7, 8], but other studies which have included other biliary malignancies (with small number of GBC) have reported better OS [9, 20]. One-year survival of 22% seems to be better than historical control of 5% [12].

Even in this small study, one patient was considered surgically resected. This signifies that responders to chemotherapy, even with stage IV should be evaluated for surgery. This requires close collaboration with surgical colleagues. Disease response and disease stabilization were only independent prognostic factors for overall survival, highlighting importance of achieving response to chemotherapy. This report in our opinion is very encouraging, though it may be argued that looking at the magnitude of problem this success is small. If achievement of pathological CR (2%) with this combination is confirmed in other studies this will translate into saving of about 20 lives/1,000 patients of GBC each year. It is possible that one patient with pathological CR here may have different genetic profile and therefore responded well. This and other issues need to be studied in future.

In summary, combination of gemcitabine and oxaliplatin reported here is feasible in unresectable GBC, with an overall response rate greater than 20%. It may even induce complete pathological response. More than 20% patients survived 1 year or more. There is a need for controlled trial to assess efficacy of this combination with other combinations especially fluoroupyridines-based combinations. Recently, we have completed a phase III trial comparing best supportive care versus 5FU-folinic acid versus GEMOX (Oxigem) and results will be available soon.

Conflict of interest statement There is no conflicts of interest by any of authors. No funding was received.

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