Original Article

Retrospective Comparative Study between Gemcitabine/Cisplatin and Gemcitabine/Capecitabine in the Treatment of Metastatic Carcinoma of Gallbladder

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Abstract

Introduction: Metastatic carcinoma of gallbladder is a disease with a dismal prognosis. Chemotherapy is mainstay of treatment. Gemcitabine/cisplatin is used as first-line chemotherapy. In some study, gemcitabine/capecitabine has been used with good result. A retrospective study has been performed to compare efficacy between these two chemotherapeutic regimens. **Materials and Methods:** The objective of this study was to compare tumor control rate, progression-free survival (PFS), overall survival (OS), and toxicity between these two chemotherapeutic regimens. In arm A, patients received gemcitabine (1000 mg/m^2 on day 1 and on day 8) and cisplatin (75 mg/m^2 on day 1). In arm B, patients received gemcitabine (1000 mg/m^2 on day 1 and on day 8) and capecitabine (1000 mg/m^2 BD from day 1 to day 14). Response evaluation has been done by response evaluation criteria in solid tumor criteria. **Results:** A total of 55 (25 in arm A and 30 in arm B) patients were included in the study. Tumor control rate was 88% in arm A and 86.7% in arm B. PFS in arm A was 7.2 months (95% confidence interval [CI]: 6.19–8.21 months) and 7.58 months (95% CI: 6.66–8.5 months) in arm B. OS in arm A was 10.8 months (95% CI: 9.51–12.09 months) and 11.57 months (95% CI, 10.3–12.84 months) in arm B. These differences between the two arms were not statistically significant. **Conclusion:** There is no statistically significant difference between gemcitabine/cisplatin and gemcitabine/capecitabine regarding disease control rate, PFS, and OS in the treatment of metastatic carcinoma of gallbladder. Hence, gemcitabine/capecitabine can also be used as first-line chemotherapy in metastatic carcinoma of gallbladder.

Keywords: *Capecitabine, carcinoma, cisplatin, gallbladder, gemcitabine*

Introduction

Prevalence of gallbladder carcinoma (GBC) shows great geographical variation. Although an uncommon malignancy, it is the fifth most common gastrointestinal malignancy (following colon, pancreas, stomach, and esophagus) and most common biliary tract malignancy in the USA. It consists of 80%–95% of biliary tract cancer worldwide.[1] It is rare in the Western world including the USA, Canada, the UK, New Zealand, and Australia. Incidence rate in these countries ranges between 0.4 and 0.8 in men and 0.6 and 1.4 in women per 100,000 population.[2] Gallbladder cancer is common in Central and South America, Central and Eastern Europe, and Japan.

Various epidemiological reviews have reported that gallbladder cancer is rare in India.[3-6] Although incidence rate varies widely throughout the country. It is more common in Northern and Central India than in the west and south. Gallbladder cancer is more common in women than in men in certain population.[7]

There are various risk factors regarding GBC. GBC occurs most commonly due to gallbladder stone. Gallstone presents in 60%–90% of patients with gallbladder cancer as compared to 20%–25% of an age-matched population. Gallstone disease was a major risk factor in a large case–control study.[8] Risk increases with increasing size of stone patients with larger stone (>3 cm) have about 10 times higher risk of having cancer as compared to smaller (<1 cm).[9] Chronic typhoid infection carriers have 3–200 times higher risk of cancer than noncarriers and 1%–6% lifetime risk of development of cancer.[10] Various single nucleotide polymorphisms have been shown to be associated with GBC. However, existing genetic studies in GBC have so far been insufficient to confirm any association.[11]

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Symptoms of GBC are vague in early stages and cannot be separated from other benign conditions such as chronic cholecystitis. Symptoms are steady pain in the right upper abdomen, weakness, loss of appetite, and weight loss. In advanced disease, common bile duct may be obstructed, most often due to infiltration of the duct by tumor, which causes jaundice.[12] Sometimes, due to extensive liver metastases, liver may be enlarged and palpable. Due to vague and nonspecific symptoms, GBC is mostly diagnosed at advanced stage.

Treatment of GBC depends on the stage of the tumor. When disease involves only lamina propria (sometimes seen as an incidental finding in simple cholecystectomy done due to chronic cholecystitis), surgery only is the treatment (in the form of simple cholecystectomy). When it involves muscle layer (T1b), extended cholecystectomy has to be done. No adjuvant therapy is required. When the disease is more advanced, adjuvant chemoradiotherapy or chemotherapy is required. Lymph node metastases beyond porta hepatis, tumor invasion of portal vein, hepatic artery, two or more extrahepatic organs (locally advanced disease), and distant metastases are contraindication for surgery. In locally advanced disease, chemoradiotherapy or chemotherapy can be given. In metastatic disease, chemotherapy is the treatment option. Other supportive procedure, such as biliary drainage, may be required depending on condition. Although chemotherapy-only treatment is preferred in metastatic GBC, results of various studies are not enthusiastic. Prognosis is dismal in metastatic GBC.

Various chemotherapeutic drugs have been used in metastatic GBC from early days of treatment. 5-fluorouracil (5-FU) has been one of the most commonly used chemotherapeutic medicines in the treatment of GBC. 5-FU is cell cycle-specific drug with activity in the S phase. 5-FU metabolite 5-Fluoro-2'-deoxyuridine-5'-monophosphate causes inhibition of thymidylate synthase. Incorporation of 5-FU metabolite 5-fluorouridine 5"triphosphate into RNA results in alteration of RNA processing. Incorporation of 5-FU metabolite fluorodeoxyuridine triphosphate into DNA results in inhibition of DNA synthesis and function. In a study done by Eastern Cooperative Oncology Group (ECOG), using 5-FU in advanced carcinoma of gallbladder, median survival was 21 weeks.

Capecitabine is fluoropyrimidine carbamate prodrug form of 5-FU. It is metabolized preferentially in tumor tissue to 5-FU. Capecitabine is also commonly used in advanced biliary tract carcinoma either as a single agent or in combination chemotherapy. In a retrospective study by Patt *et al*., 50% of patients achieved either complete response (CR) or partial response (PR). Median overall survival (OS) was 9.9 months (95% confidence interval [CI]: 4.4–15.4 months).[13]

Cisplatin is a platinum analog. It covalently binds with DNA with preferential binding to the N-7 position of guanine and adenine. It reacts with two different sites on DNA to produce cross-links, either intrastrand or interstrand. Formation of DNA adducts results in inhibition of DNA synthesis and transcription. Cisplatin has shown its activity in biliary tract carcinoma.

Gemcitabine is a new anticancer drug in the treatment of biliary tract carcinoma. Gemcitabine is a fluorine-substituted deoxycytidine analog. It exerts its action at "S" phase of cell cycle. It requires intracellular activation by deoxycytidine kinase to the monophosphate form with eventual metabolism to triphosphate nucleotide metabolite. Incorporation of this triphosphate metabolite into DNA results in chain termination and inhibition of DNA synthesis and function. Triphosphate metabolite also inhibits DNA polymerase, which in turn interferes with DNA synthesis, DNA repair, and function.

Adoption of gemcitabine as the standard treatment for patients with carcinoma of pancreas led to its use in hepatobiliary cancer. It has favorable toxicity profile.[14] In the usual dosing regimen, response of 16%–42% has been obtained. Median survival as first- and second-line treatment was 8.3 and 17 months, respectively, in a study using single-agent gemcitabine for biliary tract carcinoma.[15] One year survival was 50.9% in this study.

Two very effective drugs (gemcitabine and cisplatin) have been combined with the intent of having better results in advanced biliary tract carcinoma. In the study by Valle *et al*., gemcitabine (arm A) has been compared with gemcitabine/cisplatin (arm B) combination. Response rate was 58% versus 75%. A 6-month progression-free survival (PFS) was greater in arm B (45.5% vs. 57.1%).[16] A meta-analysis done by Yang *et al*. has shown that patients (suffering from advanced biliary tract carcinoma) treated with gemcitabine/cisplatin combination had better survival than with other regimens.[17]

Gemcitabine along with capecitabine has also been tried in some studies for better result. In a study in advanced biliary carcinoma done by Riechelmann *et al*., gemcitabine (1000 mg/m^2 on day 1 and day 8) and capecitabine (650 mg/m^2 BD from day 1 to day 14 in 21 days cycle) were used. Median PFS and OS were 6.2 and 12.7 months.[18] In another study done by Cho *et al*., 24 patients with GBC, the same dose of gemcitabine and higher dose of capecitabine (1000 mg/m^2 BD from day 1 to day 14 in 21 days cycle) was used. Median survival was 16 months.[19]

Till now, there has been no head-on trial to compare two effective chemotherapeutic regimens (gemcitabine/cisplatin and gemcitabine/capecitabine). Keeping in mind this, we have done a retrospective study to compare the efficacy of these two chemotherapeutic regimens for treatment of metastatic carcinoma of gallbladder.

Materials and Methods

Patients suffering from metastatic carcinoma of gallbladder were included in this retrospective single institutional study. Primary objective of this study was to compare tumor control rate (CR + PR + stable disease [SD]). Secondary objective was to compare PFS, OS, and toxicity between these two chemotherapeutic regimens. Patients who previously received chemotherapy for this disease were not included in this study. In arm A, patients received gemcitabine (1000 mg/m^2 on day 1 and on day 8) and cisplatin (75 mg/m^2 on day 1). In arm B, patients received gemcitabine (1000 mg/m^2 on day 1 and on day 8) and capecitabine (1000 mg/m^2 BD from day 1 to day 14). Chemotherapy continued until disease progression or excess toxicity. Clinical examination was done before each cycle of chemotherapy. Response evaluation by CECT scan (and by other imaging according to initial finding) was done after each three cycles of chemotherapy. Imaging was also done at any point of treatment due to appearance of new symptoms. Response evaluation has been done by response evaluation criteria in solid tumor criteria.

Statistical analysis

Categorical variables were compared using Chi-square test. The means of numerical data were described as a mean ± standard error and compared using independent samples *t*-test. All analyses were two tailed and statistical significance was accepted for a calculated $P < 0.05$. OS has been compared also by Kaplan–Meier survival analysis [Figure 1]. Statistical analysis has been done using statistical software (SPSS 16, SPSS for Windows, Chicago, SPSS Inc).

Result

A total of 55 (25 in arm A and 30 in arm B) patients were included in the study. Mean age in arm A was 56.36 years. Mean age in arm B was 57.4 years. Difference in mean age was not statistically significant. In arm A, 19 (76%) patients were female and 6 (24%) patients were male. In arm B, 21 (70%) patients were female and 9 (30%) patients were male. This difference was statistically insignificant. Difference between other baseline characteristics was not also statistically significant. Tumor control rate was 88% in arm A and 86.7% in arm B. No patient in either arm achieved CR. Fifteen patients in arm A and twenty patients in arm B partially responded to treatment. SD was seen in seven patients in arm A and six patients in arm B. Early disease progression occurred in three patients in arm A and four patients in arm B. Difference in response rate was not statistically significant. PFS in arm A was 7.2 months (95% confidence interval [CI]: 6.19–8.21 months) and 7.58 months (95% CI: 6.66–8.5 months) in arm B. OS in arm A was 10.8 months (95% CI: 9.51–12.09 months) and 11.57 months (95% CI: 10.3–12.84 months) in arm B. Difference in PFS ($P = 0.57$) and in OS ($P = 0.4$) between the two arms was not statistically significant.

Toxicity analysis was done according to National Cancer Institute, Common Terminology Criteria for Adverse Event, version 4 criteria. In arm A, acute Grade 3 vomiting occurred in three patients [Table 1]. Delayed Grade 3 vomiting occurred in two patients. In arm B, no patient had Grade 3 vomiting. No patient in arm B suffered from delayed vomiting. Three patients in arm B suffered from Grade 3 diarrhea. No patient in arm A had Grade 3 diarrhea. In arm A, one patient had Grade 3 anemia. Two patients suffered from Grade 3 neutropenia. One patient suffered from Grade 3 thrombocytopenia. One patient in arm B suffered from Grade 4 anemia. Five patients had Grade 3 neutropenia. Two patients suffered from Grade 4 neutropenia. Two patients had Grade 3 thrombocytopenia. Two patients in arm A and five patients in arm B suffered from febrile neutropenia. Seven patients in arm A suffered from Grade 2 peripheral neuropathy. In arm A, Grade 3

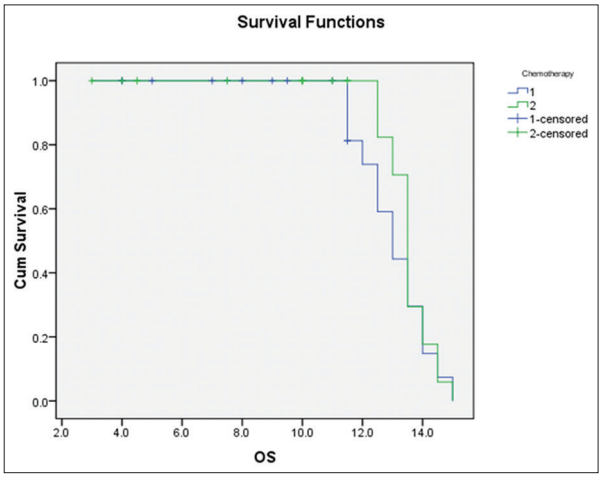

Figure 1: Survival curve

Table 1: Toxicity analysis

	Toxicity		
Name	**Grade**	**Arm-A (%)**	**Arm-B (%)**
Vomiting	Grade 2	13 (52)	5 (16.67)
	Grade 3	5 (20)	0
Diarrhea	Grade 2	4 (16)	7 (23.33)
	Grade 3	0	3 (10%)
Anemia	Grade 2	9 (36)	11 (36.67)
	Grade 3	1 (4)	4 (13.33)
	Grade 4	0	1 (3.33)
Neutropenia	Grade 2	5 (20)	8 (26.67)
	Grade 3	2 (8)	5 (16.67)
	Grade 4	0	2 (6.67)
Thrombocytopenia	Grade 2	4 (16)	5 (16.67)
	Grade 3	1 (4)	2 (6.67)
Peripheral neuropathy	Grade 2	7 (28)	0
	Grade 3	0	0
Alopecia	Grade 2	11 (44)	0
	Grade 3	4 (16)	0
Palmoplantar erythrodysesthesia	Grade 2	0	5 (20)
	Grade 3	0	3 (10)

alopecia occurred in four patients. Three patients in arm-B suffered from Grade 3 palmoplantar erythrodysesthesia.

Discussion

Gallbladder cancer is the most common malignancy in biliary tract. It is most aggressive malignancy in biliary tract.[20] Five-year survival rate is <5%.[21] Results of treatment in terms of OS in carcinoma of gallbladder have not been satisfactory. Aggressive biologic behavior and lack of sensitive screening test to detect early-stage disease are factors causing poor prognosis.[22] In most of the cases, early disease does not produce symptoms or symptoms are generalized, which cannot be separated from benign disease to this organ.[23] That is why, most of the patients suffering from carcinoma of gallbladder, present with either unresectable locally advanced state or with metastatic disease. Only 10% of patients present at a stage amenable to surgical resection.[24] Almost 50% of patients have lymph node metastasis at the time of presentation.[25] A study by Arminski has shown liver is the most common site of metastasis (76%–86%). According to the author, metastases occur to many organs including liver, lymph nodes, adrenal, kidney, spleen, brain, breast, thyroid, heart, uterus, and skeletal system.[26] In our study, most common site of metastasis was also liver.

In metastatic GBC, chemotherapy is the mainstay of treatment. Historically, 5-FU has been the most active single agent, but response rate is 10%–15%. Other agents were mitomycin, doxorubicin, nitrosourea, leucovorin, and cisplatin. To improve response rate, combination chemotherapy has been used. 5-FU, doxorubicin, and mitomycin regimen produced response in 4 out of 13 patients. Combination of 5-FU and leucovorin resulted objective response in 9 out of 28 patients. In a study, using 5-FU and cisplatin, partial response was seen 6 out of 24 patients. With the use of gemcitabine, there has been improvement in response rate. In a study by Doval *et al*., gemcitabine plus cisplatin had a tumor control rate 59.9% in patients suffering from unresectable GBC.[27] In the study by Patt *et al*., 50% treatment response was achieved with oral capecitabine chemotherapy in patients suffering from GBC. The presence of mild-to-moderate hepatic dysfunction has no significant effect on the pharmacokinetics of capecitabine. Hence, capecitabine is also useful in moderately impaired hepatic dysfunction.

In a study by Cassier *et al*., median age was 60.7 years at the time of diagnosis and 66% patients were male.[28] In another study by Kim *et al*., median age at diagnosis was 52 years.[29] In the study done by Harder *et al*., median age was 63 years and male patients were 41.9%.[30] In our study, median age at presentation was 59 years (range: 41–68 years). Hence, median age was not very different from other published studies. In our study, 72.7% patients were female. Hence, percentage of female patients was higher in our study. In a study by Knox *et al*., ECOG performance status 0–1 was 82%.[31] In our study, 61.8% patients had performance status ECOG 1, and 38.2% had performance status ECOG 2.

A study by Kim *et al*. has shown PR with chemotherapy (gemcitabine/cisplatin) was 34.5%, SD was 13.8%, and PD was 44.8%. Median PFS was 3 months (95% CI: 2.12–3.88 months) and OS was 11 months (95% CI: 5.49–16.5 months). In another study by Hwang *et al*., median PFS was 3.3 months (95% CI: 2.6–4 months), OS was 11 months (95% CI, 9.7–12.3 months) with gemcitabine/cisplatin chemotherapy. Overall response rate was 23.9%.[32] In our study, tumor control rate was 88% with gemcitabine/cisplatin chemotherapy. OS in our study was almost same as in other studies.

In a study by Iyer *et al*., response rate was 58% (95% CI: 28%–85%) with gemcitabine/capecitabine chemotherapy. Median PFS and OS were 9 months and 14 months, respectively.[33] In another study by Iqbal *et al*., PR was 25% and SD was 23.1%. Median OS was 7 months.[34] In another study by Riechelmann *et al*., overall response rate was 29%. Three patients achieved CR. Median PFS and OS were 6.2 months and 12.7 months, respectively. In our study, 66.7% patients achieved PR with gemcitabine/capecitabine chemotherapy. SD was seen in 20% patients. OS was lower in our study in comparison to other published studies.

In the study by Valle *et al*., Grade 3 or 4 toxicity in gemcitabine/cisplatin arm included anemia (2.4%), leukopenia (4.8%), neutropenia (14.3%), thrombocytopenia (14.3%), nausea/vomiting (7.1%), and anorexia (4.8%). In comparison to this study, the incidence of vomiting and anemia was higher and neutropenia and thrombocytopenia was lower in our study. In the study by Riechelmann *et al*., Grade 3 neutropenia and thrombocytopenia were seen in one patient with gemcitabine/capecitabine combination chemotherapy. One patient suffered from gastro-intestinal bleeding and another patient had sepsis. In another study, Grade 3 toxicities included liver function abnormalities, fatigue, diarrhea, hand-foot syndrome, and hematological toxicities. Nearly 7.8% patients experienced Grade 4 neutropenia, 1.9% patient had Grade 4 thromboembolism, and 1.9% patient experienced Grade 4 fatigue. In our study, Grade 3 or Grade 4 toxicities in gemcitabine/capecitabine arm included diarrhea (10%), anemia (16.66%), neutropenia (23.34%), thrombocytopenia (6.67%), and palmoplantar erythrodysesthesia (10%).

Tumor control rate was higher in arm A in our study. PFS and OS were higher in arm B, although these differences were not statistically significant. Hence, gemcitabine/capecitabine can also be used as first-line chemotherapy in metastatic carcinoma of gallbladder. Retrospective single-institutional study nature and small number of patients are limitations of this study. To have a better result, prospective randomized study with more number of patients can be considered.

Conclusion

There is no statistically significant difference between gemcitabine/cisplatin and gemcitabine/capecitabine regarding disease control rate, PFS and OS in the treatment of metastatic carcinoma of gall bladder. Keeping in mind the limitations of our study, a prospective randomized study with more number of patients can be considered.

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Conflicts of interest

There are no conflicts of interest.

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