Safety and Efficacy of Low-Dose Single-Agent Capecitabine in Inoperable Gallbladder Cancer with Jaundice Post-Single-System Single-Catheter External Biliary Drainage: a Pilot Study from a Highly Endemic Area

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Received: 27 September 2017 / Accepted: 13 July 2018 / Published online: 31 July 2018
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Abstract

Gallbladder cancer (CaGB) in the subcontinent belongs to low socioeconomic status, and at the time of diagnosis, a large number is unresectable or inoperable so the palliative treatment remains the only option. In the present study, attempt was made to see the effect and safety profile of single-agent oral capecitabine in inoperable CaGB in presence of low levels of jaundice post-single-catheter transhepatic external biliary drainage. In $N = 35$ of inoperable jaundiced CaGB, post-biliary drainage capecitabine in low dose was started when their total bilirubin levels fell to 10 mg% or below. Post-external drainage decreased bilirubin level to < 10 mg/dl within 1–4 weeks, mean 2.37 ± 0.80 weeks. Survival was 1–6 months, mean 3.26 ± 1.46 months. Catheter patency time was 1.92 ± 0.64 months (range 0–3 months). Young age, male sex, level of jaundice at presentation, and duration of decrease in jaundice after drainage were significantly associated with progressive disease course. Poor survival was significantly associated with progressive disease course, young age, and level of jaundice at admission. To the best of our knowledge, this is the first study to establish that single-agent capecitabine can be safely given in CaGB in presence of jaundice.

Keywords Low-dose capecitabine · Single-system single catheter · External biliary drainage · Inoperable gallbladder cancer · Jaundice

Previous Abstract Presentation Role of low-dose capecitabine in inoperable cancer gallbladder in presence of jaundice: a pilot study from endemic world. A Sonkar, J Kushwaha, M Kumar, A Chandra, R Gupta, D Singh, A Kumar, A A Agarwal. *Annals of Oncology* 24 (suppl 4), iv74-iv74. (Abstract in proceedings of World GI Congress).

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Introduction

Gallbladder cancer (CaGB) is a biologically aggressive tumor of unknown etiology with high incidences reported from India, Pakistan, Chile, Bolivia, and Central Americans of Mexican origin [1]. It is a leading cause of cancer deaths in many countries. India has a high incidence of CaGB with a perceptible geographic variation. Incidence of cholelithiasis and CaGB is higher in northern parts compared to southern parts of India. The incidence of CaGB has shown a rapid rise in India with more than 50% increase during the last 15 years [2]. Most of CaGB patients in India belong to low socioeconomic status, a majority of them present in inoperable stage, and palliative treatment offers the only hope in this subgroup of patients [3–8]. A majority of them present with jaundice and are beyond the scope of curative resection. These patients require need-based palliative procedures and some form of systemic chemotherapy to sustain the effect or slow the progression of

disease. Development of jaundice indicates the advanced stage of the disease precluding palliative chemotherapy [9].

Surgery in the form of bilio-enteric bypass has been the traditional palliative approach but with its own associated morbidity and mortality [10, 11]. Endoscopic retrograde stenting (ERS) and percutaneous transhepatic drainage (PTBD) have gained over surgical procedures over the period of time [12–16]. PTBD is a technically demanding procedure where in addition internal stenting is done either using a plastic or metallic stent. It has been established earlier that drainage of as little as 30% of liver parenchyma provides adequate relief from jaundice and associated pruritus. Therefore, unilateral drainage of liver may be sufficient to palliate jaundice, provide relief from pruritus, and improve the quality of life that is the ultimate goal in these patients [17–22].

There is sufficient literature on the role of palliative chemotherapy in improving quality of life and survival of patients of CaGB [23]. However, the safety of chemotherapy in CaGB in presence of jaundice remains unanswered. Capecitabine, the oral prodrug of 5-FU, is activated in the liver, and subsequently in human tumor tissue to 5-FU. 5-FU is further metabolized to dihydrofluorouracil and then α -fluoro- β -alanine. Oral capecitabine has been used, as a single agent in hepatobiliary cancers including CaGB, but its role in presence of jaundice has yet not been studied [24]. This study attempts to identify the effect and assess the safety profile of low dose oral capecitabine in inoperable CaGB in presence of low levels of jaundice post-single-catheter single-system biliary drainage.

Methods

Thirty-five patients of inoperable CaGB with obstructive jaundice presenting to the outpatient department of Surgery at the King George's Medical University from May 2011 to August 2012 were enrolled after informed written consent and institutional ethical committee approval (Ref Code: 53 E.C.M. IIB/P9). The diagnosis of obstructive jaundice was established on the basis of liver function tests (increased serum bilirubin and alkaline phosphatase levels) along with abdominal ultrasonography (US) or contrast-enhanced computed tomography scan (CECT) of the abdomen showing gallbladder mass associated with dilated intrahepatic radicles. Histologic and/or cytological confirmation of malignancy was done by a fine-needle aspiration biopsy.

Inclusion Criteria Patients of inoperable CaGB with obstructive jaundice. Women enrolled were non pregnant and advised to use contraception method for at least 3 months after the completion of six cycles of capecitabine.

Exclusion Criteria Patients with one or more of the following were excluded from the study:

- (1) Patients with resectable cancer as judged on imaging studies
- (2) Patients with poor performance status: karnofsky index < 60
- (3) Patients with previous history of chemotherapy or radiotherapy for biliary tract cancer
- (4) Patients having any serious co-existing medical condition, pregnant or breastfeeding women.

Procedure Percutaneous transhepatic single-system single-catheter biliary drainage without stenting.

Preprocedural Preparation The baseline investigations: hemoglobin, blood cell counts, blood urea, serum creatinine, serum electrolytes, blood sugar, liver functions tests, prothrombin time, and INR were obtained. A chest x-ray and an electrocardiogram were also obtained. All patients received injectable prophylactic antibiotic (ceftriaxone 1 g) for 72 h starting 12 h before the procedure. Patients were kept nil by mouth for 8 h before the procedure and were well hydrated with dextrose containing intravenous fluids. The procedure was performed under conscious analgesia (lignocaine).

Intervention Either a right- or left-sided ductal system was used for PTBD. Patients with extensive right-sided disease and/or right lobe atrophy with sparing of the left lobe were subjected to a left-sided approach and vice versa. For hilar obstruction, either the right anterior or left system was chosen.

Technique: An anterior subxiphoid approach was used for the left duct, whereas a right lateral approach was used for the right duct. The procedure was done under ultrasound guidance, and the skin entry was through the intercostal space below the costophrenic angle. Once entry was gained to a suitable duct, the standard Seldinger technique was used to place a guide wire in the biliary system. The tract was dilated, and after crossing the obstruction with a hydrophilic guide wire. A standard 8-10F-pigtail drainage catheter was placed to maintain access to the ductal system.

Chemotherapy Administration:

Twelves et al. [25] found that mild-to-moderate hepatic dysfunction (mean bilirubin, 6.5 mg/dl; range, 0.9–28.3 mg/dl) had no clinical significance on the pharmacokinetics of capecitabine. Nevertheless, no data exist for severe hepatic dysfunction [26].

The dose of administered capecitabine in the study was lower than the recommended dose of capecitabine (Xeloda,

Hoffman La Roche), i.e., 1250 mg/m² PO, twice a day from days 1 to 14 of a 3 weekly cycle with normal bilirubin levels (0.1–1.0 mg/dl).

Chemotherapy was started after the total bilirubin levels fell below ≤ 10 mg/dl post-drainage. Patients with serum total bilirubin between 1 and 5 mg% were administered 1000 mg/m² PO, twice a day from days 1 to 14 of a 3 weekly cycle.

Patients with serum bilirubin levels between 5 and 10 mg/dl were given 500 mg/m² PO, twice a day from days 1 to 14 of a 3 weekly cycle. As soon as these patients reached a further reduced levels of total bilirubin (between 1 and 5 mg/dl), dose was increased to 1000 mg/m² BD for 14 days/3 weekly cycle. All patients receiving subsequent cycles of chemotherapy were followed up for chemotherapy-related toxicities and external catheter drainage-related complications.

Outcome Measures

The primary outcome measure was safety and efficacy of capecitabine chemotherapy in inoperable CaGB in presence of jaundice. Efficacy was determined by evaluating tumor response using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. The secondary outcome measures included time to relief from itching, procedure-related complications, procedure-related mortality, 30-day mortality, catheter patency time, and survival. The procedure-related complications were defined as those occurring after catheter placement. Early cholangitis was defined as cholangitis occurring during the first 7 days after the procedure as evidenced by fever, leukocytosis with worsening biochemical parameters. A procedure-related mortality was defined as death directly related to complications of the procedure.

The duration of catheter patency was defined as the period of time from catheter insertion to catheter occlusion or pullout. The catheter was considered to be occluded when patients had decreased or absent biliary output and/or abnormal/worsening biochemical parameters and/or cholangitis. It was confirmed by biliary dilatation in the drained lobe on US. Overall survival was calculated from study entry to death.

Follow-Up

Clinical, hematologic, and biochemical parameters were assessed at days 2, 7, and 30 after stent placement and every 3 months thereafter in follow-up period. Tumor response was assessed using the RECIST 1.1 based on computed tomography scan performed at baseline and after 2nd and 6th cycle of chemotherapy. All patients were instructed to contact the hospital if any symptom suggestive of a complication appeared. Additional information regarding current status or death was

obtained directly from the referring physician or from the patient during outpatient visit or by telephone.

Safety

Safety was monitored throughout the study and for 28 days after the last study treatment. Adverse events were graded according to the National Cancer Institute–Common Toxicity Criteria (NCI-CTC). Hand foot syndrome was graded, as in previous capecitabine studies [27, 28]. Patients were educated to recognize adverse effects $>$ grade 2 and interrupt capecitabine and await further instruction from their physician.

Statistical Analysis

Continuous data were summarized in mean $\pm$ SD and discrete (categorical) in number and %. Continuous groups were compared by independent Student's *t* test while categorical by Chi-square (χ^2) test. A two-sided ($\alpha = 2$) $p < 0.05$ was considered statistically significant. All analyses were performed on Microsoft Excel software.

Results

The baseline characteristics of inoperable CaGB patients with jaundice are summarized in Table 1. Mean age ($\pm$ SD) of CaGB patients at presentation was 43.20 ± 9.22 years (range 23–70 years). Further, among patients, mostly were females (65.71%). In this study, 22 (62.85%) out of 35 patients were from rural area and 13 (37.14%) from urban area. The rural to urban ratio of the study was approximately 2:1. The level of

Table 1 Baseline characteristics of GB cancer patients with jaundice

Characteristics	Statistics ($n = 35$)
Age (years):	
Mean $\pm$ SD	43.20 ± 9.22
Range (min-max)	(23–70)
Sex:	
Males	12 (34.3%)
Females	23 (65.7%)
Level of total bilirubin at admission (mg/dl):	
Mean $\pm$ SD	15.0 ± 6.30
Range (min-max)	(6.7–27.90)
Hemoglobin (g/dl)	10.2 ± 2
Total leucocyte count ($\times 1000$)/cm	11 ± 3
ALP (IU/L)	819 ± 564
AST (IU)	78 ± 43
ALT (IU)	65 ± 34

total bilirubin of all CaGB patients at admission ranged from 6.7 to 27.90 mg/dl with mean ($\pm$ SD) 15.0 ± 6.30 mg/dl.

Evaluation of Intervention, Complications, and Treatment Response

The effects of external drainage and capecitabine on CaGB patients are summarized in Table 2. The external drainage decreased bilirubin level to < 10 mg/dl within 1–4 weeks with mean ($\pm$ sd) 2.37 ± 0.80 weeks and median 2 weeks. Majority of the patients ($\sim 86\%$) got relief from itching during the first week after drainage.

On determining the tumor response based on RECIST 1.1, 28.6% of the patients showed stable disease (SD) while 71.4% showed progressive disease (PD) with no patient demonstrating a complete or a partial response. The survival of all patients ranged from 1 to 6 months with mean ($\pm$ sd) 3.26 ± 1.46 months. Most of the procedure-related complications occurred late in the study period and included cholangitis, bile leak, and catheter pullouts. None of the patient developed catheter occlusion. Catheter patency time (i.e., duration till PTBD pullout) ($n = 13$) ranged from 0 to 3 months with mean ($\pm$ sd) 1.92 ± 0.64 months. Since it resulted in formation of biliary fistula, ostomy bag was applied. There was no procedure-related deaths and 30-day mortality was attributed to the advanced presentation of disease in these patients.

Association of Clinical Characteristics with Disease Response and Survival

The association of different variables with disease status of CaGB patients is summarized in Table 3. Young age ($\leq$

Table 2 Effect of external drainage and capecitabine in GB cancer patients with jaundice

Characteristics	Statistics
Decrease in total bilirubin level to < 10 mg% (weeks):	
Mean $\pm$ St.D	2.37 ± 0.80
Range (min-max)	1–4
Disease status:	
SD	10 (28.6%)
PD	25 (71.4%)
Survival (months)	
Mean $\pm$ St.D	3.26 ± 1.46
Range (min-max)	1–6
Procedure-related complications	15
PTBD pullout (months):	
Mean $\pm$ St.D	1.92 ± 0.64
Range (min-max)	1–3
Procedure-related death	0
30-day mortality	2

40 years) and males were significantly associated with progressive disease course. Level of jaundice at time of presentation and duration in decrease in jaundice after PTBD was also significantly associated with the course of disease. Higher level of jaundice at admission had progressive disease, so was the delay in decrease in jaundice level after drainage. Poor survival was significantly associated with progressive disease course. PTBD pullout had no significant association with disease course. Young age and levels of jaundice at admission were significantly associated with poor survival (Table 4).

Chemotherapy Complications

During study, 24 patients (68.6%) developed nausea and vomiting, 14 patients (40%) had abdominal distension, 7 patients (20%) developed joint pain/flu like symptoms, and 7 patients (20%) developed rashes, which were least common. Most of the toxicities were of grade I in presentation and there was no reported grade III and grade IV toxicities in the chemotherapy-administered group.

Discussion

CaGB causes obstruction of the biliary tree resulting in jaundice and is the presenting complaint in 30 to 60% of the patients [29]. Majority of them fall in inoperable CaGB; these patients who present with jaundice may not be a fit case for curative resection. There is dearth of chemotherapeutic regimen offering a good disease-free and overall survival. This subgroup of patients needs palliation of jaundice and palliation of disease simultaneously which is an ordeal for a treating physician. Chemotherapy has been reported to have a significant benefit over best supportive care, but no singular chemotherapy regimen has yet been identified in patients of CaGB with jaundice [24, 30]. Palliation of jaundice by PTBD, ERS etc. is associated with a delay in levels of bilirubin to fall further, leading to delay in initiation of chemotherapy. In advanced CaGB and cholangiocarcinomas, capecitabine in combination with gemcitabine has shown promising antitumor activity and a tolerable safety profile [30, 31] but neither in isolation nor in presence of jaundice.

Efficacy: Response

The study by Chowdhary et al. comes closest to this study where the effect of single-agent capecitabine in CaGB in absence of jaundice reported a high clinical benefit rate CBR (CR + PR + SD) of 82.3%: PR in 12 patients (26.08%), SD in 26 patients (56.21%), and PD in 8 patients (17.39%) [32]. Patt et al. in his retrospective analysis reported a CBR of 75% patients of CaGB treated with oral capecitabine [24]. The present study shows inferior CBR of 28.6% (all stable disease;

Table 3 Association of different variables with disease status (SD/PD) of GBC patients

Variables	SD (<i>n</i> = 10)	PD (<i>n</i> = 25)	<i>P</i> value	Survival ≤ 3 months (<i>n</i> = 20)	Survival > 3 months (<i>n</i> = 15)	<i>p</i> value
Age (years):						
< 40 years	0	14	0.002	13	1	0.0001
≥ 40 years	10	11		7	14	
Sex:						
Males	1	11	0.06	9	3	0.12
Females	9	14		11	12	
Total bilirubin at admission (mg/dl):						
< 15 mg/dl	8	8	0.01	4	12	0.0001
≥ 15 mg/dl	2	17		16	3	
Decrease in bilirubin level to < 10 mg% (weeks):						
< 2 weeks	2	1	0.12	1	2	0.38
≥ 2 weeks	8	24		19	13	
PTBD pullout:	6	7	0.07	8	5	0.68
No PTBD pullout:	4	18		12	10	
Survival (months):						
≤ 3 months	2	18	0.005			
> 3 months	8	7				

SD) and majority of the patients 71.4% had progressive disease (PD). The reason attributable to the inferior CBR could be due to use of low-dose capecitabine in presence of jaundice with dose reduction of 60% (500 mg/m² BD) when bilirubin level was 5–10 mg/dl and of 20% reduction (1000 mg/m² BD) when bilirubin levels were 1–5 mg/dl.

Efficacy: Survival

In patients of unresectable or metastatic CaGB and cholangiocarcinomas, a phase II trial of gemcitabine and capecitabine by Southwest Oncology Group (SOG), the 6-month overall survival was 55% (95% CI: 41–69%) with median survival of 7 months (95% CI: 5–8 months) [33] whereas in a study by Cho et al. in a phase II trial using the same combination of chemotherapy as first-line therapy in patients with advanced and/or metastatic biliary carcinoma, the median time to disease progression and overall survival 6.0 months (range, 3.8–8.1) and 14 months (range 11.4–16.6), respectively [31]. The study by Patt et al. for the first time in patients with unresectable CaGB reported a median survival of 9.9 months (95% CI, 4.4–15.4 months) using single-agent oral capecitabine [24]. During 1-year follow-up in the present study, the

median survival was 3.54 ± 1.33 months (range 1–6 months) with no survivors by the year-end.

There is scarce literature about use of capecitabine in advanced CaGB in presence of jaundice. The studies closest to our work have studied capecitabine alone or in combination in unresectable hepatobiliary cancers (which included gallbladder cancer in inclusion criteria) or isolated unresectable CaGB group. Present study is in disagreement with earlier studies by SOG [33], Cho et al. [31] and Patt et al. [24] as they included patients of heterogeneous group of cancers at varied stages and that too without jaundice. The inferior survival in our study largely resulted due to the presence of jaundice, and advanced CaGB, establishing that these two factors are poor independent prognostic indicators for survival.

Safety

The aim of any chemotherapy in metastatic setting is to allay the symptoms and sustain the effect of any palliative procedure whether minimally invasive or surgical. All anticancer drugs are associated with some form of toxicity and contraindicated in presence of jaundice. A rationale alternative is drainage of bile/normalization followed by administration of

Table 4 Complication of capecitabine administration

	Nausea and vomiting	Abdominal complaints	Rashes	Flu-like symptom and joint pain
Absent	11 (31.4%)	21 (60.0%)	28 (80.0%)	28 (80.0%)
Grade I	24 (68.6%)	5 (14.3%)	5 (14.3%)	3 (8.6%)
Grade II	0 (0.0)	9 (25.7%)	2 (5.7%)	4 (11.4%)

chemotherapy whenever situation demands. This leads to significant delays in administration of chemotherapy leading to dismal outcome in an already bleak scenario.

Patt et al. in his retrospective analysis of patients of hepatocellular cancers, cholangiocarcinomas, and CaGB, treated with oral capecitabine, reported that grade 1 or 2 hand-foot syndrome was the most common side effect (37%), followed by grade 1 or 2 nausea and emesis (19%), fatigue (14%), and grade 3 thrombocytopenia occurring in 8% of these patients [24]. Lately, Joerger et al. concluded that in patients with severe hyperbilirubinemia, initial monotherapy with capecitabine could be considered, followed by the addition of gemcitabine with improving hyperbilirubinemia [34].

In present study, the most common complication during chemotherapy administration was grade 1 nausea and vomiting (68.6%). Forty percent patients had grade 1 or 2 abdominal distension and 20% developed grade 1 or 2 joint pain/flu-like symptoms. Grade 3/4 toxicity was not seen and none of patients had hematological toxicities of any grade. Thus, the authors assume that the patients in present study tolerated the chemotherapy well.

The mildness of the observed toxicity could be attributed to the less aggressive starting dose (500 or 1000 mg/m² depending on bilirubin levels) used for this group of patients. The use of 1000 mg/m² capecitabine has become common in the treatment of patients with other malignancies, such as colorectal carcinoma; first reported by Borner et al. [35] also recommended the use of 1000 mg/m² twice daily when capecitabine is used in combination with oxaliplatin.

Biliary Drainage

CaGB is the most common cause of malignant hilar biliary obstruction. The three methods available for palliation of jaundice include surgical bilio-enteric anastomosis (SB), ERS, and PTBD [36, 37]. Biliary drainage aims to palliate symptoms and complications associated with extrahepatic obstruction [38]. ERS is the primary tool for drainage of distal obstruction whereas PTBD is mostly reserved for cases where block is hilar or proximal [36–39]. For treatment of patients with proximal obstruction, both endoscopic and percutaneous methods are used but the choice would depend on the specific patient circumstances as well as on local availability of resources and expertise.

In our study, 19 patients (54.16%) had jaundice level > 15 mg/dl with mean level of 15.0 ± 6.30 mg/dl. After single-catheter single-system drainage, in 90% of the patients, total bilirubin levels fell to < 10 mg/dl level within 2 weeks with a mean of 2.37 ± 0.8 weeks. In Robson's study [38], median time to achieve serum bilirubin of less than 2 mg/dl was 2.8 weeks when right or left system PTBD was done with or without internalization. Severe pruritus can be debilitating, and rapid relief after biliary decompression has been reported

in literature. Pruritus disappeared or significantly improved within 24–48 h of biliary drainage [37] and rapid relief could be obtained when transhilar metallic/plastic stent was placed [38–40].

In present study, in 28 patients (80%), itching was relieved by 1st week, 4 patients (11.42%) by 2nd week, and one patient by 3rd week of biliary drainage. The fall in bilirubin levels was in tandem with the relief from itching. However, when compared to study by Robson et al. [38], the delay in relief could be attributed to single-system single-catheter drainage without internalization. Studies by Polydorou [17], De Palma [18, 41], and Freeman [42] have endorsed the adequacy of single-system endoscopic drainage with good palliation in up to 80% of patients. A narrative review by Delden et al. [37] observed percutaneous biliary drainage and stenting for palliation of malignant obstructive jaundice to be a safe and effective technique with technical success in > 90% and clinical success > 75% in all major series. Thus, this study establishes the usefulness of single-system drainage for patients of inoperable CaGB with jaundice due to malignant biliary obstruction.

Historically, complications of PTBD include sepsis, hemobilia, bile leak, false passage, stent blockage, and liver abscess with an overall rate of 8–42%, the rate of early complications being 9.7 to 17% [43]. Demonstrating long-term results of PTBD, Born et al. [44] reported catheter dislocation rate up to 30%. The complications in the present study were higher (42.8%) with catheter dislocation reported in 37.14% patients. Higher rate of pullout in our study could be due to use of non-self-retaining catheter and poor catheter care.

Literature supports the low procedure-related mortality than the patient usually falling due to the natural course of the disease. The procedure-related mortality ranged between 0 and 3% and 30-day mortality ranged between 2 and 20% in a series by Delden et al. [37] This study also had similar results with a 30-day mortality (5.7%) including in-hospital mortality though none were procedure-related mortality.

Conclusion

Low-dose capecitabine has an acceptable safety profile in patients with drained biliary system albeit with no significant increase in overall survival in CaGB. Oral capecitabine can prove to be an effective chemotherapy regimen in patients with advanced CaGB with low levels of jaundice, but larger extensive studies are needed to formulate the dosage protocols.

This study shows that single-system, single-catheter drainage is an effective palliation techniques in patients with malignant biliary obstruction in cases of advanced CaGB specially in a resource constraint setting.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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