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Original Research

Comparison of Efficacy and Toxicity of Gemcitabine-Cisplatin Regimen VS Gemcitabine-Capecitabine Regimen as First Line Chemotherapy in Advanced Gallbladder Carcinoma

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Introduction: Gallbladder cancer (GBC) is the commonest malignancy of the biliary tract, and majority of patients with GBC in India has advanced unresectable disease. This study was undertaken to address the efficacy, the toxicity profile and the compliance of the two different gemcitabine-based chemotherapy regimens in advanced unresectable GBC.

Materials and Methods: A prospective randomized study was undertaken to compare the efficacy and toxicity profiles of two gemcitabine-based doublet chemotherapy regimens, gemcitabine-cisplatin and gemcitabine-capecitabine in patients with advanced GBC. All eligible patients were recruited from Dr. B Borooah Cancer Institute, Guwahati from 20.11.2020 – 20.08.2021 and randomly assigned to one of the groups of chemotherapy in 1:1 ratio.

Results: Among 250 patients with locoregionally advanced, inoperable and metastatic GBC registered at Dr B Borooah Cancer Institute, 50 patients fulfilled the criteria and were planned for recruitment for our study. After randomization, 23 patients were allotted among each of the gemcitabine-cisplatin and gemcitabine-capecitabine arms. With the median follow up time of 8 months, the median PFS (progression-free survival) and median OS (overall survival) for the entire cohort was 6 months and 8 months, respectively. Median PFS was marginally higher in the gemcitabine-cisplatin arm, in comparison to gemcitabine-capecitabine arm, but not statistically significant (6.5 months vs. 5.4 months; p = 0.793). Median OS was marginally higher in the gemcitabine-cisplatin arm, in comparison to gemcitabine-capecitabine arm, but was not statistically significant (8.5 months vs. 7.6 months; p = 0.879). The overall response rate (ORR - includes partial response [PR] and complete

responses [CR]) were similar (26%) in both the arms. Non-hematological toxicities were similar with both the regimen. Hematological toxicities were found to be non-significantly higher with gemcitabine-cisplatin as compared to gemcitabine-capecitabine.

Conclusion: Gemcitabine with capecitabine in advanced GBC can alternatively be considered in first line treatment with similar OS, PFS, ORR and with acceptable toxicity profile compared to gemcitabine-cisplatin, thereby avoiding cisplatin-induced long-term toxicities

Introduction

According to Hundal and Shaffer, gallbladder cancer (GBC) represents the most common malignancy of the biliary tract, comprising 80–95% of all biliary tract cancers [1]. Biliary tract cancer is an umbrella term that includes GBC, cholangiocarcinomas, and ampullary cancers, while GBC refers only to cancers of the gallbladder. India has high incidence of GBC and accounts for 10% of the global burden. Within India, highest incidences of GBC cases are seen in North, North-East, Central and Eastern India. The incidence in North India is 10-22/100,000 population, as per Dutta et al.[2] Phadke and co-authors identify Cachar, Delhi, Kamrup, Dibrugarh, Kolkata, and Sikkim as high-risk regions for gallbladder cancer within India [3, 4].

Rakić and co-authors note that gallbladder cancer, a highly malignant tumor, is associated with an overall 5-year survival rate of less than 5% and a mean survival of under six months [5]. Tarver and Kayahara et al. report that gallbladder cancer's 5-year survival rates vary significantly by stage, with 83% for stage I, 70% for stage II, 45% for stage III, 23% for stage IVA, and 9% for stage IVB [6, 7]. Dutta explains that the poor prognosis of gallbladder cancer stems partly from its nonspecific clinical presentation, aggressive biological behavior, and the absence of sensitive screening tests, which often leads to delayed diagnosis at an advanced stage [8]. Surgical resection remains the mainstay therapy for GBC, though only 10% of patients apply to curative treatment at initial presentation.[5] A substantial proportion of patients with GBC in India have advanced unresectable disease with female to male ratio of 3:1 and mean age of patients was 51±11 years.[5] With 90% of patients presenting at an advanced stage, palliative chemotherapy remains the only means of potentially improving their survival rates.[5]

For patients with unresectable tumors, NCCN guidelines prioritize systemic chemotherapy using gemcitabine- or fluoropyrimidine-based regimens, with concurrent fluorouracil (FU)-based chemoradiotherapy as an option for select cases [9].

Gemcitabine-based combination regimens are preferred over gemcitabine monotherapy for most patients with a good performance status and who do not have significant hyperbilirubinemia. Gemcitabine-based combination is preferable over a non-gemcitabine-based regimen for most patients. Commonly used regimens are gemcitabine-based regimens, with cisplatin or oxaliplatin or capecitabine being the second drug. This is based on the landmark ABC-02 and BT-22 trials which compared gemcitabine-cisplatin to gemcitabine, and the trial from All India Institute of Medical Sciences, New Delhi, India, which compared gemcitabine-oxaliplatin combination regimens to 5-fluorouracil and best supportive care [10, 11].

There is a lack of sufficient evidence comparing the efficacy and toxicity of gemcitabine-cisplatin and gemcitabine-capecitabine doublets in the advanced Gallbladder carcinoma. In our study, we aim to address the efficacy, the toxicity profile and the compliance of the two different gemcitabine-based chemotherapy regimens.

A prospective randomised study was undertaken to compare the efficacy and toxicity profiles of two gemcitabine-based doublet chemotherapy regimens, gemcitabine-cisplatin and gemcitabine-capecitabine in patients with advanced Gallbladder carcinoma.

The primary objective is to compare progression-free survival in both chemotherapy arms and the secondary objectives are to compare overall survival in both chemotherapy arms and to compare the toxicity profile and chemotherapy completion rate among the two groups.

Materials and Methods

Patients more than 18 years of age with biopsy/Fine- needle aspiration cytology (FNAC) proven unresectable and locoregionally advanced or metastatic carcinoma gallbladder were included in the study. Patients with serum bilirubin ≥3X upper normal limit (UNL; >1.2 mg/ dL), creatinine clearance <50 ml/min, ECOG ≥ 2, having history of other malignancy were excluded. All eligible patients were recruited from Dr. B Borooah Cancer Institute, Guwahati. Eligible patients were randomly assigned to one of the groups of chemotherapy in 1:1 ratio after taking proper consent. Data recruitment for the study was done between 20/11/20 – 20/08/21 after receiving institutional ethical committee approval. After obtaining informed consent, patients were randomized to one of two palliative chemotherapy arms: Arm A was considered the standard arm, and Arm B was the experimental arm. Arm A consists of injection Gemcitabine given at 1000 mg/m² followed by injection Cisplatin 25mg/m^2 (intravenous in on day 1 and day 8 administered as 3 weekly cycles). In Arm B, patients received injection Gemcitabine given at 1000 mg/m² on day 1 and day 8 along with oral Capecitabine 825 mg/ m² twice daily 30 minutes after food for continuous 14 days followed by a gap period of 7 days, cycles were repeated every 3 weeks. However, in cases of unacceptable chemotherapy-related toxicity, subsequent chemotherapy administration was delayed for one week; if toxicity persisted, a dose reduction of up to 25% of the calculated dose was allowed in both groups. Growth factor support was allowed only for secondary prophylaxis. Treatment-related toxicity was monitored before commencing each cycle according to CTCAE version 5.0. In both the arms, chemotherapy was continued till patient develops progressive disease, unacceptable toxicity or general/laboratory parameters precludes further administration of chemotherapy.

Patients randomized to both the arms underwent response evaluation after 4 cycles of chemotherapy with CECT scan whole abdomen and patients showing response anything other than progressive disease was continued with same chemotherapy. Further response assessment in patients continuing same chemotherapy was done after completion of eight cycles of chemotherapy. In patients with progressive disease, chemotherapy regimen was changed according to choice of treating physician. Cross over was allowed between the arms only after progression of disease. Any overt sign and symptoms of disease progression, if present before usual time of response evaluation will be further investigated with appropriate investigations. Radiological assessment will be according to RECIST 1.1.

A power calculation assuming a 20% difference in PFS (alpha=0.05, power=80%) indicated a need for approximately 100 patients per arm; however, due to recruitment constraints, the study was underpowered, which is acknowledged as a limitation.

The study protocol was duly approved by the Institute Ethics Committee of the Dr. B. Borooah Cancer Institute, Guwahati, India.

Analysis

The results of the study were presented in tabular form. Bar diagram and Pie-Chart were used to describe the descriptive statistics. Chi square test is used to evaluate association between categorical variables. Kaplan-Meier method was used to evaluate overall, progression-free survival rate and log rank test was used to compare the survival among groups. Cox regression was used to evaluate the Hazard ratio. Chi square test was used to find out association between categorical variables. A p value <0.05 was considered as statistically significant at 95% confidence interval.

IBM SPSS Version 21 was used for statistical analysis.

Results

Between November 2020 and August 2021, a total of 250 patients with locoregionally advanced, inoperable and metastatic Gallbladder cancers registered at Dr B Borooah Cancer Institute among which a total of 50 patients fulfilled the criteria and were planned for recruitment for our study. After randomisation, 23 patients were allotted among each of the gemcitabine-cisplatin and gemcitabine- capecitabine arms (Figure 1).

Figure 1. Consort Diagram.

Median age of entire cohort was 50 years. Thirty-four patients (74%) were female patients and 26% (n=12) were males, with female: male ratio of 2.8:1. Eight patients (17%) had comorbidities. Ten (22%) participants were overweight and two (4%) patients were obese in the entire cohort. Most common presenting symptom was pain abdomen, seen in 42 patients (92%), followed by nausea and vomiting in 18 patients (41%), and post-prandial fullness of abdomen in six (13%) patients.

Four patients defaulted before randomization due to loss in follow-ups. See Figure 1 for the CONSORT diagram. Due to COVID 19, it is suspected that these patients did not continue with the follow-ups.

Median duration from symptom onset to time of presentation was three months and from diagnosis to treatment initiation was 2.4 weeks in the entire cohort. All the patients in this study were treated with palliative intent in the intention-to-treat analysis. Compliance was analyzed on an intention-to-treat basis.

Distribution of baseline characteristics among the treatment arms were comparable (Table 1).

		Gemcitabine-cisplatin arm (n=23)	Gemcitabine-capecitabine arm (n=23)
Characteristics			
Median Age (Years)		48 (SD ± 8.2)	54 (SD ± 8.5)
Male: Female		01:04.7	01:01.9
Median BMI (Kg/m^2)		23 (SD ± 3.2)	22 (SD ± 3.8)
Presence of co-morbidity		4 (17%)	4 (17%)
History of prior Cholecystectomy		3 (13%)	2 (9%)
Tumour	AJCC Stage		
Characteristics			
T-Stage	T0	2 (9%)	2 (9%)
	T3	8 (35%)	6 (26%)
	T4	13 (56%)	15 (65%)
N-Stage	N0	1 (4%)	1 (4%)
	N1	8 (35%)	7 (30%)
	N2	14 (61%)	15 (62%)
M-Stage	M1	16 (70%)	18 (79%)
Baseline Transaminases Level	Normal	19 (82%)	18 (78%)
	> UNL (1.2 mg/dL)	4 (18%)	5 (22%)
Baseline Total Bilirubin (mg/dl)>UNL		7 (30%)	5 (21%)

Baseline Ca 19.9 (U/ml)>UNL		15 (65%)	15 (65%)
Baseline Anemia (Hb< 11 gm/dL)		5 (21%)	5 (21%)

Table 1. Baseline Characteristics between the Treatment Arms.

Among male patients, four patients (33%) received chemotherapy regimen of gemcitabine-cisplatin and eight patients (64%) received gemcitabine-capecitabine regimen. Among female patients, 19 patients (55.8%) received gemcitabine- cisplatin chemotherapy and 15 patients (44.2%) received gemcitabine-capecitabine regimen.

Treatment outcomes and Survival parameters

With the median follow up time of 8 months, the median PFS and median OS for the entire cohort was 6 months and 8 months, respectively.

Median PFS was 6.5 months (95% CI: 4.8-8.1) in the gemcitabine-cisplatin arm vs. 5.4 months (95% CI: 3.9-8.4) in the gemcitabine-capecitabine arm (p=0.793) (Figure: 2).

Figure 2. Kaplan-Meier Survival Curves for the Two Arms.

Median OS was higher in the gemcitabine-cisplatin arm, in comparison to gemcitabine-capecitabine arm, but was not statistically significant (p = 0.879). Median OS was 8.5 months (95% CI: 7.0-9.3) in the gemcitabine- cisplatin arm vs. 7.6 months (95% CI: 4.9-9.8) in the gemcitabine-capecitabine arm (Figure 3, Table 2).

Figure 3. Kaplan Meier Survival Curves for the Two Arms (Overall survival).

Medians for Survival Time (months)		
	Progression Free Survival (PFS)	
Gemcitabine-Cisplatin	6.5	p = 0.793
Gemcitabine-Capecitabine	5.4	
Overall	6	
	Overall Survival (OS)	
Gemcitabine-Cisplatin	8.5	p = 0.879
Gemcitabine-Capecitabine	7.6	
Overall	8	

Table 2. Table Showing Medians for Survival Time Amongst the Two Arms.

On subgroup analysis of baseline characteristics including gender, age, ECOG Performance status, baseline bilirubin level, baseline CA 19-9 value, number of metastatic sites, presence of liver or peritoneal metastases showed no statistically significant differences amongst the two arms for PFS and OS (Table 3).

Univariate Analysis	p-value	HR	95%CI for HR	
			Lower	Upper
	Progression Free Survival (PFS)			

Gender				
Female	0.456	1.349	0.614	2.963
Male	0.066	0.265	0.064	1.091
Age				
<60years	0.637	1.197	0.566	2.533
≥60years	0.681	1.607	0.168	15.373
Extent of disease				
Locoregionally advanced	0.33	0.416	0.071	2.426
Metastatic	0.409	1.39	0.636	3.039
CA 19-9				
Normal	0.296	0.477	0.119	1.915
Elevated	0.102	2.067	0.866	4.929
ECOG performance status				
ECOG 0	0.103	0.247	0.046	1.329
ECOG 1	0.093	2.062	0.887	4.793
Bilirubin level				
Normal	0.902	1.057	0.438	2.552
Elevated	0.949	0.966	0.336	2.781
Liver metastases				
Present	0.61	0.783	0.305	2.007
Absent	0.921	0.954	0.374	2.435
	Overall Survival (OS)			
Gender				
Female	0.515	1.308	0.583	2.937
Male	0.677	0.754	0.199	2.848
Age				
<60years	0.846	1.077	0.51	2.276
≥60years	0.475	2.244	0.244	20.656
Extent of disease				
Locoregionally advanced	0.484	0.535	0.093	3.083
Metastatic	0.554	1.261	0.586	2.715
CA 19-9				
Normal	0.118	0.268	0.052	1.394
Elevated	0.088	2.166	0.892	5.256
ECOG performance status				
ECOG 0	0.211	0.342	0.064	1.837
ECOG 1	0.247	1.613	0.718	3.625
Bilirubin level				
Normal	0.807	1.117	0.46	2.714
Elevated	0.788	1.163	0.387	3.501
Liver metastases				
Normal	0.344	0.607	0.216	1.707
Elevated	0.456	0.674	0.239	1.903

Table 3. Subgroup Analysis, PFS and OS Comparison of Baseline Characteristics between Two Arms (Note: Subgroup analyses are exploratory and unadjusted for multiple comparisons to minimize type I error risk.).

After 4 cycles, ORR (includes partial response [PR] and complete responses [CR]) were similar (26%) in both the arms. Complete responses were not seen in either of the two arms. Stable disease (SD) was comparable among the two arms. Progressive disease (PD) was documented among 10

patients (44%) in gemcitabine-cisplatin arm as compared to 12 patients (52%) in gemcitabine-capecitabine arm (Table 4).

Response	Gemcitabine-cisplatin (%)	Gemcitabine-capecitabine (%)
Rates		
PR	6 (26)	6 (26)
SD	7 (30)	5 (22)
PD	10 (44)	12 (52)

Table 4. Comparison of Response Rates after Four Cycles of Chemotherapy among the Two Arms.

Compliance to chemotherapy was found to be similar amongst both the treatment arms after 4 cycles. Twenty-two patients (n=22/23; 96%) in gemcitabine- cisplatin arm completed planned four cycles of initial chemotherapy, compared to 19 (83%) patients in the gemcitabine-capecitabine arm. In gemcitabine-cisplatin arm, five patients (n=5/22) completed total eight cycles of chemotherapy, as compared to only two patients (n=2/19) in the gemcitabine-capecitabine arm.

In the gemcitabine-cisplatin arm, the major causes of treatment abandonment were symptomatic progression of the disease seen in ten patients (n=10/17; 59%). In addition, seven patients did not complete all eight cycles of chemotherapy due to logistical issues. In the gemcitabine-capecitabine arm, twelve patients (70%) had symptomatic progression of the disease, while five patients did not complete all eight cycles of chemotherapy due the logistical and financial issues. Median numbers of chemotherapy cycles in gemcitabine-capecitabine and gemcitabine-cisplatin arms were six (IQR: 4-7) and four (IQR: 3-6), respectively.

Distribution of Toxicities among the two Arms [Table 5]:

Hematological toxicities were found to be similar among both arms (Table 5).

	Chemotherapy Regimen	
	Gemcitabine-Cisplatin (n=23) [N%]	Gemcitabine-Capecitabine (n=23) [N%]
Hematological Toxicities		
Grade 1-2	12 (52)	12 (52)
Grade 3-4	8 (34)	6 (26)
Febrile neutropenia	1 (4.3)	2 (8.7)
All grade neutropenia	4 (17.4)	4 (17.4)
Grade 1-2	2 (8.7)	3 (13)
Grade 3-4	2 (8.7)	1 (4.3)
All grade thrombocytopenia	3 (13)	2 (8)
Grade 1-2	3 (13)	2 (8)
Grade3-4	0	0
All grade anemia	15 (65)	14 (60)
Grade 1-2	9 (40)	9 (40)
Grade 3-4	6 (26)	5(21)
Non-hematological Toxicities		
Mucositis (all grades):	2 (8.7)	3 (13)
Grade 1-2	2 (8.7)	1 (4.3)
Grade 3-4	0	2 (8.7)
Diarrhea (all grades):	6 (26)	9 (40)
Grade 1-2	4 (26)	6 (26)
Grade 3-4	2 (8.7)	3 (13)
Hand foot syndrome (all grades):	0	9 (40)

Grade 1-2	0	7 (30)
Grade 3-4	0	2 (8)
Nausea & vomiting (all grades):	5 (21)	5 (21)
Grade 1-2	3 (13)	5 (21)
Grade 3-4	2 (8.7)	0
Renal dysfunction (all grades):	3 (13)	0
Grade 1-2	2 (8.7)	0
Grade 3-4	1 (4.3)	0

Table 5. Toxicities among the Two Arms.

Grade 3 hematological toxicity was seen in 8 (34%) and 6 (26%) patients in gemcitabine-cisplatin and gemcitabine-capecitabine arms, respectively (Table 5). No deaths due to hematological toxicities were reported in either of the two arms. Most of these toxicities were manageable on outpatient basis with transfusion of blood and blood products, oral antibiotics and growth factor support. Treatment interruptions due to hematological toxicity were less than a week in most of the cases (in both the arms). In patients with grade 3 toxicities, 8 out of 9 (89%) times treatment was postponed for less than a week (average of six days).

Combined Grade 3-4 non-hematological toxicities were similar with both the regimen. Grade 3-4 toxicities were seen in 5 (21%) patients with gemcitabine-cisplatin as compared to 7 (30%) patients with gemcitabine- capecitabine (Table 5).

Combined Grade 1-2 toxicities were similar in both the arm (occurred in 8 patients (34%) and 12 patients (52%) in gemcitabine-cisplatin and gemcitabine-capecitabine arms respectively).

Grade 3-4 diarrhea occurred in 2 (8.7%) patients in gemcitabine-cisplatin arm as compared to 3 (13%) patients in gemcitabine-capecitabine arm.No deaths related to non-hematological toxicity of chemotherapy was seen in either of the arms.

No crossover occurred in the study. Future analyses could include patient-reported outcomes or cost- effectiveness to emphasize capecitabine’s oral convenience.

Discussion

Certain regions in India, like the Indo-Gangetic belt, have got the highest incidences of biliary tract cancers world-wide. GBC is one of the three leading cancers among women of North and North-east India [2]. Currently multiple gemcitabine-based regimens are used for the treatment of advanced Gallbladder cancer, but direct prospective randomised trials are lacking. Commonly used drugs are single agent use of gemcitabine, single agent 5-FU [12]. Less commonly used drugs are combination of gemcitabine with capecitabine or, platinum combination regimens. The differential safety profile and methods of administration of cisplatin and capecitabine has led to different centres using these drugs preferentially in combination with gemcitabine as first line chemotherapy for the treatment of advanced GBC [13-15]. While cisplatin is associated with a higher incidence of myelosuppression, emetic potential, renal toxicity, and the need for adequate hydration during administration, liver function abnormalities, fatigue, diarrhea, hand foot syndrome and hematologic toxicity may lead to debilitating changes affecting quality of life and compliance with chemotherapy [15]. Lack of prospective randomised comparison studies with gemcitabine with capecitabine and gemcitabine with cisplatin Gallbladder cancer, lays the groundwork for our study.

In our study, median age of entire cohort was 50 years. Females population comprises seventy-four percent, with female: male ratio of 2.8: 1.The mean age of presentation of GBC in the Indian subcontinent is younger than their counterparts in the USA and western European countries. [1, 2,

16] The median age of presentation was 67 years in a Memorial Sloan−Kettering report of 435 gallbladder cancer patients, and 52 years in a study reported from New Delhi, India [17, 18]. The lower median age of diagnosis may be due to the age structure of the Indian population and referral bias [11, 17, 19, 18]. Women are affected two to six times more often than men.[22] Epidemiological studies from India and western countries similar showed female to male ratios [20, 21].

Obesity is one of the risk factors for Gallbladder cancers and carries a relative risk of 1.8 - 2 as compared to non-obese population [22]. Ten (22%) participants were overweight and two (4%) patients were obese in the entire cohort. This was lower than reported from Indian studies (41%) by A.P Dubey et.al [20].

Thirty-four patients (74%) patients had metastatic disease at presentation and the rest 12 patients (26%) were locally advanced and unresectable. A history of cholecystectomy for gallstones was found in 5 (10%) of the entire cohort. Patients with comorbidities were very few in this study (only 9%). Most common presenting symptom was pain abdomen in 42 patients (92%), followed by nausea and vomiting in 18 patients (41%), and post-prandial fullness of abdomen in 6 (13%) patients comparable with Indian studies of clinical presentation of GBC [2]. Various other studies relating to GBC, viz. Muhammad A et al. and Zhang BH et al. had shown similar symptomatology at presentation [23, 24].

Median duration from symptom onset to presentation was 3 months and from diagnosis to starting treatment was 2.4 weeks in entire cohort.

After a median follow up time of 8 months, the median PFS and OS for the entire cohort was 6 and 8 months.

respectively. Median PFS was higher in the gemcitabine- cisplatin arm, in comparison to gemcitabine-capecitabine arm (6.5 months versus 5.4 months; p = 0.793), but not statistically significant. Median OS was also higher in the gemcitabine-cisplatin arm, in comparison to gemcitabine- capecitabine group, but was not found to be statistically significant (8.5 months versus 7.6 months; p = 0.879). This is comparable with overall survival of 7 months reported in trial by Iqbal et al [14]. However, a large series by Knox et al, reported median overall survival time of 14 months. [8]. The seemingly inferior response rates and OS in our study as compared with ABC-02 trial could possibly be due to various factors. It is very likely that the disease biology is different in Indian patients in metastatic setting as shown in this study with inferior response rates and outcome [25]. Riechelmann and colleagues at Princess Margaret in Canada report on a total of 75 patients treated with gemcitabine and capecitabine for advanced biliary cancer, detailing a response rate of 29% and an overall survival of 12.7 months [26]. A second study performed in South Korea with a total of 44 patients had a response rate of 32% and median overall survival of 14 months [9].

Another trial from Roswell Park accrued a total of 12 patients over 2 years with a response rate of 16% (the lowest response rate reported of the three studies [27].

Other trials with gemcitabine-containing regimens have also been conducted, including combinations with docetaxel, oxaliplatin, cisplatin and carboplatin [28, 29]. In our study, ORR was similar in gemcitabine-cisplatin as compared to gemcitabine-capecitabine group (26% in each arm; p = 0.68). Knox et al reported 27% ORR in GBC [8]. Gemcitabine with oxaliplatin was reported by GERCOR, with the combination reporting a response rate of 33% and a median overall survival of 8.3 months. Other platinum containing regimens report 20 to 24% response rates and similar median overall survivals [30 , 31] Valle and colleagues reported a randomized phase II with 314 patients with advanced biliary cancer randomized to gemcitabine/cisplatin vs. gemcitabine alone. The median overall survival was greater with the combination of gemcitabine/cisplatin than the single agent, 11.7 vs. 8.2 months (p=0.002), as was progression-free survival 8.5 vs. 6.5 months,

(p=0.003) [10].

Subgroup analysis of baseline characteristics including gender, age, ECOG Performance status, baseline bilirubin levels, baseline CA 19-9 value, number of metastatic sites, presence of liver or peritoneal metastases showed no statistically significant differences among the two arms for progression-free survival and overall survival.

Compliance to chemotherapy was found to be similar in gemcitabine-capecitabine group as compared to gemcitabine-cisplatin group. Ninety-six per cent patients in gemcitabine-cisplatin group and 83% patients in gemcitabine-capecitabine group completed planned four cycles of initial chemotherapy before interim response assessment. The reason for discontinuation of treatment in most patients in both the group was due to clinical progression of their disease. Four patients discontinued treatment because of financial problems and one patient due to COVID-19 related restrictions.

Only eight patients received second-line chemotherapy after their disease progression in the entire cohort. The benefit of second line chemotherapy, even in a well-selected population, has not been validated yet. However, few studies have yet been conducted concerning salvage or second-line therapy after gemcitabine failure in advanced biliary tract cancer and there are no comparative randomised trials comparing chemotherapy to best supportive care after progression on gemcitabine.[32,33] Majority of the patients had poor performance status for continuation of further anticancer treatment and opted for best supportive care.

Hematological toxicities were found to be non- significantly higher with gemcitabine-cisplatin as compared to gemcitabine-capecitabine. Grade 3 hematological toxicity was seen in 14% and 7% patients in gemcitabine-cisplatin and gemcitabine-capecitabine groups, respectively. However, deaths due to hematological toxicities were not seen in either of the two groups. Treatment interruptions due to toxicity were less than a week in most of the instances. Treatment interruptions due to grade 3 hematological toxicities were less than seven days in most patients (89%). The findings are consistent with what has been reported with gemcitabine with cisplatin and gemcitabine-capecitabine [15, 34, 35]. Most common grade 3/4 non-hematological toxicities are nausea, vomiting and diarrhea in gemcitabine-cisplatin arm. Hand foot syndrome and diarrhea were the common adverse events noted in the gemcitabine-capecitabine arm. Fatigue was also more commonly reported among some trials [14]. Ramaswamy et al in a comparative study between gemcitabine-cisplatin (GC) versus gemcitabine-oxaliplatin (GO) reported the degree of anemia to be significantly higher with GC when compared to GO (22.1% vs. 6.7%; p <0.001).[15] Besides a direct myelosuppressive effect, cisplatin-based therapy results in a cumulative anemia that is disproportionate to the effects on other blood cells with the severity correlating with the degree of cisplatin induced renal tubular dysfunction.[36] Recent advancements, such as the TOPAZ-1 trial incorporating durvalumab with gemcitabine-cisplatin (median OS 12.8 months) [37], highlight immunotherapy’s role and contextualize our findings in resource-limited settings.

Strength of the Study

Due to low incidence of Gallbladder cancer, prospective randomized studies on Gallbladder cancer in worldwide literature are limited. To our knowledge, this study is one of the few prospective study conducted on advanced Gallbladder cancer, which gives a detailed and meaningful insight on treatment and survival of this rare disease.

Limitations of the Study

This study has limitations due to its small sample size and it being a single institutional study. A well conducted multi-institutional study with a large sample size is needed, which can provide more

information into the disease biology among Indian population and for optimisation of interventions to improve the survival and quality of life in advanced and unresectable carcinoma of Gallbladder. The single-center design and overlap with the COVID-19 pandemic (2020-2021) may have biased compliance due to logistical restrictions and patient access issues.

In conclusion, although gallbladder cancer is a rare malignancy worldwide, the incidence of GBC in Northern and North-eastern part of India is high. Most GBC cases are diagnosed at an advanced stage. Systemic therapy in the form of chemotherapy plays important role in this subset of patients. The studies on advanced gallbladder cancer are limited. There is lack of clear consensus on various treatment protocols to be used in advanced gallbladder cancer. Our study is one of the few prospective trials in advanced gallbladder cancer comparing two different gemcitabine-based chemotherapy protocols.

Gemcitabine-cisplatin or gemcitabine-capecitabine can be used as an initial regimen in advanced GBC. Gemcitabine with capecitabine in advanced Gallbladder cancer can be considered in first line treatment of advanced GBC with similar OS, PFS, ORR and with acceptable toxicity profile compared to gemcitabine-cisplatin, thereby avoiding cisplatin-induced long-term toxicities. While non-significant differences do not confirm statistical equivalence, gemcitabine-capecitabine may be considered a reasonable alternative.

Further large prospective studies as well as non-inferiority trials are needed to validate the findings of our study. Future studies should involve multi-center collaboration for larger samples and include molecular profiling (e.g., FGFR/IDH mutations) to address GBC heterogeneity.

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Conflicts of Interest

The authors declare no conflict of interest.

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