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Gemcitabine and Carboplatin in Inoperable, Loco-Regionally Advanced and Metastatic Gallbladder Cancer- A Study from Northern Indian Cancer Institute

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Authors' contributions

This work was carried out in collaboration between all authors. Author VT designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author DCD managed the analyses of the study. Authors VG and SR managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The primary objective of this study was to determine the response rates of the gemcitabine and carboplatin combination chemotherapy in treatment naïve patients with inoperable gall bladder cancer. The secondary objectives were to evaluate the toxicity, progression free survival (PFS), and overall survival (OS).
Methodology: Treatment naïve patients with histologically proven inoperable gall bladder cancer treated with gemcitabine and carboplatin chemotherapy between February 2011 and December 2014 were included in this study. The dose of gemcitabine was 1 gm/m^2 on day 1 and 8, and carboplatin [target AUC (area under the concentration versus time curve in mg/ml) of 5] on day 1, in a 21 day cycle. CT scan was used for response assessment.

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Results: There were 32 men and 92 women with a median age of 59 years (range 26-75 years). Of the 124 patients, 9 (7.3%) patients achieved a complete response and 54 (43.5%) patients achieved a partial response for an overall response rate of 50.8%. The median PFS was 4.6 months [95% confidence interval (CI) 4–5.5 months], with 1-year survival rate of 20.2%. Common toxicity criteria (CTC) grade 3 anaemia was seen in 6 (4.8%) patients. Grade 3 and 4 neutropenia was observed in 11 (8.9%) and 4 (3.2%) patients respectively, whereas 9 (7.3%) patients experienced Grade 3 thrombocytopenia.
Conclusion: The combination of gemcitabine and carboplatin is active in advanced gall bladder carcinoma with mild toxicity.

Keywords: GBC; PFS; OS; GCSF.

1. INTRODUCTION

Worldwide, gallbladder cancer (GBC) is the most common malignant tumor of the biliary tract apart from being the sixth most common gastrointestinal cancer [1]. Although, GBC is one of the rare cancers in many parts of the world with an annual incidence rate of 2.2 per 100,000 population, it is more prevalent in several regions of East Asia and Latin America. In India, GBC is more prevalent in northern and northeastern states of Uttar Pradesh, Bihar, Orissa, West Bengal and Assam with southern regions having a 10 times lower incidence as compared to northern region [2,3]. Also female to male ratio of GBC in India is 2:1 as compared to 3:1 in the western world [3,4]. The peak age-specific incidence rate is generally seen in the seventh and eighth decade in either sex.

Majority of the patients with GBC have advanced unresectable disease at the time of presentation due to the lack of characteristic early signs and symptoms. Over two-thirds of the patients are diagnosed either during surgery or postoperatively due to a non-specific clinical presentation [5-9]. Patients of advanced GBC has dismal prognosis with OS of less than 1 year and 5-year survival of less than 5% [10,11]. Early surgical resection remains the best approach for improving the overall long term survival of GBC patients. As majority of the patients present with advanced, inoperable disease, clinicians have to depend on palliative chemotherapy for the management of disease [12].

Before, gemcitabine and platinum based chemotherapy regimens have shown good response rate and survival benefit in advanced GBC and systemic chemotherapy with agents like 5-FU, leucovorin, mitomycin, cisplatin, adriamycin and capecitabine have been extensively studied in various trials. Gemcitabine (difluorodeoxycytidine), an analog of cytosine arabinoside is a pyrimidine antimetabolite that has the potential to be synergistic with cisplatin by virtue of its mechanism of action [13]. An impressive response rate of 36-48% and median OS of 4.7-7 months has been reported with gemcitabine and cisplatin combination chemotherapy in advanced GBC [14,15]. The results of ABC-02 study from the UK and BT22 study from Japan has established gemcitabine and cisplatin combination chemotherapy as a standard of care in the management of advanced unresectable GBC [16,17]. A pooled analysis comprising of 104 trials and 2810 patients have suggested that gemcitabine and platinum combinations may improve survival in GBC as compared to other regimens [18]. This analysis did not address the superiority of one platinum salt over other in GBC and till date no clinical trial have undertaken a direct comparison of different platinum salts.

Carboplatin is an analog of cisplatin and when administered alone or in combination therapy has shown lower nephro and neurotoxicity as compared to cisplatin [19]. Further, carboplatin offers the possibility of ambulatory administration and this could be a great treatment advantage in low resource countries. Based on these facts, we undertook a retrospective study of gemcitabine and carboplatin combination chemotherapy in treatment naïve patients with inoperable GBC. The primary objective of this study was to determine the response rates of the gemcitabine and carboplatin combination chemotherapy and the secondary objectives were to evaluate the toxicity, PFS and OS.

2. METHODOLOGY

2.1 Study Population

Treatment naïve patients with histologically proven inoperable gall bladder cancer treated with gemcitabine and carboplatin chemotherapy

between February 2011 and December 2014 were included in this study. Patients were required to have a bi-dimensionally measurable disease with an age > 18 years. Patients who had received prior radiotherapy were eligible, provided that the irradiated area was not the only source of measurable disease and a minimum of 3 weeks had elapsed between the completion of radiotherapy and enrolment into the study. All the patients included in this study had a very poor performance status and were not fit for treatment with cisplatin. Complete blood count and clinical assessment of nonhaematologic toxicities were carried out at baseline, first and third week of a 21 day cycle. CT scan of the abdomen was done for response assessment at baseline, 3rd and 6th cycle and thereafter every 6 months or earlier as per the clinical judgement. The study was conducted according to the ethical principles stated in the latest version of Helsinki Declaration, and the applicable guidelines for good clinical practice (GCP).

2.2 Treatment

Patients received 1 gm/m^2 of gemcitabine on days 1 and 8 and carboplatin (target AUC of 5) on day 1, in a 21 day cycle. Patients were supported with Granulocyte colony stimulating factor (GCSF) in order to reduce the myelosuppression and enhancing the tolerability. Treatment was continued every three weeks until disease progression or patient's withdrawal from the study. CT scan was used for response assessment. A complete response (CR) was defined as the disappearance of all known disease and a partial response (PR) was defined as at least a 50% decrease in measurable disease with no evidence of any new lesions or progression of any existing lesions. An inability to demonstrate a 50% decrease in tumour size or a 25% increase in the size of one or more lesions, as well as no new lesions was defined as stable disease (SD). A 25% increase in the size of one or more measurable lesions, or the appearance of any new lesions was defined as progressive disease (PD).

2.3 Efficacy and Safety Assessment

All patients who received at least one dose of the study drug were included in the efficacy and safety assessment. Response rate was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0). Survival was calculated from the start of chemotherapy until death or last follow-up using the Kaplan-Meier method.

2.4 Statistical Analysis

The primary endpoint of this study was response rate. The width of the resultant confidence intervals (CI) for parameters to be estimated was constructed with a significance level of 0.05, i.e., a 95% CI. OS and PFS were analyzed with the use of Kaplan-Meier survival analysis and estimates were provided with 95% confidence intervals. Statistical analysis was performed using SAS 8.02 (SAS Institute Inc.). Statistical analysis was done based on intention to treat (ITT) principle. The ITT population included all the patients who have been determined to be eligible for study participation based on eligibility and exclusion criteria. This was a non randomized study and all the patients received at least one dose of chemotherapy.

3. RESULTS

A total of 124 patients were included in this study between February 2011 and December 2014. There were 32 men and 92 women with a median age of 59 years (range 26-75 years). Main baseline patient characteristics are enumerated in Table 1. The median number of chemotherapy cycles administered were 3 (range 1-6). Of the 124 patients, 9 (7.3%) patients achieved a complete response and 54 (43.5%) patients achieved a partial response for an overall response rate of 50.8%. 8 (6.5%) patients achieved stable disease, 25 (20.2%) patients achieved disease progression whereas response could not be ascertained in 28 (22.6%) patients. The median PFS was 4.6 months [95% confidence interval (CI) 4–5.5 months; Fig. 1]. At a median follow-up of 6 months (range 0.3-43.5 months), the median OS was 5.9 months [95% CI; 5.1-7.8 months; Fig. 2], with 1 and 2 year survival rate of 20.2% and 7.3% respectively. CTC grade 3 anaemia was seen in 6 (4.8%) patients. Grade 3 and 4 neutropenia was observed in 11 (8.9%) and 4 (3.2%) patients respectively whereas 9 (7.3%) patients experienced Grade 3 thrombocytopenia (Table 2). All grade toxicities are also included in Table 2.

4. DISCUSSION

Gemcitabine in combination with different platinum compounds have shown an impressive response rates in GBC. Various phase 2 studies

evaluating the efficacy of gemcitabine and cisplatin combination chemotherapy in patients with advanced GBC and biliary tract cancer reports the response rate and median OS in the range of 21-35% and 8.4-11 months respectively [20,21]. Studies evaluating the efficacy of gemcitabine and oxaliplatin combination chemotherapy in patients with advanced GBC and biliary tract cancer reports response rate ranging between 22-50% and median OS ranging between 7.6-14 months [22,23]. To date, there is only one phase 3 trial from India that compared the combination of gemcitabine plus oxaliplatin (GemOx) to flurouracil plus folinic acid (FUFA) and to best supportive care. The study showed significantly longer (9.5 months) OS in GemOx group as compared to best supportive care (4.5 months) group. The response rate in GemOx group was 30.8% as compared to 0 and 14.3% in the best supportive care and FUFA group [24]. Studies evaluating the efficacy of gemcitabine and capecitabine combination chemotherapy in patients with advanced GBC and biliary tract cancer reports a response rate of 17-32% and median OS of 12.7-14 months [25,26].

Table 1. Baseline patient characteristics

Enrolled	124
Evaluable for response	124
Evaluable for toxicity	124
Gender, n (%)	
Male	32 (26)
Female	92 (74)
Age (years)	
Median	59
Range	26-75
Performance Status, n (%)	
2	112 (90.3)
3	12 (9.7)
Histopathology Grade, n (%)	
Well differentiated	3 (2.4)
Moderately differentiated	25 (20.2)
Poorly differentiated	22 (17.7)
Unknown	74 (59.7)
Prior radiation, n (%)	5 (4)

Carboplatin, an analog of cisplatin have shown lower non-haematological toxicity such as nausea, vomiting, nephropathy and neuropathy when administered alone or in combination therapy as compared to cisplatin [19]. Gemcitabine and carboplatin combination chemotherapy have been successfully assessed in various phase 3 trials involving lung and bladder cancer [27,28]. With a response rate of 50.8% and median PFS of 4.6 months, our study confirms the advantage of gemcitabine and carboplatin combination chemotherapy in advanced GBC. The response rate in our study is higher than the one reported in the previous studies involving different platinum compounds along with gemcitabine. The GBC subset of the famous phase 3 ABC-02 trial from UK had 76 patients on gemcitabine arm and 73 patients on gemcitabine plus cisplatin arm with a response rate of 37.7% in gemcitabine plus cisplatin arm as compared to 21.4% in the gemcitabine arm [16]. The addition of cisplatin to gemcitabine significantly improved OS (11.7 vs. 8.1 months; $p<0.001$) as well as median progression-free survival (8 vs. 5 months; $p<0.001$) establishing this combination as the standard of care for advanced inoperable GBC. Another similar study from Japan BT22 investigated the same treatment regimens with 42 patients on gemcitabine arm and 41 patients on gemcitabine plus cisplatin arm [17]. The study reports a response rate of 19.5% in gemcitabine plus cisplatin arm as compared to 11.9% in the gemcitabine arm. The median survival time (11.2 months vs 7.7 months) and median progression free survival (5.8 months vs 3.7 months) were better in gemcitabine plus cisplatin arm though the same was not statistically significant. With a total of 124 patients, our study had more number of patients on gemcitabine plus carboplatin combination chemotherapy as compared to the GBC subset of gemcitabine plus cisplatin arm of ABC-02 (73 patients) and BT22 (41 patients) trials. The only phase 2 trial on gemcitabine and carboplatin combination chemotherapy in GBC from India, reported a response rate of 37% and median OS of 11 months [29]. Similarly, Williams et al reported a median OS of 10.6 months (95% CI, 8.8 to 14.2) with gemcitabine and carboplatin combination chemotherapy in 48 patients of biliary tract cancers [30]. The response rate of 50.8% achieved in our study is way higher than the one reported in all previous trials involving different platinum compounds along with gemcitabine.

The median PFS of 4.6 months in our study is comparable to 5.8 reported in BT22 trial and 5.4 months reported in a study by Talwar V et al. [31] but is lower to the 8 months reported in ABC-02 trial. The median OS of 5.9 months reported in our study is very much lower to 11 and 10.6 months reported in other two studies of gemcitabine and carboplatin combination chemotherapy in GBC and biliary tract cancer respectively.

Table 2. CTC all grade toxicities

Toxicity	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Anaemia	9 (7.3%)	8 (6.5%)	6 (4.8%)	-
Neutropenia	24 (19.4%)	14 (11.3%)	11 (8.9%)	4 (3.2%)
Thrombocytopenia	17 (13.7%)	13 (10.5%)	9 (7.3%)	-
Nausea	-	24 (19.4%)	-	-
Vomiting	14 (11.3%)	10 (8.1%)	-	-
Diarrhea	10 (8.1%)	6 (4.8%)	-	-

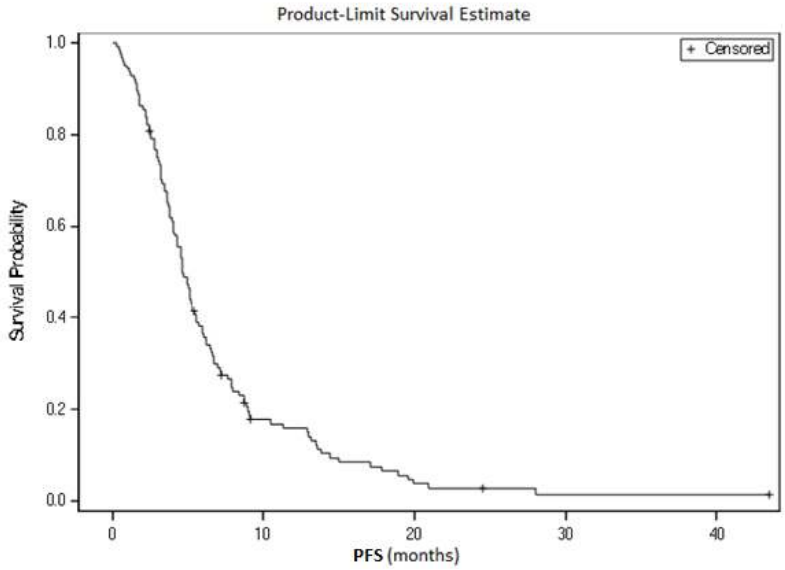

Fig. 1. Kaplan Meier survival analysis for progression free survival

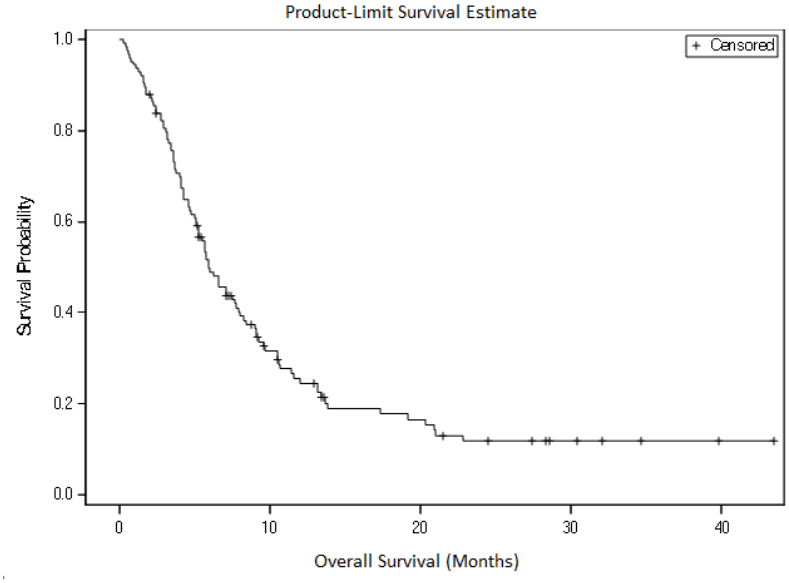

Fig. 2. Kaplan Meier curve for overall survival

The gemcitabine plus cisplatin arm of ABC-02 trial reported grade 3 or 4 toxicities in 70.7% patients with decreased neutrophil counts, abnormal liver function, fatigue and infection

being the most frequently reported adverse events. The most common grade 3 or 4 toxicities in the gemcitabine plus cisplatin arm of BT22 trial were neutropenia (56.1%), thrombocytopenia (39%), leucopenia (29.3%) and ɣ-glutamyltransferase (29.3%). Similarly, grade 3 or 4 toxicities observed in GemOx group of the only phase 3 trial from India were vomiting, myelosuppression, neurotoxicity and transaminitis in 7.7%, 38.5%, 11% and 15% patients respectively [24]. The 24.2% of grade 3 or 4 toxicities reported in our study is lower to the one reported in all previous studies.

5. CONCLUSION

The encouraging results of gemcitabine and carboplatin combination chemotherapy in the present study suggest the potential role of this combination in the management of advanced inoperable GBC. Mild toxicity observed in our study as well as the ease of ambulatory administration especially in low resource countries establishes the advantage of gemcitabine and carboplatin combination chemotherapy over other chemotherapeutic regimens. In conclusion, our study suggests the relevance of treating patients having advanced inoperable GBC with gemcitabine and carboplatin combination chemotherapy, as an alternative of gemcitabine and cisplatin regimen in patients that are not fit for treatment with cisplatin. Prospective studies using this regimen in GBC patients with poor performance status seems warranted.

6. LIMITATIONS OF STUDY

Some of the limitations of the present study are its retrospective nature, poor patient compliance and lost to follow-up resulting in shorter overall survival.

CONSENT

Being a retrospective study, consent form waiver was obtained from the institutional ethics committee and the study data was collected in a de-identified fashion from the available medical records and charts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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