

Efficacy and Safety of FOLFOX as a Second-Line Chemotherapy for Patients with Locally Advanced and/or Metastatic Carcinoma Gall Bladder – Experience from a Tertiary Care Center in India

Abstract

Background: Carcinoma gallbladder is mostly diagnosed in locally advanced, inoperable, or metastatic stage. Best supportive care with or without palliative chemotherapy is the only feasible treatment option. Gemcitabine and platinum agents' combination is the most effective first option with no well-established second-line regimen. **Objectives:** We planned to study the response rate, safety, the progression-free survival (PFS), and overall survival (OS) on the second-line FOLFOX-4 chemotherapy. **Methods:** This is a prospective single-arm observational study of 29 eligible patients. Patients were studied for response to the second-line FOLFOX-4 chemotherapy. Positron emission tomography/computed tomography scans were done for response assessment; chemotherapy toxicity was graded using National Cancer Institute clinical toxicity criteria; and survival rates (PFS and OS) were studied. **Results:** Among the 39 patients with gemcitabine-based chemotherapy (CT-1), the median PFS-1 was 6.5 months. Twenty-nine patients received second-line chemotherapy (CT-2). Responses observed complete response in 2/29, partial response in 7/29, stable disease in 1/29 patients, and progressive disease in 19/29. The overall response rate was 9/29 (31.0%). Grades 2–4 toxicities were anemia (17.95%), thrombocytopenia (12.82%), neutropenia (12.82%), and peripheral neuropathy (7.69%). The median OS was 9.13 months. Late PFS-1 (>median PFS-1) patients had significantly lower mortality as compared to early PFS-1, odds ratio of 0.251 ($P = 0.002$), and median PFS-2 was 2.53 months. **Conclusion:** After the failure of gemcitabine and platinum-based chemotherapy, FOLFOX-4 is modestly effective, fairly well tolerated and this needs to be proven in a larger randomized phase 3 study. Further research into the pathogenesis of biliary tract cancer with the aim to identify new targets for treatments is required.

Keywords: Carcinoma gallbladder, FOLFOX-4, gemcitabine and platinum, second-line palliative chemotherapy

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Introduction

Carcinoma gallbladder is a dreaded disease with dismal prognosis. Most of the patients are diagnosed in advanced inoperable stage, and best supportive care (BSC) with or without palliative chemotherapy is the only feasible treatment option.

At present, cytotoxic chemotherapy comprising a combination of gemcitabine and cisplatin is held as the most effective first-line regimen,^[1] providing a tumor control rate of 81.4%, median progression-free survival (PFS) of 11.7 months versus gemcitabine alone (71.8%, 8.1 months), as reported by the phase 3 ABC-02 study.

GEM-OX is another well-accepted first-line regimen with nearly similar efficacy and

less toxicity, as evidenced in the phase 2 study by Sharma *et al.*^[2] After disease progression on the first-line chemotherapy, the efficacy of the second-line chemotherapy is less well established with no definitive recommendations.

We planned to study the tumor response rate, safety, the PFS, and overall survival (OS) on the second-line FOLFOX-4 chemotherapy.

Methods

This was a prospective single-arm, single-center, observational study. The study was conducted over a period of 2 years from July 2014 to June 2016.

Inclusion criteria are as follows:

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- Histologically/cytologically confirmed, nonresectable or recurrent/metastatic adenocarcinoma of the gallbladder
- Who had failed one prior course of gemcitabine-based chemotherapy
- Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–2
- Adequate bone marrow reserves and acceptable renal and liver functions (serum creatinine <1.5 times upper limit of normal (ULN), creatinine clearance ≥ 30 ml/min, total bilirubin <1.5 mg/dL and ALT, AST and alkaline phosphatase $\leq 5 \times$ ULN).

Thirty eligible patients were planned to be enrolled for the second-line chemotherapy in this study. Eligible patients who progressed on gemcitabine and platinum-based chemotherapy (CT-1) were treated using the FOLFOX regimen (CT-2). This regimen consisted of:

- Oxaliplatin (85 mg/m²) and leucovorin (200 mg/m²) on day 1, followed by a 5-FU bolus (400 mg/m²/day) and 22-h infusion of 5-FU (600 mg/m²/day) for 2 consecutive days.

Each cycle consisted of two doses of chemotherapy, 2 weeks apart. Tumor response was radiologically assessed with positron emission tomography and/or Computed tomography scan after 3 and 6 cycles of chemotherapy using the PERCIST and RECIST criteria version 1.1. Toxicity of chemotherapy was graded using standard CTC criteria on clinical examination and blood investigation reports. The overall response rate (ORR) was calculated as the sum of rates of partial response (PR) and complete response (CR).

PFS was defined as the time from start of treatment to the first radiologic confirmation of disease progression, or death from any cause within 60 days after the last assessment, whichever came first. PFS on the first-line gemcitabine and platinum-based chemotherapy (CT-1) was designated as “PFS-1,” and PFS on the second-line FOLFOX regimen (CT-2) was designated as “PFS-2.” OS was defined as the time period from the first administration of study treatment (CT-1) to death from any cause.

Data analysis

The median OS and PFS were estimated using the Kaplan–Meier method, Kaplan–Meier with log rank test. Univariate cox proportional hazard regression analysis of the link between each variable and OS was performed, and univariate logistic regression analysis was performed to find

the risk factors of early recurrence. A value of $P < 0.05$ was considered statistically significant. IBM Statistical Package for the Social Sciences (IBM SPSS®) Statistics version 21 was used for statistical analysis.

Results

A total of 58 patients of CA GB were enrolled for the management during study period. Ninety-five percent patients (56 out of 58) had adenocarcinoma histology. One patient had adenosquamous histology and one had neuroendocrine carcinoma and both were not eligible for this study. Of this cohort, another 19 patients could not receive any chemotherapy due to their poor general condition or no patient consent. Thus, a total of 39 patients could receive the first-line chemotherapy (CT-1). The population included 28 females and 11 males (ratio, 2.6:1), with a median age of 54 years (range, 34–72 years). About 87.1% of eligible patients had an ECOG PS of 0–1. Figure 1a-c depicts the study population characteristics.

A total of 39 patients who received CT-1 (gemcitabine plus cisplatin or carboplatin) the PFS-1 ranged from 1.43 to 16.57 months with a median PFS-1 of 6.5 months [Figure 2]. All of these patients progressed on or after completion of gemcitabine-based first-line chemotherapy. Twenty-nine of these 39 patients fulfilled the eligibility criteria for the second-line chemotherapy and the rest were either in poor general condition or refused further chemotherapy. The best tumor response observed was CR in 2/29 patients, PR in 7/29 patients, SD in 1/29 patients, and 19/29 patients had PD with no radiological response at all. Thus, the ORR (rate of PR + SD) was 9/29, i.e., 31.0% only. Patients were followed at regular intervals until progression or death till the study cutoff date. The PFS-2 ranged from 1.27 to 9.33 months [Figure 3], with a median PFS-2 of 2.53 months. Forty-one percent of the patients developed Grades 2–4 toxicities.

The most common Grade 3 or 4 toxicities observed were anemia (17.95%), thrombocytopenia (12.82%), neutropenia (12.82%), peripheral neuropathy (7.69%), hand-foot syndrome (2.56%), and electrolyte imbalance (2.56%). Dose reduction by 25% was needed in one-third of our study patients [Figure 4].

At the end of study period, six patients were alive (OS not reached). The median OS among the rest was 9.13 months. On univariate analysis, it was observed that late PFS-1 patients have significantly lower chances of

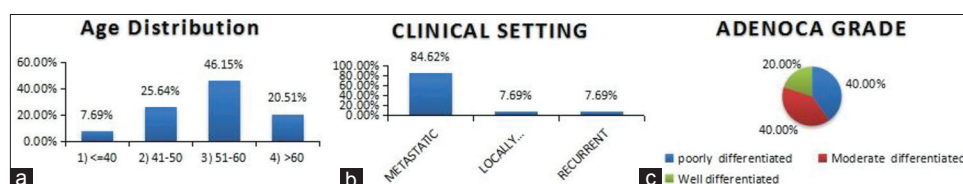


Figure 1: (a) Age distribution of population. (b) Disease status of patients. (c) Histopathology grade of carcinoma gallbladder

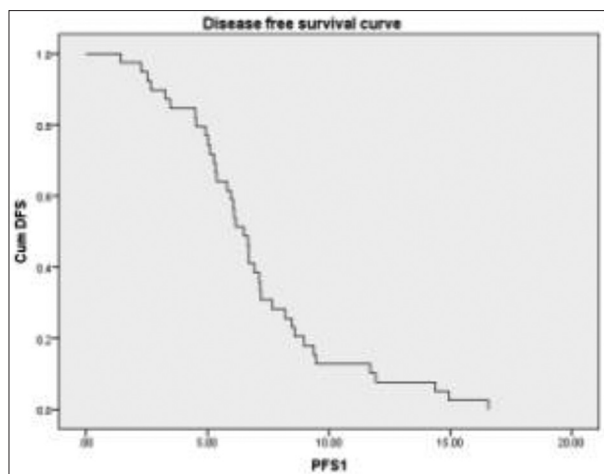


Figure 2: Kaplan–Meier curve depicting progression-free survival-1, which ranged from 1.4 to 14.9 months with a median progression-free survival-1 of 6.5 months

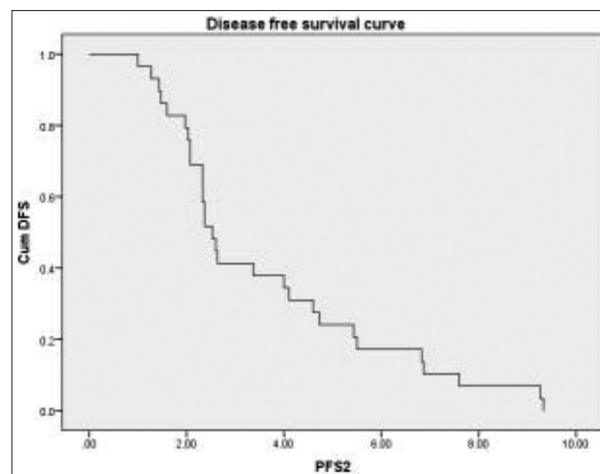


Figure 3: Kaplan–Meier curve depicting progression-free survival-2, which ranged from 1.27 to 9.33 months, with a median progression-free survival-2 of 2.53 months

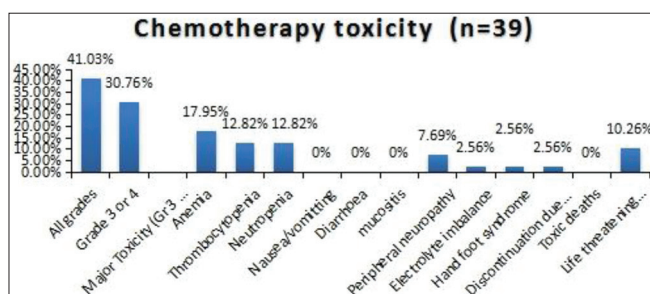


Figure 4: Toxicity profile of the second-line FOLFOX-4 in carcinoma gallbladder patients

death as compared to early PFS-1 with an odds ratio (OR) of 0.251 ($P = 0.002$) [Figure 5].

Discussion

There are limited clinical data to suggest a clinical benefit of the second-line chemotherapy in advanced biliary tract cancer, and there is no regimen considered as standard in this setting. In our study, the ORR was 31.0%. He *et al.* have reported an ORR of 21.6% to FOLFOX chemotherapy^[3] whereas Ramaswamy *et al.*^[4] from Mumbai have reported an ORR of 21.8% to CAPIRI chemotherapy. The multicenter French study by Briau *et al.*,^[5] which used multiple CT-2 regimens, reported ORR ranging from 10% to 13.5% with no statistically significant difference between the various CT-2 regimens. This numerically large difference in ORR between our study and the French study, however, did not translate into much difference in survival data (PFS and OS). The median PFS for the second-line chemotherapy was 2.53 months in our study. The median PFS reported by Briau *et al.*^[5] and Fiteni *et al.*^[6] are 3.40 and 4.0 months, respectively, to various second-line chemotherapy regimens. This is quite similar to our observation, suggesting that probably there is not much difference in efficacy among the various 5FU, capecitabine, oxaliplatin, and irinotecan-based mono- or

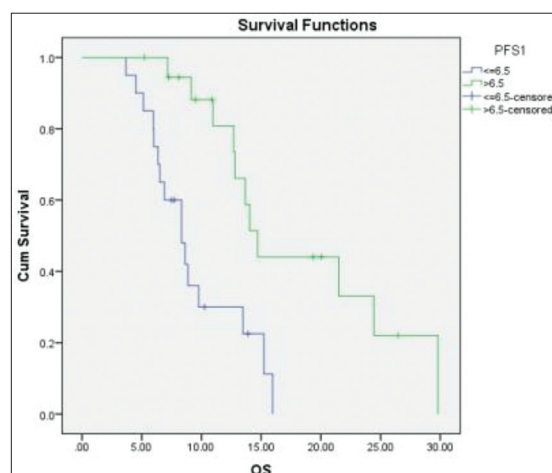


Figure 5: Kaplan–Meier curve depicting overall survival. The median overall survival among the rest was 9.13 months

polychemotherapy regimens. Ramaswamy *et al.*^[4] from Mumbai have reported a median PFS of 6.0 months with CAPIRI regimen. However, the superior PFS reported by them did not translate into superior OS. The median OS was 9.1 months in our study. The median survival reported by Briau *et al.*^[5] and Ramaswamy *et al.*^[4] were 6.7 and 8.0 months, respectively.

In Mane *et al.*^[7] phase-2 study, capecitabine with oxaliplatin regimen was studied in 17 cases of unresectable biliary tract cancer in the second-line setting. They have reported a disease control rate of 22%, PFS of 15 weeks (95% CI: 6.6–23.3), and OS of 19 weeks (95% CI: 10.4–27.5). These survival data are similarly dismal and emphasize the unmet need for effective second-line chemotherapy regimens.

Grade 3 or 4 toxicity was observed in 31% of patients in the current study, necessitating dose reduction by 20% in these cases. Only one patient could not be continued on chemotherapy due to Grade 4 myelo-Univariate

analysis-patients having late PFS-1 (more than 6.5 months) have significantly lower chances of death as compared to early PFS-1 with an OR of 0.251 ($P = 0.002$). Logrank test also inferred that mortality is significantly higher in patients who progressed earlier on the first-line chemotherapy (with PFS-1 less than the median PFS-1 of 6.5 months, $P < 0.001$). Other variables such as age, sex, ECOG-PS, adenoca grade, bilirubin, and CA 19.9 level were not associated with statistically significant difference in survival outcome on univariate analysis and logistic regression.

Brieau *et al.*^[5] observed CA 19.9 level >400 IU/ml, ECOG-PS 2 or higher and median PFS <6.5 months on the first-line chemotherapy to be associated with poor prognosis on multivariate analysis suppression. In all rest but one of these patients, the FOLFOX regimens were fairly well tolerated.

Conclusion

Our study concluded that after the failure of gemcitabine and platinum-based first-line chemotherapy, FOLFOX is modestly effective and fairly well-tolerated regimen for the second-line treatment.

Whether second-line chemotherapy is conclusively better than BSC, needs to be proven in a larger randomized phase 3 study. Definite practice changing recommendations cannot be drawn.

Further research into the pathogenesis of biliary tract cancer with the aim to identify new targets for treatments is urgently required.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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