Original Article

Best supportive care compared with chemotherapy and radiotherapy for unresectable gallbladder cancer: A tertiary care institute experience

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ABSTRACT

Context: Gallbladder represent the most common cancer among biliary tree, complete surgery offers only chance of cure, but most of patients with unresectable or metastatic stage, in such patients only palliative treatment be given. **Aims:** The aim of this retrospective study is to evaluate efficacy of chemotherapy with gemcitabine and oxaliplatin (GEMOX), and or with radiotherapy over best supportive care (BSC)) in unresectable gallbladder cancer (GBC). **Materials and Methods:** Patients with unresectable GBC were evaluated from our center between 2008 and 2011. Three cohorts were identified. Group A, BSC, Group B chemotherapy with GEMOX two weekly for maximum of six cycles. Group C, Chemotherapy with GEMOX and Radiotherapy. Patients underwent percutaneous transhepatic biliary drainage (PTBD) or Endoscopic retrograde cholangiopancreatography (ERCP) when required. **Results:** Total 50 patients included in analysis. 19 are male and 31 are female. 14 patients in Group A. 18 patients in Group B and 18 in Group C. Median follow up was 8.8 month. The progression free survival (PFS) of patients who received of BSC at 15 month was 18%. PFS of patients who received chemotherapy (CCT) at 28 month was 30%. PFS of patients who received CCT Chemotherapy and radiotherapy PFS at 15 month was 38%. When compared all three group none is statically significant ($P = 0.538$). **Conclusion:** Judicious used of BSC along with chemotherapy and or with radiotherapy may help in increase in period of stable disease along with overall survival (OS) in selected group. In our retrospective analysis CCT with GEMOX and with radiotherapy has helped in improving the OS and PFS in few patients who had good performance status.

Key words: Chemotherapy, endoscopic retrograde cholangiopancreatography, gallbladder, percutaneous transhepatic biliary drainage, radiotherapy

INTRODUCTION

Gallbladder cancer (GBC) is the most common biliary tract cancer. For some unknown reason, GBC is a common type of cancer among the females in the northern part of India. Incidence varies by geographic region and racial ethnic group. Age-adjusted incidence of GBC among females in Delhi is 7.4 persons/100,000 population per year (it is the fourth most common cancer in females after breast, cervix, and ovary).[1] The reasons for high incidence in this population are not well-understood. Chile and Bolivia (10-15 persons/100,000 population/year) are other high incidence areas.[2] One of the highest incidences in India has been reported from Kamrup Urban District (10.2/100,000 female).[3] Only 10% of patients are suitable for surgery, and the rest of the patients present in advanced and unresectable stage and are candidates for palliative treatment only. Currently, there is no standard chemotherapy for GBC, and the majority of studies have included patients from all subsites of biliary tract cancers. With various chemotherapeutic agents (with or without fluorouracil (FU)) response rates were reported in 0-36% of patients.[4-10] Median survival for patients presenting with unresectable disease is 2 to 4 months, with fewer than 5% patients surviving 1 year.[11] Gemcitabine and

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.130214

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oxaliplatin as single agents or in combination (GEMOX) with other drugs have shown activity in adenocarcinoma of pancreas, gallbladder, and biliary tracts.[6-8,12-15,18,19] Most of the reported studies have included patients with all subsites of biliary tract cancers. However, biliary tract cancer includes cholangiocarcinoma, GBCs, and ampullary tumors. These various tumors are likely to have a different biology and clinical course as evidenced by the fact that patients with cholangiocarcinoma have a better median survival than patients with GBC. Median survival reported for GBC in various studies is in the range of 4-11 months, studies involving mainly cholangiocarcinoma have reported median survival of 15-16 months suggesting a difference in the biology of the two diseases. Gemcitabine is among several new anticancer drugs under investigation in the treatment of biliary tract cancer. Objective responses of up to 36% have been reported in different series.[5,7,9,11] Combinations of gemcitabine and cisplatin have been studied with somewhat higher response rates. Two phase II studies and one phase III study have reported using this combination. Response rates of 28-38% and median survival of 4.6-8.4 months was reported.[8,16] A randomized trial tried to address the issue of chemotherapy in biliary tract malignancy recently.[17] Of 410 total patients, who were randomly assigned between gemcitabine with cisplatin and gemcitabine alone, only 36% had GBC as primary site. Median overall survival (OS) was 11.7 versus 8.2 months ($P = 0.002$). Patients with primary GBC also had a similar benefit with gemcitabine and cisplatin as seen in subgroup analysis. Oxaliplatin is a third-generation platinum compound with much less emetic and renal toxicity compared with high-dose cisplatin. Combination GEMOX may be a suitable alternative to gemcitabine and cisplatin.

MATERIALS AND METHODS

This was a retrospective analysis of 50 patients. Inclusion criteria included patients who had biopsy or fine needle aspiration cytology—proven unresectable or metastatic adenocarcinoma of gallbladder. Three arm study: Group A, best supportive care (BSC); Group B chemotherapy with GEMOX 2 weekly for maximum of six cycles; and Group C, CCT with GEMOX and radiotherapy. Baseline characteristics of enrolled patients are presented in Table 1. Patients were underwent percutaneous transhepatic biliary drainage (PTBD) or endoscopic retrograde cholangiopancreatography (ERCP) when required. In BSC patients received only symptomatic treatment. Patients receiving chemotherapy response assessed after three cycles and if favorable response than continue up to six cycle. Radiotherapy given dose of 30-45 Gy in 10-25 fractions by three-dimensional conformal radiotherapy (3DCRT). Treatment for patients with grade 3 or 4 toxicity was either delayed until resolution of toxicity or return of toxicity to lower than grade 2. Chemotherapy dose was reduced by 25% and rounded off in cases of grade 4 neutropenia or thrombocytopenia. Response Evaluation Criteria in Solid Tumors (RECIST) was used for assessment of complete response (CR), partial response (PR), stable disease, and progressive disease. Response assessment was done by repeat computed tomography (CT) scan after three cycles and six cycles in the GEMOX arm. This was done so patients had assessment after completing half of the planned chemotherapy. During follow-up, CT scan was done every 3 months and thereafter every 6 monthly. Patients who developed progressively increasing jaundice during the follow-up were considered to have progressive disease. For statistical analysis data was arranged in Statistical Package for Social Sciences (SPSS), version 19. Descriptive studies were done for parameter, survival, progression free survival and OS for the entire cohort. The log-rank test was used to analyze prognostic factors for the entire cohort. Kaplan-Meier analysis used for survival analysis. P value < 0.05 is considered as statically significant.

Table 1: Patient's characteristics

Patient characteristic	RT+CCT	CCT alone	BSC
Age (years)			
<50	8 (44.44)	8 (44.4)	6 (42.85)
>50	10 (55.55)	10 (55.55)	8 (57.13)
Sex			
Male	9 (50.00)	6 (33.3)	4 (28.57)
Female	9 (50.00)	12 (66.6)	10 (71.42)
KPS			
70-80	6 (33.33)	4 (22.00)	12 (85.68)
90-100	12 (66.67)	14 (78.00)	2 (14.28)
Stage			
II	7 (38.85)	2 (11.10)	0 (0)
III	6 (33.33)	9(49.50)	4 (28.57)
IV	5 (27.75)	7 (38.50)	10 (71.42)
Charlson index			
0	10 (55.5)	12 (66.6)	6 (42.85)
1	5 (27.75)	6 (33.34)	8 (57.13)
2	3 (16.65)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)
No ERCP/PTBD	8 (44.44)	4 (22.00)	10 (71.42)
ERCP/PTBD	10 (55.55)	14 (78.00)	4 (28.85)
Hb			
<10	6 (33.33)	6 (33.3)	6 (42.85)
>10	12 (66.67)	12 (66.6)	8 (57.13)

KPS: Karnofsky performance scale, ERCP: Endoscopic retrograde cholangiopancreatography, PTBD: Percutaneous transhepatic biliary drainage, HB: Hemoglobin, BSC: Best supportive care, CCT: Chemotherapy, RT: Radiotherapy

RESULTS

Total 50 patients included in analysis, 19 are male and 31 are female. Fourteen patients in Group A, 18 in Group B, and 18 in Group C. Median follow-up was 8.8 months. The progression free survival (PFS) of patients who received of BSC at 18 month was 10%. PFS of patients who received CCT at 18 month was 28%. PFS of patients who received CCT and radiotherapy PFS at 18 month was 38% [Figures 1-3]. When compared all three group none is statically significant ($P = 0.538$). All three arms

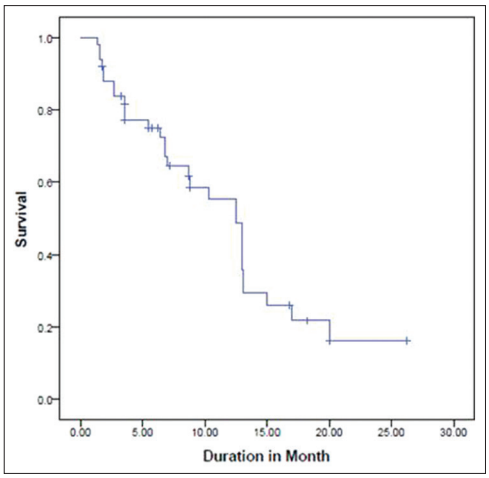

Figure 1: Kaplan-Meier estimation of survival of patients

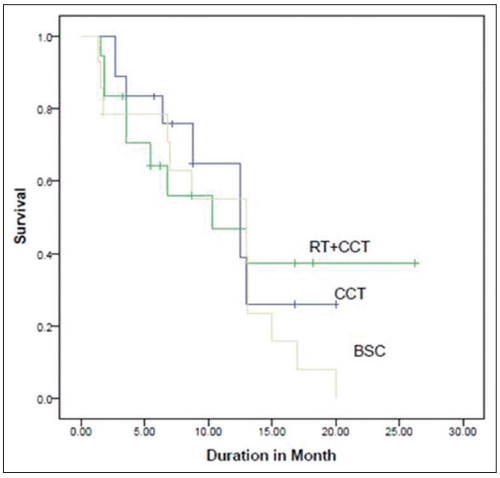

Figure 2: Kaplan-Meier estimation of survival of patients who received best supportive care (BSC), CCT, and CCT with radiotherapy

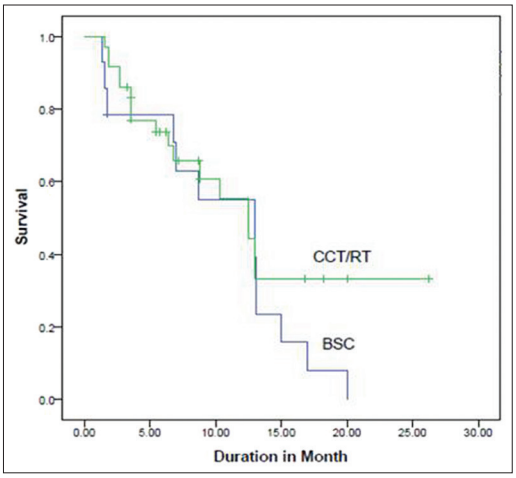

Figure 3: Kaplan-Meier estimation of survival of patients who received BSC and CCT and or radiotherapy

were well-balanced with regards to age, sex, presenting symptoms, liver metastases and prior surgical interventions in form of ERCP or PTBD. Only four patients experience grade 4 neutropenia, which was managed by granulocyte colony-stimulating factor (G-CSF) and antibiotics.

DISCUSSION

GBC is one of the most common biliary malignancies. Currently, there is no standard chemotherapy protocol for unresectable GBC, and median survival for patients presenting with unresectable disease is 2-4 months, with 1-year survival lower than 5%.[11] There were only two randomized trials comparing BSC and chemotherapy in biliary tract cancer (not limited to GBC only) using FU-based chemotherapy when this trial was conceived. In the study by Glimelius *et al.*,[20] patients were randomly assigned to FU-based chemotherapy or BSC. Median OS was 6.5 months in the chemotherapy group and 2.5 months in BSC group ($P = 0.1$). It was possible that because of the small sample size, statistical significance could not be achieved. In another study by Takada *et al.*,[10] chemotherapy was compared to BSC. Patient population was heterogeneous including pancreatic, GBC, and biliary tract cancers. No significant improvement was seen with use of chemotherapy. GEMOX are emerging as commonly used drugs, either as a single agent or in combination. The study by Doval *et al.*,[8] using gemcitabine and cisplatin reported 38% response rates and 4.8 months of median survival. Andre *et al.*,[9] reported a median PFS of 5.7 months compared with the 8.5 months reported in this study. However, in that study, GEMOX were used in doses of 1,000 and 100 mg/m^2, respectively, every 2 weeks. In another study, median PFS of 3 months was reported.[12] Modified GEMOX (mGEMOX) was more toxic than fluorouracil and folinic acid (FUFA). The most common toxicities were vomiting, myelosuppression, neurotoxicity, and transaminitis. Administration of GEMOX on 2 days (days 1 and 8) was reason for more myelosuppression (38%) seen in them GEMOX arm. In our study mGEMOX was used in which gemcitabine (800 mg/m^2) and oxaliplatine (80 mg/m^2) were used for 2 weekly maximum six cycles. There was no toxic death and a greater number of patients could complete mGEMOX therapy; transaminitis was significantly more common in mGEMOX arm. Riechelmnn *et al.*[21] It is comparable to other gemcitabine-based studies.[7-9,12,17] Andre *et al.*,[22] recently reported a phase II trial of biliary tract cancer. In our analysis, the objective response rates for GBC was only 4.3% and OS and PFS for the whole group were 8.8 and 3.4 months, respectively. CCT with mGEMOX and with radiotherapy has helped in improving the OS and PFS in few patients who had good performance status. BSC remains important integral in management of carcinoma gallbladder.

CONCLUSION

In summary, carcinoma gallbladder remains a lethal malignancy, in majority of patients who presented

with advance stage, surgery was not possible and palliative treatment was the only option. Our survival and progression free survival are similar to those as reported in literature. Our series suggests that used of BSC along with chemotherapy and or with radiotherapy may help in increase in period of stable disease along with OS in selected group. Chemotherapy with GEMOX and or with radiotherapy has helped in improving the OS and progression free survival in some patients who had good performance status.

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Cite this article as: Singh PK, Kapoor R, Kumar R, Bahl A, Kumar N, Gupta R, Sharma SC. Best supportive care compared with chemotherapy and radiotherapy for unresectable gallbladder cancer: A tertiary care institute experience. Clin Cancer Investig J 2014;3:153-6.

Source of Support: Nil, **Conflict of Interest:** None declared.