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ORIGINAL RESEARCH

A Prospective Analysis of Clinical Characteristics, Treatment and Outcome of Patients with Locally Advanced or Metastatic Gall Bladder Cancer

Dr Prashant kumbhaj[1], Dr Vishesh Gumdal[2], Dr Vinay Kumar Mahala[3], Dr Deepak Singla[4], Dr Dinesh Yadav[5], Dr Prakash Chitalkar[6]

[1]Associate Professor, Medical Oncology Department, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur.
[2]Assistant Professor, Medical Oncology Department, ESIC Medical College, Sanathnagar, Hyderabad.
[3]Assistant Professor, Surgical Gastroenterology Department, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur.
[4]Consultant Medical Oncologist, Indus International Hospital, Derabassi, Mohali, Punjab.
[5]Associate Professor, Surgical Oncology Department, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur.
[6]Prof and Head, Medical Oncology Department, Sri Aurobindo Institue of Medical Sciences, Indore.

ABSTRACT

Background: Gallbladder cancer (GBC) is a major cause of cancer mortality in parts of the world where it is common including India. Gemcitabine with cisplatin is currently the standard of care for pateints with advanced biliary tract cancers. The aim of the study is to Determine The Clinical Characteristics, Treatment And Outcome of Patients With Locally Advanced Or Metastatic Gall Bladder Cancer.

Materials and Methods: This is a prospective study of metastatic and unresectable gall bladder carcinoma patients presented in Sri Aurobindo Institute of Medical Sciences from Feb 15 to Dec16.Total 30 patients were evaluated with initial clinical characteristic like jaundice, leukemoid reaction, hepaticencephalopathy, Metastatic sites, Ascites, Tumor Markers. Chemotherapy, Gemcitabine 1000mg/m2 D1 and D8 combined with Oxaliplatin 100mg/m2 D1 Every 21 days were given. Interim Response was assessed after 3-4 cycles and after completion of treatment .Patients progressing on initial chemotherapy were offered 2nd line chemotherapy or best supportive care according to performance status.

Results: Median age was 60 years. There were 17(57%) women and 13(43%) men diagnosed with advanced GBC. Out of 30 patients 7(23%) had encephalopathy and 23(76%) had ascites. The median CA19.9 was 23 U/mL, median CEA 3.01 ng/mL, median billirubin 11.72 mg/dl, median leucocyte count 14700, median AFP 2.1ng/ml .Site of metastases was nodal in 17(56%), Liver (10(33.3), peritoneal in 3(10%) and bilateral ovarian in 1(3.3%) patient. Extrabdominal 1(3.3%). Total 30 patients received Gemcitabine with oxaliplatin chemotherapy. The median number of cycles administered was 4 (Range 1-6). 30 Patients were evaluated for response ,out of which 1 (3.3%) had CR, 9(30%) had PR, 2(6.6%) had SD, and 18 (60%) had progressive disease as their best response with first line chemotherapy. The grade 3 & 4 toxicities reported on treatment included, thrombocytopenia in 4 (13%) patients, neutropenia in 2 (6%),Liver Toxicity occurred in 3 (10%) patients, platinum induced peripheral

neuropathy interfering with daily activities was documented in 3 (10%) and diarrhea requiring hospital treatment occurred in 4 (13 %).
Conclusion: This is the prospective study to show tolerance and efficacy of Gem-Ox in patients with advanced GB cancer. The clinical benefit rate is low at 40 % suggesting that the biology of advanced GB cancers patients is likely to be aggressive and needs to be studied in large prospectively designed studies with newer chemotherapy or targeted therapies.
Keywords: Complete remission, Partial remission, Gall bladder cancer, Gemcitabine.

Corresponding Author: Dr Dinesh Yadav, Associate Professor, Surgical Oncology Department, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur.

INTRODUCTION

Gallbladder carcinoma (GBC) is a major cause of mortality in cancer in areas of the world where it is diagnosed. The prognosis associated with GBC is poor predominantly due to advanced stage at diagnosis, which is often related to lack of or nonspecific symptoms during the early stages of disease .Its incidence varies 20-fold based on geographic region due to marked ethnic and geographical variations. Chile, North India, Pakistan, Ecuador and Poland reported highest incidence. Surgery is the only curative modality that provides a chance of cure. However recurrence is common in the form of distant metastasis and long term survivors are less than 30 percent.[1,2] The incorporation of systemic chemotherapy and novel agents have been tested in many clinical trials to improve the chances of cure in resectable disease and improve survival in advanced disease.

Treatment of gall bladder cancer has been studied along with other biliary tract neoplasm. Studies of gallbladder cancers alone have reported worse outcomes compared to studies including cholangiocarcinoma. Due to its aggressive behaviour and varied epidemiology it has to be studied exclusively and separately from other biliary cancers. The data reported from studies shows a more aggressive biology and inferior outcomes. It is a very common malignancy diagnosed in north India especially along the Ganges belt. There is limited data available on treatment outcomes of Indian patients with GBC. So we have done a study to determine the clinical characteristics, treatment and outcome of patients with locally Advanced or metastatic all bladder cancer.

MATERIALS & METHODS

The Present Study is a prospective observational study of Metastatic and unresectable Gall Bladder Carcinoma Patients admitted in SAIMS, Indore.

Patients fulfilling following criteria were included in the study:

All patients aged >18 years diagnosed as advanced Carcinoma of the gallbladder, in SAIMS, metastatic and unresectable locally advanced Gallbladder carcinoma (Histologically adenocarcinoma), patients having ECOG performance status 0-2 and adequate renal, hepatic and hematopoeitic functions

Other patients who were having any other chemotherapy prior to inclusion in this study, patients who were partially treated outside, who had localized or resectable disease at presentation, patients who have undergone surgery and having histology other than Adenocarcinoma were excluded from study.

Patient were treated with Gemcitabine-oxaliplatin combination at SAIMS Indore from Feb 2015 to Dec 2016.After fulfilling all criteria for study ,30 Subjects included in the study were analyzed with respect to their demographic parameters and clinical characteristics, Including Icterus, Hepatic Encephalopathy, Metastatic Sites, Ascites, Leukomoid reactions, Tumour Markers [Ca 19.9 ,AFP, CEA] .

The Response Rate, Toxicity, Progression-Free Survival And Overall Survival of Patients With Advanced Gallbladder Carcinoma Treated With Gemcitabine-Oxaliplatin (Gem-Ox) Chemotherapy were estimated.

Following was the chemotherapy protocol.

(1) Gemcitabine 1000mg/m2 D1 and D8 over 30 mins combined with Oxaliplatin 100mg/m2 D1 over 2 hrs every 21 days for 6 cycles.

After 3 cycles, if there was a progressive disease, further treatment with second line chemotherapy was offered for good perfomence status patients. Best supportive care including analgesics, blood transfusions and any other symptomatic treatment was offered with low performance status patients progressing on GEM-OX chemotherapy.

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% or rounded off in cases of grade 4 neutropenia or thrombocytopenia.

Response evaluation was done by Computed Tomography (CT) scan was done after 3 and 6 cycles of chemotherapy according to RECIST criteria. (Response evaluation criteria in solid Tumors). During follow up, CT scan was done every 3 months for 1 year and thereafter every 6 months.

Patients were assessed for toxicity. National cancer Institute common toxicity criteria were used for defining toxicity .Evaluation of toxicity is done by NCI common toxicity criteria.

RESULTS

This is a Prospective analysis of a total of 30 patients registered at SAIMS from February 2015 to February 2017. Median age was 60 years (range, 49-78), there were 17(57%) women and 13(43%) men diagnosed with advanced GBC. Out of 30 patients 7(23%) had encephalopathy and 23(76%) had ascites. and The median CA19.9 was 23 U/mL (Range 2.45-1200); median CEA 3.01 ng/mL (Range 1-24.6); median billirubin 11.72 mg/dl (Range 0.55 to 37.5);median leucocyte count 14700 (Range 5600-49500); median AFP 2.1ng/ml (Range 1 to 15.02);site of metastases ,nodal in 17(56%), Liver (10(33.3), peritoneal in 3(10%) and bilateral ovarian in 1(3.3%) patient. Extrabdominal 1(3.3%). Total 30 patients received Gemcitabine with oxaliplatin chemotherapy. The ECOG performance status was 0-1 of patients.

The baseline characteristics are presented in the table 1,2,3.

The chemotherapy regimen used in the treatment of advanced GBC was Gemcitabine 1000mg/m2 D1 and D8 over 30 mins combined with Oxaliplatin 100mg/m2 D1 over 2 hrs every 21 days. Response was assessed after 3& 6 cycles.

All analysis were performed on an intention to treat basis. Overall survival and progression free survival were analyzed with the use of Kaplan –Meier curves. Of the 30 patients treated with GEM-OX, the median number of cycles administered was 4 (Range 1-6). 30 Patients were evaluable for response, out of which 1 (3.3%) had CR, 9(30%) had PR, 2(6.6%) had SD, and 18 (60%) had progressive disease as their best response with first line chemotherapy. The median progression free survival was 4 months (1.8-5.9) and the median overall survival was 5.5 months (2.9-8). On comparing the clinical benefit rate and survival from this study to the published ABCO2 trial & AIIMS Study, it is evident that the our patients with gall bladder carcinoma have a poorer outcome. In locally advanced and inoperable in the absence of distant metastatic disease the clinical benefit rate from the gemcitabine -oxalipatinum combination was better at 53 % as compared to only 18 % in patients with distant metastasis. The median progression free survival of locally advanced unresectable patients was 6.2 months with an overall survival of 9.1 months.

The grade 3 & 4 toxicities reported on treatment included, thrombocytopenia in 4 (13%) patients, neutropenia in 2 (6%),Liver Toxicity occurred in 3 (10%) patients, platinum induced peripheral neuropathy interfering with daily activities was documented in 3 (10%) and diarrhea requiring hospital treatment occurred in 4 (13 %) patient.
There is no standard treatment for patients who progress on first line chemotherapy. Capecitabine based regimen and best supportive care were offered for patients progressing on Gemcitabine-oxaliplatin based chemotherapy according to performance status.

Table 1: Baseline characteristic of patients treated for advanced GBC

Clinic Characterstics	**Numbers (Percentage)**
Total number	30
Age Median Range	 60.5 49-78
Male	13(43%)
Female	17(57%)
CA19.9 Median Range	11(37%) 23 2.45 to 1200
CEA Median Range	8(27%) 3.01 1 to 24.6
AFP Median Range	 2.17 1 to 15.02
Ascites	23(76%)
Leukocytosis Median Range	24(80%) 14700 5600 to 49500
Hepatic Encephalopathy	7(23%)
Hyper billirubinemia Median Range	 11.7 0.55 to 37.5

Table 2: Response to first line chemotherapy as per RECIST criterion

	Mid cycle assessment (%)	**End of treatment assessment (%)**
CR	0	1(3.3%)
PR	12(43%)	9(30%)
SD	4(13%)	2(6.6%)
PD	14(46.6%)	18(60%)
CBR	17(53.3%)	12(40%)

Table 3: Comparison of results with the ABCO2 and AIIMS

	SAIMS (30)	**ABC02 trial (61)**	**AIIMS Study (26)**
CR	1(3.3%)	0	2(7.7%)
PR	9(30%)	23(37%)	6(23%)
SD	2(6.6%)	29(47%)	10(38%)
PD	18(60%)	9(14.8%)	8(31%)
CBR	12(40%)	52(85.2%)	18(69.2%)

PFS	4 Months	8 Months	8.5 Months
OS	5.5 Months	11.7 Months	9.5 Months

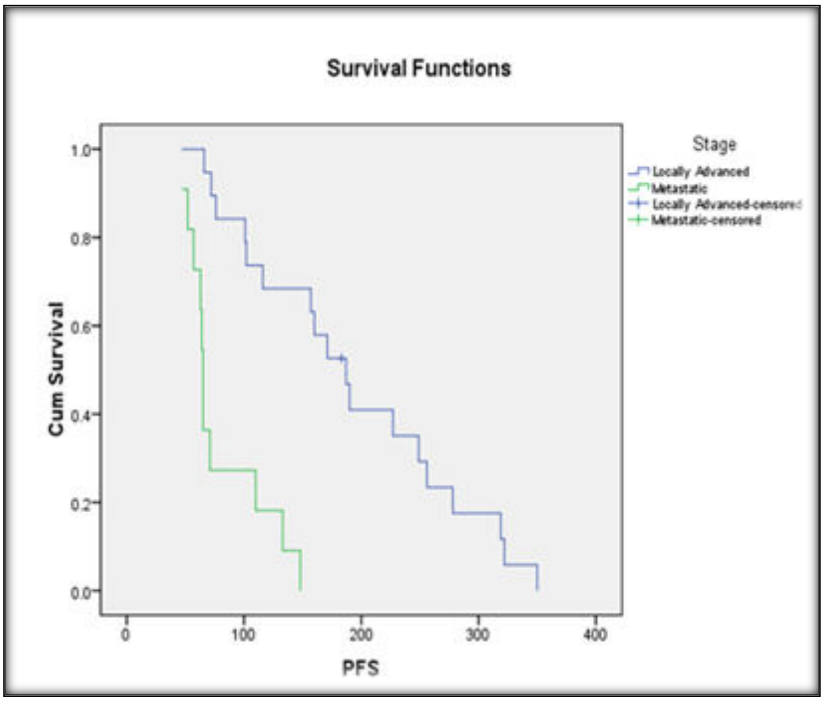

Figure 1: Progression free survival of (a) metastatic disease (b) locally advanced and the estimated progression free survival for the locally advanced GBC Patients is 6.2 months (95% CI, 4.8 to 7.5) and for metastatic GBC patients is 2.1 months (95%CI,2.06-2.23) with p value <0.0001 using log rank test.

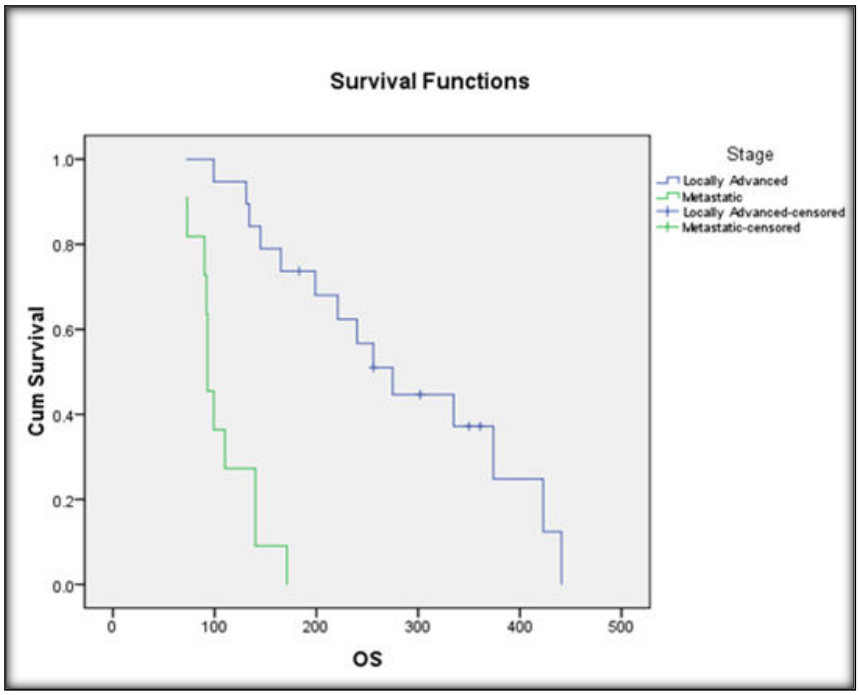

Figure 2: Overall survival of (a) metastatic disease. (b) locally advanced and The estimated overall survival for the locally advanced GBC Patients is 9.1 months (95% CI, 6.9 to 11.4) and for metastatic GBC patients is 3.1 months (95%CI,2.8-3.3) with p value <0.0001 using log rank test.

DISCUSSION

This is a prospective observational study was performed at a multi-disciplinary cancer centre. Patients from 17 districts have access to this centre. This study was done with the aim to determine the treatment outcomes in advanced GBC treated at our institute in central India . The median survival for patients presenting with unresectable disease is 2 to 4 months, with 1-year survival lower than 5%.[3] A systematic review in 2005 identified 13 studies of the use of gemcitabine alone or in combination with other agents in the treatment of advanced biliary cancers which included GBC and cholangiocarcinoma.[4] Three of these studies involved the use of a cisplatin–gemcitabine regimen and showed median survivals of 4.6, 6.5, and 10.4 months. The main drawbacks of the published literature in this field are: small number of patients, inclusion of bile duct and ampulla of Vater cancers in the studies.

In our study the combination of Gemcitabine with oxaliplatin as palliative chemotherapy was shown to be an effective first line therapy. With a clinical benefit rate (CR+PR+SD, as by RECIST criteria) of 53% at mid cycle assessment and 40% at end of treatment assessment. This treatment option provides modest gains in terms of symptom relief and duration of life.

The Estimated median PFS of 4 months and OS of 5.5 months with the combination chemotherapy though show that like other aggressive biliary cancers the response in GBC is also not durable in nature.

UK ABC-02 trial tried to address the issue of chemotherapy in biliary tract malignancy.[5] Of 410 total patients, who were randomly assigned between gemcitabine and cisplatin and gemcitabine alone, only 36% had GBC as primary site. Median overall survival (OS) was 11.7 versus 8.2 months (P = .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.[5]

Sharma et al,[6] compared 27 patients treated with mGEMOX combination chemotherapy to single agent 5FU and best supportive care. The Median OS was 4.5 months for the BSC arm; 4.6 months for the FUFA arm, and 9.5 months for the mGEMOX arm. The clinical benefit rate (40%) in our study is less compared to study from from Sharma et al which is around 68%. Andre et al,[7] reported a median PFS of 6 months using the same chemotherapy regimen as used in our study, compared with the 8.5 months reported in the study from Sharma et al where different dosing of Gemcitabine 900 mg/m2 and Oxaliplatin 80 mg/m2 IV infusion (mGEMOX) on days 1 and 8 every 3 weeks were used. In another earlier study, by Sharma et al, a median PFS of 3 months was reported.[8] Another Indian study by Doval et al,[9] who treated 30 patients using gemcitabine and cisplatin reported 38% response rates and 4.8 months of median survival. Valle JW et al also showed improvement in PFS and OS.[10]

In fact the Estimated median OS and PFS reported in our study are inferior to the results of other treatments in the population of patients with biliary tract cancers where GBC is studied along with cholangiocarcinoma but comparable to other studies which have included only GBC.

Oxaliplatin based chemotherapy is reported to be less toxic and safer as compared to intravenous regimens containing Cisplatin and infusional 5 flurouracil. Our study shows that this therapy has managable toxicity and can be safelyadministered as outpatient basis. Hematological toxicities were more common than non-hematological toxicities.Study by Sharma et al showed greater incidence of grade 3/4 hematological toxicity. Our study also shows high incidence (16%)of grade 3/4 hematological toxicity. This may probably be accounted for, by the day1 and day8 scheduling of Oxaliplatin. After hematological toxicity diarrhea was most common (13%). Grade 3 or 4 neuropathy secondary to Oxaliplatin was reported in 10% of patients which is comparable to study done by Sharma et al. Single agent

Capecitabine based regimen(39%) and best supportive(61%) care were offered for patients progressing on Gemcitabine-oxaliplatin based chemotherapy according to performance status of patients. Common reasons which led to delay in treatment treatment and need for chemotherapy dose modification were infections like cholangitis, thrombocytopenia, febrile neutropenia and liver toxicity or peripheral neuropathy.

Our study analyses all the patients who received chemotherapy ranging from 2 cycle to 6 cycles. One of the reason for lower response rates in our study is due to inclusion of patients with lower performance status (upto and including ECOG 2). Patients with a good PS (0-1) appear to derive greater benefit from combination chemotherapy.

Our results suggest palliative chemotherapy, for locally advanced or metastatic gallbladder cancers produces modest benefits and should be compared in large prospective studies with newer treatment strategies.

Genetic profiling and discovery of the molecular pathways driving this deadly disease will result in a better understanding of this disease and needs to be studied exclusively for GBC.

CONCLUSION

This is the prospective study to show tolerance and efficacy of Gem-Ox in patients with advanced GB cancer. the clinical benefit rate is low at 40 % suggesting that the biology of advanced GB cancers patients is likely to be aggressive and needs to be studied in large prospectively designed studies with newer chemotherapy or targated therapies.

Limitations:

This study has some limitations including the numbers of patients and the associated biases if any. All efforts were made to include every single patient treated during the study duration. Patients who is not able to come hospital or lost to follow up, was done by telephonic contacts and encouraged for follow up and to complete chemotherapy cycles.

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