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A Prospective Study Comparing Oxaliplatin & 5-Fu with Gemcitabine & Cisplatin in Advanced Stage Carcinoma Gall Bladder

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Abstract
Background: *Overall incidence of Gallbladder (GB) malignancy is rare but it is the most common primary hepatobiliary carcinoma. Its incidence is highest in India and median survival is less than 6 months. Different chemotherapy regimens have been tried. These days Gemcitabine with cisplatin is the most preferred therapeutic approach but still less number of patients are achieving the 1 year survival. But studies on oxaliplatin and fluropyrimidine combination shows appreciative results in term of overall survival .These evidences led us for current prospective study to compare these two regimens in locally advanced carcinoma GB.*
Aim: *The primary objective was to compare the overall survival while secondary objectives were to assess* the response *rate & toxicity.*
Method and Material*: This single institution study included 50 cytopathologically proven advanced stage Carcinoma GB patients and randomized into ARM A (gemcitabine and cisplatin) and ARM B (oxaliplatin and 5FU). 4*
Result: *OS for arm A was 5± 0.504(95%CI, 4.012-5.988) months and for arm B was 5.5 ±.542 (95%CI , 44.37-65.63)months. Most common side effects were nausea/vomiting and Anemia for arm A and arm B respectively.*
Conclusion: *Oxaliplatin and 5-FU regimen can be considered as first line chemotherapy or second line chemotherapy in patients with advanced stage carcinoma GB. To confirm these results, study on larger number of patients population with advanced carcinoma GB needs to be undertake with randomization.*
Keywords: *Carcinoma Gall Bladder, Gemcitabine , Cisplatin,Oxaliplatin,5-FU.*

INTRODUCTION

Overall incidence of Gallbladder (GB) malignancy is rare but it is the most common primary hepatobiliary carcinoma and the 5th most common malignancy of the gastrointestinal tract. It shows a marked geographic and ethnic variation (Baillie J[1]). The highest incidence are reported in Indians, Pakistanis, Chileans, Bolivians, Central Europeans Israelis, Native Americans and Americans of Mexican origin (Lazcano-Ponce EC et al 2001[2]).Unfortunately, it is often diagnosed at advanced stage and the median survival is less than 6 months (Perpetuo et al[3]). Till date, only palliative chemotherapy is the primary therapeutic approach for advanced stage.

Different chemotherapy regimens have been tried, but only few of them shows the encouraging results e.g. Gemcitabine and cisplatin; Gemcitabine and oxaliplatin; Gemcitabine and Capectabine; Oxaliplatin and 5-FU; Oxaliplatin and Capecitbine etc. These days Gemcitabine with cisplatin is the most preferred therapeutic approach but still less number of patients are achieving the 1 year survival. But studies on oxaliplatin and fluropyrimidine combination show appreciative results in term of overall survival. In spite of their beneficial results none of them become standard of treatment because all these studies were having less number of advance staged GB cancer patients and most of them are non randomized. These factors led us for current randomized prospective study comparing the combination of Gemcitabine and Cisplatin Vs Oxaliplatin and 5-FU in advanced stage carcinoma GB. The primary objective was to compare the overall survival while secondary objectives were to assess the response rate & toxicity.

PATIENTS AND METHODS

This single institution, randomized prospective study included 50 cytopathologically proven advanced stage Carcinoma GB patients between July 2014 and May 2015. Written Informed consent has been taken from all the patients before initiation of this study.

Eligibility criteria

Eligible patients met the following criteria: cytopathologically confirmed, unresectable, locally advanced, and metastatic adenocarcinoma of the GB; age >18 years; ECOG status 0–2; adequate bone marrow function (Hb ≥10gm% , white blood cell count ≥3500 cells/mm³, platelets ≥ 1,00,000cells/mm³). Patients may have prior placement of stents or shunts to relieve obstruction. Patients were excluded if having any serious comorbid condition; bilirubin ≥1.5 times the upper limit of normal (ULN) despite adequate endoscopic biliary drainage; creatinine ≥2mg/dl; pregnancy and lactation ;earlier chemotherapy; suspicious brain metastases and prior peripheral neuropathy ; another malignancy of any other site. Supportive care was permitted.

Treatment plan

All Patients were randomized (by computerized random numbers) into two groups ARM A and ARM B.

ARM A has received injection Gemcitabine in dose of 1000mg/m^2 in 500 ml normal saline via intravenous infusion over 30–60 min on days 1 and 8 of a 21-day cycle and injection Cisplatin, 70 mg/ m^2, diluted in 500 ml of 0.9% normal saline, intravenously on day 1& 2, after completing the Gemcitabine dose. Cisplatin dose was also preceded by pre-hydration and electrolyte supplementation.

ARM B has received injection Oxaliplatin in dose of 100mg/m^2, diluted in 500 ml of D-5 given intravenously 2hr infusion on day 1 and injection 5-FU, 1000 - 1200mg/m^2 diluted in normal saline, intravenously 8 hr infusion on day 1 and 2.

Before treatment, patients were assessed by taking complete history and physical examination (general and systemic), Performance status measured by Zubrod's score, blood investigations like full blood count, Kidney Function Test (KFT), serum electrolytes and Liver function Test (LFT), Chest X-Ray PA view, Ultrasonography whole abdomen, CECT whole abdomen. During the study, complete history and physical examination, same prior blood investigations were performed prior to each cycle of treatment. Tumor response assessment was done by USG whole abdomen, CECT whole abdomen, and CXR at 12, 24 & 36 wks.

RESULTS

26 patients were randomized to arm-A and 24 patients to arm-B. Median follow up was performed for 11 months or till death. Male to female ratio was 1: 3.54. The patient characteristics shown in Table 1.

Table 1. Patient characteristics

Characteristics	**No.(%)**
Median age(range)	50(32-79)yr
Sex	
Male	11(22%)
Female	39(78%)
Associations	
Pain	49(98%)
Mass	42(84%)
Cholelithiasis	40(80%)
Vomiting	12(24%)
Distended abdomen	9(18%)

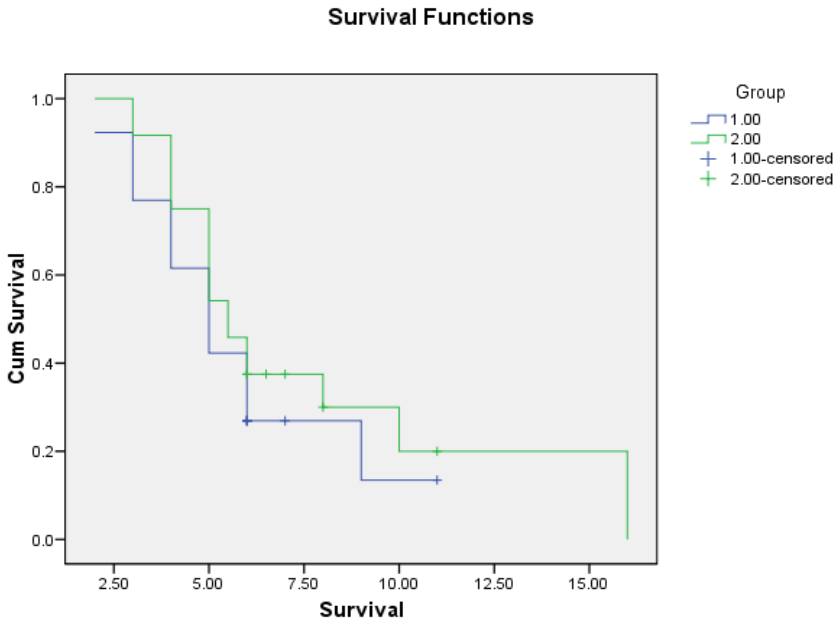
Among 50 patients, 32 (64%) Patients presented with metastatic lesion and 18 (36%) patients presented with locally advanced Gall Bladder cancer. Disease status has shown in table 2.

Table 2. Stagewise distribution in both arms

Disease status	**ArmA ,N=26(%)**	**Arm B, N=24(%)**
Stage IIIA	-	1
Stage IIIB	3	1
Stage IVA	-	-
Stage IVB	23	22
Metastatic subsites		
RPLN	12(46%)	14(58%)
Omental	11(42%)	8(33%)
Liver	8(30%)	14(58%)
Other abdominal sites	11(42%)	5(20%)

Efficacy and survival

Overall survival for arm A was 5± 0.504(95%CI, 4.012-5.988) months and for arm B was 5.5 ±.542 (95%CI , 44.37-65.63)months. Kaplan meier curve for overall survival is given below.



1= arm A, 2= arm B

In both arms none has achieved complete response. At the end of this study, only 6 patients are alive in each arms but 20 and 18 patients has died in arm A and arm B respectively. Response rate showed in table 3.

Table 3 Response rate for each arm

Overall response	Arm A(n=26)		Arm B (n=24)	
	No.	%	No.	%
PD	8	30.8	5	20.8
PR	6	23.1	5	20.8
SD	12	46.2	14	58.3
CR	0	0	0	0

TOXICITY

A total of 114 cycles of chemotherapy has been given in each arm. The median number of chemotherapy cycles was 5 for Arm A (range 1-5) and 6 (range 2-7) for Arm B. In ARM-A, the most common side effect was nausea/vomiting (non-hematological). It occurs in 80% of the patients including 12% grade 3 toxicity while in ARM-B anemia (hematological) was the most common toxicity along with 44 % having grade 1 & 2.

Table 4. NCI CTC toxicities

Symptoms	GRADE 1	GRADE2	GRADE3	GRADE4
Non Hematological	**N(%)**	**N(%)**	**N(%)**	**N(%)**
Nausea/Vomiting				
Arm -A	36(32%)	41(36%)	14(12%)	-
Arm -B	14(12%)	23(20%)	-	-
Diarrhoea				
Arm-A	14(12%)	14(12%)	-	-
Arm-B	18(16%)	5(4%)	-	-
Infection				
Arm-A	23(20%)	-	-	-
Arm-B	5(4%)	-	5(4%)	-
Peripheral Neuropathy				
Arm-A	-	-	-	-
Arm-B	7(6%)	4(3%)	-	-
Hematological				
Anemia				
Arm-A	46(40%)	18(16%)	-	-
Arm-B	46(40%)	5(4%)	-	-
Neutropenia				
Arm-A	14(12%)	5(4%)	5(4%)	-
Arm-B	-	9(8%)	-	-
Thrombocytopenia				
Arm-A	5(4%)	5(4%)	-	-
Arm-B	-	5(4%)	5(4%)	-

Second Line chemotherapy

Two patients of arm A has also received oxaliplatin and 5-FU regimen as a second line chemotherapy and both were alive at the end of this study (i.e. up to 11 months).

DISCUSSION

Till date, there is no standard of treatment for advanced stage carcinoma GB. Only palliative chemotherapy is the standard of therapy. Various chemotherapy alone or in combination have been tried including 5-FU, gemcitabine, cisplatin, capecitabine, doxorubicin, mitomycin C, methotrexate (Hejna et al 1998[4]; Penz et al, 2001[5] ; Knox et al, 2005[6]; Harder et al, 2006[7]) resulting in response rate of 10- 26% . Now a days Gemcitabine with cisplatin is the most preferred therapeutic approach but still less number of patients are achieving the 1 year survival. But Studies on oxaliplatin and fluropyrimidine combination (O Nehls et al 2002[8]; O Nehls et al 2008[9]) shows appreciative results in term of overall survival. These evidences led us for current prospective study for comparison between these two regimens in locally advanced carcinoma GB.

In current study no patient has achieved complete response in both arms which is similar to O Nehls et al 2002[8] (oxaliplatin,5FU and leucovorin), AD Wagner et al2006[10] (gemcitabine, oxaliplatin and 5FU). But most of the studies shows the complete response in unresectable carcinoma GB patients including Rachel P. Riechelmann et al 2007[11](gemcitabine and capecitabine),T. Andre et al 2004[12] (gemcitabine and oxaliplatin), DC Dovel 2004[13] (gemcitabine and cisplatin), O Nehls et al 2008[9] (oxaliplatin and capecitabine) and Juan Valle et al 2010[14] (cisplatin and gemcitabine vs gencitabine alone). In these studies they didn't mention the stage of carcinoma GB. So there is a doubt, whether these patients of locally advanced carcinoma GB could ever achieve the complete response or not. In current study among 50 patients, 76 % (38) died. It appears that both regimens of chemotherapy have similar overall survival. Median overall survival for arm A was 5 months, also seen in DC Dovel et al[13] (OS: 20 weeks) but 2 patients has survived up to 11 months. In arm B median OS is 5.5months which is less than other similar studies O Nehls 2002[8](OS=9.5 months) and O Nehls 2008[9](OS=12.8 months). Only 2 patients survived for 11 months and 1 for 16 months. These varied results may be due to the more metastatic staged patients in current study. But this is unavoidable because in our setup most of the patients consulted to us in very advanced staged or in metastatic stage.

In conclusion, oxaliplatin and 5-FU regimen can be considered as first line chemotherapy or second line chemotherapy in patients with advanced stage carcinoma GB and along with kidney related disorder. It also prolongs OS and relieves symptoms like Gemcitabine and Cisplatin. So, we may also use this regimen in chemotherapy naïve patients. To confirm these results, study on larger number of patient population with advanced carcinoma GB needs to be undertaken with randomization.

REFERENCES

1. Baillie J: Tumors of the gallbladder and bile ducts. J Clin Gastroenterol 1999;29:14-21
2. Lazcano-Ponce EC, Miquel JF, Munoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001;51:349
3. Perpetuo MD, Valdivieso M, Heilbrun LK, et al. Natural history study of gallbladder cancer: a review of 36 years experience at M. D. Anderson Hospital and Tumor Institute. Cancer 1978;42:330.
4. Hejna M, Pruckmayer M, Raderer M. The role of chemotherapy and radiation in the management of biliary cancer: a review of the literature. Eur J Cancer. 1998;34:977–986. [PubMed]
5. Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger W, Lenauer A, Depisch D, Krauss G, Schneeweiss B, Scheithauer W

(2001) Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. Ann Oncol 12: 183–186

6. Knox JJ, Hedley D, Oza A, Feld R, Siu LL, Chen E, Nematollahi M, Pond GR,Zhang J, Moore MJ (2005) Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 23:2332– 2338
7. Harder J, Riecken B, Kummer O, Lohrmann C, Otto F, Usadel H, Geissler M, Opitz O, Henß H (2006) Outpatient chemotherapy with gemcitabine and oxaliplatin in patients with biliary tract cancer. Br J Cancer 95:848–852
8. Nehls O, Klump B, Arkenau HT, Hass HG, Gregor M, Porschen R (2001) A phase II trial of oxaliplatin, fluorouracil and leucovorin for advanced biliary system adenocarcinomas. Br J Cancer 87: 702 – 704
9. Nehls O, Oettle H, Hartmann JT, Hofheinz RD, Hass HG, Horger MS,Koppenhofer U, Hochhaus A, Stieler J, Trojan J, Gregor M, Klump B (2008) Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. Br J Cancer 98: 309–315
10. AD Wagner, P Buechner-Steudel, M Moehler, H Schmalenberg3, R Behrens4, J Fahlke5, A Wein6, S Behl, O Kuss, G Kleber and WE Fleig(2009) Gemcitabine, oxaliplatin and 5-FU in advanced bile duct and gallbladder carcinoma: two parallel, multicentre phase-II trials.Br J Cancer 101, 1846 – 1852
11. Rachel P. Riechelmann, Carol A. Townsley, Sheray N. Chin, Gregory R. Pond,Jennifer J. Knox (2007). Expanded Phase II Trial of Gemcitabine and Capecitabine for Advanced Biliary Cancer. American cancer society September 15, 2007 / Volume 110 / Number 6: DOI 10.1002/cncr.22902
12. Andre´ T, Tournigand C, Rosmorduc O, Provent S, Maindrault-Goebel F,Avenin D, Selle F, Paye F, Hannoun L, Houry S, Gayet B, Lotz JP, de Gramont A, Louvet C (2004) Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol 15: 1339–1343
13. DC Doval, JS Sekhon, SK Gupta, J Fuloria, VK Shukla, S Gupta and BS Awasthy(2004). A Phase II study of gemcitabine and cisplatin in chemotherapy naive, unresectable gall bladder cancer. British Journal of Cancer (2004) 90, 1516 – 1520
14. Juan Valle, Harpreet Wasan, Daniel H. Palmer,David Cunningham, Alan Anthoney, Anthony Maraveyas, Srinivasan Madhusudan, Tim Iveson, Sharon Hughes,Stephen P. Pereira, Michael Roughton and John Bridgewater for the ABC-02 Trial Investigators(2010) Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. n engl j med 362;14