



## A Comparative Randomise Study of Chemotherapy versus Chemoradiation in Unresectable Locally Advanced Gallbladder Carcinoma

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### INTRODUCTION

Gall bladder (GB) carcinoma is most common biliary tract malignancy worldwide. <sup>(1)</sup> The incidence is increasing globally and also in India. Recently, the Indian Council of medical research (ICMR) has reported that incidence rates of GB cancer in women in Northern India (more than 9 per 100000 per year) are one of the highest in the world. Cholelithiasis is frequently associated with GB cancer in up to 40%-90% patients and is the most common associated factor independent of age or sex. <sup>(2)</sup> Surgery is potentially curative treatment in early stage of GB cancer. But vague presenting symptoms often delay the diagnosis of GB cancer, thus contributing to its overall progression and poor outcome. Overall mean survival is six months, while 5- year survival rate is only 5%. <sup>(3)</sup> Palliative therapy is the treatment which alleviates the distressing symptoms caused by advanced cancer. Palliative chemotherapy or radiotherapy helps to improve quality of life,

reduces risk of complications and also has some survival benefit. In an effort to improve survival rates and quality of life, neoadjuvant or concurrent chemotherapy has been used. Radiation therapy is safe and tolerable as palliative therapy in unresectable GB cancer to relieve symptoms like abdominal pain and obstructive jaundice. It acts by shrinking tumors that are blocking passage ways for blood or bile or are pressing on nerves. <sup>(4)</sup>

The goal of the study was to evaluate the efficacy and safety of chemotherapy alone as Gemcitabine and Cisplatin versus continuous daily Capecitabine with radiotherapy in patients with previously untreated locally advanced unresectable GB carcinoma. The primary end point was radiologic response and symptomatic evaluation. The secondary end point included overall survival and tolerability.

## MATERIAL AND METHODS

One hundred histologically conformed untreated patients of adenocarcinoma of GB were randomly enrolled for study from 1<sup>st</sup> September 2013 to 31<sup>st</sup> August 2014, out of 224 patients total enrolled during one year. Staging was done as per TNM-Staging system. Routine hematological and radiological investigations were done before starting the treatment. The mean age of patients was 52 years (range 30-75years). The Table no-1 describes the baseline characteristics.

## CONTROL GROUP

Control group patients were treated with chemotherapy only, in form of Gemcitabine (1000 mg/m<sup>2</sup>/day on day 1 and day 8) and Cisplatin (75 mg/m<sup>2</sup>) for total 6 cycles each cycle given after 21 days.

## STUDY GROUP

Study group patients were treated with external beam radiotherapy, 2.0 Gy per fraction, 5 days per week for 5 weeks, total 22 fractions to a total dose of 44Gy followed by a boost of 3 fraction of 2.0 Gy each to the tumor bed and regional lymph nodes. Total dose was 50.0Gy. Concurrent chemotherapy was administered in form of oral Capecitabine. Capecitabine was administered at planned escalating doses of 1000-1,250 mg/m<sup>2</sup> B.D. The first daily dose was given 2 hours before radiation therapy and second dose was given 12 hr. after the first dose, and followed by Capecitabine monotherapy 3 weekly, one week rest, continue for 6 cycles.

## RADIOTHERAPY

Tumor bed was marked using ultrasonography. EBRT was delivered to the tumor bed and lymphatics through parallel opposed anterior and posterior portals using cobalt-60 gamma rays. The field included tumor bed, porta-hepatic, pancreatico-duodenal nodes, celiac nodes and retroperitoneal nodes. Blocks were used to exclude stomach, small-intestine, kidney and liver. The primary goal was to optimize loco-

regional control. The overall treatment time of radiotherapy was approximately 6 weeks. Study group patients were monitored weekly during radiation treatment and thereafter, every 3 weeks during treatment with Capecitabine monotherapy and then patients were followed up every 3 months. Physical examination, routine hematological tests and radiological examinations were done as per the standard schedule. Response evaluation was done using response evaluation criteria in solid tumors (RECIST-Criteria). The median follow up time was 2 years. Information concerning disease status, complications and death was available through follow up, institutional records, letters and telephonic contact directly with the patients or relatives.

## STATISTICAL ANALYSIS

Symptomatic and radiological response rates of disease were calculated after the one month of treatment and then patients were followed up every 3 months up to 2 years. Signs, symptoms and adverse events during treatment were recorded from the date of initiation of treatment to the last follow up. Overall survival was estimated by Kaplan-meier method. For statistical analysis, data was arranged using SPSS 21 version. Toxicity was assessed by using the RTOG-criteria.

## RESULTS

One hundred patients were randomized from 1<sup>st</sup> September 2013 to 31<sup>st</sup> August 2014, out of which 50 patients each in control (chemotherapy) and study (chemo-radiation) groups were assessable for efficacy and safety. The median follow up was 8.5 months (range 0.8-24 months). The results were calculated from the date of initiation of treatment to the occurrence of any event or death.

## DISEASE RESPONSE TO TREATMENT

After three month of the completion of treatment, according to the RECIST-criteria, objective response (complete + partial response) was attained in 34 (68.0%) and 28 (56.0 %) patients, in

the study group and control group, respectively (Table- 2). Stable disease was observed in 5 (10.0 %) and 6 (12.0 %) patients in study and control group, respectively and progressive disease in 4 (8.0 %) and 6 (12.0%) patients in study and control group, respectively. 7 (14.0 %) and 8 (16.0 %) patients of study and control group respectively, expired at the end of three months follow up. At the end of 2 years, objective response (complete + partial response) was observed in 6 (12.0%) patients in study group and 2 (4.0 %) patients in control group. There are 43 (86.0%) patients in study group and 46 (92.0 %) patients in control group who expired.

### OVERALL SURVIVAL

Patients who were treated by chemo-radiation (study group) has a improvement in overall median survival (7.5 months) compared with chemotherapy alone (control group) 5.8 months ( $P < 0.05$ ). The two years overall survival rate of control group was 8.0% and study group was 14 %. Patients died due to systemic and locally progressive disease. Among study group 43 (86.0%) and control group 46(92.0%) patients died at the end of 2 years follow up.

### SYMPTOMATIC BENEFIT

Significant symptomatic benefit can be achieved with relief of biliary obstruction (relieves pruritus and hepatic dysfunction). After chemotherapy 20 % and chemoradiation 25% patient didnot need percutaneous transhepatic cholangiography (PTC), drainage endoscopic retrograde cholangio-pancreatography (ERCP) guided stenting or surgical bypass. Local response rate which reflected the reopening of occluded bile duct was 74 % in control group and 82 % in study group. Abdominal pain was relieved in 55 % cases. Nausea and vomiting were relieved initially but increased after using chemotherapy. No change in feeling of abdominal lump by patients. Overall 60 % patients showed symptomatic relief for a mean duration of  $4.7 \pm 3.5$  months. Recurrence developed in 12 (66.7 %) patients in a period of

two years of follow up. Metastasis occurred in 48 cases, in which 24 metastasized to liver, 8 to lungs, 3 to ovaries, 4 to supraclavicular lymph nodes (left) , 7 to peritoneum and 2 to bones.

### COMPLICATIONS AND REACTIONS

In the study three patients develops hemetemesis due to duodenal perforation. Two patients had stricture developed at the junction of first part of duodenum and pylorus in study chemoradiation group. In 18 cases, recurrent ascites with repeated tapping led to shock and death. Fever persisted in 8 cases and led to death due to severe infection. Grade 3 Hand-Foot Syndrome (HFS) develop in 6 % ( $n=3$ ) after 6 weeks at dose level of  $> 1,000$  mg/m<sup>2</sup> B.D./day and 1 (2%) cases develops grade-3 reactions during 6<sup>th</sup> cycle of Capecitabine monotherapy. Chemotherapy and concurrent chemo-radiation led to development of anorexia (grade-3 & 4) in 35 % cases, stomatitis (grade-3) in 12 % cases. Adverse events according to Maximum National Cancer Institute Common Toxicity Criteria are as follows, Nausea (grade-3 in 4% ), Vomiting (grade-3 in 6% ), Diarrhea in (grade-3 in 2% ), grade-2 fatigue develops in 10% cases when dose level  $> 1,000$ mg/m<sup>2</sup> B.D. of Capecitabine. Dose reductions were done after grade-2 and grade-3 toxicity. Treatment interrupted and treat all cases symptomatically and when the toxicity resolved treatment was continue without dose adjustment.. WHO- grade 3 and 4 febrile neutropenia developed in 8 % cases, 12 % cases needed blood transfusion for anaemia grade 3 and 4 whereas grade 3 and 4 thrombocytopenia was seen in 10 % cases. The toxicity management was according to standard guidelines.

**Table No.1** Baseline characteristics of the patients

Characteristics		Observation			
		Study Group n=50	%	Control Group n=50	%
Background	Rural	34	68.0	36	72.0
	Urban	16	32.0	14	28.0
Age	30-50 yr	22	44.0	21	42.0
	51-75 yr	28	56.0	29	58.0
Gender	Male	18	36.0	17	34.0
	Female	32	64.0	33	66.0
KPS Score	70	14	28.0	13	26.0
	80	31	62.0	30	60.0
	90	5	10.0	7	14.0
Sign and Symptoms	Jaundice	32	64.0	29	58.0
	Abdominal pain	28	56.0	29	58.0
	Ascites	4	8.0	6	12.0
	Fever	3	6.0	5	10.0
	Nausea	25	50.0	22	44.0
	Vomiting	18	36.0	20	40.0
Incidence of Gall stone	Palpable mass	16	32.0	21	42.0
	present	44	88.0	46	92.0
	Absent	6	12.0	4	8.0
	III-A (T <sub>3</sub> N <sub>0</sub> M <sub>0</sub> )	14	28.0	16	32.0
Stage TNM	III-B (T <sub>2</sub> N <sub>1</sub> M <sub>0</sub> )	24	48.0	26	52.0
	IV-A (T <sub>4</sub> N <sub>0</sub> M <sub>0</sub> )	12	24.0	8	16.0
	Well differentiated	16	32.0	14	28.0
Histopathology Adenocarcinoma	Moderately	24	48.0	23	46.0
	Poorly/ Undifferentiated	10	20.0	13	26.0

**Table No.2** Disease – Status (According to RECIST – Criteria)

S.N.	Disease Status	Group	Follow up at													
			3 Month	%	6 Month	%	9 Month	%	12 Month	%	18 Month	%	24 Month	%		
1	Complete Response	Study	10	20.0	10	20.0	7	14.0	6	12.0	4	8.0	4	8.0		
		Control	8	16.0	7	14.0	6	12.0	6	12.0	4	8.0	2	4.0		
2	Partial Response	Study	24	48.0	18	36.0	9	18.0	5	10.0	2	4.0	2	4.0		
		Control	20	40.0	16	32.0	8	16.0	3	6.0	0	0.0	0	0		
3	Stable Disease	Study	5	10.0	4	8.0	3	6.0	3	6.0	1	2.0	0	0		
		Control	6	12.0	5	10.0	3	6.0	0	0	0	0.0	0	0		
4	Progressive Disease	Study	4	8.0	2	4.0	5	10.0	4	8.0	4	8.0	1	2.0		
		Control	8	16.0	5	10.0	4	8.0	6	12.0	5	10.0	2	4.0		
5	Total Death	Study	7	14.0	16	32.0	26	52.0	32	64.0	39	78.0	43	86.0		
		Control	8	16.0	17	34.0	29	58.0	35	70.0	41	82.0	46	92.0		

**DISCUSSION**

Historically, GB carcinoma has carried a dismal prognosis. Approximately 70 to 80 % of patients present in stage III and IV.<sup>(7)</sup> This has been attributed to the late presentation of patients and the technical difficulty of an adequate surgical resection in the presence of advanced local and regional involvement. There has been an improvement in the modern imaging techniques but still GB carcinoma is diagnosed late due to its vague symptoms. More effective therapies have

emerged with improvement in the survival of patients with invasive cancer<sup>(4)</sup>.

The location, size, extension and stage at presentation of the tumor are important for determining prognosis. Larger tumors are less likely to respond to radiotherapy because their poor vascular supply reduces radiosensitivity. Concurrent chemotherapy leads to radiation sensitization, secondary to synergistic DNA damage, cell cycle synchronization and inhibition of repair and resistance pathways. Chemotherapy

alone or with radiation improves local tumor control, reduces micrometastases and decreases the risk of distant metastasis <sup>(1)</sup>. Sixty percent of patients of study group were free from distressing symptoms of abdominal pain and obstructive jaundice. With improvement in nutrition, there was significant weight gain after treatment <sup>(5)</sup>.

Treatment of unresectable locally advanced GB carcinoma usually consists of various palliative strategies which provide only a modest survival benefit <sup>(5)</sup>. Mostly patients received 5-Flourouracil based chemotherapy so we also tried. Capecitabine is a oral prodrug converted in 5-FU and works as radiosensitizer if it is taken at least 2 hours prior to irradiation <sup>(5)</sup>. Gemcitabine has excellent clinical activity against solid tumors. Gemcitabine-based combination chemotherapy is widely accepted with gemcitabine and cisplatin combination chemotherapy as one of the most commonly used regimens <sup>(8)</sup>. Exposure to normal tissues to 5-FU within the radiation field is likely to be lower with oral Capecitabine compared with intravenous 5-FU. Capecitabine-based chemoradiation may have enhanced therapeutic ratio compared with 5-FU based treatment in patients. Capecitabine also avoids the potential complications associated with indwelling central venous catheters, such as infections, sepsis, thrombosis and blockage. Chemotherapy and concurrent chemo-radiation provide immediate symptomatic relief by arresting growth, shrinkage of tumor, decreasing risk for loco-regional failure and hence improving survival. In recent years, several groups have reported that chemotherapy and concurrent chemo-radiation improves the survival and symptomatic relief.

In case of chemotherapy alone, Malik *et al* showed that gemcitabine and cisplatin chemotherapy had 9% complete response, 55% partial response and 64% overall response rate. Median overall survival was 42 weeks <sup>(8)</sup>. Shewach *et al* showed that in gemcitabine and cisplatin combination chemotherapy 9.5 % cases showed complete response and 38.09 % showed partial response. The median survival time was 7

months and toxicity was reasonable <sup>(9)</sup>. Doval *et al* showed 13.3% complete response, 23.3% partial response, 23.3% stable disease and 13.2% progressive disease. The median time to progression was 18 weeks and median overall survival was 20 weeks. One year survival rate was 18.6 %. Gemcitabine and cisplatin combination is well tolerated <sup>(10)</sup>. In our study 2 year survival rate were 8.0 % and chemotherapy is well tolerated. Yamashita *et al* showed that 33.3 % cases show partial responses, 57.2 % show stable disease and 9.5 % complete response. The median overall survival time was 18.8 months and median time to progression was 13.4 months <sup>(11)</sup>. In our study objective response (complete + partial response) 28 (56.0 %) was observed and overall median survival 5.8 months Stable disease was observed in 6 (12.0 %) patients and progressive disease in 6 (12.0%) patients. Overall 52 % patients showed symptomatic relief for a mean duration of  $4.9 \pm 3.1$  months. Recurrence developed in 6 (30 %) patients in a period of two years of follow up. And in case of chemo-radiation Singh *et al* showed that oral capecitabine regimen has shown the best survival benefit in chemoradiation in unresectable GB carcinoma. The mean survival was 2.6 years whereas other regimens had mean survival of 8 to 16 months and those who received only best supportive care had mean survival of 3.6 months <sup>(12)</sup>. Kapoor *et al* showed that patients on combined chemotherapy and radiotherapy had better 2-years disease free survival (DFS) of 60 % as compared to those who did receive single modality of treatment. Liver infiltration by tumor was found to be a bad prognostic factor with DFS at one year of 0.8 vs 0.5 patients with no liver infiltration ( $P=0.06$ ) <sup>(7)</sup>. Park *et al* showed that local response rate (reopening of occluded bile duct) was 89.5%. 36.6% showed overall response. Longest survival time was 52 months and median survival time was 14 months. One and two year survival rates were 82.2% and 31.6% respectively <sup>(13)</sup>. In our study 32.0 % cases reopen the occluded bile duct. Engineer *et al* showed that complete metabolic and radiological response was observed

in 66.6 % and partial response i 33.4 %. Median overall survival was 20 weeks <sup>(4)</sup>. Gallardo *et al* reported the results of a series of 26 patients with metastatic and unresectable GB carcinoma. He observed a 36 % response rate and 30 months of median survival <sup>(14)</sup>.

Capecitabine, an orally administered systemic 5-fluorouracil prodrug, has been tested in GB carcinoma. One of the main positive effects of this drug is its capacity to lead to 5FU concentrations in tumors 125 times greater than serum concentrations. The effect of capecitabine on GB carcinoma was evaluated by Patt Y, who showed a 50% response rate and median overall survival of 10.1 weeks <sup>(15)</sup>. Knox *et al* reported combination of gemcitabine and capecitabine showing overall objective response rate of 31 %, 42 % patients had stable disease and disease control rate of 73 %. The median overall survival time was 14 months and median progression-free survival time was 7 months. Tolerance was good even in patients with liver dysfunction or biliary stents. Median overall survival was 14 weeks <sup>(16)</sup>. In our study objective response (complete + partial response) 34(68.0 %) was observed and overall median survival 7.5 months Stable disease was observed in 5 (10.0 %) patients and progressive disease in 4 (8.0%) patients. Overall 68 % patients showed symptomatic relief for a mean duration of 5.6 ± 3.8 months. Recurrence developed in 6 (30 %) patients in a period of two years of follow up.

## CONCLUSION

GB cancer remains a lethal malignancy. In this study chemo-radiation had overall survival, symptom free rates and local control rates similar to those reported in literature but better than chemotherapy alone in patients with stage III or IV disease. This study reports a single institution experience of using chemotherapy alone or with radiation in patients with GB carcinoma (stage III-A, III-B & IV-A), which gave better symptomatic relief and was well tolerated. Gemcitabine, cisplatin and capecitabine are effective as adjuvant therapy in carcinoma GB to improve

treatment outcome. Both chemotherapy and radiotherapy have superior survival outcomes. Improvements in treatment are still required. Unique method but still under investigational process and larger randomized trials are needed to verify these good results.

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