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Scientific Research

Role of Combination Chemotherapy with 5-Fluorouracil, Cisplatin and Paclitaxel for Advanced Gall Bladder Cancer

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Abstract

Aim: The prognosis for patients with advanced Gallbladder carcinoma is poor. Due to unresectability and relatively ineffective chemotherapy available, a need exists for effective chemotherapeutic regimen. The aim of this study was to determine the efficacy and safety profile of 5-fluorouracil, cisplatin and paclitaxel in patients with advanced Gallbladder cancer. Material and Methods: From January 2002 to July 2004, 40 patients of advanced carcinoma Gallbladder received 5-fluorouracil, cisplatin and paclitaxel. On day 1, paclitaxel was given (150 mg/m^2), cisplatin was given on day 2 (50 mg/m^2) and 5-fluorouracil was given from day 1 to day 3 (500 mg/m^2). This cycle was repeated every three weeks and patient assessment was done. Results: Forty patients were enrolled in this study. Thirty-five were assessed for response. Five patients were lost in follow up. There were thirty females and ten males. A median of three cycles of treatment (range one to seven) was administered. Two patients achieved complete response and eleven had partial responses giving an overall response rate of 32.5% in the intention-to-treat population (95% confidence interval 11.1% to 46.5%). The median response duration was 5.3 months. The median time to progression and overall survival was 4.1 months and 11.2 months, respectively. The most common grade 3 adverse effects were neutropenia (30%), nausea (20%), vomiting (15%), diarrhea (10%), stomatitis (5%), and peripheral neuropathy (5%). Only one case had febrile neutropenia. There was no treatment related death. Conclusions: The combination of 5-fluorouracil, cisplatin and paclitaxel has promising anti-tumor activity and is well tolerated in patients with advanced and metastatic Gallbladder cancer.

Keywords

Advanced Gallbladder Carcinoma; Combination Chemotherapy; Prognosis

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1. Introduction

Gallbladder cancer is one of the most aggressive human malignancies. It is notorious for clinical detection in advanced stages with unresectability and refractoriness to chemotherapy. When patients come to hospital with pain abdomen, lump abdomen or jaundice is diagnosed of Gallbladder cancer, they have almost lost possibility of a curative resection. Only a small subset of patients of Gallbladder cancer has a curative surgical resection potential. Prognosis for metastatic and advanced disease is dismal with median survival usually <4 months in patients not treated with chemotherapy [1] [2]. Most primitive and most extensively studied chemotherapeutic agent in biliary malignancy to date has been 5-fluorouracil (5-FU), although response rate has been around only 10% - 13% [3] [4]. Similar results are seen for single agent like cisplatin (8%) in advanced cancer of Gallbladder and bile ducts [5].

Due to poor response to single chemotherapeutic agent, different randomized trials of combination chemotherapy were done which showed improved survival. In phase II studies, 5-day continuous infusion 5-FU and cisplatin have demonstrated a response rate of 24% in patients with advanced biliary cancer [6]. Different trials of Gemcitabine alone or in combination with cisplatin have shown response rate of 10 to 40% [7]-[10]. In other phase II trials of 5-FU, epirubicin, cisplatin (ECF regimen), response rate is around 29% - 40% [11]-[14]. Multi-drug chemotherapy due to its better results motivated us to do a trial of 5-FU + Paclitaxel + Cisplatin for advanced Gallbladder cancer. Patients were evaluated for response rate in terms of time to progression, overall survival and safety of the combination regimen.

2. Material and Methods

All patients had cytologically confirmed advanced or metastatic carcinoma of gall bladder with at least one unidimensionally measurable lesion (diameter ≥ 2 cm as assessed by physical/X-ray/Ultrasound/CT scan examination). Other eligibility criteria were age 20 - 70 years and Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2 [3]. Patients had received no prior chemotherapy or radiotherapy. Patients with hematological (hemoglobin ≥ 8 gm/dl, total leukocyte count $\geq 4.0 \times 10^9$/L, absolute neutrophil count $\geq 2.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L), hepatic (total bilirubin ≤3 mg/dl, total protein ≥ 6 gm/dl, serum transaminases ≤3 × normal limit or ≤5 × normal limit in cases of hepatic metastases), and renal (serum creatinine ≤1.6 mg/dl) parameters were included. All patients were given proper and adequate information and written consent was taken before enrollment.

Chemotherapy Schedule

Forty patients were enrolled for this study. All patients received three drugs.

DAY 1: Paclitaxel 150 mg/m^2 on day 1 dissolved in 300 ml normal saline and infused over 30 minutes.

DAY 2: Cisplatin 50 mg/m^2 dissolved in 150 ml normal saline and infused over 30 minutes.

DAY 1 - 3: 5-Fluorouracil 500 mg/m^2 dissolved in 540 ml dextrose normal saline and infused over 4 hours.

Cycle was repeated every 3 weeks. Treatment was continued until development of unacceptable toxicity, progression of disease or patient deciding not to continue the treatment.

Complete blood count and biochemical tests to assess renal and hepatic functions were done before and on day 15 of each cycle of chemotherapy. Tumor size was assessed after completion of each cycle and it was carried on till patient developed progressive disease. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumor Guidelines [15]. Patients with complete response or partial response required a confirmatory disease assessment at least 4 weeks later.

The trial was conducted according to the two-stage Gehan design [16] with overall response as the primary end point. Assuming a true response rate of at least 15%, initially 19 patients were accrued. Because the probability of obtaining no response in 19 patients was <0.05, the trial was to be abandoned if no response were observed. Study was continued if at least one treatment response was observed and six additional patients were added according to the rules, to obtain an accuracy of 0.10 for the final response rate. According to this design, the probability of completing the trial was >95% if the true response rate was at least 15%. However accrual was continued to a total of 40 patients so that the proportion of patients responding could be better defined.

Duration of response, time taken to progression and survival were calculated as secondary end points by the Kaplan-Meier Method. The duration of response was defined as the interval from the onset of complete response

or partial response until evidence of progressive disease was found. Time taken to progression (TTP) was estimated from date of entry to the date of progression of disease. Overall survival was measured from the date of entry to the date of death.

3. Results

A total of 40 patients were registered between January 2002 and July 2004. The median age was 48 years (range 24 to 67 years) (**Table 1**). Most of the patients (75%) had good performance status (0 or 1 on ECOG scale). Five patients had undergone surgery for biliary decompression and four received endoscopic stents for palliation of obstructive jaundice. Hepatic metastases were present in 40% patients at the time of enrollment for chemotherapy. Abdominal lymph nodes were enlarged in 25% patients. Other metastatic sites were lungs, supraclavicular lymph nodes, and bones.

A total of thirty-five patients were evaluated for response. The remaining five patients were not assessable for response because of loss to follow-up. The overall response rate in intention-to-treat population was 32.5%, including two confirmed complete responses and eleven confirmed partial responses. When eleven patients with stable disease were included, tumor growth control was achieved in 60% of patients (**Table 2**). The median duration of response in thirteen responding patients was 5.3 months.

Table 1. Patients profile.

Characteristic	No. of patients	Percentage
No. of patients enrolled	40	100
Assessable for response	35	87.5
Lost to follow-up	05	12.5
Age (Years)		
Median (48)		
Range (24 - 67)		
Sex		
Male	10	25
Female	30	75
Performance status (ECOG scale)		
0	24	60
1	06	15
2	10	25
Extent of disease		
Locally advanced	04	10
Metastatic	30	75
Recurrent	10	25
Metastatic Sites		
Liver	16	40
Abd. Lymph nodes	10	25
Lung	05	12.5
Supraclavicular lymph nodes	03	07.5
Peritoneum	08	20
Bone	02	5

Table 2. Anti-tumor activity (Intention-to-treat analysis).

Response	No. of patients	Percentage
Confirmed response	13	32.5
Complete response	02	5.0
Partial response	11	27.5
Stable disease	11	27.5
Progressive disease	11	27.5
Not assessable	05	12.5

The median time taken to progression for all patients was 4.1 months (95% confidence interval {CI} 2.7 - 5.6) and the median survival was 11.2 months (95% CI 7.2 - 14.1).

A total of 142 treatment cycles (median three, range one to seven) were administered, of which 135 cycles were assessable for safety. The remaining seven cycles in five patients were not assessable for safety. The frequencies of hematological and non-hematological adverse events are shown in **Tables 3** and **4** respectively. The most common grade 3 hematological adverse events were neutropenia, which occurred in 30% of the patients. One patient experienced febrile neutropenia. The most common grade 3 non-hematological adverse event was nausea (20%) followed by vomiting (15%), diarrhea (10%), stomatitis (5%), peripheral neuropathy (5%). Grade 3 hand-foot syndromes occurred only in 5% of the patients. There were no treatment related deaths during the study.

Treatment was delayed in 46 cycles and dose was reduced in 8 cycles. Treatment doses were modified in patients suffering from for hematological toxicity, nausea, vomiting, diarrhea, stomatitis, peripheral neuropathy, and hand-foot syndrome.

4. Discussion

Many chemotherapy trials have been focused on biliary tract cancer with mixed results [1]-[6] [8] [10] [11] [13] [16]-[20]. Gall bladder cancer behaves differently from the rest of the biliary tract due to its different etiology, biological behavior and response to modality of treatment. Isolated chemotherapy trials for carcinoma Gallbladder have been difficult due to less number of patients in different geographical regions [7] [9] [12] [14]. However Gangetic belt is a fertile ground for carcinoma Gallbladder [21].

Response rate and overall survival with ECF regimen have been reported to be 29% - 40% and 6.4 - 11 months [11]-[14]. Gemcitabine either alone or in combination has shown improved survival rate with median overall survival of 11.5 months [7]-[10] [17] [18]. A phase II study combining fractionated cisplatin and de Gramont (5-FU and Leucovorin) regimen suggested improvement compared with classical 5-FU and cisplatin combination [11]-[13], and in terms of safety and efficacy [19]. A prospective phase III study using numerous chemotherapy agents has been reported with better results. Large randomized prospective studies on the

Table 3. Hematological adverse effects.

Hematological complications	Grade (Percentage of cycles)				Grade (Percentage of patients)			
	1	2	3	4	1	2	3	4
Anemia	48	12	3	1	33	30	7	5
Leucopenia	32	8	2	0	35	15	10	5
Neutropenia	17	12	3	0	10	12	30	0
Thrombocytopenia	22	5	2	2	40	15	5	0

Table 4. Non-hematological adverse effects.

Hematological complications	Grade (Percentage of cycles)				Grade (Percentage of patients)			
	1	2	3	4	1	2	3	4
Nausea	28	20	5	0	37	15	20	0
Vomiting	20	17	3	0	32	10	15	0
Diarrhea	15	12	5	0	25	5	10	0
Stomatitis	5	10	2	0	10	10	5	0
Peripheral neuropathy	5	5	2	0	10	5	5	0
Hand-foot syndrome	30	5	2	0	40	20	5	0
Myalgia	15	5	5	0	30	15	5	0

use of adjuvant therapy are lacking, and any recommendations are based on small studies and meta-analysis [22].

The results of the present study suggest that combination of 5-fluorouracil, cisplatin and paclitaxel is active and well tolerated as first-line chemotherapy for advanced gall bladder cancer. The overall response rate (32.5%), median time taken to progression (4.1 months) (**Figure 1**) and median survival (11.2 months) (**Figure 2**) following treatment with 5-fluorouracil, cisplatin and paclitaxel are comparable with results reported previously. Toxicity profile of 5-fluorouracil, cisplatin and paclitaxel is acceptable with the only major grade adverse effect being neutropenia.

5. Conclusion

Carcinoma Gallbladder is one of the most aggressive malignancies and complete resection is the only hope for cure. Most patients come at a very advanced stage with surgically unresectable tumor. Adjuvant therapies with

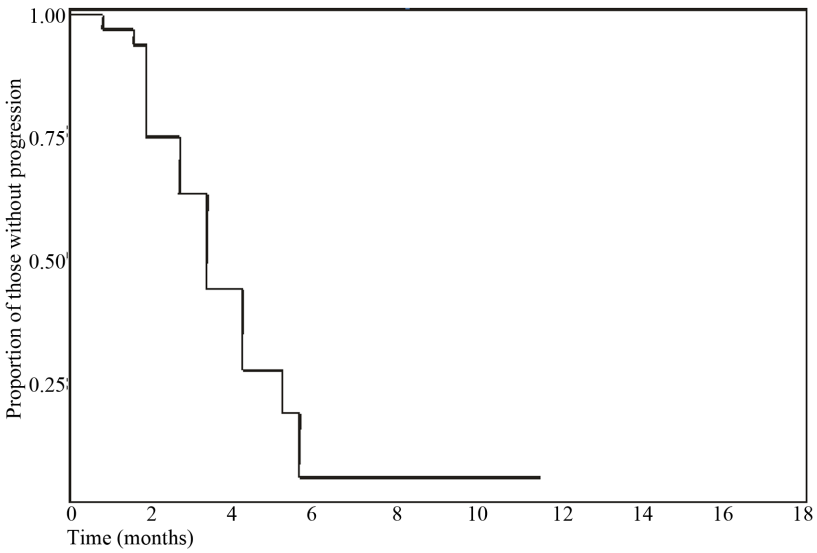

Figure 1. Kaplan Meier Curve for time to progression.

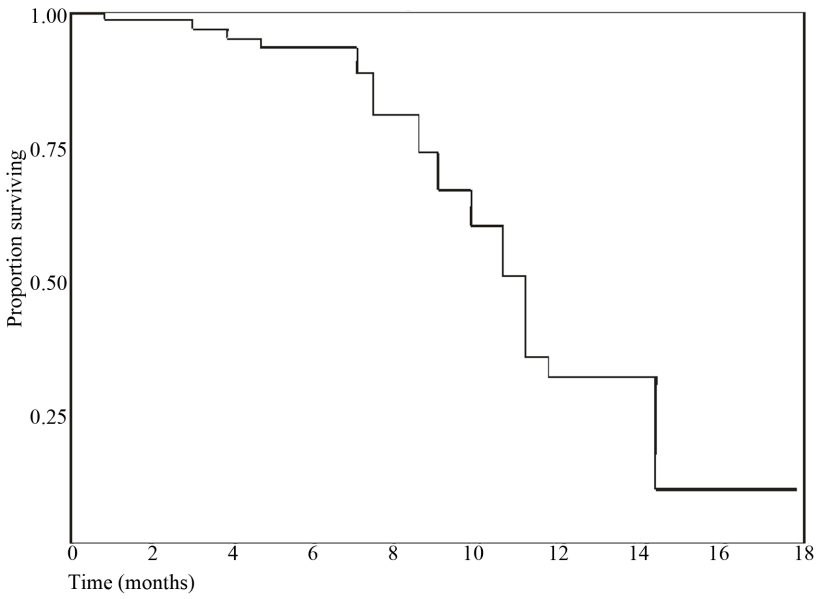

Figure 2. Kaplan Meier Curve for overall survival.

5-fluorouracil, pacliatxel and cisplatin are well tolerated. Large prospective randomized trials are required to compare its efficacy and low toxicity.

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