ORIGINAL ARTICLE

Clinical Efficacy of Adjuvant Therapy in Unresectable Gallbladder Cancer: our experience from south Punjab

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ABSTRACT

Aim: Gallbladder carcinoma (GBC) commonly present at an advanced unresectable stage. We sought to compare efficacy of gemcitabine alone and in combination with radiotherapy as adjuvant treatment of GBC.
Study Design: Quasi-experimental study.
Place & Duration of Study: Nishtar Hospital Multan from July 2012 to June 2013.
Methods: Fourty six confirmed cases of unresectable GBC were randomly allocated in two groups. Group-I received gemcitabine alone and Group-II received gemcitabine and radiotherapy.
Results: Combination of gemcitabine and radiotherapy achieved better clinical efficacy as adjuvant treatment.
Conclusions: Radiation therapy using Gemcitabine as radiosensitizer is more beneficial in control of disease.
Keywords: Gallbladder carcinoma, gemcitabine, radiotherapy.

INTRODUCTION

Gallbladder cancer (GBC) is the most common and most aggressive hepato biliary tree cancer. The reported incidence of the disease varies by geographic region and racial-ethnic groups. Pakistan is amongst the countries with the highest incidences of GBC including India, Chile, Bolivia, and Israel. In Pakistan, the incidence of disease is has been reported as 3-5% in certain high risk populations [1]. At present, there is no clear understanding on the reasons for high incidence in these populations. The important risk factors associated with GBC include chronic gall stones, porcelein gallbladder, inflammatory bowel disease, occupational chemical exposure, estrogen excess, chronic typhoid infection, obesity and multiparity. Females have preponderance of disease especially early in life as compared to males [2]. Symptoms of GBC are non-specific in early course of disease and cannot be differentiated from other common conditions like chronic cholecystitis. Therefore, early diagnosis of GBC is an incidental finding on cholecystectomy samples. Tumors restricted to lamina propria only are surgically curative. The patients suitable for curative surgery include only 10% and the rest are diagnosed in advanced and unresectable stage. At the time of diagnosis, 50% are found to have metastasis to lymph nodes making them candidates for palliative treatment only. GBC has an abysmal prognosis and untreated patients have a median survival of 6 months[3]. To provide palliation of symptoms, radiation therapy (RT) with or without concurrent chemotherapy is used. Historically, 5-fluouracil has been in advanced disease as a bolus or as an infusion with response rates of 10-24%. Presently, clear standards for chemotherapy in GBC do not exist[4].

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Since gallbladder is embryologically similar to pancreas, for this reason Gemcitabine was tried in biliary malignancy recently. Gemcitabine is a cystidine analog and interferes with S phase of cell cycle by inhibiting ribonucleotide reductase. Gemcitabine offers a favorable toxicity profile and has shown to increase survival in a study using gemcitabine as a single agent for GBC. During palliative treatment, chemotherapeutic agents tend to act as radiosensitizer leading to reduction of radiation dose and producing a better response. Gemcitabine has been described as a potent radiosensitizer but still there is no consensus on the optimal radiosensitizing dose [5]. This study was designed to compare the efficacy of Gemcitabine as a single agent and its role as a radiosensitizer combined with RT in terms of response rate and relief of symptoms in patients of advanced unresectable GBC.

SUBJECTS AND METHODS

This experimental study was conducted at Nishtar Hospital Multan from July 2012 to June 2013 after taking approval from hospital ethical review board. All the females and male patients with histopathologically proven diagnosis of gallbladder carcinoma presenting in Department of Oncology of Nishtar Hospital and no prior chemotherapy or radiotherapy history were enrolled for this study. Criteria for inclusion in the study: a) adequate marrow reserve (Hemoglobin level >9g/dl, Total leucocyte count >4000/mm^3, Absolute Neutrophil Count >2000/mm^3, Platelet count >100,000/mm^3); b) renal parameters within normal range; c) liver function tests not deranged; d) Karnofsky performance score of 60 or above; e) Life expectancy of 3 months or greater; and f) normal x-ray chest [6]. The patients who refused to participate in the study, had prior chemotherapy or radiotherapy were excluded. Thorough evaluation of all the study patients was done including history of the patient indicating the history of present illness, duration of symptoms, presenting symptoms (pain in right hypochondrium, nausea, vomiting, anorexia, weight loss, and palpable mass), past medical history, personal history (dietary habits, any drug abuse,

any chronic ailment), socio-economic status and family history was recorded. Physical examination of patients included recording of pulse, blood pressure, temperature, respiratory rate, signs of jaundice and abdominal inspection and palpation for any mass. All patients required a pre-treatment abdominal ultrasound and abdominal computed tomography (CT) imaging indicative of the current status of disease, a size of mass or residual lesion in at least two dimensions. The presence or absence of ascites was recorded. Blood counts, renal parameters and liver function tests were obtained prior to start of therapy.

The patients were randomly allocated to one of the two study groups. Group-I received Gemcitabine 1000 mg/m^2 and Group-II received Gemcitabine 200 mg along with radiation therapy. The primary end point was the determination of response rate in two study arms. Secondary end point was the alleviation of symptoms. The protocol was carried out according to the plan. The patients receiving chemotherapy alone (Group-I) received Gemcitabine in doses of 1000 mg/m^2 on day 1, 8, and 22 of therapy for a total of three cycles. The patients receiving chemo-radiation (Group-II) were given Gemcitabine 200 mg starting on day one of planned radiation and followed on weekly basis till the completion of radiation. Planned radiation dose was 4500 centigray (cGy) midpoint tumor dose being delivered to right hypochondrium using shrinking field technique. Dose was 180 cGy per day, five days a week and the total span of radiation therapy was five weeks. Initial port was marked encompassing the gallbladder bed and regional lymph nodes and radiation dose of 180 cGy was delivered for first 14 days. After 14 days, by ultrasound evaluation the portal was reduced to the tumor site. This technique was adopted keeping in view the tolerance limit of liver. Later with reduced portal, the tumor area was radiated for the remaining period. Patients were evaluated by taking history and a detailed physical examination at each follow up visit. The response was categorized as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) on the basis of complete disappearance of all clinically detectable disease, 50 % reduction in measurable disease, neither is there regression nor progression of the disease and disease worsens in spite of treatment respectively. Data was entered and analyzed on SPSS version 17.

For continuous variables, mean and standard deviation (age, height, weight) were calculated and presented in tabulated form while simple frequencies and corresponding percentages of the categorized variables were calculated and presented in tabulated form. Association among different variables was calculated through Chi square Test and its significance was checked through its corresponding P-value. P-value equal to or less than 0.05 had been taken as statistically significant to show association for factors responsible.

RESULTS

The study participants were 46 patients with histopathologically proven GBC. At workup, all had advanced/unresectable disease. They consisted of 20% male and 80% female patients. As shown in Table 1, the median age was 62 years (range 40-72 years). In Arm A (Gemcitabine alone) stable disease was seen in 10 patients (%) while 13 patients (44%) showed progressive disease. In Arm B (Gem+RT), 18 patients (56%) had stable disease while 5 patients (16%) suffered from progressive disease. There was no complete response (CR) in either of the two arms. Regarding symptom relief, 8 patients (32%) in Arm A had pain relief and improvement of appetite while 17 patients (68%) didn't show any benefit. In Arm B 20 patients (80%) had symptom relief while 5 patients (20%) had stable symptoms. When the response rates were adjusted for variables such as age, sex, performance status, number of metastatic lesions, prior surgery, there was no statistically significant correlation between response rates and these variables. Pearson Chi Square test (P>0.05) was applied to determine the statistical significance of the study as the analysis was mainly qualitative in nature (Table 2). The test indicated that chemo radiation using Gemcitabine as a radiosensitizer is a better modality for the control of disease & offers a better palliation.

Table 1. Distribution of study participants according to age-groups

Age (years)	n
40-50	05(12%)
51-60	18(38%)
61-70	22(48%)
71-80	01(2%)
Total	46(100%)

Table 2. Contingency table showing treatment outcome of two study arms calculating significance of Pearson's Chi-square statistic

Groups	Stable	Progressive	Total
Gemcitabine alone	10	13	23
Radiotherapy plus Gemcitabine	18	05	23
Total	28	18	46

The chi-square statistic is 4.47 (Yates correction).
The P-value is 0.034.
The P-value is significant at $P < 0.05$.

DISCUSSION

There is no standard treatment regimen for advanced/unresectable GBC, thus requiring adjuvant therapeutic agents including radiation therapy and chemotherapy. Previously 5FU has remained the mainstay for chemotherapy but recently newer drugs like Gemcitabine, has shown promising results[7]. This study was conducted using quasi-experimental study design to compare the efficacy of Gemcitabine as a single agent against Gemcitabine as radiosensitizer combined with radiation therapy among patients with advanced, unresectable GBC. Based on the data of studies from advanced pancreatic cancer, gemcitabine has also been evaluated in biliary cancers. As a single agent, gemcitabine showed only moderate efficacy with response rates (RRs) ranging from 0% to 30% [8]. Gemcitabine has been found to be able to achieve a longer overall survival time (9.1 vs. 2.9 months, respectively) than any of the best supportive care strategies examined, yielding a disease control rate of 69.2% at the 1-year post-chemotherapy follow-up [9]. One study conducted in Pakistan revealed that combination chemotherapy using Gemcitabine and Cisplatin in

advanced Gallbladder cancer is more effective in control of disease[10].

Similarly the role of chemo-radiation has been investigated in a few trials and showed promising results. Application of radiation therapy in addition to chemotherapy or the drug used as radiosensitizer has been tried using 5FU, Cisplatinand Gemcitabine[11]. It is well-known that radiation therapy is effective in control of pain and reduces the pressure effects. Similarly many advanced stage patients have benefited from radiotherapy alone for palliation[12]. Published data reveals that radiation therapy has been applied in various forms i.e. conformal RT, intra-operative RT, and ERT [13]. Studies have highlighted that addition of radiotherapy to surgery or chemotherapy has produced positive results in terms of disease control without pronounced side-effects[14,15]. Keeping in view these findings, we planned this clinical trial to see the outcome of two therapies in terms of response and alleviation of agony in our population where the disease is usually inoperable or unresectable.

CONCLUSIONS

Our study has revealed that radiation therapy using Gemcitabine as radiosensitizer is more beneficial in control of disease as response rate of 84% was observed in patients who received radiation therapy along with Gemcitabine.

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