Original Article

Effects of chemotherapy on patients with unresectable or metastatic adenocarcinoma of gallbladder

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Abstract

Objective: To evaluate the effect of combination chemotherapy on disease status, toxicity and survival of patients with unresectable locally advanced or metastatic adenocarcinoma of gallbladder.

Methods: Single arm study of twenty patients, with unresectable locally advanced or metastatic adenocarcinoma of gallbladder, who presented to oncology clinic at Ziauddin Hospital Nazimabad Karachi from January 1997 to December 1998. Patients received combination of 5-Fluorouracil (5FU) and Folinic Acid daily for five days.

Results: Out of twenty patients, two (10%) were males and eighteen (90%) were females. Twelve (60%) patients showed symptomatic relief for a mean duration of 4.7 $\pm$ 3.2 months. Disease remained stable in ten (50%) patients, progressed in nine (45%), and one (5%) showed partial remission of disease. Toxicity with chemotherapy was acceptable, without severe side effects. None of the patients suffered from febrile neutropenia. Overall survival was 13.6 $\pm$12.3 months.

Conclusion: 5-Fluorouracil with Folinic acid therapy does not result in significant objective responses, however, stabilization of disease process occurred in 55% of patients. Symptomatic relief was observed more frequently. This combination deserves further evaluation (JPMA 57:71;2007).

Introduction

Primary gallbladder carcinoma (GBC) is the most common malignant tumor of the biliary tract and the fifth most common cancer of the digestive tract.[1] In the United States and European countries, carcinoma of the gallbladder is an uncommon tumor accounting for less than 2% of all cancers reported annually. There are 6000 to 7000 new cases of gallbladder cancer reported annually in the United States.[2]

However, in certain parts of the world, it is a very common disorder. The reasons for these geographical or ethnic variations for biliary tract cancer are not clear, but some unknown environmental risk factors or a genetic susceptibility are suspected.[1]

The frequency of the gallbladder tumour is higher in Pakistan as compared to other countries like Iran, Turkey and Bangladesh.[3] Similarly, it is the most lethal cancer observed in Chilean women.[4] Comparable rates have been reported from Bolivia and Mexico. In Thailand, cancer of the biliary tract is the commonest cancer observed.[5]

The frequency increases with age and reaches a maximum during the seventh decade of life. The higher frequency of gallbladder tumour in females is also notable and it has been reported as the second commonest malignancy of gastrointestinal origin in females.[6] The tumour is associated with gallstones in more than 70% of case s and cholelithiasis played a significant role. Despite this observation there is still a debate about the true relationship between the two conditions.[7]

There seems to be a higher risk of carcinoma in a gallbladder with a calcified wall: i, e. porcelain gallbladder. Some reported that gallbladder cancer is associated with an anomalous high union of pancreatic and common bile ducts.[8]

The commonest histological type is adenocarcinoma. This may be glandular, medullary, scirrhous, papillary or colloid. It appears that papillary form may have a better prognosis than the nodular infiltrate form. Occasionally, undifferentiated carcinoma, squamous cell carcinoma, adenoacanthoma, carcinoma in situ and a mixed group of rarities are reported.[9]

Gallbladder cancer is an aggressive disease and carries extremely poor prognosis. Tumors are usually asymptomatic until they reach an advanced stage. Hence, most patients present with extensive disease. Overall survival rate is about 5% and median survival is 6 months.[10]

There is no effective therapy for vast majority of patients with gallbladder cancer who present with either locally advanced or metastatic disease. The role of aggressive surgery in gallbladder cancer has remained controversial.[11]

Till now chemotherapy or radiation therapy have not proved to be of substantial benefit.[12] A number of chemotherapeutic regimens have been developed to treat

unresectable cancer of the gallbladder. These regimens have generally used 5-fluorouracil (5FU) alone and in combination with a variety of other agents. But none appears to be more effective. Response rate to chemotherapy is low, duration of response is short and there is no improvement in overall survival.[13] Response rate to 5-Fluorouracil is about 20%. Combination chemotherapy may yield slightly higher response rate, however, it is more toxic and no survival benefit is observed.

Due to lack of any effective treatment, we prospectively treated 20 patients, with locally advanced or metastatic adenocarcinoma of gallbladder, with 5FU, which has been used widely in gastrointestinal malignancies and Folinic Acid was added to enhance the efficacy of 5FU.

Patients and Methods

This single arm study was started after approval from hospital ethics review committee. Twenty patients with unresectable locally advanced or metastatic adenocarcinoma of gallbladder were selected, presenting to oncology clinic at Ziauddin Hospital, Karachi from January 1997 to December 1998. Record forms, flow sheets and toxicity cards for each study patient were filled and maintained regularly. Toxicity was recorded according to National Cancer Institute (NCI) common toxicity criteria (CTC). All patients provided informed consent before starting treatment.

Histologically confirmed, radiotherapy or chemotherapy naïve patients with unresectable, locally advanced or metastatic adenocarcinoma of gallbladder, age > 18 years, with Eastern Cooperative Oncology Group (ECOG) performance status of <3 were included. They were also required to have at least one bidimentionally measurable lesion, either by physical or radiological examinations. Liver enlargement due to metastases was acceptable as measurable disease if it extends more than 5 cm below the costal margin in the mid clavicular line. Liver metastases were acceptable as measurable disease if the largest diameter of at least one of the lesion was 4 cm or more on ultrasonography or CT Scan. Other eligibility criteria included adequate haematological, hepatic and real function tests as defined by WBC > 4000/cmm, platelets >100,000/cmmm, creatinine within normal range and creatinine clearance of >60 ml/minute, bilirubin, SGOT, SGPT< twice normal. Non-pregnant and non-lactating patients, and able to give written informed consent were included.

Patients who had received prior chemotherapy or radiotherapy to the only area of measurable disease, and patients who were infected or had serious complications of surgery were excluded.

Patients suffering from severe cardiovascular disease such as myocardial infarction in the last 3 months, unstable angina, uncontrolled hypertension and significant arrhythmias, or patients suffering from central nervous system disease or psychosis were also excluded.

Patients with a prior or concomitant second primary tumor except for non-melanoma cancer of skin or carcinoma in-situ of cervix were not included.

Complete history and physical examination including detailed account of the prior surgery and determination of the performance status were recorded.

Determination of height weight and surface area and measurement of disease parameters were noted. Complete blood counts, Urine analysis, Blood biochemistry including LFT's, alkaline phosphates, serum albumin and LDH, Renal function tests, Serum CEA levels were checked. Radiological studies including chest X-ray, CT Scan and Ultrasound were done.

Treatment consisted of a 3-week cycle. The drug was administered as follows:

Inj: Folinic acid 20mg/m^2 (D1 to D5)

Inj: 5FU 425mg/m^2 (D1 to D5)

Daily on day care basis for 5 days, and was repeated after 28 days. Folinic Acid was given before 5-FU as intravenous infusion in 60 minutes and then 5-FU was given as slow I.V.push.

At least 2 cycles of chemotherapy were given before the first evaluation.

A patient who developed grade III or IV gastrointestinal, haematological or renal toxicity would have a 25% reduction in the dose of chemotherapeutic agents.

Therapy would be delayed in the presence of grade III and IV toxicity (except nausea, vomiting, or alopecia) till recovery from these side effects.

Patients who would have more than 4 weeks delay in therapy due to toxicity would be excluded from the study.

Use of any other cytotoxic drug or hormonal therapy was not permitted. Other drugs such as for diabetes, hypertension, were permissible. Type of anti-emetic therapy was at the discretion of the investigator.

Results

Twenty patients (2 males and 18 females, ratio 1:9) were enrolled according to the inclusion and exclusion criteria. Thirteen patients had stage IVa and seven had stage IVb disease.

The mean age of the patients was 52.8 $\pm$ 8.4 years (range 35-66). Eight percent of patients had ECOG performance status of 0; 12% had performance status of 1, 46% had performance status of 2, and 34% of patients had performance status of 3.

Among all patients, a total of 87 chemotherapy cycles were delivered (Mean 4.3 with a minimum of 2 cycles). One patient had a partial response and 10 had stable disease. Nine patients showed progressive disease.

Survival was calculated from the date of starting chemotherapy. Median survival was 6 months and overall survival was 6.8 (3.7) months. All the responders achieved response after the second cycle.

Duration of relief / response was 5.9 $\pm$ 3.3 months, and overall survival was 6.8 $\pm$3.7 months.

Toxicity profile was acceptable. None of the patients suffered febrile neutropenia, therefore no dose reduction was required. Chemotherapy side effects included, anorexia 35%, stomatitis 25%, nausea 15%, and diarrhoea 10%.

Discussion

A higher frequency of gallbladder cancer (GBC) has been observed in Pakistan as compared to other countries.[3] The frequency varies from 6-8%. GBCs were found in 1% to 2% of surgeries on the biliary tract.[1] Surgery is the standard treatment for gallbladder and biliary tract cancer. However, curative tumor resection is possible only in a small number of the patients who are otherwise surgical candidates. Despite recent advances made in early detection and surgical management of other cancers related to better radiological and surgical techniques, improved delivery of anaesthesia and supportive care, prognosis of patients with these cancers has not improved significantly and no progress has been made in the treatment of gallbladder malignancy.[11]

Little data is available in literature for comparison of results. Most series include gallbladder cancer in biliary system along with bile duct cancers. Therefore direct comparison is difficult.

There are several trials reported in the literature utilizing systemic chemotherapy for the management of these patients. Most of these studies are based upon small number of patients. Response to 5-fluorouracil was observed in 10 out of 70 patients reported in three different trials.[14-16] Similarly disappointing results have been reported with the use of streptozocin, and methyl-CCNU.[14] Response rate of 47%to mitomycin-C was reported in a small series[15], which could not be confirmed in a subsequent study. 5-fluorouracil has been widely used in the oncologic practice and it has shown some efficacy in Gallbladder malignancy.[16] It has been demonstrated that concurrent administration of Folinic acid with 5-fluorouracil enhance the efficacy of 5-fluorouracil and thereby increasing the cytotoxicity of 5-fluorouracil.[17] Many clinical trials have demonstrated that efficacy of 5-fluorouracil can be enhanced by giving Folinic acid before the delivery of 5-fluorouracil.[18] Recently in phase II trials gemcitabine with cisplatin have been used in patients with unresectable or metastatic gallbladder cancer. These trials have shown better results as compared to previously used regimens in this type of malignancy[19,20] but currently none of the regimen is established as standard of care in this type of malignancy.

Approximately 30% response rate has been observed with Gemcitabine. Other drugs such as Cisplatin and Capecitabine have also been used. These agents have been tried in too small a number of patients to be clinically meaningful. Similarly, combination chemotherapy has resulted in disappointing results. There is a desperate need to identify new agents and combinations that may be effective in the management of locally advanced or metastatic gallbladder cancer.

Conclusion

5-Florouracil with Folinic acid therapy does not result in significant objective responses, however, stabilization of disease process occur in several patients. Symptomatic relief was observed more frequently. This combination deserves further evaluation and might need addition of other cytotoxic drugs.

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