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Original Article

A Retrospective Study on Demographic Characteristics, Response, and Survival of Unresectable or Metastatic Gallbladder Cancer Patients Treated with Chemotherapy

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Abstract

Introduction: Gallbladder cancer (GBC) is the most common biliary tract malignancy worldwide. It arises from the epithelial lining of the gallbladder or the cystic duct. It manifests either as a gallbladder wall thickening or a mass lesion in the fundus, body, or neck of the organ. Other biliary tract malignancies include intrahepatic and extrahepatic cholangiocarcinoma. In most of the clinical trials, these entities have been clubbed together as one disease and treated similarly. GBC represents 80–95% of biliary tract cancers worldwide, according to autopsy studies.

Materials and Methods: The present study was single-institution retrospective cohort study. This study was conducted from January 1, 2017, to June 31, 2020, at Apollo Multispecialty Hospitals Ltd., Kolkata.

Results: In our study, 61.3% of patients had gallbladder stone and 38.7% did not. We documented gallbladder stone in our study population from a history or baseline imaging study. Our study revealed a lower proportion of gallbladder stone associated with cancer which was probably because a majority of GB stones are radiolucent and hence missed on X-ray-based imaging like computed tomography scan.

Conclusion: Overall response rate and progression-free survival to second-line chemotherapy were 37.5% and 2.85 months, respectively. Some of the patient and disease characteristics such as low body mass index, poor performance status, and metastatic disease adversely affected survival.

Key words: Computed tomography scan, Extrahepatic and carcinoma, Gallbladder cancer

INTRODUCTION

Gallbladder cancer (GBC) is the most common biliary tract malignancy worldwide. It arises from the epithelial lining of the gallbladder or the cystic duct. It manifests either as a gallbladder wall thickening or a mass lesion in the fundus, body, or neck of the organ. Other biliary tract malignancies include intrahepatic and extrahepatic cholangiocarcinoma. In most of the clinical trials, these entities have been clubbed together as one disease and treated similarly. GBC represents 80–95% of biliary tract cancers (BTCs) worldwide, according to autopsy studies.[1] The global rates for GBC exhibit striking variability, reaching epidemic levels for some regions and ethnicities. In most instances, GBC develops over 5–15 years, when metaplasia progresses to dysplasia, carcinoma *in situ*, and then, invasive cancer. Progression is frequently rapid and silent, portending an abysmal prognosis. The dismal prognosis, in part, relates to the gallbladder lacking a serosal layer adjacent to the liver, enabling hepatic invasion and metastatic progression. Silent in its infancy, this malignancy remains asymptomatic until aggressive disease has progressed to an advanced and non-curative stage. It is either detected incidentally at the time of cholecystectomy or when it presents with complications due to local spread of the malignancy in the form of jaundice, hepatomegaly, ascites, or duodenal

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obstruction. A satisfactory outcome depends on an early diagnosis and surgical resection. Despite this potential for cure, <10% of patients have tumors that are resectable at the time of surgery, while nearly 50% have lymph node metastasis. Even after surgery, most progress to metastatic disease, highlighting the importance of improving adjuvant therapies.[2] Advanced, unresectable, or metastatic disease is incurable and usually treated with palliative chemotherapy. However, even with chemotherapy, the median survival has failed to go beyond a year. There is no salvage chemotherapy regimen approved so far. Hence, there is an unmet need to develop newer strategies in this patient group to improve outcome.

Vague abdominal symptoms often mask a more worrisome diagnosis contributing to its overall progression and poor outcome. Patients with GBC may present with a number of nonspecific complaints, such as anorexia and weight loss, as a precursor to jaundice. Imaging can detect malignancy. Ultrasound, readily available, might reveal a polypoidal gallbladder mass and perhaps invasion of adjacent structures. Incidental findings include the presence of cholelithiasis and calcification, in the form of the porcelain gallbladder. Wall thickness (>3 mm) and enhanced vascularity are sonographic features that can also signify potential malignancy.[3] Computerized tomography (CT) helps identify any extension to lymph nodes, liver involvement, or distant metastases. Fluorodeoxyglucose positron emission tomography (PET) scanning captures the uptake of fluorodeoxyglucose by tumor cells. PET scans are useful in differentiating malignant from benign disease. Based on three well conducted randomized controlled trials, the current standard of care for advanced GBC (A-GBC) is a gemcitabine-platinum doublet which entails a median survival of 9.5–11.7 months.[4] The first trial that established the doublet therapy was the ABC-02 trial which cemented the place of gemcitabine-cisplatin combination chemotherapy in the first-line setting. The combination of gemcitabine and oxaliplatin (GEMOX) has shown promising activity in this setting as well. An international Phase II study evaluated the efficacy and safety of GEMOX as first-line therapy in patients with advanced BTCs. In this study, GEMOX, albeit, demonstrated activity in non-gallbladder BTCs, but poor activity in gallbladder carcinoma.[5]

Aims and Objectives

The aim of the study is to evaluate the demographic characteristics of the patients and their response to treatment and survival and also analyze the various palliative chemotherapy regimens used in the 1st and 2nd line setting of unresectable or metastatic carcinoma of gallbladder in terms of response rate, progression-free and overall survival.

Objectives

Demographic characteristics

The objectives of the study were to evaluate demographic characteristics of patients with unresectable or metastatic carcinoma of gallbladder.

Response rates

The objectives of the study were to calculate response rates of patients with unresectable or metastatic carcinoma of gallbladder treated with chemotherapy.

Progression-free survival (PFS)

The objectives of the study were to analyze PFS in patients with unresectable or metastatic carcinoma of gallbladder after being treated with the 1st or 2nd line chemotherapy.

Overall survival

The objectives of the study were to analyze overall survival of patients with unresectable or metastatic carcinoma of gallbladder treated with palliative chemotherapy.

MATERIALS AND METHODS

Study Site

Apollo Multispecialty Hospitals Ltd., Kolkata (formerly, Apollo Gleneagles Hospital, Kolkata).

Study Population

Patients diagnosed with unresectable or metastatic gallbladder cancer, who received palliative chemotherapy in the Department of Medical Oncology in Apollo Multispecialty Hospitals Ltd., Kolkata (formerly, Apollo Gleneagles Hospital, Kolkata).

Study Design

This was a single-institution retrospective cohort study.

Study Period

The study period was from January 1, 2017, to -June 31, 2020.

Inclusion Criteria

The following criteria were included in the study:

- Patients with histopathology or cytology-proven diagnosis of gallbladder carcinoma
- Patients with unresectable or metastatic disease – Stages III (inoperable)-IV disease by AJCC TNM staging with appropriate imaging as per clinical practice
- Age ≥18 years
- Patients who are either treatment naïve or did not receive more than 1 line of chemotherapy
- Patients who received chemotherapy (at least one cycle) at Apollo Hospital, Kolkata.

Exclusion Criteria

The following criteria were excluded from the study:

- Those who received chemotherapy or targeted therapy elsewhere
- Those who received radiotherapy with curative intent
- Those who have hyperbilirubinemia (serum bilirubin over 3 mg/dl).

Statistical Analysis

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS 24.0 and GraphPad prism version 5. A Chi-squared test (χ^2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a Chi-squared distribution when the null hypothesis is true. Without other qualification, "Chi-squared test" often is used as short for Pearson's Chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. $P \leq 0.05$ was considered for statistically significant.

RESULTS AND DISCUSSION

The aim of this study was to acquire knowledge about the demographic characteristics of the patients afflicted with unresectable or metastatic gallbladder cancer who came for treatment at our institute.

Body Mass Index (BMI)

BMI is a statistical index using a person's weight and height to provide an estimate of body fat in males and females of any age. The National Institute of Health (NIH) now uses BMI to define a person as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2).[6] Baseline BMI of all patients was calculated from height and weight documented on the day of administration of first cycle chemotherapy. They were then classified into the above-mentioned four groups. Various studies from India, mostly of case–control design, revealed that patients with GBC have lower BMI compared to their healthy counterparts. In our study, 85.5% of patients had a BMI of <30 kg/m^2 while only 14.5% of patients were obese. This finding is at par with the figures found in various Indian series. Low BMI is generally a surrogate for poor or malnutrition, which may be associated with suboptimal immune status and a pro-inflammatory state secondary to micronutrient and antioxidant deficiency; both of which, in turn, can promote malignancy. In our study, only 6 patients (9.6%) were underweight. Being a tertiary care private institution, usually patients from medium to high socioeconomic strata are treated here. Hence, this low incidence of underweight patients in our study population may not be representative of the true picture prevailing in the country.

Gallbladder Stone

Various studies in India have documented presence of gallstone in 70–90% of patients with GBC. Certain studies have a lower rate, possibly due to problems with detecting them on ultrasound when they are entrapped within a mass. Another reason is that most gallstones are radiolucent and they may or may not be picked up on CT scan.

In our study, 61.3% of patients had gallbladder stone and 38.7% did not. We documented gallbladder stone in our study population from a history or baseline imaging study. Our study revealed a lower proportion of gallbladder stone associated with cancer which was probably because a majority of GB stones are radiolucent and hence missed on X-ray-based imaging like CT scan. Even with this limitation in documentation of gallstones in our patients, our percentage of gallstones (61.3%) was close to the Indian data (70%).

Treatment Received 1st Line Chemotherapy

In the first-line setting, patients received a variety of chemotherapy regimens. Of the 62 who received chemotherapy, majority of patients (56.5%) got gemcitabine plus cisplatin regimen. The second most common regimen was gemcitabine plus oxaliplatin (17.7%). About 14.5% of patients received gemcitabine monotherapy. Others received gemcitabine plus carboplatin, gemcitabine plus capecitabine, and gemcitabine plus nab-paclitaxel. Only one patient received non-gemcitabine-based chemotherapy with capecitabine.

PFS to 1st Line Chemotherapy

Median PFS was 5.33 months (0.2–34.8) in our study. Gemcitabine monotherapy produced a median PFS of 2.87 months. Gemcitabine plus cisplatin doublet showed a median PFS of 5.43 months while the third group where patients received gemcitabine doublets other than with cisplatin had a median PFS of 6.73 months. The difference was statistically significant. Hence, gemcitabine-based doublet is significantly superior to gemcitabine monotherapy in terms of PFS. In our study, patients who received gemcitabine in combination with platinum agents (cisplatin, carboplatin, or oxaliplatin) showed significant improvement in PFS over those who did not (6.73 months vs. 2.87 months). In the ABC 01 trial, median progression-free survival was 8.0 months in the cisplatin plus gemcitabine group and 5.0 months in the gemcitabine-only group. A small study[7] was undertaken to evaluate the efficacy and safety of combined chemotherapy of gemcitabine and carboplatin in 20 patients. The median time to progression of the tumor was 33.8 weeks or 7.8 months. To sum up, PFS to first-line chemotherapy in A-GBC is approximately 8 months with doublet chemotherapy and 5 months with gemcitabine monotherapy. In our study, the PFS was on the

lower side due to a few reasons. First, the study population received a variety of chemotherapy regimens from single-agent therapy to doublet chemotherapy. Second unlike the clinical trials, we included a number of patients who had a performance status (PS) of ECOG 2. Patients with poor PS who had poor prognosis from the outset brought down collective PFS of the whole study population.

Overall Response Rate (ORR) to 2nd Line Chemotherapy

ORR was 37.5%. There was no complete response. Progressive disease was seen in 8 patients (50%). In 2 patients (12.5%), the disease was stable. Six patients (27.3%) could not be evaluated for response as they died even before the first imaging study could be done after start of 2nd line chemotherapy. ORR in our study was slightly higher than what we find in literature. Of the six patients who showed partial response, four had received capecitabine plus oxaliplatin (CAPOX) chemotherapy. The other two responses were to capecitabine monotherapy and paclitaxel. CAPOX chemotherapy was the only regimen that stood out among all other 2nd line agents with 80% success rate. Here, by success rate, we mean the rate of responses produced by one particular chemotherapy regimen. Success rates of paclitaxel and capecitabine monotherapy were 50% and 16.6%, respectively.

Overall Survival

In our study, the median overall survival of all patients who received systemic chemotherapy was 8.9 months. Systemic chemotherapy has shown significant but modest survival benefit in the management of A-GBC. Most studies have included gallbladder cancer in the fold of BTCs. Only few clinical trials were performed exclusively in patients with GBC. In these earlier trials, overall survival was around 7 months. A pooled analysis suggested differences in effectiveness of chemotherapy between gallbladder and other BTCs. Subgroup analysis showed shorter overall survival for GBC compared to cholangiocarcinoma (7.2 vs. 9.3 months). In the seminal ABC 2 trial, median overall survival was 11.7 months in the cisplatin-gemcitabine group and 8.1 months in the gemcitabine group.[8] The groupe coopérateur multidisciplinaire en oncologie study evaluated 56 patients with gallbladder and BTCs. These patients were treated with GEMOX combination. The median overall survival of patients with good PS was almost double that of patients with poor PS (15.4 months vs. 7.6 months). Gemcitabine plus carboplatin regimen produced similar result. In most studies, gemcitabine monotherapy produced a median survival of 11 months or less.

To compare the effect of various chemotherapy regimens on overall survival, we divided the chemotherapy into three groups. In our study, patients who received 1st line chemotherapy with gemcitabine and cisplatin had a median survival of 9 months, the second group of other gemcitabine doublets (gemcitabine plus oxaliplatin, gemcitabine plus carboplatin, gemcitabine plus capecitabine, and gemcitabine plus nab-paclitaxel) showed a median survival of 10 months and gemcitabine monotherapy had a median survival of 4.9 months. The difference in survival was statistically significant. When we compared gemcitabine plus platinum combination to other chemotherapy, those who received gemcitabine-platinum combination in our study had a significant improvement in overall survival of 9.9 months compared to 4.45 months in those who did not.

i. Most clinical trials include patients with PS of 0 or 1, while we included a considerable number of patients (21%) with ECOG PS of 2 or more
ii. We had a considerable number of patients (16.1%) who received monotherapy. Overall survival is low with single-agent chemotherapy even in worldwide literature
iii. Most of the clinical studies calculated survival of biliary tract cancers as a group and very few analyzed survival of gallbladder cancer separately. A pooled analysis revealed that the survival of gallbladder cancer with systemic chemotherapy is generally inferior than other biliary tract cancers like cholangiocarcinoma.[9]
    - Taking all these factors into account, we may conclude that the overall survival data generated in our study are at par with other published literature
    - Effect of demographic characteristics, patient, and tumor factors on overall survival.

BMI – we classified BMI as per the WHO/NIH criteria and tried to know if the BMI has any effect on overall

Table 1: Distribution of gallbladder stone in the study population

GB stone	Frequency	Percent
No	24	38.7
Yes	38	61.3
Total	62	100.0

Table 2: Distribution of various chemotherapy regimens in first-line setting in the study population

CT – 1ST line	Frequency	Percent
CAPE	1	1.6
GEM	9	14.5
GEM-CAPE	1	1.6
GEM-CARBO	4	6.5
GEM-CIS	35	56.5
GEM-NABPACLI	1	1.6
GEM-OX	11	17.7
Total	62	100.0

survival. The median survival in underweight patients was 4.3 months, in healthy patients 8.57 months, in overweight patients 10.0 months, and in obese patients 14.57 months. This difference was statistically significant. This shows that underweight patients have significantly poorer survival outcome than those who are not. Low BMI has a direct correlation with under and/or poor nutrition. Moreover, under or poor nutrition is associated with poorer survival. Usually, these patients have poor tolerance to chemotherapy and hence treated with suboptimal treatments in the form of single-agent chemotherapy.

Stage – theoretically, it seems that the patients who are non-metastatic should have better prognosis than those with metastatic disease because they have comparatively less advanced disease with lower disease burden. Indeed, that was the precise inference from our study too. Patients, who were non-metastatic, but could not receive curative surgery due to reasons like comorbidities, unresectability, or patient's preference, had significant survival advantage over metastatic disease (14.57 months vs. 8.5 months) [Tables 1 and 2].

CONCLUSION

The demographic characteristics obtained in our study were similar to those found in Indian and worldwide literature. Median age at presentation was 57 years. Almost three-fourth of our patients were female. Very few patients were underweight which may not be a true representation of the community scenario. Over 90% of patients had adenocarcinoma histology. Most patients received gemcitabine-based doublet chemotherapy in the first-line setting. Of them, the majority had platinum compounds, most commonly cisplatin as a partner to gemcitabine. ORR, median overall survival, and PFS to first-line chemotherapy was 53.3%, 8.9 months, and 5.33 months, respectively. Gemcitabine-based doublet especially with platinum produced the best result in this setting. Only 44% of the patients received second-line chemotherapy which included capecitabine, gemcitabine, irinotecan, or paclitaxel-based regimens. CAPOX was the most efficacious among the second-line regimens. ORR and PFS to second-line chemotherapy were 37.5% and 2.85 months, respectively. Some of the patient and disease characteristics such as low BMI, poor PS, and metastatic disease adversely affected survival.

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