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Gastrointestinal Cancer

Treatment Outcomes of Advanced Cholangiocarcinoma: A Single-Center Experience from India

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Abstract

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Background Survival data for patients with advanced cholangiocarcinoma are very sparse in India. We performed this study to find the median overall survival of patients with advanced cholangiocarcinoma and to identify prognostic factors for survival.

Methods This is a retrospective study of 30 patients with inoperable and metastatic cholangiocarcinoma treated with cisplatin and gemcitabine chemotherapy. Overall survival was estimated by the Kaplan–Meier method. Univariate and multivariate analyses were performed to determine the impact of age, gender, performance status, carbohydrate antigen (CA) 19.9, liver function test on survival. Data were analyzed using SPSS version 21.

Results The mean age of the population was 47.5 years ($\pm$14.5). The most common presenting complaint was jaundice followed by abdominal pain. Extrahepatic cholangiocarcinoma comprised of 86%. Median number of cycles was 4 and the response rate was 46.6% (partial response and stable disease) The median overall survival was 9 months (95% confidence interval = 6.0–11.8 months). The median survival of patients with Eastern Cooperative Oncology Group performance score <2 and ≥ 2 were 15.6 and 4.2 months ($p = 0.002$), respectively. The median overall survival for patients with albumin >3.0 g/dL was 12.1 and 4.5 months for <3.0 g/dL ($p = 0.039$). Patients with CA 19.9 <200 U/mL had a better overall survival (13.2 months) than those above 200 U/mL (5.6 months) ($p = 0.001$). In the multivariate analysis, performance status was found to be the only independent prognostic factor.

Conclusion Advanced cholangiocarcinoma has a poor prognosis. Performance status, serum albumin, and CA 19.9 were found to be prognostic.

Keywords

- cholangiocarcinoma
- chemotherapy
- survival

Introduction

Biliary tract cancer comprises of gall bladder cancer and cholangiocarcinoma. Cholangiocarcinoma comprises of intrahepatic, perihilar, and distal cholangiocarcinoma. Due to rarity of the disease, cholangiocarcinomas are mostly combined with gall bladder cancers for randomized control trails.[1] Median overall survival is less than 1 year.[2] Majority of cases present with advanced disease. Palliative chemotherapy is the only treatment prolonging the survival. 5-fluorouracil as single agent or in combination is the most tested chemotherapeutic agent in cholangiocarcinoma. Various other chemo regimes have been

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tried. Highest response rate obtained was in the phase III ABC 02 trial, where they used cisplatin and gemcitabine combination regimen.[3] The aim of the study is to evaluate overall survival in patients with unresectable cholangiocarcinoma receiving cisplatin gemcitabine chemotherapy and identify the prognostic factors affecting the survival.

Methodology

The study sample was drawn from a database of patients treated at the Department of Medical Oncology, Madras Medical College, Chennai, India, between January 2015 and January 2018. Using the database, we identified all patients who were diagnosed histologically with cholangiocarcinoma treated with chemotherapy. The patient charts were reviewed to select those who had unresectable or metastatic disease. Patients' demographics, radiological and histopathological findings, presenting complaints, course of illness, chemotherapy details, and survival were collected retrospectively from the medical records. Informed written consent was obtained from all the patients before start of the treatment. The study was approved by the Institute Ethics Committee

A total of 42 patients with cholangiocarcinoma from our department database were selected. Six patients received adjuvant therapy. Four patients had incomplete details. Two patients had expired because of postoperative morbidity before initiation of treatment. A total of 30 patients with cholangiocarcinoma who were treated with chemotherapy were analyzed retrospectively. Baseline CA 19.9 levels were noted. Patients received injection cisplatin 25 mg/m^2 and inj gemcitabine 1 g/m^2 on day 1 and day 8, every 21 days for a maximum of 6 cycles. Chemotherapy was given full dose if the absolute neutrophil count (ANC) > 1,500/µL, platelet count > 100,000/µL, total bilirubin < 5.0 mg/dL, aspartate transaminase/alanine aminotransferase (AST/ALT) < 2.5 above normal upper limit, and serum creatinine less than 1.5 mg/dL.

Dose Modifications

If the ANC was 500 to 1,000 /µL, the dose of gemcitabine was reduced by 25%. If the creatinine clearance was between 45 and 50 mL/min, then cisplatin dose was reduced by 50%. If the creatinine clearance was less than 45 mL/min, then the chemotherapy was delayed. Granulocyte colony-stimulating factor support was not routinely used. Patients were assessed for toxicities during the day 1 and day 8 of each cycle. Toxicity was assessed using CTCAE v 4.03. Response assessment was performed using contrast-enhanced computed tomography abdomen after 6 cycles and was assessed using response evaluation criteria in solid tumors (RECIST) criteria v 1.1.

Statistical Analysis

Descriptive statistics were summarized as percentages or proportions. Continuous variables were summarized as mean with standard deviation or median with interquartile range. The survival time was measured from the date of diagnosis until the time of death or last patient contact. The Kaplan–Meier method was used to summarize the overall and median survival times. We evaluated the significance of the age, gender, performance status, site of disease, in predicting the survival. The log–rank test was used to determine whether a statistically significant difference existed between the patient groups for each comparison. Correlation between AST, ALT, alkaline phosphatase (ALP), serum bilirubin, CA 19.9, and survival was performed by spearman or Pierson correlation. Statistical significance was defined as a two-sided p-value of 0.05 or less. Statistical analyses were performed using SPSS software version 21.

Results

Patients Characteristics

Mean age of the population was 47.5 ($\pm$14.5). Sixty-three percent of patients were males. An Eastern Cooperative Oncology Group (ECOG) performance status of <2 was seen in 53% ($n = 16$) of patients. Most common presenting complaint was jaundice, seen in 82% followed by abdominal pain in 20%. Cholelithiasis was seen in five patients and three patients had choledochal cyst. Distal cholangiocarcinoma was the most common type (46%) followed by hilar (42%) and intrahepatic (14%). Mean tumor size was 4.5 cm ($\pm$ 2.1). Intrahepatic cholangiocarcinoma was larger in size than perihilar and distal tumors. The mean size of intrahepatic tumors (9.4 cm [$\pm$ 2.9]) was significantly larger than that of perihilar (3.7 cm [$\pm$ 1.3]) and distal tumors 3.9 cm [$\pm$ 2.3] [p =0.01]). Unresectable disease was seen in 43% and 57 % had metastatic disease. Liver was the most common site of metastasis followed by bone, peritoneum. The most common histology was adenocarcinoma, as seen in 28 patients and the remaining 2 patients had neuroendocrine tumor. Among the adenocarcinoma patients, 55 patients had poorly differentiated tumor.

Treatment Details

The median baseline CA 19.9 was 213.5 U/mL (46.1–834.4). The median serum total bilirubin was 8.6 mg/dL (4–16.1). The median serum AST was 50 U/L (27.7–72.5). The median serum ALT was 51 U/L (40.5–91.8). The median serum ALP was 278.5 U/L (181.5–444.1). The median serum albumin was 3.2 g/dL (2.9–3.7). Biliary drainage procedure in the form of either stenting or percutaneous transhepatic biliary drainage was done in 30% ($n = 9$) of patients. Median number of cycles was 4 (2–5). None of the patient achieved a complete response. In 10%, the response could not be assessed. A partial response was seen in 26.6%, while 20% had stable and 43.3% had progressive disease. Around 47% required gemcitabine dose reduction at least for 1 cycle and 20% required cisplatin dose reduction. Grade 3 or 4 anemia was 28%, neutropenia was 22%, and thrombocytopenia was 8%. The most common nonhematological toxicity was fatigue seen in 68% of the patients.

Survival

The median overall survival was 9 months (95% confidence interval= 6.0–11.8 months). ►Fig. 1 shows the Kaplan–Meier analysis of overall survival. Patients with more than 50 years had a survival of 7.2 months, compared with 10 months for age less than 50 years ($p = 0.28$). For patients with ECOG performance score < 2, the median overall survival was 15.6 months, which is

significantly longer than 4.2 months for those with a performance status ≥2 ($p = 0.002$). Patients with tumor size < 4 cm and female gender had better survival but was not statistically significant. ►Table 1 gives us the results of univariate analysis. The median overall survival for patients with unresectable disease was 15.8 months when compared to just 6.3 months for metastatic disease ($p = 0.001$). Intrahepatic cholangiocarcinoma has a trend toward better survival compared to distal or perihilar cholangiocarcinoma. Among the liver function test (LFT) parameters, albumin levels correlated with median overall survival (0.036, respectively). The median overall survival for patients with albumin > 3.0 g/dL was 12.1 versus 4.5 months for patients with < 3.0 g/dL ($p = 0.039$). Patients with CA 19.9 less than 200 U/mL had a median overall survival of 13.2 months when compared to 5.6 months for patients with CA 19.9 above 200 U/mL ($p = 0.001$). Bile drainage did not influence the survival. In the multivariate analysis, performance status was found to be the only independent prognostic factor.

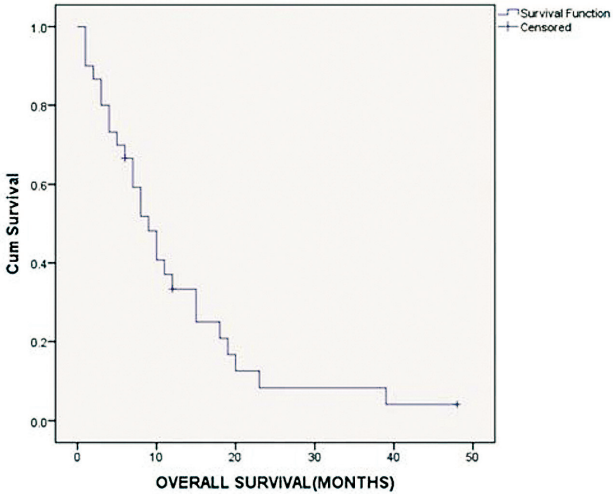

Fig. 1 Kaplan–Meier curve showing the overall survival of the entire population. The median overall survival was 9 months (95% confidence interval = 6.0–11.8 months).

Table 1 Univariate analysis of prognostic factors for overall survival of 30 patients with advanced cholangiocarcinoma

Variable	Subgroup	Median overall survival (mo)	*p*-Value
Age	≥50 <50	7.2 10.0	0.28
ECOG performance status	<2 ≥2	15.6 4.2	0.002
Site	Intrahepatic Perihilar Distal	15.0 5.3 9.2	0.13
Gender	Male Female	7.1 9.9	0.32
Stage of the disease	Unresectable Metastatic	15.8 6.3	0.005
Tumor size (cm)	<4.0 >4.0	9.7 4.3	0.14
Albumin (g/dL)	>3.0 <3.0	12.1 4.5	0.039
CA 19.9 (U/mL)	<200 >200	13.2 5.6	0.01

Abbreviations: CA, carbohydrate antigen; ECOG, Eastern Cooperative Oncology Group.

Discussion

We assessed the survival of patients with unresectable or metastatic cholangiocarcinoma attending our department. The median overall survival in our study population was 9 months. This is similar to 7 to 11 months reported in the literature.[1,2,4,5] We also tried to identify prognostic factors affecting survival. We found patients with performance status 0-1 had better survival, coinciding with the results of study reported by Wiazzane et al (►Fig. 2).[6] Age, gender, and tumor size did not affect the survival. With respect to the site of tumors, intrahepatic cholangiocarcinoma had a better survival compared to extrahepatic subtypes.[3,6]

Among the LFT parameters, albumin correlated with survival that is similar to the findings in the study done by Waghray et al where patients with albumin > 3.0g/dL had a better survival.[7] CA. 19.9 was found to be a negative predictor of survival.[7,8] In our study, patients with CA 19.9 > 200 U/mL had poor survival. The median overall survival with single agent gemcitabine or fluoropyrimidines is around 5 to 10 months.[6] In ABC 02 trial combination of cisplatin and gemcitabine gave a median overall survival of 11.7 months.[3] From Indian perspective, a study done by Babu et al, the median overall survival was 10.3 months when treated with cisplatin and gemcitabine.[2] As shown in ►Table 2, the median overall survival in our study was comparable to the Indian data. Moreover, in Babu et al study, only intrahepatic cholangiocarcinoma was included.

In addition to palliative chemotherapy, surgical resection is one way to improve the survival.[12,13] The future treatment

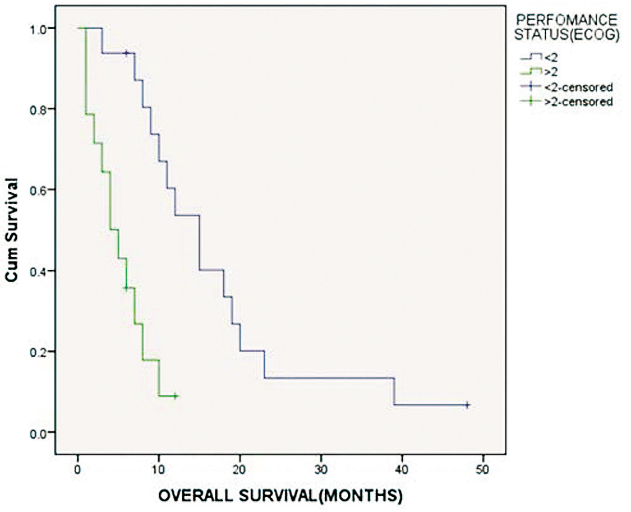

Fig. 2 Kaplan–Meier curve showing the overall survival between patients with Eastern Cooperative Oncology Group performance status ≥2 and <2. The median survival of patients with performance status ≥2 and <2 were 4.2 and 15.6 months, respectively ($p = 0.002$).

Table 2 Comparison of overall survival of inoperable cholangiocarcinomas treated with gemcitabine-based chemotherapy

Sr. No.	Study	Year	Site	Chemotherapy	Median overall survival (mo)
1	ABC 02[3]	2010	Biliary tract cancer	CDDP + gemcitabine	11.7
2	Babu et al[2]	2019	Intrahepatic cholangiocarcinoma	Carboplatin+ gemcitabine	10.3
3	Charoentum et al[10]	2007	Cholangiocarcinoma	CDDP + gemcitabine	10.8
4	Pracht et al[1]	2012	Cholangiocarcinoma	GEMOX + cetuximab	10.0
5	Wiazzane et al[7]	2013	Cholangiocarcinoma	Gemcitabine based	27.7
6	Carraro et al[11]	2008	Biliary tract cancer	CDDP + gemcitabine	11.3
7	Okusaka et al[12]	2010	Biliary tract cancer	CDDP + gemcitabine	11.2

Abbreviations: CDDP, Cis-Diamine-Dichloro Platinum (Cisplatin); GEMOX, gemcitabine-oxaliplatin.

strategy for these cholangiocarcinomas should be personalized medicine. Next-generation sequencing can be used to identify any targetable mutation like FGFR (Fibroblastic Growth Factor Receptor)/IDH (Isocytrate Dehydrogenase)/NTRK (Neurotrophic Tyrosine Kinase) and tailor the treatment accordingly. There are few limitations of this study. First, it is a retrospective study. Hence, it comes with its own inherent methodology issues like bias. Second, our study has a smaller sample size. Third, S.CEA (Serum Carcinoembryonic Antigen) was not performed for all patients, thus limiting us in identifying its prognostic role in survival.

Conclusion

To conclude, inoperable cholangiocarcinoma has poor prognosis. Performance status, serum albumin, and CA 19.9 were found to be prognostic. Therapy with cisplatin and gemcitabine is still a well-tolerated therapeutic option for unresectable and metastatic cholangiocarcinoma.

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Conflict of Interest

None.

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