ORIGINAL ARTICLE

Treatment Response and Survival with Chemotherapy for Unresectable, Nonmetastatic Cholangiocarcinoma

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Abstract

Background and objectives: Limited studies have dwelt upon the treatment of unresectable, nonmetastatic cholangiocarcinoma as a separate entity. Hence, the management protocols are not clearly defined for this subgroup of patients. We aimed to analyze patients treated for unresectable, nonmetastatic cholangiocarcinoma.

Materials and methods: We analyzed the treatment of patients with unresectable, nonmetastatic cholangiocarcinoma retrospectively.

Results: A total of 162 cases of cholangiocarcinoma were reported to our center from 2016 to 2019, out of which 54 were unresectable and nonmetastatic. Thirty patients opted for treatment and were the subjects of this study. Of 30 patients, 24 had hyperbilirubinemia, out of which 10 received chemotherapy after biliary drainage procedure. Out of 30 patients, a total of 16 patients had received chemotherapy, while 14 did not. Gemcitabine/Cisplatin was the first-line chemotherapy administered to 9 patients, whereas 5 received Gemcitabine/Capecitabine and 2 received single-agent gemcitabine. Partial response was documented in 6 patients, and 4 patients had stable disease. The median overall survival was 12.04 months in patients who had received chemotherapy and 6.02 months in those who did not receive chemotherapy ($p = 0.005$). The median progression-free survival was 6.53 months for patients who had received chemotherapy. The aHR for mortality with chemotherapy compared with no chemotherapy was 0.353 (95% CI: 0.154–0.807).

Conclusion: The study data demonstrate that gemcitabine combined with cisplatin- or capecitabine-based chemotherapy prolongs survival in patients with unresectable and nonmetastatic cholangiocarcinoma. In patients with cholangiocarcinoma associated with jaundice, biliary drainage procedure enables giving chemotherapy. Hyperbilirubinemia persisting despite drainage procedures portends poor prognosis and represents an unmet need.

Keywords: Biliary tract neoplasms, Biliary tract cancers, Cholangiocarcinoma, Chemotherapy, Unresectable.

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Introduction

Cholangiocarcinoma (CCA) represents 3% of all malignancies of the gastrointestinal tract.[1] There are reports dealing with the increasing incidence of this malignancy.[2–5] Surgery presents the best possibility for cure, however, only a minority of tumors are resectable.

The patients with advanced cancer of the biliary tract comprise both the locally advanced and metastatic disease making it a heterogeneous group with inclusion of a range of primary tumor sites, i.e., intrahepatic bile duct, extrahepatic bile duct, ampulla, and gallbladder. In most studies, patients with CCA have been clubbed together with other biliary cancers, and data pertaining to CCA only are lacking.[1–8] This heterogeneity complicates assessment of treatment efficacy. The resectability rates are higher for CCA at the distal site as compared with the proximal (both intrahepatic and perihilar). Patients who have had surgical resection of disease have better prognosis.

Most studies have clubbed unresectable and nonmetastatic tumors along with the metastatic tumors; hence, the data regarding the treatment efficacy and approaches in the nonmetastatic, unresectable subgroup are not clearly delineated. Thus, optimal treatment strategies for patients falling in the nonmetastatic, unresectable category are yet to be defined.

Systemic chemotherapy plays an important role in advanced disease. The ABC-02 study provided evidence for the efficacy of gemcitabine with cisplatin-based chemotherapy for the treatment of advanced CCA and showed better overall survival (OS) compared with gemcitabine alone without an increase in the toxicity.[2] We retrospectively analyzed CCA patients treated with chemotherapy from 2016 to 2019 at our center for understanding the demographics, clinical presentation, treatment response,

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and survival in this subgroup of patients with unresectable and nonmetastatic disease.

Materials and Methods

Study Design and Inclusion Criteria

The retrospective study was conducted in a tertiary care referral center for hepatobiliary diseases in North India among patients with CCA. All patients with nonmetastatic, unresectable CCA who opted for treatment at our center were taken up for the study. The patients had given informed consent forms for the procedures and treatments. In the forms, the patients had given consent for publication of their clinical information in a journal with due efforts to conceal their identity. The inclusion criteria were age of >18 years, histologic or cytologic diagnostic confirmation of intrahepatic or extrahepatic CCA, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Other eligibility criteria were adequate hematologic and biochemical function with serum creatinine below 2 mg/dL. While chemotherapy was administered to the patients with serum bilirubin below 3 mg/dL, all patients with deranged liver functions who underwent any therapeutic procedure [endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic biliary drainage (PTBD)] regardless of whether they ultimately received chemotherapy or not were taken in the intent-to-treat analysis. The patients were followed up to February 2021, up till disease progression or death.

Study Procedures

Chemotherapy Schedule: Gemcitabine-based chemotherapy was most commonly used. Gemcitabine/cisplatin regimen was given as gemcitabine 1000 mg/m^2 body surface area (BSA), cisplatin 25 mg/m^2 and both administered intravenously, days 1 and 8 every 21 days for four cycles. Gemcitabine/Capecitabine was given as gemcitabine 1000 mg/m^2 intravenously on days 1 and 8. Capecitabine 650 mg/m^2 was given orally twice daily for 14 days. The chemotherapy cycle was repeated every 21 days. Gemcitabine alone was given at 1000 mg/m^2 on days 1, 8, and 15 every 28 days for three cycles. If there was no disease progression at 12 weeks, the same regimen was given for another 12 weeks. The modifications in chemotherapy dose and delays were allowed as per tolerance and toxicity. The treatment was discontinued at progressive disease or unacceptable adverse effects. Upon disease progression, second-line chemotherapy, with one of the following regimens: Capecitabine and oxaliplatin (CAPOX); 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX); 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI); or single-agent capecitabine was considered.

Assessment of Tumor Response and Survival

Treatment response was recorded by imaging with computed tomography (CT) or 18fluorine-fluorodeoxyglucose positron emission tomography–computed tomography (18F-FDG PET–CT) scans. The same modality was followed for comparison as had been initially employed for staging work-up. The responses were classified on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[9] Progression-free survival (PFS) was calculated from the day of the diagnosis to the day that progressive disease was recorded. Overall survival was calculated from the day of the diagnosis till the last date of follow-up or the date of death. To observe adverse effects, clinical history, physical examination, and blood investigations were carried out before every cycle of chemotherapy.

Statistical Analysis

Descriptive statistics were calculated as mean (SD) or median (IQR). Progression-free survival and OS were calculated using the Kaplan–Meier analysis, and survival was compared using the log-rank test. Cox proportional hazards regression was employed to calculate adjusted hazard ratios for survival. SPSS software 23.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Patient Characteristics

Of 162 patients with CCA who reported to our center between 2016 and 2019, 79 (48.7%) had metastatic disease, while 29 (17.9%) were operable. Of these, 54 (33%) patients were unresectable and nonmetastatic, out of which 30 opted for treatment at our center and were the subjects of this study. The mean age was 60.9 years (range 45–71 years). There were 13 male and 17 female patients. Hilar CCA was the most prominent site in 20 (67.7%), followed by intrahepatic CCA in 7 (23.3%), and distal CCA in 3 (10%). Of 30 patients, 6 patients without hyperbilirubinemia received chemotherapy. Hyperbilirubinemia >3 mg/dL was present in the remaining 24 out of 30 patients. Despite the procedures—PTBD in 16 patients and ERCP in 8 patients—10 patients were able to get chemotherapy, and the remaining 14 patients could not on account of nonresolving hyperbilirubinemia. At diagnosis, the mean CA19.9 levels were 3660 (1–58,800) and mean CEA levels were 18.4 (0.8–141). The patient characteristics are mentioned in Table 1.

Treatment Response and Survival

Gemcitabine/Cisplatin was the first-line chemotherapy administered to 9 patients, whereas 5 received Gemcitabine/Capecitabine and 2 patients received single-agent gemcitabine. The number of chemotherapy cycles ranged from 3 to 8 with a median of 4. Partial response was documented in 6, and stable disease in 4 patients. Six patients had received second-line chemotherapy upon disease progression (CAPOX and FOLFOX in 2 patients each, and FOLFIRI and single-agent capecitabine in 1 patient each), however, all had progressive disease. The median OS was 12.04 months in patients who had received chemotherapy and 6.02 months in those who did not receive chemotherapy (p = 0.005). The median PFS for patients who received chemotherapy was 6.53 months. Overall, 4 patients (13.3%) survived at 2 years, i.e., 2 patients each out of those that did and did not receive chemotherapy. Figure 1 depicts the comparison of survival experience of patients who had received chemotherapy to those who could not. The cumulative survival for the chemotherapy group was better with a statistically significant difference (p = 0.01). The aHR for mortality on adjusting for age was 0.353 (95% CI: 0.154–0.807).

Discussion

The present report demonstrates the feasibility of treatment of unresectable, nonmetastatic CCA with gemcitabine-based chemotherapy. Patients receiving chemotherapy demonstrated better overall survival compared with the group that did not receive chemotherapy due to nonresolving hyperbilirubinemia. This group of patients has been clubbed with patients having metastatic disease in most studies. Few studies have addressed the treatment of nonmetastatic, unresectable CCA separately. Hence, the therapeutic strategies for these patients vary from center to center.

Table 1: Characteristics of patients with cholangiocarcinoma

Parameters	*Number (percentage)*
Total cases	162
Operable	29 (17.9%)
Metastatic	79 (48.7%)
Unresectable, nonmetastatic	54 (33.3%)
Unresectable, nonmetastatic received treatment	30
Subsite	
Hilar	20 (67.7%)
Intrahepatic	7 (23.3%)
Distal	3 (10%)
Gender	
Male	13
Female	17
Age (years)	Mean 60.9 (45–71)
Serum Ca 19.9 (U/mL)	Mean 3,660 (1–58,000)
Serum CEA (ng/mL)	18.4 (0.8–141)
Hyperbilirubinema >3 mg/dL	24 (80%)
Biliary drainage procedure	
PTBD	16 (52%)
ERCP	8 (28%)

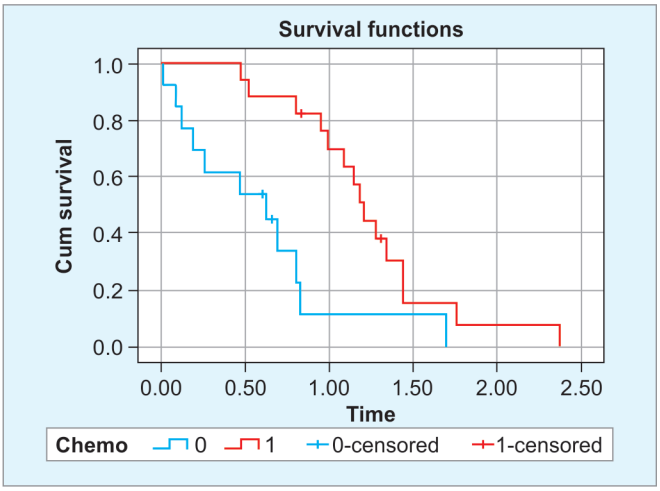

Fig. 1: Effect of chemotherapy vs no chemotherapy on survival

The trial (ABC-02)-based gemcitabine and cisplatin combination chemotherapy was the main regimen used in this study. In the ABC-02 study, the median OS was 11.7 months in the patients treated with gemcitabine and cisplatin (n = 204), while it was 8.1 months in those treated with gemcitabine (n = 206). In this study, the median OS was 12.04 months in the patients given chemotherapy and 6.02 months in those who were not given chemotherapy, which was similar to the results obtained in the ABC-02 trial.[1] These results indicate that with a chemotherapy-only approach, the survival of locally unresectable disease matches that seen in metastatic disease. Hence, other treatment modalities need to be incorporated to improve survival in this subset of patients with nonmetastatic disease.

There have been studies reporting on treatment with a combination of chemotherapy with radiotherapy in CCA. In a Korean study on intrahepatic CCA, of 92 patients in which 27.1% had received cisplatin- and capecitabine-based chemotherapy along with radiotherapy and the remaining had received chemotherapy alone. The rates of OS 9.3 vs 6.2 months and PFS 4.3 vs 1.9 months were significantly more in the combination chemoradiotherapy arm vs chemotherapy arm.[3] A study revealed that external radiotherapy relieved jaundice and prolonged survival in the patients with unresectable intrahepatic CCA with a 1-year OS 38.5% and a median OS of 9.5 months.[4] In a study[5] on inoperable intrahepatic CCA, 79 patients had received definitive radiotherapy and a subset of patients had also received a biological equivalent dose (BED) of above 80.5 Gy. Most patients also received chemotherapy either concurrently or prior to RT. The 3-year OS was 44%, and it was significantly higher for those receiving a BED of more than 80.5 Gy (73%) as compared with lower BED (38%). The corresponding local control rates were significantly higher at 78% vs 45%.[5] For unresectable, nonmetastatic extrahepatic CCA, conventional-dose chemoradiotherapy also has a role and helps in biliary decompression.[6–8] Treatment with stereotactic body radiation therapy (SBRT) has been studied in a report with 31 patients mostly with unresectable extrahepatic and some with intrahepatic CCA. The OS rates were 59% and 33% at 1 and 2 years, respectively, and median survival of 15.7 months.[10] Five patients had undergone resection or liver transplantation after SBRT.

Targeted treatments are also available for CCA. Tumors having *neurotrophic tyrosine receptor kinase (NTRK)* gene rearrangements can benefit from TRK inhibitor therapy for TRK fusion-positive cancers, viz., larotrectinib or entrectinib.[11] BRAF V600E-mutated cancers have benefited from dabrafenib plus trametinib.[12] Pemigatinib in mutations of fibroblast growth factor receptor 2,[13] ivosidenib in isocitrate dehydrogenase (IDH) mutation,[14] and pembrolizumab in patients with deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) are other promising drug interventions.[15,16] In addition, regimens with bevacizumab, erlotinib, cetuximab, and panitumumab combinations with chemotherapy have been described with varying results.[17–21]

In this study, 16 of the 30 patients (53%) were able to receive chemotherapy, while the remaining could not because of uncontrolled hyperbilirubinemia despite a biliary drainage procedure. Of the 30 patients, 24 (80%) had hyperbilirubinemia. Despite a procedure, 14 out of 24 (58.3%) were not able to get chemotherapy and only 10 of 24 (41.6%) were able to receive chemotherapy. This is an unmet need, and the evolution of treatments that could be effective in the setting of CCA with jaundice needs to be considered. A better survival was seen in the patients who were given chemotherapy as compared with the patients who were not able to receive chemotherapy. However, the response to second-line chemotherapy was dismal. Incorporation of targeted therapy, immunotherapy, radiation, and other techniques needs to be devised to fit in the treatment algorithm.

The limitations of the present report are largely due to the lack of randomization and imbalance of unmeasured prognostic factors as it is a retrospective analysis. The patients who could not receive chemotherapy represent the cohort that were unable to achieve resolution of hyperbilirubinemia, and hence are expectedly prognostically worse.

This study reports the effectiveness of chemotherapy in unresectable, nonmetastatic cholangiocarcinoma. This series of cases contributes information in accruing data for this rare disease.

The study data demonstrate that gemcitabine combined with cisplatin- or capecitabine-based chemotherapy prolongs survival in patients with unresectable and nonmetastatic cholangiocarcinoma. In patients with cholangiocarcinoma associated with jaundice, biliary drainage procedure enables giving chemotherapy. Hyperbilirubinemia persisting despite drainage procedures portends poor prognosis and represents an unmet need. Newer treatment modalities need to be incorporated for further improving survival in patients with unresectable, nonmetastatic cholangiocarcinoma.

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