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Presentation and Outcomes with First-Line Chemotherapy in Advanced Cholangiocarcinomas—A Relatively Rare Component of Biliary Tract Cancers in India

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Abstract

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Background Biliary tract cancers (BTCs) are a rare group of cancers with limited data with respect to advanced unresectable cholangiocarcinoma (CCA).

Materials and Methods The study is a retrospective study of patients with advanced unresectable/metastatic CCA, who received first-line palliative chemotherapy (CT1) from January 2014 to March 2019 at the Tata Memorial Hospital, Mumbai. Baseline clinical characteristics, chemotherapeutic regimens, and toxicities were evaluated.

Results One hundred and forty patients satisfied criteria for evaluation. Median age of the entire cohort was 57 years (range: 32–80). There were 87 patients (62.1%) with intrahepatic CCA, 35 patients (25%) with perihilar CCA, and 14 patients (10%) with distal CCA. One hundred and twelve patients (80%) had metastatic disease at presentation. Commonest CT1 regimens were gemcitabine–cisplatin (GC) in 89 patients (63.5%) and gemcitabine–oxaliplatin (GO) in 34 patients (24.3%). Sixty-three patients (45%) received second-line chemotherapy. With a median follow-up of 27 months, median progression-free survival for the entire cohort was 7.56 months (95% confidence interval [CI]: 6.23–8.88), and median OS was 12.16 months (95% CI: 10.08–14.24). Common chemotherapy-related grade 3/4 side effects included vomiting in 25 patients (17.9%), diarrhea in 23 patients (16.4%), and thrombocytopenia in 22 patients (15.7%).

Conclusion The current study in advanced CCAs is the largest of its nature from India. The common regimens used as first line were GC and GO. Tolerance and overall survival appear similar to previously published data.

Keywords

- biliary tract cancers
- first-line palliative chemotherapy
- gemcitabine–cisplatin
- India
- unresectable cholangiocarcinoma

Introduction

Biliary tract cancers (BTCs) are a rare group of tumors, with wide geographical variance in prevalence.[1] India is one of the regions with a high incidence of gallbladder cancers (GBCs) and there are a large number of epidemiological and clinical studies which have reported on these measures in GBC.[2-5] However, there is limited evidence as to

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the epidemiological factors as well as clinical outcomes in patients with advanced cholangiocarcinomas (CCAs) in India.

Advanced CCAs are treated with palliative first-line chemotherapy (CT1), usually a gemcitabine-based doublet, though there is some evidence for the use of external beam radiotherapy concurrent with chemotherapy in unresectable but nonmetastatic CCAs.[6-9]

A recently published study from India highlighted outcomes in CCA with the gemcitabine–carboplatin regimen and showed reasonable tolerance and outcomes.[10] With this background, we conducted a retrospective study evaluating outcomes of patients with CCA treated with CT1.

Materials and Methods

Data for this study were extracted from a prospective database of all patients with BTC. Patients between January 2014 and March 2019 were screened from the database. The study was conducted according to the principles of the Declaration of Helsinki, and guidelines for good clinical practice.

The decision on unresectability and/or metastatic disease of CCA was made by a dedicated team comprising a surgical oncologist, medical oncologist, radiation oncologist, and radiologist.

Patients satisfying all the following criteria were included in the analysis:

1. Histologically proven CCA. In cases where histology was not feasible despite repeated attempts, patients were treated based on clinical presentation and radiological evaluation.
2. ECOG (Eastern Cooperative Oncology Group) PS 0–2.
3. Metastatic or unresectable CCA.
4. Administered at least one cycle of CT1 in our hospital.

First-line chemotherapeutic regimens, toxicity assessment, and responses were retrieved from database. Toxicity assessment was recorded as per NCI-CTCAE (National Cancer Institute- Common Terminology Criteria for Adverse Events) version 4.0 and grades 3 and 4 toxicities are reported. Responses to treatment were evaluated three to four cycles of chemotherapy or earlier as per physician decision. Responses were calculated by response evaluation criteria in solid tumors RECIST (Response Evaluation Criteria in Solid Tumors) criteria, with responses reported as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), where feasible. If RECIST was not calculable, then the response was quantified based on collusion between treating physician and the GI radiologist as follows: CR—disappearance of all baseline lesions; PR—significant regression of lesions at baseline; SD—no significant regression of baseline lesions and no new lesions; PD—appearance of new lesions or significant increase in baseline lesions. Response rates and clinical benefit rate (CBR) were reported as percentages.

Progression-free survival (PFS) was calculated from date of diagnosis to date of progression, cessation of chemotherapy due to adverse events, withdrawal from therapy or death (in case of no documented progression). Overall survival (OS) was calculated from date of diagnosis to date of death. Patients who were lost to follow-up were considered as dead for the purpose of statistical evaluation of OS.

Clinical Data Collection and Statistics

Demographic and clinical data were entered into SPSS version 25 with descriptive statistics being used to measure median and frequencies for categorical variables. Median EFS and OS were calculated using Kaplan–Meier's estimates. Potential prognostic variables assessed by chi-square test for significance on univariate analysis included the presence versus absence of obstructive jaundice, intrahepatic cholangiocarcinoma (iCCA) versus others, and unresectable nonmetastatic disease versus metastatic disease.

Results

Baseline Characteristics

A total of 140 patients satisfied the inclusion criteria for analysis. Briefly, median age of patients was 57 years (range: 32–80). Eighty-seven patients (62.1%) had iCCA, 35 patients (25%) had perihilar cholangiocarcinoma (pCCA), and 14 patients (10%) had distal cholangiocarcinoma (dCCA). Other characteristics are detailed in ►Table 1.

Chemotherapeutic Regimens and Toxicities

The most common regimens used as CT1 were gemcitabine–cisplatin (GC) in 89 patients (63.5%) and gemcitabine–oxaliplatin (GO) in 34 patients (24.3%). Concurrent chemoradiation was administered in 11 patients (7.9%).

Table 1 Baseline characteristics

Characteristic	Number (%)
Median age (y)	57 (range: 32–80)
Gender	
Women	58 (41.4)
Men	82 (58.6)
Location of tumor	
Intrahepatic cholangiocarcinoma	87 (62.1)
Perihilar cholangiocarcinoma	35 (25)
Distal cholangiocarcinoma	14 (10)
Multifocal	4 (2.9)
Disease status	
Unresectable, nonmetastatic	28 (20)
Metastatic	112 (80)
Previous history of radical resection	
Yes	11 (7.9)
No	129 (92.1)
Presence of obstructive jaundice at baseline	
Yes	43 (30.7)
No	97 (69.3)
Sites of metastasis	
Hepatic	87 (62.1)
Nonregional nodes	70 (50)
Pulmonary	15 (10.7)
Peritoneal	15 (10.7)
Osseous	3 (2.1)
Adrenal	2 (1.4)

Table 2 Chemotherapeutic regimens and toxicity profiles

Characteristics	Number (%)
First-line chemotherapeutic regimens	
Gemcitabine–cisplatin	89 (63.5)
Gemcitabine–oxaliplatin	34 (24.3)
Gemcitabine	12 (8.6)
Others	5 (3.5)
Grades 3 and 4 toxicity	
Vomiting	25 (17.9)
Stomatitis/oral mucositis	5 (3.6)
Diarrhea	23 (16.4)
Neutropenia	20 (14.3)
Febrile neutropenia	8 (5.7)
Thrombocytopenia	22 (15.7)
Anemia	13 (9.3)
Neuropathy (grades 2 and 3)	13 (9.3)

Sixty-three patients (45%) of patients received a second-line chemotherapeutic regimen postprogression, the commonest of which was capecitabine–irinotecan (62%; $n = 63$).

Common grades 3 and 4 toxicities with first-line chemotherapy included vomiting in 25 patients (17.9%), diarrhea in 23 patients (16.4%), and thrombocytopenia in 22 patients (15.7%). Other details are mentioned in ►Table 2.

Response Rates and Survival Outcomes

Radiological responses were available in 123 patients. Fifty-one patients (36.4%) had PR, and 35 patients (25%) had SD as best response on first-line chemotherapy, for a CBR of 61.4%. Thirty-seven patients (26.4%) had PD as best response on first-line chemotherapy.

With a median follow-up of 27 months, 123 patients had PD, resulting in a median PFS of 7.56 months (95% confidence interval [CI]: 6.23–8.88). Of the cohort of 140 patients, 111 patients had expired due to disease progression, 17 patients were alive, and 12 patients were lost to follow-up. The median OS of the entire cohort was 12.16 months (95% CI: 10.08–14.24). There was no difference in OS between patients with unresectable nonmetastatic disease and patients with metastatic disease (13.6 vs. 11.7 months, $p = 0.47$), presence versus absence of obstructive jaundice (13.6 vs. 11.7 months; $p = 0.36$), and iCCA versus others (12.9 vs. 12 months; $p = 0.722$).

Discussion

A majority of CCAs present with advanced disease (55–90%), thereby ruling out surgery or liver transplant as treatment options. Systemic therapy, predominantly chemotherapy remains the major modality of management in such tumors. The results of the ABC-02 and BT-22 trials, showing superiority of GC over gemcitabine alone in advanced BTC, remain the gold standard in terms of systemic therapy for patients with these malignancies.[6,11] Various monoclonal antibodies have systematically failed to show survival benefit above chemotherapy alone, while there has also been a dearth of viable targetable mutations identified in these cancers.[12] This, coupled with the rarity of CCAs in India, means retrospective data on first-line chemotherapy still has value in terms of adding to existing literature.

The current study, to our knowledge, is the largest of its kind with respect to advanced CCA from India. Though the CCAs are usually clubbed together in terms of treatment strategies, it is interesting to note that the commonest subtype in our cohort was the iCCAs (62%). A similar pattern was noted in the Japanese BT-22 study as well.[11] Obstructive jaundice is a common presentation in pCCAs and dCCAs and was seen in 30.7% of patients in the study,

As expected, a gemcitabine–platinum combination (GC or GO) was the most commonly used regimen in this study, with a handful of patients receiving other protocols such as mFOLFIRINOX (modified fluorouracil, leucovorin, irinotecan, and oxaliplatin) and gemcitabine–capecitabine. Despite small studies showing good tolerance to intensive regimens such as FOLFIRINOX in advanced BTC, the lack of larger randomized studies means these protocols are rarely used in clinical practice.[13]

The median PFS (7.56 months) and OS (12.16 months) seen in the current study are very similar to those seen in the seminal ABC-02 (median PFS—8 months; median OS—11.7 months) and BT-22 (median PFS—5.8 months; median OS—11.2 months) studies. This is heartening to note, considering the real-world nature of the patients in the current study. The survivals are superior to those seen with advanced GBC previously published from our institution (median OS—7.65 months) and are consistent with evidence that CCAs survive longer than advanced GBCs.[14] An additional point of note is the percentage of patients who were able to receive second-line chemotherapy (45%). This is a fair proportion, considering the lack of standardization or known efficacy of second-line regimens in advanced BTC.[15] It is also indicative of the relatively maintained general condition and fitness of patients with CCA on radiological progression, as opposed to advanced GBCs where deterioration is more rapid. The common CT2 used in our institution is capecitabine–irinotecan and we have published data on the same previously.[16]

The chemotherapy-related side-effect profile in the current study cannot be attributed to a single regimen because a significant proportion received GC or GO. Besides grade 3/4 vomiting (15.7%), which is higher compared with published data, other side effects were in the expected range.

While the survivals seen with CCA in this study are acceptable, they are still in the range of ~12 months only. There is an urgent need to find better treatment strategies in these rare tumors and BTCs as a whole. Some encouraging results have been seen with first-line triplet GC-nab-paclitaxel regimen,

ivosidenib in IDH1 mutated multiply pretreated CCA and pemigatinib in FGFR rearranged iCCAs.[17,18] The gains seen in these studies have been modest but are a step in the right direction.

Conclusion

In conclusion, the current study in advanced CCAs is the largest of its nature from India. The common regimens used as first line were GC and GO. Tolerance and OS appear similar to previously published data. Further studies are required to improve survivals in this cancer which is relatively rare in India.

Funding
None.

Conflict of Interest
None declared.

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