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ORIGINAL ARTICLE

Patients with advanced cholangiocarcinoma benefit from chemotherapy if they are fit to receive it: single center experience

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Summary

Purpose: *The purpose of this study was to report the clinical course and outcome of patients suffering from advanced cholangiocarcinoma (CCA).*

Methods: *The medical records of 93 patients with unresectable or metastatic CCA were retrospectively analyzed.*

Results: *Out of 93 patients, 53 (64.9%) were initially managed with palliative biliary drainage (PBD). Cisplatin-based regimens were administered to 18 (19.3%) patients, and non-cisplatin regimens (mainly 5-fluorouracil [5-FU]-based) were administered to 23 (24.8%) patients. Of all 93 patients 53 (55.9%) did not receive chemotherapy. The median overall survival (OS) for all patients was 6.1 months and was significantly higher in patients treated with chemotherapy as compared to those without chemotherapy (p=0.002). However, no difference in OS was seen in patients treated with cisplatin- or 5-FU-based chemotherapy. We noticed that a high number of patients were not referred to a medical oncologist even for advice.*

Conclusion: *The relief of bile duct obstruction is an important part of the initial patient management. One of the main observations of this study was that systemic chemotherapy significantly improved survival. Increased awareness of the medical oncologists' role in the management of CCA can increase the number of patients who can have access to chemotherapy.*

Key words: advanced cholangiocarcinoma, chemotherapy, palliative biliary drainage, survival

Introduction

CCA including bile duct cancers arises from the intrahepatic, perihilar, and extrahepatic biliary tree. Although, this disease has a relatively lower incidence rate, it causes serious morbidity and mortality than other gastrointestinal malignancies, thus making its treatment important [1]. Surgical resection seems to be the only hope for cure in early stages; most of the cases are, however, diagnosed at an advanced stage. Cytotoxic chemotherapy has been increasingly used in advanced stages and there is sufficient data showing a positive effect of chemotherapy on overall survival [2-12].

Data from clinical trials may not always be consistent with clinical practice. Sometimes regimens in those trials may be too toxic and the inclusion criteria may be too strict. CCA is a good example for this scenario. Most of the CCA patients cannot use this chance since the initial presentation with local tumor complications is usually followed by infectious complications and deteriorated the performance status. Additionally, unawareness of the chemotherapy benefit in this rare tumor type by other departments is an additional obstacle. Therefore, it is worth publishing clinical experience that reflects the real life experiences in terms of chemotherapy effectiveness in CCA patients. In this study, we aimed to evaluate the clinical features, disease course, therapeutic options, and chemotherapy exposure rate, response and survival rates of CCA patients at our institution.

Methods

The medical records of histologically confirmed CCA patients at Baskent University, Adana Research and Training Center treated between 2003 and 2009

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were reviewed. Demographics and clinical characteristics including age, sex, body mass index, Eastern Cooperative Oncology Group (ECOG) performance status score, presence of cholelithiasis, histological subtypes, serum markers for hepatitis and AIDS were considered in this study. The primary treatment modality, chemotherapy, and response rates were also documented.

Statistical analysis

All of the results were presented as a rate for categorical values, and mean and median values for continuous variables. The survival curves were estimated according to the Kaplan-Meier method and log-rank test was used for univariate statistical comparisons. Progression free (PFS) and OS were determined, respectively, as the time period (months) between histological diagnosis and progression or death, and between histological diagnosis and death. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were used for estimation. For dichotomous variables, x^2 test and Fisher's exact test for 2×2 cross tables were used for comparison. All of the data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL) and a two-sided p value of ≤0.05 was considered statistically significant.

Results

Included were 93 patients with a median age of 63 years (range 34-87) with unresectable locally advanced or metastatic disease. There were 41 men (44.1%) and 52 (55.9%) women. Detailed demographic characteristics are listed in Table 1. Out of 83 patients PBD was the initial interventional modality in 53 (63.9%) of them. No information on PBD in the remaining 10 patients was available (Table 2). PBD was used more frequently in Klatskin and distal bile duct tumors than in proximal biliary tumors (p=0.0001).

Chemotherapy was administered to 41 patients (44.1%). The median number of chemotherapy cycles was 3 (range 1-6) and the different regimens administered are described in Table 2. No complete response (CR) was achieved. Partial response (PR) and stable disease (SD) were limited to 3 (7.1%) and 13 (38.1%) patients, respectively. Disease control rate (CR+PR+SD) was significantly higher in patients treated with cisplatin-based chemotherapy (cisplatin plus 5-FU; n=14; cisplatin plus gemcitabine; n=4) as compared to those treated with 5-FU-based regimens (n=23; p=0.048). Median OS was 6.1 months (95% CI 3.1- 9.2) in the whole patient group. Furthermore, the patients who received chemotherapy had a higher median OS rate (12.9 months, 95% CI 4.6-21.1) as opposed to the OS rate of 2.1 months (95% CI 0.5-3.6) for the patients without chemotherapy. The difference in OS was statistically significant as shown in Figure 1 (p=0.002). The median PFS was 3.5 months (95% CI 2.4-4.6). The median OS with cisplatin-based chemotherapy combinations (12.8 months, 95% CI 2.5-23.2) was not statistically superior (p=0.66) than with non-cisplatin combinations (10.8 months, 95% CI 4.6-21.1) (Figure 2), neither was PFS (3.5 months, 95% CI 2.0-4.9 vs. 4.0 months, 95% CI 3.4-4.7), respectively (p=0.56).

ECOG performance status in the chemotherapy group was significantly better than in the non-chemotherapy group (p=0.045). Even if we excluded patients with ECOG performance status of 3 and 4, OS in the chemotherapy group (12.8 months, 95% CI 4.5-21.2) was still statistically better than in the non-chemo-

Table 1. Patient clinical characteristics and risk factors

Characteristics	*n (%)*
Gender (female)	52 (55.9)
Age, years, median (range)	63 (34-87)
Hepatitis C infection (n=66)	5 (7.6)
Diabetes mellitus (n=61)	16 (26.2)
Obesity (n=50)	8 (16.0)
Cholelithiasis (n=78)	28 (35.9)
ECOG PS (n=88)	
0	44 (50.0)
1	13 (14.8)
2	23 (26.1)
3	8 (9.1)
Tumor location	
Intrahepatic	17 (18.3)
Klatskin tumor	39 (41.9)
Distal bile duct	16 (17.2)
Gallbladder	21 (22.6)

ECOG PS: Eastern Cooperative Oncology Group performance status

Table 2. Local and systemic therapies

Therapies	*n=93 (%)**
Biliary drainage (n=83)	53 (63.9)
Chemotherapy	
Yes	41 (44.1)
No	52 (55.9)
Cisplatin-based chemotherapy	18 (19.3)
Cisplatin-calcium folinate-fluorouracil	14 (15.1)
Cisplatin-gemcitabine	4 (4.2)
Non- cisplatin-based chemotherapy	23 (24.8)
Mayo[1]	15 (16.2)
FAM[2]	5 (5.4)
UFT (uracil-tegafur)[3]	3 (3.2)

*Because of rounding, sum of percentages may not be 100%
[1]Fluorouracil 425 mg/m^2 and calcium folinate 20 mg/m^2 for 5 consecutive days. [2]Fluorouracil 600 mg/m^2 on days 1 and 8, adriamycin 30 mg/m^2 on days 1 and 29, mitomycin 10 mg/m^2 every 8 weeks. [3]UFT 300 mg/m^2 PO on weekdays

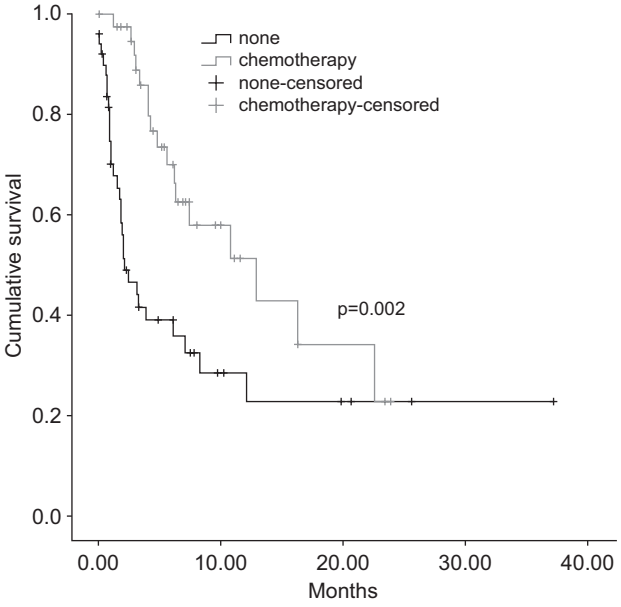

Figure 1. Overall survival of patients treated with systemic chemotherapy vs. those untreated. Significant difference favored systemic chemotherapy (p=0.002).

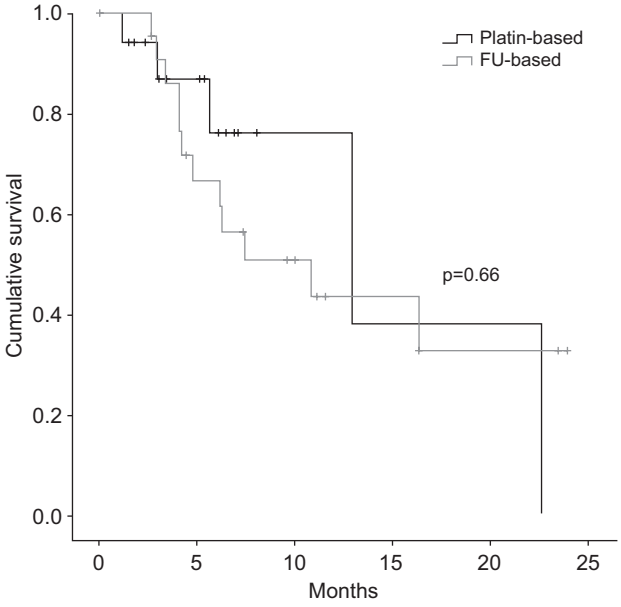

Figure 2. Overall survival for patients treated with cisplatin-based chemotherapy vs. 5-FU based-chemotherapy. No difference between the 2 groups (p=0.66).

therapy group (2.0 months, 95% CI 0.3-3.8, log-rank p=0.04). Only ECOG performance status and systemic chemotherapy exhibited statistically significant impact on OS in the univariate analysis. After 1st-line chemotherapy 13 (31.7%) patients received 2nd-line and 4 (9.8%) patients 3rd-line chemotherapy.

Discussion

CCA accounts for 2% of all the malignancies and bears a poor prognosis [13]. Most of the patients are diagnosed at advanced stages and die within in one year from diagnosis. The present article summarizes data from a significant number of CCA patients treated and followed from 2004 till 2009 at our center, including basic demographic characteristics, treatment modalities, and chemotherapy effectiveness in terms of response and survival. This study first underlines the importance of PBD in CCA because over 50% of the patients were initially handled with PBD. None of our patients had a well defined predisposing factor. This study also supports the findings of other investigators regarding the beneficial effect of cytotoxic chemotherapy in CCA [2-12]. There was a significant OS benefit with chemotherapy. Despite the favorable impact of chemotherapy, unexpectedly low chemotherapy exposure rate of such patients was observed which might be at least partly due to the low referral rate to a medical oncologist. When we checked our patients' charts, we saw that many patients had not been consulted the medical oncology department, probably because either surgeons or gastroenterologists did not think that palliative chemotherapy could be beneficial to patients. This was probably secondary to lack of multidisciplinary team work.

CCA may present with obstructive painless jaundice that can be complicated with life-threatening cholangitis and sepsis. Therefore, a significant proportion of cases need to be treated with PBD initially. In our analysis we found that the first therapeutic intervention was PBD (63.9% of the patients). It is suggested that successful PBD can have a positive impact on OS [14,15]. In this study we could not show a significant effect of PBD on survival, so this observation might be due to the heterogeneity of our group since we included intrahepatic CCA into the study which usually does not need a PBD.

In the literature, the most important predisposing factors for CCA are primary sclerosing cholangitis, choledochal cyst, and cirrhosis [7]. In this study none of our patients had these well defined predisposing factors. Less defined risk factors include diabetes, obesity, and cholelithiasis [16,17]. The frequencies of these factors are listed in Table 1.

Systemic chemotherapy has been increasingly used for patients with CCA. In the literature, the beneficial effect of chemotherapy was first reported in a trial that included 90 patients, of whom 37 had CCA [4]. In that study, the authors observed that 5-FU-based chemotherapy significantly increased OS compared to best supportive care (BSC) (6 vs. 2.5 months). Recently, systemic chemotherapy gained popularity after the publication of several studies [2-12]. Gemcitabine,

5-FU, cisplatin, oxaliplatin, and docetaxel are active chemotherapeutics in CCA. They are used as single agents or in combination. Combination regimens are usually composed of gemcitabine and 5-FU with or without cisplatin. The studies with combination regimens usually report 25-35% response rates with 6-11 months OS [2,3,6]. A pooled analysis of 2810 patients with CCA concluded that combination regimens offered higher response and disease control rate as compared to single-agent chemotherapy. However, this did not translate into significant benefit in the OS and PFS [18]. The superiority of the combination of cisplatin plus gemcitabine over gemcitabine alone was shown in the pivotal ABC-02 trial [6]. In this trial combination chemotherapy yielded superior median OS and PFS rate as compared to gemcitabine alone. ABC-02 was the reference trial that clearly demonstrated superiority of combination chemotherapy in CCA. In our analysis, we observed 6.1 months of OS for the whole group and were able to show that combination chemotherapy increased OS significantly (12.9 months). Patients treated with chemotherapy usually had a significantly better performance status. After exclusion of patients with low performance score, survival advantages of chemotherapy were, however, still significant. In this retrospective analysis, cisplatin-based combination regimens failed to show a survival advantage over the 5-FU-based chemotherapy in terms of both OS and PFS. The disease control rate was, however, significantly higher for cisplatin-based regimens as compared to 5-FU-based regimens, which was in line with the current evidence [6]. Our attempt to identify other factors associated with survival, e.g., gender, systemic disease, age, obesity, failed to show any survival advantage for any of them, even if some were shown to be important previously [15,19].

In our institution we noticed that these patients were never referred to a medical oncologist even for advice.

In conclusion, a significant number of CCA patients cannot receive chemotherapy. Apart from individual patient factors, the low referral rate from gastroenterologists and surgeons seems to be an important obstacle for chemotherapy administration, the single most important treatment modality for patients with advanced CCA. This may be due to the wrong impression among those disciplines that CCA patients do not benefit from chemotherapy. In a clinical setting, we demonstrated that chemotherapy is beneficial for advanced CCA patients. Multidisciplinary collaboration starting from disseminating the achievements in systemic treatment to related disciplines can optimize the care of these patients.

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