JBUON 2021; 26(6): 2678-2687
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Chemotherapy in cholangiocarcinoma - experience of a tertiary cancer center from Romania

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Summary

Purpose: *Advanced and metastatic cholangiocarcinoma prognosis is poor, and current palliative treatment is limited. The present study aimed to analyze the prognostic factors for survival in patients with advanced cholangiocarcinoma treated by various lines of chemotherapies.*

Methods: *The clinical data of 120 consecutive patients with cholangiocarcinoma treated between January 2008 and December 2018 at one comprehensive cancer center were retrospectively analyzed. Survival curves were drawn using the Kaplan-Meier method. The log-rank test was used for survival analysis.*

Results: *The progression-free survival in the first-line treatment was 5.6 months. Almost half of the first-line therapy patients received a second-line regimen with a progression-free survival of 3.8 months. In patients treated with third-line regimens, the progression-free survival was 6.8 months, however, only 20.53% of the initial patient cohort was eligible for third-line treatments. Time to treatment failure was 9.37 months, and overall survival was 12.73 months. No correlation was found between body mass index, gender, and progression-free survival, or overall survival. The type of metastasis seemed not to influence the survival rate or time to treatment failure.*

Conclusions: *Tumor extent at diagnosis influences the prognosis of advanced cholangiocarcinoma. First-line treatment selection impacts second-line survival and overall survival. Different chemotherapy regimens are equally effective in assuring tumor control. Neutrophil to lymphocyte ratio (NLR) is associated with poor prognosis.*

Key words: *cholangiocarcinoma, hepatobiliary, prognosis, chemotherapy, survival*

Introduction

Cholangiocarcinoma (CCA) is an entity comprising diverse epithelial tumors expressing features of cholangiocyte differentiation, which may arise at each point of the biliary tree. CCAs are rare tumors that frequently present in an advanced stage and are often challenging to diagnose and

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Received: 02/09/2021; Accepted: 05/10/2021

treat. Generally regarded as rare tumors, they are classified according to their location as intrahepatic, perihilar, and distal with a significant intertumoral variation.

CCAs embody nearly 3% of all gastrointestinal cancers diagnosed worldwide. The incidence of CCA in the western world is modest between 0.35 to 2 per 100000 annually but has steadily risen in the last 30 years. Additionally, the prevalence in China, Thailand, and other parts of Asia can be up to 40 times the rate observed in the United Kingdom, making CCAs an important health problem [1].

The 5-year survival rate for intrahepatic and extrahepatic CCAs are 24% and 13% for localized disease, and 1% for metastatic disease [2]. Surgery with complete resection is the only treatment with curative intent. However, most patients are diagnosed at an advanced stage, and more than 1/3 of the patients considered resectable have unresectable disease [3]. Recurrence after curative surgery affects almost half of CCA patients. Data regarding surgical treatment after recurrence is limited. Frequently therapy for recurrent disease consists of chemotherapy and or radiotherapy. A retrospective analysis by Takahashi et al. compared patients with recurrent disease who received systemic treatment with those who underwent surgical treatment. Survival was significantly better with surgery – 3-year survival 32% vs. 3%. Prognostic factors for reoperation were: disease-free interval of 2 years, locoregional recurrence, absence of lymph nodes involvement [4].

The use of neoadjuvant and adjuvant chemotherapy results in better survival and lower recurrence rates compared to adjuvant or no therapy, as proven by Hong et al [5]. Gemcitabine-based chemotherapy has better response rates and tumor control than fluoropyrimidine regimens; adding a platinum compound results in increased tumor control and response rates compared to monotherapy [6]. However, as known, the platinum compounds are responsible for allergic reactions, which could raise some concerns regarding the completeness of the systemic treatment. On the other hand, the cardiotoxicity is less than 5%, which could be used for a continuous administration strategy [7].

The majority of the patients with cholangiocarcinoma have unresectable disease, and a noteworthy proportion of patients treated with resection present with recurrent disease. Median survival for patients with unresectable disease is 4-8 months [8]. Local progression of CCA can lead to pain, biliary obstruction, liver failure, biliary stenting, and palliative local radiation therapy may be appropriate for these patients [9]. Palliative chemotherapy increases survival in unresectable and metastatic cholangiocarcinoma patients.

Methods

The current study is a single-center, retrospective analysis conducted in a tertiary cancer center, the "Prof. Dr. Ion Chiricuță" Institute of Oncology in Cluj-Napoca, one of the most important in Romania, concerning CCA patients treated in a 10-year time interval between 2008-2018. This study received the institutional Ethics Com-

Table 1. Patient characteristics

Number of patients (n=112)	*n (%)*
Age (years)	
Mean	61.27
Min - max	35 - 82
Gender	
Female	56 (50)
Male	56 (50)
TNM Stage	
T	
1	3 (2.7)
2	25 (22.3)
3	23 (20.5)
4	13 (11.6)
N	
0	2 (1.8)
1	43 (38.4)
x	67 (59.8)
M	
0	20 (17.9)
1	92 (82.1)
Grade of malignancy	
1 & 2	21 (18.8)
3	91 (81.2)
Type of cholangiocarcinoma	
Intrahepatic	84 (75.0)
Extrahepatic - perihepatic	12 (10.7)
Extrahepatic - distal	16 (14.3)
Surgery before systemic treatment	
Yes	23 (20.5)
No	89 (79.5)
Number of metastatic lesions	
1	7 (6.3)
>1	105 (93.7)
Sites of metastasis	
Peritoneal	2 (1.8)
Lung	11 (9.8)
Liver	46 (41.1)
Other	39 (34.8)
Treatment setting	
Initial	106 (94.6)
Relapse	6 (5.4)
Body mass index	
Mean	25.49
Min – Max	16.52 - 41.66

mittee board approval No. 42/8 Dec 2015. Research was conducted in accordance with the Declaration of Helsinki. All patients treated in our Institute should complete and sign a written informed consent before commencing treatment. All data were anonymized before the analysis implied by the study as per the General Data Protection Regulations.

Inclusion & exclusion criteria

Patients were searched retrospectively in the Institute database. Criteria for case inclusion were: age ≥ 18 years, histologically confirmed diagnosis of cholangiocarcinoma, Eastern Cooperative Oncology Group (ECOG) performance 0-2, a total serum bilirubin level of 1.5 times above the upper limit of normal (ULN) range or maximum 3 mg/dL, liver-enzyme (ALAT or ASAT) levels of 5 times the ULN range or less, INR less than 1.4, levels of serum urea and serum creatinine of 1.5 times the ULN range or less and availability of the clinicopathologic and laboratory monitored features, adequate response evaluation, and survival data. Patients with additional cancers were excluded, as well as those with previous chemotherapy administration for the metastatic disease, uncontrolled comorbidities, poor performance status (ECOG≥3), inadequate lab tests, hypersensitivity to the active substance, heart failure (NYHA grade >2), uncontrolled hypertension, acute myocardial infarction (within 6 months prior to chemotherapy initiation) and pregnancy. All patients were evaluated by CT scan or MRI according to RECIST 1.1.

Of the initial 120 patients identified in the given time, one was excluded due to a concurrent metastatic nasopharyngeal cancer, and seven due to incomplete clinical or treatment data.

Statistics

For statistical analysis, we defined overall survival (OS) as the period of time between the first cycle of chemotherapy and death, time to treatment failure (TTF) as the time interval between the first and the last cycle of chemotherapy (whatever line of treatment was administered), progression-free survival during first-line therapy (PFS1) as the time between the first and the last cycle of first-line chemotherapy, progression-free survival during second-line treatment (PFS2) as the time between the first and the last cycle of the second-line chemotherapy, and progression-free survival during third-line of chemotherapy (PFS3) as the time frame between the first and final cycle of the third line of therapy. Selected patient characteristics are summarized in Table 1. Data analysis was performed using IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

Treatments

Patients were treated with regimens consisting of a platinum derivative (carboplatin, oxaliplatin, or cisplatin) most often in association with gemcitabine, taxanes (docetaxel) or fluoropyrimidines (5FU, capecitabine) or with gemcitabine, taxanes, fluoropyrimidines, irinotecan, anthracyclines monotherapy. Table 2 summarizes the administered chemotherapy regimens.

Results

Median progression-free survival in the first-line setting was 3.7 months. 41.96% of the initially selected patients were given a second-line treatment with a median progression-free survival of

Table 2. Chemotherapy regimens administered in included patients

Regimen & duration	*Drugs & duration*	*Doses*	*Number of patients n (%)*
5FU & prodrug	Capecitabine length of a cycle - 21 days	2500 mg/m^2 / day 14 days of 21	32 (28.57)
Platin derivates in combination	5Fu - every 14 days	400 mg/m^2 followed by continuous infusion 600 mg/m^2 days 1,2 of 14	102 (91.07)
Cisplatin	every 14 days	25 mg/m^2/ day day 1 & 8 of the cycle	12 (10.71)
Oxaliplatin	cisplatin every 21 days	80 mg/m^2/ day	15 (13.39)
Carboplatin	oxaliplatin every 14 days	AUC 5	75 (66.96)
Gemcitabine	carboplatin every 21 days	1000 mg/m^2/ day day 1 & 8 of a 21 day length cycle OR 1000 mg/m^2/ day every 14 days for a cycle with length 14 days	8 (7.14)
Anthracycline - doxorubicin	every 21 days	minimum 60 mg/m^2	6 (5.35)
Docetaxel	every 21 days	75-100 mg/m^2	17 (15.17)
Irinotecan	every 14 days	180 mg/m^2	7(6.25)

2.9 months. However, only 20.53% of all patients could receive a third line of chemotherapy with a progression-free survival of 4 months. The median time to treatment failure was six months. Overall survival data were available for 105 patients with a median survival of 9.06 months. Detailed survival analysis is summarized in Table 3.

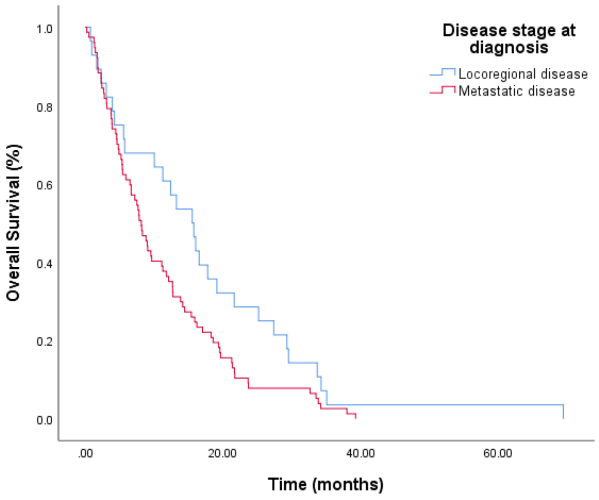

Figure 1. Overall survival according to the clinical stage at diagnosis.

Overall survival was analyzed depending on multiple items such as gender, age, body mass index, histologic type, grade of malignancy, status at treatment initiation - initial or relapsed disease, serum biochemical analysis, and a variety of chemotherapy regimens.

Disease stage at diagnostic seemed to influence overall survival, as seen in Figure 1 significantly. Locoregionally advanced disease, even non-operable, had better survival than metastasis at diagnosis. For TTF, the results were better for the locoregional disease, p value displaying a slight tendency to statistical significance (p=0.094, Table 4).

To assess the prognostic value of metastases location, we classified patients based on the location of their metastatic lesions - liver, peritoneal, lung, bone, lymph node, brain. Metastasis location did not influence PFS1(p=0.704), PFS2 (p=0.857), PFS3 (p=0.328), OS (p=0.429), or TTF (p=0.745). Since most patients presented with liver metastases, we further stratified patients into two categories – those with hepatic versus extrahepatic

Table 3. Overall results of the chemotherapy regimens in the first three lines of the systemic treatments

Survival	*Mean* (*95% confidence interval*)	*Median* (*95% confidence interval*)	*Number of patients* *n (%)*
PFS 1	5.6 (4.3 - 6.9)	3,7 (2.8 - 4.5)	112 (100)
PFS 2	3.8 (2.6 - 5.03)	2.9 (2.36 - 3.43)	47 (41.96)
PFS 3	6.8 (4.14 - 9.50)	4 (3.58 - 4.41)	23 (20.53)
TTF	9.37 (7.47 - 11.27)	6.00 (3.63 - 8.36)	112 (100)
OS	12.73 (10.55 - 14.92)	9.06 (6.19 - 11.94)	105 (93.75)

OS: overall survival, PFS1: progression-free survival for first-line of treatment, PFS2: progression-free survival for second-line of treatment, PFS3: progression-free survival for third-line of treatment, TTF: time to treatment failure

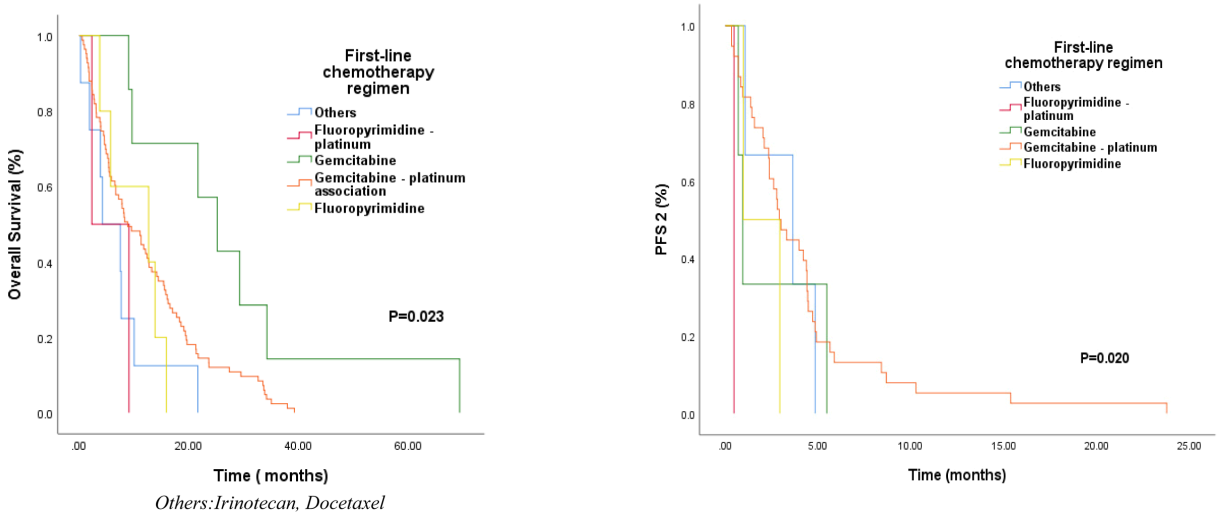

Figure 2. OS and PFS 2 depending on first-line treatment choice.

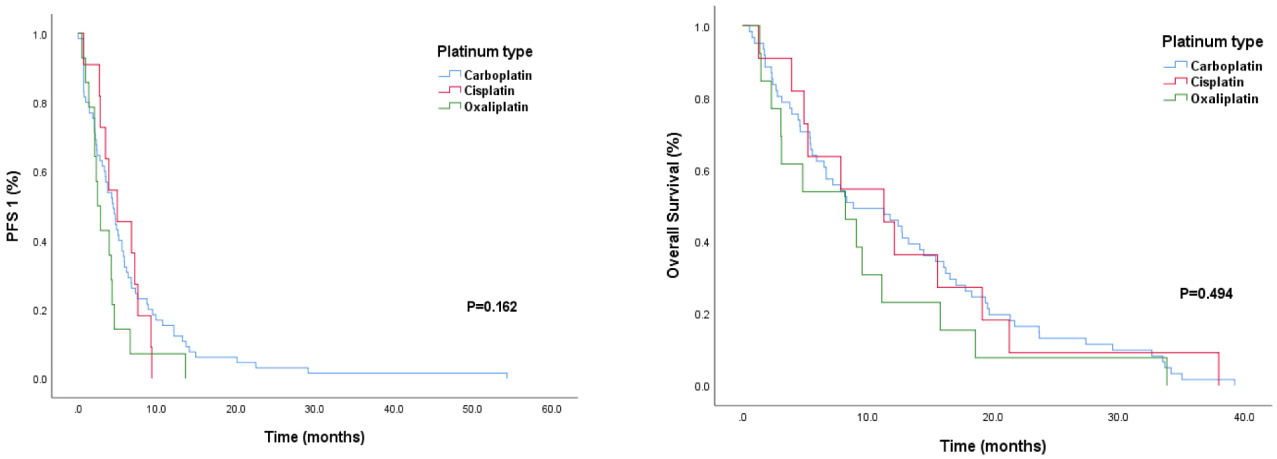

Figure 3. OS and PFS 1 depending on the platinum backbone.

Table 4. Items without statistical significance in terms of OS, PFS1, PFS2, PFS3, TTF

Item / p value	*OS*	*TTF*	*PFS1*	*PFS2*	*PFS3*
Age	0.878	0.644	0.658	0.846	0.273
Gender	0.440	0.154	0.115	0.701	0.893
BMI	0.257	0.278	0.168	0.780	0.881
Type of cholangiocarcinoma					
CD	0.420	0.535	0.200	0.373	0.468
CI					
CP					
Grade of malignancy	0.255	0.407	0.942	0.207	0.394
Metastasis	0.023	0.108	0.225	0.459	0.735
M0					
M1					
Type of metastasis	0.429	0.745	0.704	0.857	0.328
Hepatic					
Extra-hepatic +/- hepatic					
Surgery performed versus none	0.114	0.925	0.413	0.621	0.757
Stage at initial diagnosis	0.041	0.094	0.289	0.572	0.735
Loco regional versus metastatic					
Type of chemotherapy regimen in first-line	0.023	0.222	0.112	0.020	0.339
Type of chemotherapy regimen in second-line	0.362	0.601	N/A	0.053	0.487
Type of platin-derivate	0.494	0.305	0.162	0.722	0.998
Mono versus polychemotherapy	0.182	0.419	0.473	0.304	0.437
CA 125	0.544	0.374	0.913		
CEA	0.755	0.764	0.630		
GGT	0.335	0.449	0.166		
FA	0.486	0.057	0.024	Not performed- too few cases	
Bilirubin total before first line	0.331	0.036	0.051		
Haemoglobin before first line	0.017	0.003	0.035		
Neutrophils / lymphocytes	0.004	0.009	0.010		

BMI: body mass index, CD: distal cholangiocarcinoma, CI: intrahepatic cholangiocarcinoma, CP: perihepatic cholangiocarcinoma, CEA: carcinoembryonic antigen, GGT: gamma-glutamyl transpeptidase, FA: alkaline phosphatase, OS: overall survival, PFS1: progression-free survival for first-line of treatment, PFS2: progression-free survival for second-line of treatment, PFS3: progression-free survival for third-line of treatment, TTF: time to treatment failure

metastatic lesions - but no statistically significant correlation was found.

Regarding the type of chemotherapy regimens used in the first-line setting (mono versus polychemotherapy), no differences were retrieved in terms of OS (p=0.182) or PFS1 (p=0.473). Furthermore, no statistically significant benefit for using polychemotherapy over monotherapy could be observed in second- (p=0.304) or third-line treatment (p=0.437).

As seen in Figure 2, both OS and PFS2 were significantly influenced by the type of chemotherapy used in the first-line, but not by the second-line treatment choice (p=0.362, respectively p=0.053- very close to statistical significance).

For those patients where physicians opted for a chemotherapy regimen comprising of a platinum-based treatment association, we analyzed if there is a correlation between survival and platinum compound choice. An analysis was performed for OS and PFS1 in correlation with the type of platin-derivate: carboplatin, cisplatin, or oxaliplatin. Neither platinum compound was linked to a significant survival benefit- as seen in Figure 3.

We tried to correlate multiple clinical, biochemical, tumoral, or treatment-related items with predefined types of survival. A comprehensive list of analyzed items and statistical p-values is summarized in Table 4.

Discussion

Cholangiocarcinoma remains one of the most difficult digestive pathology to treat for oncologists due to several issues. Genetic alterations, the ontogenetic origin appears to differ in various types of biliary tract malignancies, which could explain their heterogeneity in aggressiveness and response to available chemotherapy regimens [10]. Gemcitabine, 5-Fluorouracil/Capecitabine, platinum derivates – cisplatin, carboplatin, and oxaliplatin have demonstrated efficiency in cholangiocarcinoma. The vast majority of the patients will be diagnosed in an advanced stage of the disease – loco-regionally or metastatic spread. Currently, the recommended standard of care, according to both the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), is represented by the combination of gemcitabine and cisplatin for good clinical performers (oxaliplatin or carboplatin may be used where renal comorbidity raise concerns). Gemcitabine monotherapy represents an option for patients considered unfit for the previously mentioned regimen[11].

Our cohort of patients had OS around 12.73 months which is comparable with previously published data [12]. 20.5% of them had surgery with curative intent in their history of the disease, which is similar to available data on published populations of treated patients, our patients being real-life ones. Intrahepatic cholangiocarcinoma represented 75% of the included cases, gallbladder 14.3%, and peri-hepatic 10.7%, slightly different from the Valle et al. published trial [13]. We sought to analyze the influence of histological subtype on survival. No significant difference was identified between the aforementioned histological subtypes in terms of OS, PFS1,2,3, TTF. These results could contrast with published data by Marcano-Bonilla et al, who anticipate that these three entities' molecular and genetic particularities are translated in prognostic and survival differences [15]. Some data suggest that extrahepatic biliary cancer may have a more favorable prognostic due to a relatively better response to chemotherapy [15,16].

Patients treated at an earlier extent of the disease had better OS, even if they presented with inoperable disease. The presence of metastasis was associated with lower overall survival in our study. The type of metastasis – hepatic versus extrahepatic (patients presenting with liver and extrahepatic disease included in the latter) does not influence OS and TTF. Yusoff et al. found in a univariate analysis that early stage and intrahepatic variants are linked with better survival [17].

As mentioned in the result section, in our study, one of the statistically significant items linked to OS and PFS2 was the type of chemotherapy used in the first-line treatment. Regarding the platin-derivate type, our analysis retrieved the same results and OS (p value >0.05), no matter what compound was administrated during treatment. Moreover, even the comparison between polychemotherapy and monotherapy found no difference in OS, PFS1,2,3, and TTF. These findings could have multiple consequences for clinical practice. In the face of a complex disease and lack of active therapy, the oncologist faces a challenging choice - to favor the response rate or to adapt the treatment to the patient's tolerance to have a more favorable therapeutic index which may presume a potential dose reduction or changing the chemotherapeutic agent, for example, cisplatin with a less toxic better-tolerated compound. Mohring et al analyzed 58 cholangiocarcinoma patients treated with two lines of chemotherapy; 71% of them needed a de-escalation of their treatment without losing OS (compared with published randomized phase 2/3 trials), and with a more favorable profile of toxicity [12]. Our findings underline the importance of choosing the optimal first-line treatment for these patients to maximize the results and prolong survival. Similar

to other difficult oncological pathologies, the patients will progress under this initial therapy, but more than 50% of them will remain candidates for further systemic treatments [18]. For second-line regimens, no actual recommendation is available, due to lack of scientific proof regarding the survival improvement, thus rendering treatment selection based on physician's choice.

In recent years, the progress of systemic therapy for various primary malignancies has made it challenging to attain a significant overall survival advantage. These limitations can also be applied to treatment-resistant malignancies. To avoid dismissing a possible valuable treatment, some researchers proposed using a surrogate for OS, which could be PFS. The heterogeneity of the clinical trials where this model was first applied questions the wide use of this concept without clear guidelines due to the significant discrepancies between authors and external revision. These differences may be as substantial as 27% to 75%, as mentioned in the meta-analysis published by Belin et al [19]. In another article, Giessen et al analyzing metastatic colorectal cancer patients included in more than 50 trials (over 22,000 patients included) demonstrated a correlation between OS and PFS for the chemotherapies used in the included trials [20]. Sidhu et al, in a pooled analysis of 24 randomized trials, which included 69 treatment arms with more than 20,000 patients, concluded that PFS is significantly linked to OS (more than the rate of response RR) and could be considered as a valid substitute for OS [21].

In our experience, PFS2 was not linked to a specific chemotherapy regimen, although the p value was close to statistical significance. In the second line of treatment, there are no recommended regimens. No statistical differences were noted in our study between the various chemotherapy regimens administered. As previously mentioned, neither in the second-line setting, the choice of platin-derivate type didn't seem to matter. The type of regimen - mono versus combination was not statistically significant for OS, TTF, or PFS2. PFS2 was 3.8 months, comparable with 3.3 months in Mohring et al [12]. In our study, PFS2 was linked to first-line chemotherapy regimen but not second-line, which raises some questions. One particularity of the patient`s treatment was that chemotherapy was continuously administered as maintenance therapy until disease progression or unacceptable toxicity compared with a fixed six-month period in ABC-06 [22]. In our study, only 41.96% of initial patients were candidates for second-line therapy. More than 20% of the initial cohort will receive a third line of treatment. Lamarca et al., in their meta-analysis, reported a PFS between 2.8-3.5 months (phase 2 trial, respectively retrospective reports) [23]. Ying et al reported a PFS in the second-line setting of 2.6 months [18]. ABC-06 is the first trial to demonstrate the beneficial effect on OS of second-line of therapy in cholangiocarcinoma [24]. Platinum derivatives as cornerstone for first-line therapy could have as side-effect allergic reactions which could compromise the continuous therapy strategy for these patients [25].

The tumor immune microenvironment plays a crucial role in tumor progression by promoting angiogenesis, tumor cell proliferation, survival, matrix degradation, and metastasis [26]. Several studies have underlined neutrophil involvement in oncogenesis. Neutrophils promote cancer cell proliferation and survival through the secretion of tumor-promoting inflammatory cytokines such as tumor necrosis factor, interleukin 1, interleukin 6, and vascular endothelial growth factor [27-29]. On the contrary, lymphocytes play an essential role in the immune antitumoral defense. Tumor-infiltrating CD 4+ T cells promote tumor control via activation of CD 8+ and natural killer cells, direct cytotoxic activity, or inhibition of tumor growth through interferon γ and tumor necrosis factor secretion. But, CD8+ T cells are the primary cell type responsible for tumor defense via apoptosis [30]. The neutrophile-lymphocyte ratio (NLR) is a readily available, inexpensive biomarker that offers an insight into the complex process of tumoral inflammation. NLR has been linked to poor outcomes in several solid tumors, including breast, colon, prostate, melanoma, lung, pancreas, urogenital cancers, as well as hematologic malignancies [31-35]. Increasing evidence indicates that NLR is a valuable biomarker in patients with cholangiocarcinoma. A meta-analysis conducted by De-Wen Tan et al [36], consisting of 12 studies with a total of 2093 cholangiocarcinoma patients, found high NLR associated with poorer survival HR of 1.449 (95% CI: 1.296-1.619, $p<0.001$). Furthermore, high preoperative NLR was linked to poor prognosis, advanced disease, and shorter relapse-free survival in cholangiocarcinoma patients [37-40]. Omichi et al found NLR>3 to be associated with lymph node metastasis, shorter disease-free survival, and OS in patients with intrahepatic cholangiocarcinoma treated with neoadjuvant chemotherapy followed by hepatectomy [41]. Two additional studies reported high (>5) NLR to be associated with poor chemotherapy response, shorter PFS, and OS [42,43]. Increased NLR was also correlated with high programmed death-ligand 1 (PD-L1) expression by Sangkhamanon et al [44], underlying the potential predic-

tive value of NLR in cholangiocarcinoma patients. In line with currently available data, we also demonstrated the prognostic value of NRL. NRL was significantly associated with poor outcomes in terms of OS (p=0.004), time to treatment failure (p=0.009), and first-line progression-free survival (p=0.010).

Anemia is one of the most frequent findings in cancer patients 40% of cancer patients present with anemia; this percentage rises to 80% for patients with advanced and metastatic disease [45]. Cancer-related anemia has been associated with poor prognosis in a wide range of cancers, including but not limited to lung cancer, gynecological cancer, urogenital cancers, head and neck cancer, sarcoma, and hematologic malignancies. Anemia is linked to lower treatment response rates and lower quality of life [46,47]. To find novel accessible and cost-efficient biomarkers, we also investigated the correlation between pretreatment anemia and survival. Pretreatment hemoglobin levels were significantly associated with improved progression-free survival, overall survival, and time to treatment failure.

Conclusion

For patients with advanced or metastatic cholangiocarcinoma, selecting the optimal first-line regimen increases the overall survival and disease control in the second-line of therapy (PFS2). Patients with locoregional disease extension seemed to have better survival than those with a metastatic stage at initial work-up. Initial immunologic status (neutrophils/ lymphocytes ratio) and good hemoglobin level have better overall survival and treatment associated disease control rate – overall and in the first-line of therapy (TTF and PFS1).

Acknowledgements

Knowledge transfer in clinical trials of biogenomics in oncology and related domains -BIOGENONCO, MySMIS Code: 105774, Financing contract No: 10/01.09.2016.

Conflict of interests

The authors declare no conflict of interests.

References

1. Bridgewater JA, Goodman KA, Kalyan A, Mulcahy MF. Biliary Tract Cancer: Epidemiology, Radiotherapy, and Molecular Profiling. 2019; Am Soc Clin Oncol Educ Book 2016;35:e194-203. doi: 10.1200/EDBK_160831
2. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ CK. Colorectal Cancer - Cancer Stat Facts SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. [cited 2019 Feb 11]. Available from: https://seer.cancer.gov/statfacts/html/colorect.html
3. Endo I, Gonen M, Yopp AC et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008;248:84-96. Available from: https://insights.ovid.com/crossref?an=00000658-200807000-00013
4. Takahashi Y, Ebata T, Yokoyama Y et al. Surgery for recurrent biliary tract cancer: A single-center experience with 74 consecutive resections. Ann Surg 2015;262:121-9.
5. Hong JC. Comparative Analysis of Resection and Liver Transplantation for Intrahepatic and Hilar Cholangiocarcinoma. Arch Surg 2011;146:683-9. Available from: http://archsurg.jamanetwork.com/article.aspx?doi=10.1001/archsurg.2011.116
6. Eckel F, Schmid RM. Chemotherapy and targeted therapy in advanced biliary tract carcinoma: A pooled analysis of clinical trials. Chemotherapy 2014;60:13-23.
7. Maniu DR, Blag C, Popa G et al. The role of biomarkers and echocardiography in the evaluation of cardiotoxicity risk in children treated for leukemia. JBUON 2018;2323;122-31.
8. Park J, Kim M-H, Kim K et al. Natural History and Prognostic Factors of Advanced Cholangiocarcinoma without Surgery, Chemotherapy, or Radiotherapy: A Large-Scale Observational Study. Gut Liver 2009;3:298-305. Available from: http://www.gutnliver.org/journal/DOIx.php?id=10.5009/gnl.2009.3.4.298
9. Tan Y, Zhu JY, Qiu BA, Xia NX, Wang JH. Percutaneous biliary stenting combined with radiotherapy as a treatment for unresectable hilar cholangiocarcinoma. Oncol Lett 2015;10:2537-42.
10. Cardinale V, Carpino G, Reid L, Gaudio E, Alvaro D. Multiple cells of origin in cholangiocarcinoma underlie biological, epidemiological and clinical heterogeneity. World J Gastrointest Oncol 2012;4:94-102. doi: 10.4251/wjgo.v4.i5.94.
11. Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016;27:v28-v37.
12. Möhring C, Feder J, Mohr RU et al. First Line and Second Line Chemotherapy in Advanced Cholangiocarcinoma and Impact of Dose Reduction of Chemotherapy: A Ret-

rospective Analysis. Front Oncol 2021;10;11:717397. doi: 10.3389/fonc.2021.717397. eCollection 2021.

13. Valle J, Wasan H, Palmer DH et al. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer 2010;362:1273-81.
14. Marcano-Bonilla L, Mohamed EA, Mounajjed T, Roberts LR. Biliary tract cancers: epidemiology, molecular pathogenesis and genetic risk associations. Chinese J Clin Oncol 2016;5:61-92.
15. Gonzalez-Carmona MA, Bolch M, Jansen C et al. Combined photodynamic therapy with systemic chemotherapy for unresectable cholangiocarcinoma. Aliment Pharmacol Ther 2019;49:437-47.
16. Hang H, Jeong S, Sha M et al. Cholangiocarcinoma: anatomical location-dependent clinical, prognostic, and genetic disparities. Ann Transl Med 2019;7:744-56.
17. Yusoff AR, Razak MMA, Yoong BK, Vijeyasingam R, Siti ZM. Survival analysis of cholangiocarcinoma: A 10-year experience in Malaysia. World J Gastroenterol 2012;18:458-65.
18. Ying J, Chen J. Combination versus mono-therapy as salvage treatment for advanced biliary tract cancer: A comprehensive meta-analysis of published data. Crit Rev Oncol Hematol 2019;139:134-42. Available from: https://doi.org/10.1016/j.critrevonc.2019.01.001
19. Belin L, Tan A, De Rycke Y, Dechartres A. Progression-free survival as a surrogate for overall survival in oncology trials: a methodological systematic review. Br J Cancer 2020;122:1707-14.
20. Giessen C, Laubender RP, Ankerst DP et al. Progression-Free Survival as a Surrogate Endpoint for Median Overall Survival in Metastatic Colorectal Cancer: Literature-Based Analysis from 50 Randomized First-Line Trials. Clin Cancer Res 2012;19:225-35.
21. Sidhu R, Rong A, Dahlberg S. Evaluation of Progression-Free Survival as a Surrogate Endpoint for Survival in Chemotherapy and Targeted Agent Metastatic Colorectal Cancer Trials. Clin Cancer Res 2013;19:969-76.
22. Lamarca A, Palmer DH, Wasan HS et al. ABC-06 | A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated. https://doi.org/101200/JCO20193715_suppl4003. 2019 May;37(15_suppl):4003-4003.
23. Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. Ann Oncol Off J Eur Soc Med Oncol 2014;25:2328-38.
24. Rizzo A, Ricci AD, Tober N et al. Second-line Treatment in Advanced Biliary Tract Cancer: Today and Tomorrow. Anticancer Res 2020;40:3013-30.
25. Gheorghe-Cetean S, Cainap C, Oprean L et al. Platinum derivatives: a multidisciplinary approach. JBUON 2017;22:568-77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28730758
26. Misra S, Hascall VC, Markwald RR, O'Brien PE, Ghatak S. Inflammation and Cancer. In: Wound Healing Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2017. P 239-74. Available from: https://onlinelibrary.wiley.com/doi/10.1002/9781119282518.ch18
27. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. Science 2011;331:1565-70.
28. Sparmann A, Bar-Sagi D. Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. Cancer Cell 2004;6:447-58. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1535610804003009
29. Hofman PM. Pathobiology of the neutrophil-intestinal epithelial cell interaction: Role in carcinogenesis. World J Gastroenterol 2010;16:5790-800. Available from: http://www.wjgnet.com/1007-9327/full/v16/i46/5790.htm
30. van der Leun AM, Thommen DS, Schumacher TN. CD8+ T cell states in human cancer: insights from single-cell analysis. Nat Rev Cancer 2020;20:218-32.
31. Stefaniuk P, Szymczyk A, Podhorecka M. The Neutrophil to Lymphocyte and Lymphocyte to Monocyte Ratios as New Prognostic Factors in Hematological Malignancies - A Narrative Review. Cancer Manag Res 2020;12:2961-77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32024970
32. Templeton AJ, McNamara MG, Šeruga B et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis. J Natl Cancer Inst 2014;106:1-11.
33. Ethier J-L, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. Breast Cancer Res 2017;19:2-15. Available from: http://dx.doi.org/10.1186/s13058-016-0794-1
34. Yin Y, Wang J, Wang X et al. Prognostic value of the neutrophil to lymphocyte ratio in lung cancer: A meta-analysis. Clinics 2015;70:524-30. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4498150/?report=classic
35. Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med 2020;18:360-376. Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01817-1
36. Tan D-W, Fu Y, Su Q et al. Prognostic Significance of Neutrophil to Lymphocyte Ratio in Oncologic Outcomes of Cholangiocarcinoma: A Meta-analysis. Sci Rep 2016;6:33789. Available from: http://www.nature.com/articles/srep33789
37. Beal EW, Wei L, Ethun CG et al. Elevated NLR in gallbladder cancer and cholangiocarcinoma – making bad cancers even worse: results from the US Extrahepatic Biliary Malignancy Consortium. Hpb 2016;18:950-7. Available from: http://dx.doi.org/10.1016/j.hpb.2016.08.006
38. Huang H, Wan X, Bai Y et al. Preoperative neutrophil–lymphocyte and platelet–lymphocyte ratios as independent predictors of T stages in hilar cholangiocarcinoma. Cancer Manag Res 2019;11:515762. Available from: https://www.dovepress.com/preoperative-neutrophilndashlymphocyte-and-plateletndashlymphocyte-rat-peer-reviewed-article-CMAR
39. Miyahara Y, Takashi S, Shimizu Y, Ohtsuka M. The

prognostic impact of neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) in patients with distal bile duct cancer. World J Surg Oncol 2020;18:1-7. Available from: https://wjso.biomedcentral.com/articles/10.1186/s12957-020-01847-2

40. Buettner S, Spolverato G, Kimbrough CW et al. The impact of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio among patients with intrahepatic cholangiocarcinoma. Surgery 2018;164:411-8. Available from: https://doi.org/10.1016/j.surg.2018.05.002
41. Omichi K, Cloyd JM, Yamashita S et al. Neutrophil-to-lymphocyte ratio predicts prognosis after neoadjuvant chemotherapy and resection of intrahepatic cholangiocarcinoma. Surgery 2017;162:752-65. Available from: http://dx.doi.org/10.1016/j.surg.2017.05.015
42. Huh G, Ryu JK, Chun JW et al. High platelet-to-lymphocyte ratio is associated with poor prognosis in patients with unresectable intrahepatic cholangiocarcinoma receiving gemcitabine plus cisplatin. BMC Cancer 2020;20:1-13. Available from: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-020-07390-3
43. Lin G, Liu Y, Li S et al. Elevated neutrophil-to-lymphocyte ratio is an independent poor prognostic factor in patients with intrahepatic cholangiocarcinoma. Oncotarget 2016;7:50963-71. Available from: https://www.oncotarget.com/lookup/doi/10.18632/oncotarget.7680
44. Sangkhamanon S, Jongpairat P, Sookprasert A et al. Programmed Death-Ligand 1 (PD-L1) Expression Associated with a High Neutrophil/Lymphocyte Ratio in Cholangiocarcinoma. Asian Pac J Cancer Prev 2017;18:1671-4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28670887
45. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med 2004;116:11-26. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002934303007708
46. Clarke H, Pallister CJ. The impact of anaemia on outcome in cancer. Clin Lab Haematol 2005;27:1-13. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2257.2004.00664.x
47. Blohmer J-U, Dunst J, Harrison L et al. Cancer-Related Anemia: Biological Findings, Clinical Implications and Impact on Quality of Life. Oncology 2005;68:12-21. Available from: https://www.karger.com/Article/FullText/83129