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ORIGINAL ARTICLE

Efficacy of a sequential treatment strategy with GEMOX-based followed by FOLFIRI-based chemotherapy in advanced biliary tract cancers

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ABSTRACT

Background: Gemcitabine (GEM)-platinum chemotherapy stands as first-line therapy for patients with recurrent/advanced biliary tract cancer (BTC), yielding progression-free survival (PFS) of 3.4–6.4 months. No standard second-line chemotherapy after GEM-platinum failure exists and data on survival benefit remain limited.

Material and methods: We retrospectively reviewed patients with recurrent/advanced BTC who received gemcitabine-oxaliplatin (GEMOX)-based chemotherapy followed by 5-fluorouracil-irinotecan (FOLFIRI)-based chemotherapy to evaluate the efficacy of the sequential treatment strategy. Overall survival (OS) and PFS were calculated by Kaplan–Meier method.

Results: Fifty-two patients were analyzed, 21 (40%) had intrahepatic, 14 (27%) had hilar/extrahepatic, and 17 (33%) had gallbladder cancer. Median age was 64 years (range 38–79 years). Prior curative intent resection of the primary tumor was performed in 23 (44.2%) patients and GEMOX adjuvant chemotherapy was given in 12 (23.1%) patients. After a median follow-up of 36.3 months, 47 (90.4%) patients completed the treatment strategy. First-sequence GEMOX and second sequence FOLFIRI achieved 4.8 months and 3.2 months median PFS, respectively. The global OS for the sequential chemotherapy was 21.9 months. The sequence of FOLFIRI resulted in a median OS of 8.4 months.

Conclusion: The sequence of GEMOX-FOLFIRI is a potential treatment strategy for patients with recurrent/advanced BTC.

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Biliary tract carcinomas (BTC), is the second most common primary liver tumor after hepatocellular carcinoma [1]. Depending on the anatomic location, BTC are classically divided into intrahepatic, hilar, extrahepatic, and gallblader tumors. As most BTC are diagnosed at a late stage precluding complete surgical resection, patients with BTC display poor prognosis among patients with digestive cancers. The five-year survival rate is of 25–40% if curative surgery is feasible and drops to 5–10% in the advanced, unresectable setting, which reflects the aggressiveness of the disease and the need of efficient treatments [2,3]. The incidence and mortality rates associated with intrahepatic cholangiocarcinoma (CK) are increasing worldwide, whereas extrahepatic CK seem to be declining. The pathogenesis of BTC remains incompletely elucidated, however, it is thought to be related to biliary tract malformations and chronic inflammatory disease, such as primary sclerosing cholangitis, and chronic hepatic disease (including alcohol-induced, hepatitis B and C virus).

Chemotherapy is the standard of care for patients with advanced or recurrent BTC, with gemcitabine (GEM)-platinum combinations, and other GEM- or fluoropyrimidines-based regimen being the most commonly used [4–6]. The combined use of GEM with platinum agents, such as cisplatin or oxaliplatin, have been shown to have better survival outcomes compared to GEM alone or to 5-fluorouracil (FU)/folinic acid ($p < 0.001$) in a meta-analysis reported by Yang et al. [7]. Similarly, the study of Valle et al. demonstrated that GEM plus cisplatin was associated with a significant survival advantage without adding substantial toxicity [4].

Several phase II studies that evaluated the activity of the GEM-oxaliplatin (GEMOX) combination in the first-line setting, proved its efficacy and a favorable safety profile in patient with advanced BTC [8–12]. The median PFS and OS of GEMOX first-line therapy in our previous study were, respectively, 3.4 and 8.8 months in the whole population and 3.8 and 11.0 months in the non-gallbladder population [12].

Only few studies in the second-line setting have been reported in BTC patients. Moretto et al. evaluated the activity and safety of the 5-FU/irinotecan combination as first- or second-line chemotherapy in patients with pancreatic or BTC. In second-line setting, FU/irinotecan produced 42.9% of stable disease (SD) and a median progression-free survival (PFS) and overall survival (OS) of 3.5 and 6.2 months, respectively [13]. More recently, a retrospective multicenter analysis of

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196 patients with advanced BTC by the French AGEO group reported that FOLFIRI was the most frequently used second-line treatment (32.7%) after failure of GEM-platinum first-line chemotherapy [14]. In the present study, we conducted a retrospective analysis of the effectiveness of sequential GEMOX-FOLFIRI-based chemotherapy in a cohort of 52 patients with recurrent or advanced BTC.

Patients and methods

Patients and data collection

All consecutive patients with histologically proven, primary resectable or recurrent unresectable (locally advanced or metastatic) intrahepatic, hilar, extrahepatic CK, or gallbladder cancer treated at two French hospitals (Beaujon University Hospital, Clichy and Saint-Antoine University Hospital, Paris) between October 2004 and October 2013 were retrospectively reviewed. All patients who received a therapeutic strategy with GEMOX, until disease progression (PD) or limiting toxicity, followed by FOLFIRI were selected for analysis. The decision for delivering the first- and second-line chemotherapy was at the discretion of the treating physician according to the hospital protocol and was validated in multidisciplinary tumor board for all patients. The following data were collected from the hospitals records and analyzed retrospectively: age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), primary tumor location, initial tumor stage, prior surgery, number of treatment cycles per sequence of therapy, subsequent therapies after the GEMOX-FOLFIRI sequence, progression status per sequence of therapy, and living/deceased status. Tumor assessment was performed using computer tomography scan every 2–3 months and evaluated according to the Response Evaluation Criteria in Solid Tumors criteria (RECIST, version 1.0).

Therapeutic strategy

The study strategy consisted of first-sequence of therapy with GEMOX-based chemotherapy, followed by second sequence FOLFIRI-based chemotherapy. Both regimens were continued until progression or limiting toxicity. The GEMOX regimen consisted of GEM 1000 mg/m^2 given as a single infusion at 10 mg/m^2/min on Day 1, followed by oxaliplatin 85–100 mg/m^2 as a two-hour infusion on Day 2. This cycle was given intravenously every two weeks. The FOLFIRI regimen comprised intravenous irinotecan 180 mg/m^2 and leucovorin 200 mg/m^2, followed by 5-FU 400 mg/m^2 bolus on Day 1 and 5-FU 2400 mg/m^2 continuous intravenous infusion over 46 hours on Days 1–2. The treatment cycles were repeated every two weeks. Dose reductions or treatment modifications were made according to hospital protocols at the discretion of the treating physician. If disease relapse occurred within six months after the end of adjuvant chemotherapy with GEMOX (early relapse), the adjuvant chemotherapy was considered as first-line treatment for recurrent/advanced disease, whereas if disease relapsed beyond six months from the end of adjuvant chemotherapy (late relapse), treatment after relapse was considered as first-line chemotherapy for recurrent/advanced disease.

Statistical analysis

The primary objective of this study was to evaluate the effectiveness of the sequential treatment strategy of GEMOX followed by FOLFIRI regimen. OS for the GEMOX-FOLFIRI sequential strategy ($OS_{strategy}$) was defined as the time interval from the date of starting treatment strategy (first cycle of GEMOX) to the date of death from any cause. OS from FOLFIRI ($OS_{FOLFIRI}$) was defined as the time interval from the date of starting the second sequence of therapy (first cycle of FOLFIRI) to the date of death from any cause. All patients who were still alive at the time of $OS_{strategy}$ and $OS_{FOLFIRI}$ analysis were censored at the last date they were known to be alive, either during study treatment period or during follow-up period. PFS was defined as the time interval from starting GEMOX (PFS_{GEMOX}) or FOLFIRI ($PFS_{FOLFIRI}$) to the date of first documented PD or death from any cause, whichever occurs first. Time to failure of strategy (TFS) was defined as the

Table 1. Patient characteristics and study treatment.

Variable	No. of patients (n = 52)	%
Gender		
Male	32	61.5
Female	20	38.5
Age at diagnosis		
<70	36	69.2
≥70	16	30.8
Primary tumor location		40.4
Intrahepatic	21	11.5
Hilar	6	32.7
Gallbladder	17	15.4
Extrahepatic	8	
Tumor stage at diagnosis (extension)		
Localized	9	17.3
Locally advanced	18	34.6
Liver metastasis/multifocal	19	36.5
Peritoneum involvement	4	7.7
Mediastinal involvement	2	3.9
Primary tumor resection		
No	29	55.8
Yes	23	44.2
Adjuvant chemotherapy (if resected, n = 23)		
No	11	47.8
Yes	12	52.2
GEMOX/FOLFIRI sequence		
Adjuvant/First-line	8	15.4
First/Second-line	44	84.6
GEMOX regimen		
GEMOX	50	96.1
GEMOX-cetuximab	2	3.9
ECOG PS (before GEMOX)		
0	21	45.7
1	22	47.8
2	3	6.5
FOLFIRI regimen		
FOLFIRI	50	96.2
FOLFIRI3	1	1.9
FOLFIRI-bevacizumab	1	1.9
ECOG PS (before FOLFIRI)		
0	13	25.0
1	20	38.5
2	13	25.0
3	1	1.9
Missing	5	9.6

ECOG PS: Eastern Cooperative Oncology Group performance status; FOLFIRI: 5-fluorouracil/irinotecan; GEMOX: gemcitabine/oxaliplatine.

duration from the initiation of the strategy sequence to the date of first following event: death, PD on the last received planned sequence, or initiation of a new (unplanned) therapeutic agent.

Table 2. Outcomes for first-line GEMOX and second-line FOLFIRI.

	First-sequence of treatment GEMOX		Second sequence of treatment FOLFIRI	
Median, months	(n = 52)	95% CI	(n = 52)	95% CI
No of cycles, median	9.0	6.0–12.0	5.0	4.0–7.4
PFS	4.8	3.2–7.9	3.2	2.2–4.0
TFS	12.4	8.4–18.4	–	–
OS	21.9	13.2–31.7	8.4	6.0–17.7

CI: confidence interval; OS: overall survival; PFS: progression-free survival; TFS: time to failure of strategy.

Time to event endpoints and follow-up were estimated using the Kaplan–Meier method and the reverse Kaplan–Meier method, respectively, and were described using the median with its 95% confidence interval (CI). The association between treatment sequence group and survival was explored using univariate and multivariate Cox proportional hazard regression analyses for all parameters listed in Table 1. Factors shown to be significant at $p \leq 0.10$ level in the univariate analysis were considered eligible for inclusion in the final model as potentially associated with OS and PFS. All statistical analyses were performed with SAS (SAS Institute, Cary, NC).

Patients were classified into three groups demonstrating high, intermediate, or low sensitivity to the GEMOX or FOLFIRI

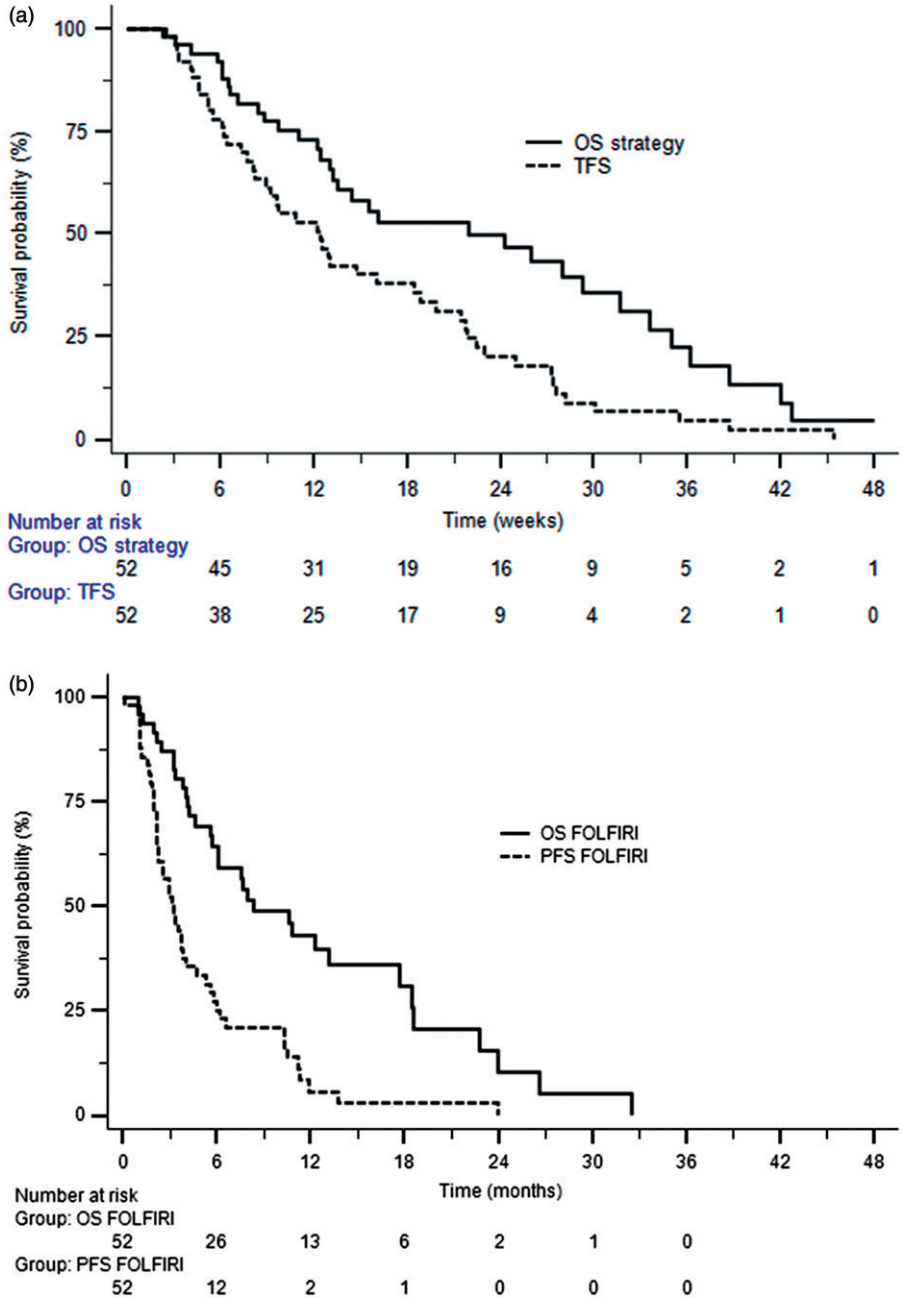

Figure 1. Kaplan–Meier estimates of study endpoints. (a) Survival for the whole strategy (GEMOX followed by FOLFIRI). (b) Survival for the FOLFIRI sequence. OS FOLFIRI: overall survival for the FOLFIRI sequence; OS strategy: overall survival for the sequential GEMOX-FOLFIRI strategy; PFS FOLFIRI: progression-free survival from FOLFIRI; TFS: time to failure of strategy.

regimens based on the PFS_{GEMOX} or $PFS_{FOLFIRI}$ values, respectively. A high sensitivity to GEMOX was defined as patients with $PFS_{GEMOX} \geq 6$ months and low sensitivity to GEMOX was defined as patients with $PFS_{GEMOX} < 3$ months. A high sensitivity to FOLFIRI was defined as patients with $PFS_{FOLFIRI} \geq 4$ months and low sensitivity to FOLFIRI was defined as patients with $PFS_{FOLFIRI} < 2$ months.

Treatment activity was evaluated by the growth modulation index (GMI), defined as the $PFS_{FOLFIRI}/PFS_{GEMOX}$ ratio. The treatment sequence was considered to have significant benefit in counteracting the progression of the disease if the GMI index was greater or equal to 1.33 [15].

Results

Patient population and characteristics

A total of 52 patients with recurrent or advanced BTC were treated with the GEMOX-FOLFIRI-based sequence and were eligible for this study (Table 1). The median age of patients was 64 years (range 38–79), including 32 men and 20 women. Twenty-one (40%) patients had intrahepatic CK, 14 (27%) had hilar or extrahepatic CK, and 17 (33%) had gallbladder cancer. Prior to first-line chemotherapy, 49 (94%) and three (6%) patients had an ECOG PS 0-1 and ECOG PS 2, respectively; and before the FOLFIRI regimen 14 (27%) had an ECOG PS 2-3. Twenty-three (44.2%) of the 52 patients underwent prior primary tumor resection with curative intent. Among 12 (23.1%) patients who received adjuvant chemotherapy with GEMOX, eight had an early relapse (<6 months) and four had a late relapse (>6 months). After a median follow-up of 36.3 months (95% CI 19.6–49.6), 47 (90.4%) patients completed the treatment strategy, and five (9.6%) patients were still on treatment. Of the 23 (44.2%) patients who received a third-line therapy after FOLFIRI, nine were given a platinum compound, two received taxane-based regimen, seven were given an antiangiogenic agent, and three an EGF receptor inhibitor agent.

Therapeutic outcomes and prognostic factors

Patients received a median of 9.0 (95% CI 6.0–12.0) cycles of GEMOX (Table 2). A dose reduction was performed in 19 (36.5%) patients. The median PFS_{GEMOX} was 4.8 months (95% CI 3.2–7.9) in the whole population (n = 52; Table 2), 4.1 months (95% CI 3.2–9.0) in 12 patients with prior adjuvant therapy and 4.8 months (95% CI 3.2–7.9) in 40 patients with no prior adjuvant therapy (p = 0.48). The six-month and one-year PFS_{GEMOX} rates were 41.2% (SD of 6.9%) and 17.7% (SD of 5.3%), respectively. The median TFS and median $OS_{Strategy}$ were 12.4 months (95% CI 8.2–18.4) and 21.9 months (95% CI 13.2–31.7; Figure 1(a)). The median number of cycles of FOLFIRI was 5.0 (95% CI 4.0–7.4; Table 2). Of the 52 patients, 15 (28.8%) received chemotherapy with reduced dose of FOLFIRI. Forty-six (88.5%) patients experienced PD or died during the FOLFIRI sequence treatment. Among 37 (71.2%) patients who had a distant progression, the two most common metastatic sites were the liver (n = 22) and peritoneum (n = 10). The median $PFS_{FOLFIRI}$ was 3.2 months (95% CI 2.2–4.0) in the whole population (n = 52; Table 2), 3.1 months (95% CI 2.2–10.3) in 12 patients with prior adjuvant therapy and 3.2 months (95% CI 2.2–4.7) in 40 patients with no prior adjuvant therapy (p = 0.55). The six-month and one-year $PFS_{FOLFIRI}$ rates were 25.7% (SD of 6.4%) and 5.7% (SD of 3.8%), respectively. The median $OS_{FOLFIRI}$ was 8.4 months (95% CI 6.0–17.7; Figure 1(b)).

In univariate/multivariate analysis, no patient characteristic was prognostic; only peritoneal tumor involvement at diagnosis (p = 0.06) and ECOG PS 2 (p = 0.12) displayed a trend toward poor prognostic factor for OS (Table 3).

Table 3. Univariate and multivariate analysis for overall survival of the two-line sequence (n = 52).

		Univariate				Multivariate	
Variable	n	E/C	Median (95% CI)	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age at diagnosis							
<70	36	22/14	25.9 (12.4–33.5)	1.0	0.877		
≥70	16	11/5	16.2 (13.0–38.6)	1.06 (0.51–2.20)			
Gender							
Male	32	20/12	25.9 (13.0–35.0)	1.0	0.540		
Female	20	13/7	16.2 (12.4–33.5)	1.24 (0.60–2.54)			
Center							
Beaujon	27	16/11	25.9 (12.4–33.5)	1.0	0.822		
Saint-Antoine	25	17/8	21.9 (13.0–36.1)	0.92 (0.47–1.83)			
Adjuvant CT							
No	40	25/15	17.2 (14.4–33.8)	1.0	0.489		
Yes	12	8/4	32.3 (15.7–37.8)	0.76 (0.36–1.60)			
Tumor stage							
Localized	11	4/7	38.6 (13.0–42.7)	1.0	0.063	0.51 (0.20–1.24)	0.139
LA/metastatic	37	26/11	21.9 (12.4–29.3)	2.42 (1.10–5.28)			
Peritoneum	4	3/1	4.1 (2.5–14.4)	5.20 (0.79–34.16)			
First-line ECOG PS							
0	21	13/8	25.9 (13.6–35.0)	1.0	0.119	1.63 (0.83–3.18)	0.156
1	22	14/8	16.2 (9.7–31.7)	1.20 (0.58–2.51)			
2	3	2/1	6.1 (6.1–11.0)	4.19 (0.28–61.7)			
Primary tumor location							
Biliary tract	35	20/15	29.3 (15.5–35.0)	1.0	0.255		
Gallbladder	17	13/4	12.4 (8.8–21.9)	1.49 (0.71–3.12)			

CI: confidence interval; CT: chemotherapy; E/C: events/censored; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ration; LA: locally advanced.

Sensitivity to the sequence strategy

Among 21 (40.4%) patients highly sensitive to GEMOX (Figure 2(a)), 13 (61.9%) demonstrated high sensitivity to FOLFIRI with median $PFS_{FOLFIRI}$ of 5.3 months (95% CI 3.7–10.3; Figure 2(b)). Among 17 (32.7%) patients with low sensitivity to GEMOX, two (11.8%) demonstrated high sensitivity to FOLFIRI (Figure 2(a)). The FOLFIRI sensitivity according to prior GEMOX sensitivity was statistically significant ($p < 0.01$).

Activity of the sequence strategy

Ten (19.2%) patients had a GMI greater or equal to 1.33, showing a 33% improvement in counteracting the progression of the disease with the second-line FOLFIRI sequence. However, there was neither correlation between OS and PFS_{GEMOX} ($r^2 = 0.41$) nor between OS and $PFS_{FOLFIRI}$ ($r^2 = 0.34$) in contrast to OS and DDC ($r^2 = 0.70$) or TFS ($r^2 = 0.88$).

Discussion

GEM-platinum chemotherapy is a validated treatment of choice for advanced BTC in the first-line setting, however, in second-line clinical data are sparse to suggest a survival benefit of chemotherapy and there is no standard second-line chemotherapy after GEM-platinum failure. Presently,

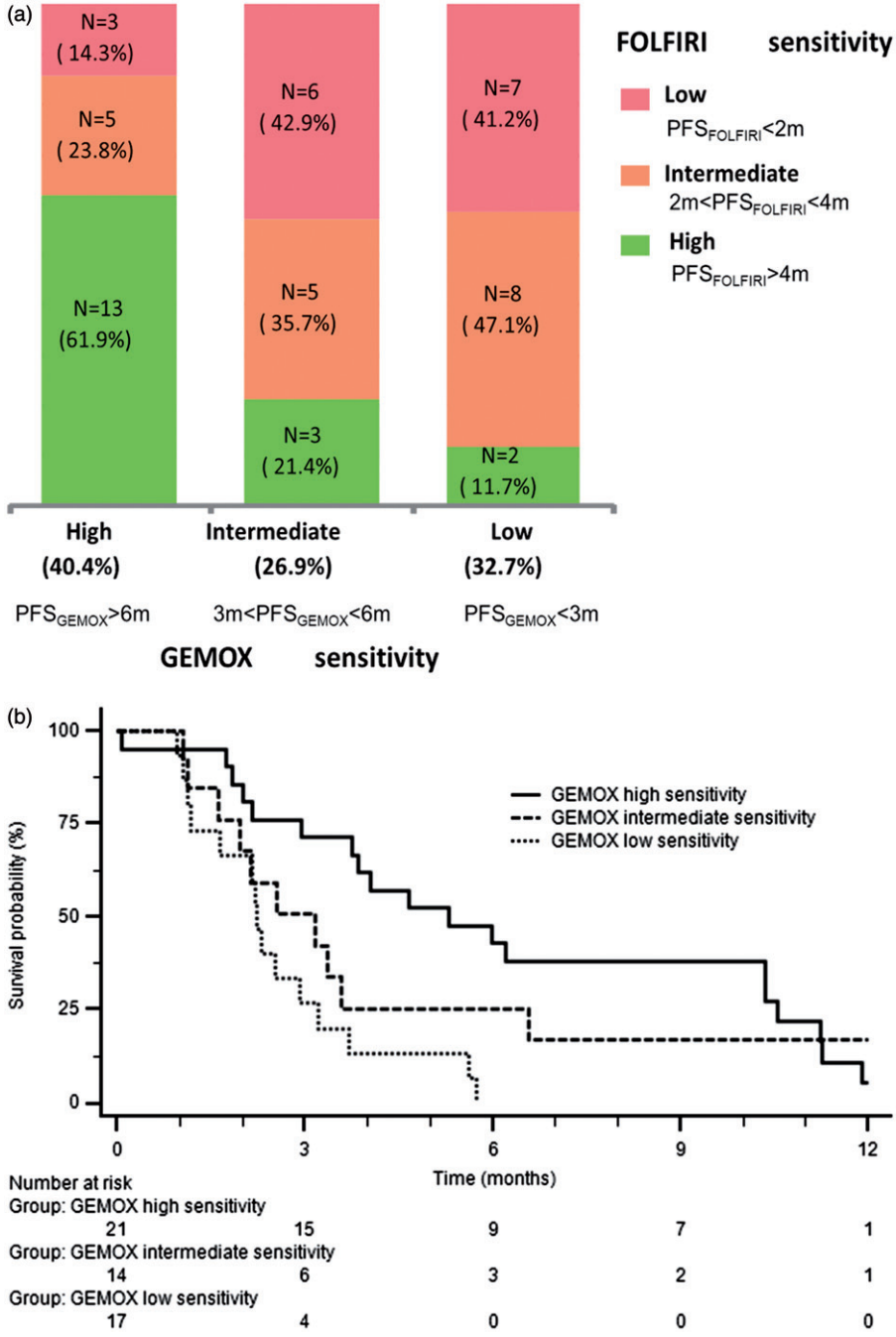

Figure 2. Relation between GEMOX and FOLFIRI sensitivity. (a) Patients repartition according to GEMOX and FOLFIRI sensitivity. (b) $PFS_{FOLFIRI}$ in patients treated with FOLFIRI according to GEMOX sensitivity. PFS_{GEMOX}: progression-free survival from GEMOX; $PFS_{FOLFIRI}$: progression-free survival from FOLFIRI.

clinical management of BTC is not influenced by biological considerations. In this retrospective study, we explored whether patients with recurrent or advanced BTC benefit from the sequential administration of GEMOX followed by FOLFIRI-based chemotherapy. Given a median OS of 21.9 months, our analysis shows that the sequence of GEMOX-FOLFIRI can be a potential treatment strategy for patients with recurrent/advanced BTC. Moreover, our data show how clinical outcome of BTC patients treated with chemotherapy is different in terms of outcomes according to tumor chemosensitivity.

Several studies evaluated the GEMOX regimen as first-line therapy in advanced BTC [8–12,16–24] (Table 4). In these reports, the median PFS ranged between 3.4 and 6.4 months and the median OS between 6.8 and 15.4 months. Neither response rate nor disease control rate are strongly correlated with OS in BTC meta-analysis experience [5]. A recent systematic review comparing the efficacy and toxicity of GEM-cisplatin and GEMOX across 33 studies highlighted that the small advantage of GEM-cisplatin in term of survival was associated with increased toxicities, which may explain why GEMOX is often preferred to GEM-cisplatin in the advanced patient population [25].

Few data on GEM second-line chemotherapy in patients with BTC are available. The present results are in line with these prior findings [14,26–28]. We found that the GEMOX-FOLFIRI sequence resulted in OS of 21.9 months and PFS of 4.8 and 3.2 months for first-line GEMOX and second-line FOLFIRI, respectively. However, neither PFS_{GEMOX} nor $PFS_{FOLFIRI,}$ ($r_1^2 = 0.41$ and $r_2^2 = 0.34$, respectively) were associated with OS. The most important prognostic factors associated with reduced OS was initial peritoneal tumor involvement (HR 5.2; $p = 0.06$).

In addition to the inherent weakness of a retrospective cohort, studies on therapeutic strategies over several lines of treatment are lacking in advanced BTC, which make the comparison with historical data quite hazardous. Moreover, this retrospective cohort has an evident selection bias due to the fact that receiving the second-line therapy was part of the inclusion criteria. This means that patients were fit and devoid of contraindications, such as inappropriate biological parameters or biliary obstruction, which indeed gave them a survival advantage.

Our analysis revealed that 35% of BTC patients (18 of 52 patients) benefited from second-line FOLFIRI regimen and that the sensitivity to this second sequence of chemotherapy was correlated ($p = 0.007$) with the sensitivity to GEMOX (the prior sequence of therapy), suggesting the existence of two BTC phenotypes: one being more sensitive to chemotherapy and for which a second-line and maybe a third-line of treatment are feasible, and another poor prognostic subtype with unclear benefit from chemotherapy. Differences in prognosis or tumor biology may also explain why first- and second-line PFS were correlated, which may be a complementary interpretation to the differences observed in tumors chemosensitivity. This observation highlights the importance of discriminating particular BTC's phenotype for individuals' stratification in future clinical trials. Indeed, due to the mild success of the available second-line treatments for patients with advanced BTC, new therapeutic options based on the molecular profile and phenotypic heterogeneity are currently under evaluation. Of note, it is important to consider that other factors independent of intrinsic BTC chemosensitivity may also affect BTC outcome, such as baseline ECOG, bilirubin level, and peritoneal carcinomatosis. Indeed, in the study of Brieau et al., ECOG PS 2-3, carbohydrate antigen 19.9 levels of >400 UI/l, and disease control by first-line chemotherapy were extracted as factors significantly associated with shorter OS [14].

In conclusions, our study suggests that the GEMOX-FOLFIRI chemotherapy sequence is a potential treatment strategy for patients with recurrent or advanced BTC. Further studies

Table 4. Efficacy of GEMOX as first-line therapy in advanced cholangiocarcinoma.

Author	No. of patients	Tumor location	Chemotherapy	PFS (months)	OS (months)
André et al. 2008 [12]	70	BTC	GEMOX	3.4 (2.5 GBC; 3.8 non-GBC)	8.8 (6.1 GBC; 11 non-GBC)
Woo et al. 2013 [20]	40	GBC	GEMOX	5.8[a]	6.8
Lee et al. 2012 [21]	268	BTC	GEMOX	4.2	9.5
			GEMOX+/-erlotinib	5.8	9.5
Andre et al. 2004 [19]	56	BTC	GEMOX Group A	5.7[b]	15.4
			GEMOX Group B	3.9 [b]	7.6
Jang et al. 2010 [16]	53	BTC	GEMOX	4.5	8.3
Manzione et al. 2007 [10]	34	BTC	GEMOX	9[c]	10
Verderrame et al. 2006 [9]	24	BTC	GEMOX		12
					18c
Hollebecque et al. 2010 [8]	44	BTC	GEMOX	5	11
Li et al. 2010 [11]	34	BTC LAPC	GEMOX	7	11.6
Kim et al. 2009 [17]	40	BTC	GEMOX	4.5	8.5
J Harder et al. 2006 [18]	31	BTC	GEMOX	6.4	11
Sharma et al. 2010 [24]	82	GBC	mGEMOX	8.5	9.5
Malka et al. 2014 [22]	150	BTC	GEMOX	5.5	12.4
			GEMOX- cetuximab	6.1	11.0
Chen et al. 2015 [23]	122	ABTC	GEMOX	4.1	9.8
			GEMOX- cetuximab	6.7	10.6

ABTC: advanced biliary tract cancer; BTC: biliary tract cancer; GBC: gallbladder cancer; GEMOX: gemcitabine and oxaliplatin; LAPC: locally advanced pancreatic cancer; mGEMOX: modified GEMOX; OS: overall survival; PFS: progression-free survival.
[a]TTP: time to progression; [b]Group A: performance status (PS) 0-2, bilirubin <2.5× normal and GEMOX as first-line chemotherapy; Group B: PS >2 and/or bilirubin >2.5× normal and/or prior chemotherapy; [c]Responders.

exploring molecular-targeted therapy and specific biomarkers for treatment efficacy are needed.

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Disclosure statement

The authors report no conflicts of interest.

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