Fluoropyrimidines plus Cisplatin versus Gemcitabine/ Gemcitabine plus Cisplatin in Locally Advanced and Metastatic Biliary Tract Carcinoma – A Retrospective Study

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Abstract

Aim: This is a retrospective study of patients with advanced biliary tract carcinoma (BTC), who were treated with different regimens of chemotherapy. **Methods**: We studied patients with advanced BTC registered at the Department of Oncology at the Fundeni Clinical Institute between 2004 and 2008. The following data were analyzed: rate of response, progression free survival (PFS) to first and second line of chemotherapy, overall survival (OS) and drug toxicity. Ninety-six patients were eligible having either advanced intra or extrahepatic cholangiocarcinoma, or gallbladder cancer with no prior chemotherapy. **Results**: Out of 96 patients, 57 (59.4%) received fluoropyrimidines (FP)+cisplatin and 39 (40.6%) gemcitabine (Gem)+/-cisplatin. The median PFS for FP+cisplatin was 5.9 months (95%CI 5-6.9) and for Gem+/-cisplatin 6.3 months (95%CI 5.4-7.1), p=0.661. Median OS for FP+cisplatin was 10.3 months (95%CI 7.5-13.1) and for Gem+/-cisplatin 9.1 months (95%CI 7.0-11.2), p=0.098. On disease progression, 46 patients received second line CT (Gem or FP+/-platinum compounds). Median OS for patients with FP based first line and Gem+/-cisplatin in second line was 19 months (95%CI 8.9-29) higher than for the reverse sequence: 13.2 months (95%CI 12-14.4), but not statistically significant (p=0.830). All patients were evaluated for toxicities. Most patients (75.5%) reported at least one adverse event. **Conclusion**: Our results through direct comparison of FP+cisplatin with Gem+/-cisplatin as first line treatment did not show any statistical differences in terms of rate of response, PFS and OS. However, our study showed that FP+cisplatin as first line and Gem based second line therapy gave a better OS rate.

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Key words

Advanced biliary tract cancer – fluoropyrimidines – gemcitabine – cisplatin – second line chemotherapy.

Abbreviations

BTC: biliary tract cancer; CR: complete response; DCR: disease control rate; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FP: fluoropyrimidines; Gem: gemcitabine; HFS: hand-foot syndrome; OS: overall survival; PD: progressive disease; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; RR: response rate; SD: stable disease.

Introduction

Biliary Tract Cancer (BTC) is one of the most aggressive human malignancies [1]. Most patients are diagnosed in advanced stages with limited treatment options [2-4]. Fluoropyrimidines (FP), gemcitabine (Gem) and platinum compounds are the main drugs used in the treatment of BTC. There was no standard chemotherapy to offer to these incurable patients until 2010, when two randomized trials provided evidence that the regimen with Gem+cisplatin is an effective therapy for advanced biliary cancer. In ABC-02 and BT trial, the overall survival (OS) was 11.7 and 11.2 months for combined therapy vs. 8.1 and 7.7 months for Gem alone [3, 5, 6]. Based on these trials and on phase 2 trials, NCCN and ESMO updated its clinical practice guidelines [7, 8]. To our knowledge, only one retrospective study which directly compares Gem with FP based regimens has been published [9]. We retrospectively reviewed the records from our Department of Oncology, from 2004-2008, to evaluate all patients with advanced BTC. We analyzed the efficacy and the toxicity of FP and Gem-based regimens, and also whether the second line chemotherapy could play a significant role in the treatment.

Methods

Between January 2004 and July 2008, 96 patients with advanced BTC were treated in the Department of Oncology of the Fundeni Clinical Institute. The study material consisted of patients with primary or recurrent unresectable intrahepatic or extrahepatic (hilar or pedicular) cholangiocarcinomas, gall bladder or metastatic disease. The eligible patients had cytologically or histologically proved BTC. We performed this retrospective study for the evaluation of the effectiveness in daily practice of two types of chemotherapy: FP and cisplatin vs. Gem/Gem plus cisplatin. At the time of the present study analysis, the fact that Gem and cisplatin is better than Gem alone was not known; this is why we put the two regimens in one group. All data was prospectively recorded and only the outcomes were updated at the time of analysis. All patients gave written informed consent prior to receiving chemotherapy, according to our institutional guidelines and the study was reviewed and approved by the Fundeni Clinical Institute Board. The decision for delivering the chemotherapy was, in all cases, at the discretion of the physician and in the context of the clinical trials. In case of disease progression, patients were crossed over to the second line treatment.

Study design

The patients received FP+cisplatin or Gem+/-cisplatin. The FP used in our study were 5fluorouracil (5FU) or capecitabine. 5FU+cisplatin consisted of 5FU administered intravenously (i.v.) at a dose of 1000mg/m^2 in 10 hours, day 1 to day 4, and cisplatin 60mg/m^2, day 1 every 3 weeks [9]. Capecitabine was administered orally at a dose of 1000mg/m^2 b.i.d. day 1 to day 14 and cisplatin 60 mg/m^2 day1, every 3 weeks [10]. Gem was administered at a dose of 1000mg/m^2 i.v. over 30 min, day 1, 8, 15 every 4 weeks alone or combined at the same dose day 1 and 8 with cisplatin 60mg/m^2 day1 i.v. every 3 weeks [6,11-19]. The treatment continued until progressive disease (PD), unacceptable toxicity, or until the patient and/or the doctor decided to discontinue the treatment. Toxicity was evaluated before each treatment cycle according to the NCI CTCAE, version 3.0. Tables for dose modification based on summary of product characteristics were used to ensure the treatment. Patients with ECOG 0-2, with evidence of PD for first line and with adequate bone marrow, kidney and liver function were crossed over to the second line treatment. As second line treatment, patients received Gem in a weekly infusion for 3/4 weeks or Gem plus cisplatin for FP group, and FP for the Gem group, as follows: xeloda (capecitabine) plus cisplatin, xeloda plus oxaliplatin, mFOLFOX 6 or 5FU+LV (Mayo regimen) [9, 13, 16, 20-25]. The disease status was checked every three months by physical examination and radiological investigation used at baseline and classified based on the RECIST 1.0 criteria. Progressive disease was defined as the appearance of new malignant lesions, an increase of more than 20% in measurable disease or an increase in ECOG PS of one/two levels.

Statistical analysis

Summary statistics, such as the median and proportion described the patients' and disease characteristics. The primary endpoints of this study were progression free survival (PFS)1, for the first line of chemotherapy, PFS2 for the second line and OS. PFS1 and PFS2 were calculated from the initiation of the corresponding line until first/second disease progression/death from any cause. Overall survival (OS) was defined as the duration from the date of starting the first line of therapy to the date of patient death, or last follow-up. Times to event curves were estimated with the Kaplan Meier method and were compared using the log rank test. The secondary endpoints were the rate of response for the first line of chemotherapy (RR1) and for the second line (RR2) and the disease control rate (DCR) defined as the percentage of patients who achieved complete response (CR), partial response (PR) and stable disease (SD). All tests were considered posthoc analysis and no multiplicity adjustments were performed. The statistical significance was considered for p levels <0.05 (two-sided). Data management and statistical analysis was performed using IBM SPSS Statistics v 19 (copyright SPSS Inc). The database was updated for analysis in March 2011.

Results

Patients' characteristics

The data of 96 patients (61 males and 35 females) with advanced BTC were analyzed. As first line of chemotherapy, 57 patients received FP+cisplatin and 39 patients underwent Gem+/-cisplatin. The median follow-up duration was 14.1 months (95% CI 12.5-15.8).

Forty-nine patients had intrahepatic cholangiocarcinoma, 19 Klatskin tumors, 14 common bile duct tumors and the other 14 had gallbladder carcinoma. The median age of the patients was 56.7 years (26-81). ECOG PS at baseline, for FP+cisplatin group was 0/1/2:32/20/5 and for Gem+/-cisplatin group: 0/1/2:15/21/3. Demographics and tumor characteristics are listed in Table I. All 96 patients had the pathological examination (94 adenocarcinoma and 2 squamous cell carcinoma). Thirty-three patients had unresectable recurrence after curative surgical interventions, and 29 patients underwent palliative surgery. Percutaneous biliary drainage was performed in 4 patients. Thirty eight patients had percutaneous liver biopsy. As first line treatment, 30 patients received 5FU+cisplatin and 27 patients, xeloda+cisplatin; 26 patients were treated with Gem+cisplatin and 13 with Gem. They received a median of 6.1 cycles (range 2-12). The cisplatin dose was 60 mg/m^2 due to the adverse effects, and 23 patients (12 in FP+cisplatin group and 11 in Gem+/-cisplatin group) stopped cisplatin after a median of 3.5 months of therapy; they continued on Mayo regimen or Gem and were analyzed as part of the respective group. Of the 96 patients, 90 patients developed PD during the study (13 patients clinically progressed, 5 patients progressed locoregionally, 65 patients at distant sites

and 7 patients progressed in both local and distant sites). Forty-six patients received the second line therapy: 29 from FP+cisplatin group received Gem based regimen and 17 from Gem+/-cisplatin group received FP regimens (Table I). The second line was stopped due to disease progression in 28 patients and clinical deterioration of ECOG PS in 12 patients. Further third line chemotherapy was offered to nine patients after second-line failure.

Efficacy

First line of chemotherapy

Of all 96 patients, 92 were evaluable for response: of these, 17 patients had a rapid PD within the first 2 months of therapy (14 patients from FP+cisplatin group and 3 patients from Gem+/-cisplatin group). Of 57 patients on FP+cisplatin group, 3 patients had PR for 6.67 months (95% CI 3.2-12.9) and 37 patients had SD for 4.37 months (95% CI 2.1 – 8.0). In the Gem+/-cisplatin group, 34 patients had SD for 3.2 months (95% CI 2.0-5.3) and 1 patient had PR for 4.1 months. The RR for FP+cisplatin group was 5.5% and the DCR was 74%; for Gem+/-cisplatin group, the RR was 2.6% and the DCR 92.1% (Table II). The median PFS1 for the first line for FP+cisplatin group was 5.9 months (95%CI 5.0-6.9) and for Gem+/-cisplatin group 6.3 months (95% CI 5.4-7.1) (p=0.661) (Table II, Fig.1). The median PFS1 for intrahepatic cholangiocarcinoma was 5.7 months (95%CI 4.6-6.8), for Klatskin tumors, 7.1 months (95%CI 6.4-7.7), for common bile duct tumors, 6.0 months (95%CI 2.6-9.4) and for gallbladder tumors, 5.8 months (95% CI 5.4-6.2) with no statistical significance among disease types (Table III).

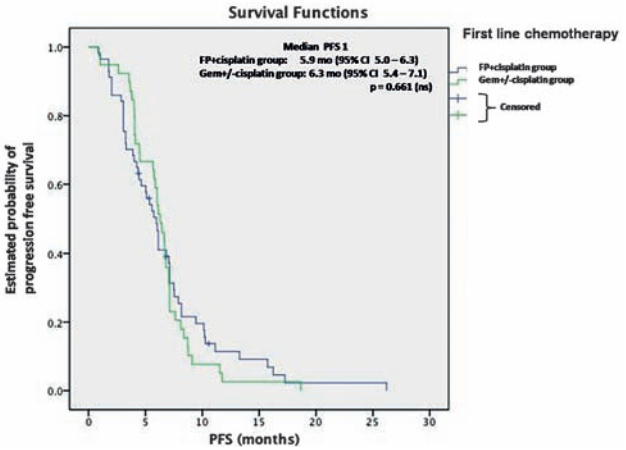

Fig 1. Kaplan-Meier plot of progression free survival for first line of chemotherapy (PFS1) for fluoropyrimidines + cisplatin group and gemcitabine +/- cisplatin group.

Table I. Patients' demographics and tumor characteristics

FIRST LINE THERAPY	5FU+ cisplatin	Xeloda+ cisplatin	Gem+cisplatin	Gem
n (number of patiens)	30	27	26	13
Age (range) -years	56.4 (26-76)		57 (36-81)	
ECOG at baseline 0/1/2	32/20/5		15/21/3	
Male/Female	35/22		26/13	
Primary site (n/%)				
Intrahepatic cholangiocarcinoma	37 (65%)		12 (31%)	
Klatskin tumors	8 (14%)		11 (28%)	
Common bile ducts tumors	5 (8.7%)		9 (23%)	
Gallbladder carcinoma	7 (12.3%)		7 (18%)	
Extent of disease (n/%)				
Locally advanced	12 (21%)		7 (18%)	
Metastatic	9 (15.8%)		15 (38.5%)	
Locally advanced +metastases	30 (52.7%)		10 (25.6%)	
Locoregional recurrence	4 (7%)		6 (15.4%)	
Locoregional recurrence +metastases	2 (3.5%)		1 (2.5%)	
Prior therapies (n/%)				
Curative surgery of primary tumors	11 (18.6%)		22 (56.4%)	
Adjuvant chemotherapy	7 (12.3%)		6 (15.4%)	
Paliative surgery	16 (28%)		13 (33%)	
a) resected with macroscopic residual	5 (8.7%)		6 (15.4%)	
b) abdominal laparatomy /scopy with biopsy	7 (12.3%)		3 (7.7%)	
c) Surgical biliary drainage	4 (7%)		4 (10%)	
Radiological biliary drainage	2 (3.5%)		2 (5%)	
SECOND LINE THERAPY (n/%)	29(50.8%)		17(43.6%)	

	Gem	Gem+cisplatin	5FU	mFOLFOX 6	XELODA	XELOX	XELODA+cisplatin
	24	5	8	5	1	2	1

Second line of chemotherapy

Of 46 patients with second line therapy, 43 patients were evaluated for response, 10 patients had a rapid PD within the first 2 months and 33 patients had SD for 5.13 months (95%CI 2.0-9.7). For the patients who received FP second line treatment, DCR was 71.4% and for patients who received Gem-based second line, DCR was 79.3% (Table IV). PFS2 for FP-based regimen second line was 3.2 months (95% CI 1.2-6.9) and for Gem-based regimen second line, 6.1 months (95% CI 3.1-9.0) (p=0.092) (Table IV, Fig.2).

Overall survival

Ninety-six patients were assessed for OS. The median survival for FP+cisplatin group was 10.3 months (95%CI 7.5-13.1) and for Gem+/-cisplatin group: 9.1 months (95%CI 7-11.2) (p=0.098) (Table II, Fig.3). The median OS for the patients who received second line treatment (46 patients) was 13.6 months (95% CI 11.2-16) with a better OS for patients with FP+cisplatin first line and Gem second line, 19 months (95%CI 8.9-29) versus 13.2 months (95%CI 12-14.4) for patients with Gem+/-cisplatin first line and FP second line but with no significant difference (Table IV, Fig.4). Univariate analysis was performed for the main known prognostic factors for advanced BTC: tumor location, metastatic versus locally-advanced disease, gender, age, previous therapy: curative versus palliative surgery, first and second line of chemotherapy, number of lines administered. Multivariate analysis, incorporating all factors isolated from the univariate analysis, identified two potential prognostic factors associated with longer survival: number of chemotherapy lines and the two lines sequence. The adjusted hazard ratio (HR) for OS for the patients with second line vs. patients with one line was 0.25 (95% 0.08-0.76, p=0.015). For patients with Gem+/-cisplatin first line and FP+platinum second line versus FP+cisplatin first line and Gem+/-cisplatin second line adjusted HR for OS was 3.69(95% CI 1.04-13.14, p=0.043). Our results indicate that the patients treated with FP+cisplatin based treatment in first line and Gem+/-cisplatin in second line had a better survival than vice versa. According to disease site, the median survival time is shown in Table III.

Table II. Patients' characteristics and outcomes for the first line chemotherapy

	FP+cisplatin	Gem+/-cisplatin
Patients (n)	57	39
Patients evaluable for response(n)	54	38
PR (n)	3	1
SD (n)	37	34
PD (n)	14	3
RR (PR) (%)	5.5%	2.6%
DCR (PR+SD) (%)	74%	92.1%
PFS1 (months) p=0.661	5.9 (95%CI: 5.0-6.9)	6.3 (95%CI: 5.4-7.1)
OS (months) p=0.098	10.3 (95%CI: 7.5-13.1)	9.1 (95%CI: 7-11.2)

PR-partial response, n-number, SD-stable disease, PD-progressive disease, RR-response rate, DCR-disease control rate, PFS-progression free survival, OS –overall survival, (ns)-nonsignificant, CI-confidence interval

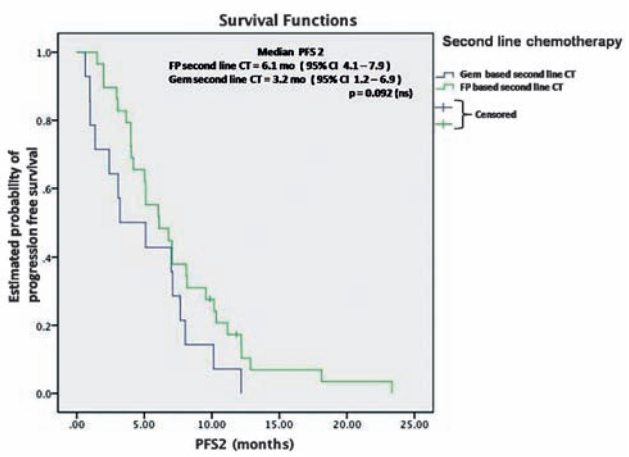

Fig 2. Kaplan-Meier plot of progression free survival (PFS2) for the second line chemotherapy: gemcitabine based 2nd chemotherapy and fluoropyrimidines based 2nd chemotherapy.

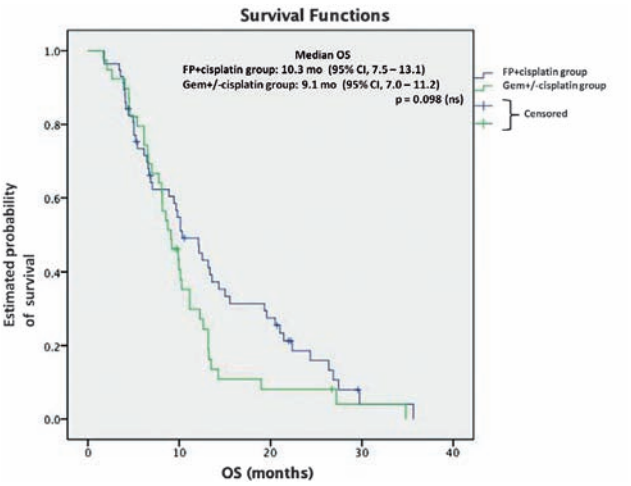

Fig 3. Kaplan-Meier plot of overall survival: fluoropyrimidines + cisplatin group and gemcitabine +/- cisplatin group.

Table III. Patients' outcomes according to disease type

	No. of patients	PFS (months)	OS (months)
Intrahepatic cholangio-carcinoma	49	5.7 (95%CI 4.6-6.8)	10.1 (95%CI 8.5-11.7)
Klatskin tumors	19	7.1 (95%CI 6.4-7.7)	10.2 (95%CI 6.7-13.8)
Common bile duct tumors	14	6.0 (95%CI 2.6-9.4)	10.1 (95%CI 5.2-15.0)
Gallbladder carcinoma	14	5.8 (95%CI 5.4-6.2)	7.7 (95%CI 4.2-11.2)
p		0.309	0.377

For abbreviations, see Table II

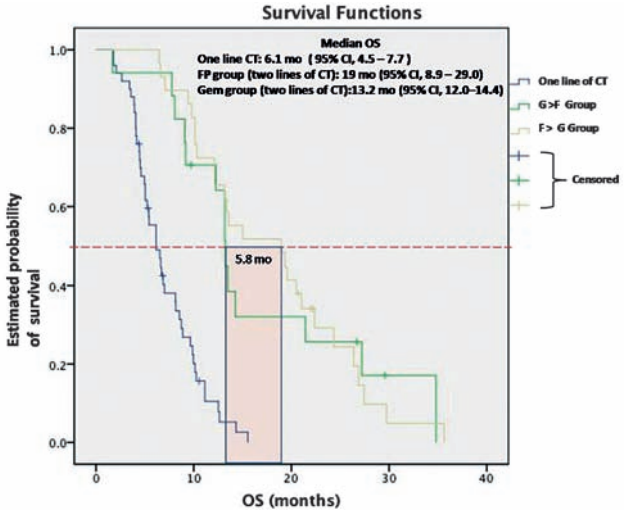

Fig 4. Kaplan-Meier plot of overall survival for patients with one line of chemotherapy (CT) and patients with two lines of CT: Group G>F (gemcitabine+/-cisplatin 1st line CT and continued with FP based second line CT); Group F>G (fluoropyrimidines + cisplatin 1st line CT and crossed over Gem based second line).

Table IV. Patients' characteristics and outcomes for second line chemotherapy

Variable	Gem+/-cisplatin first line + FP second line	FP+cisplatin first line + Gem second line
Patients(n)	17	29
Patients evaluable for response(n)	14	29
SD	10	23
PD	4	4
DCR (%)	71.4%	79.3%
PFS 2(months) p=0.092	3.2 (95%CI: 1.2-6.9)	6.1 (95%CI: 3.1-9)
OS(months) p=0.830	13.2 (95%CI: 12.0-14.4)	19.0 (95%CI: 8.9-29)

SD-stable disease, PD-progressive disease, DCR-disease control rate, OS –overall survival, CI-confidence interval, n-number

Safety

We evaluated the toxicity for patients of first line chemotherapy. Most patients (75.5%) reported at least one adverse event. Hand-foot syndrome (HFS), stomatitis and diarrhoea grade 1/2 were more frequent with FP+cisplatin. The rate of patients who experienced haematological adverse events grade 1/2 was higher with Gem+/-cisplatin. Liver related events and biliary sepsis were more frequent in the Gem+/-cisplatin group (Table V). FP+cisplatin and Gem+/-cisplatin were similar in terms of the percentage that experienced grade 3/4 treatment-related adverse events. Grade 3/4 haematological adverse events were comparable in both groups, except thrombocytopenia and leukopenia which were more common with Gem+/-cisplatin. Nausea and vomiting grade 3/4 were similar in both groups. Hand-foot syndrome, diarrhoea and stomatitis grade 3/4 were more frequent but nonsignificantly with FP+cisplatin. The incidence of grade 3/4 laboratory abnormalities and biliary sepsis was higher in the Gem+/-cisplatin group (Table VI). Adverse events (nausea, vomiting and renal insufficiency) which led to cisplatin interruptions occurred to 12 (21%) patients in the FP+cisplatin group and to 11 (28%) patients in the Gem+/-cisplatin.

Discussion

The results of our study, through direct comparison of FP+cisplatin with Gem+/-cisplatin in the first line showed a better efficacy in terms of DCR (74.0% versus 92.1%) and PFS (5.9 vs. 6.3 months) for Gem+/-cisplatin but not statistically significant. Although the median OS for the first group was longer than for the second group (10.3 vs. 9.1 months), the difference was not statistically significant.

It must be added that in the second group, 13 patients received Gem alone versus 26 with Gem+cisplatin, possibly jeopardizing partially the results, and therefore, we might not be able to conclude that FP+cisplatin is better than Gem+cisplatin. The retrospective study published by Kim et al on 243 patients and the pooled analysis of clinical trials conducted by Eckel showed similar efficacy in terms of DCR, PFS and OS for FP-based regimens and Gem-based regimens, but showed a benefit from adding cisplatin to Gem or FP [9, 26]. In our study, the RR was lower (5.5% and 2.6%) than in other reported studies but with a high DCR (stabilization) (74% and 92.1%), practically a stop of progression. This could be explained by the selection bias and by the scanning frequency, because in daily practice a 3-month interval of imaging is feasible. In the ABC-02 study the tumor control was 81.4% in Gem+cisplatin arm and 71.8% in the Gem arm and it demonstrated that the 12-week interval scanning was sufficient even within phase III studies [27]. Moreover, 29 patients (30%) had locally advanced disease or locoregional recurrence, and therefore 30% of them were very difficult to assess radiologically in 2004-2006 (i.e. the difference between PR and SD). This could explain the low rate of response mainly using conventional CT scan and only the deterioration of the performance status to 3 or 4, or the appearance of another metastasis differentiates between SD and PD.

Few significant survival differences between different tumor locations were found (Table III), although the median OS for gallbladder carcinoma was slightly lower than the others, possibly reflecting its more aggressive biology [26, 28, 29, 30].

What is surprising is that out of the patients who received two lines of chemotherapy, those who started with FP+cisplatin and continued with Gem+/-cisplatin had a better median OS than the patients with the reverse sequence (Gem based first line and FP based second line). Nevertheless, these results need to be interpreted with caution as they come from a retrospective study with several biases.

A standard second line of chemotherapy after Gem or FP has not been developed until now, but 48% of our patients failing previous treatment, had good PS (0, 1 and 2) and were willing to undergo further treatment. In our study, the percentage of patients (48%) who received the second line

Table V. Grade 1 or 2 toxicities -first line chemotherapy

	FP +cisplatin (n=57)		Gem+/-cisplatin (n=39)		Fisher exact test (2-sided)
	n	%	n	%	p
Hematologic					
Neutropenia	12	21	10	25.6	0.628
Leukopenia	8	14.0	14	35.9	0.015
Thrombocytopenia	4	7.0	12	30.8	0.004
Anemia	6	10.5	10	25.6	0.092
Hepatic					
Bilirubin > 1.5 x ULN	3	5.3	4	10.3	0.437
ALT > 5 x ULN	2	3.5	6	15.4	0.059
AST > 5 x ULN	2	3.5	5	12.8	0.116
Renal					
Creatinine > 1.5 x ULN	2	3.5	2	5.1	1.000
Nausea/vomiting	4	7.0	3	7.7	1.000
Diarrhoea	4	7.0	1	2.6	0.645
Constipation	0	0	2	5.1	0.163
Stomatitis	5	8.8	0	0	0.078
Hand-foot syndrome	5	8.8	0	0	0.078
Fatigue/asthenia	8	14.0	7	17.9	0.776
Weight loss	9	15.8	7	17.9	0.787
Anorexia	10	17.5	10	25.6	0.444
Flu-like syndrome	0	0	6	15.4	0.004
Peripheral oedema	3	5.3	6	15.4	0.152
Neuropathy	2	3.5	2	5.1	1.000
Biliary sepsis	4	7.0	4	10.3	0.711

Note: Severity was graded according to National Cancer Institute Common Toxicity Criteria (NCI CTCAE), version 3.0.

chemotherapy was higher than in ABC-02 (17%), but lower than in BT22 (75%) without differences in OS [5, 6, 27].

The last results of the FFCD study in pancreatic cancer showed that the second line may be offered to patients with good prognostic factors (ECOG 0, 1); FOLFOX following Gem or Gem following FOLFIRINOX, but the difference regarding sequence was not statistically significant [20].

Although our study is retrospective and might thus have inclusion bias, the results provide evidence that patients with first line chemotherapy failure may derive a benefit from second line chemotherapy.

To our knowledge, this is the first study evaluating a strategy with a second line of therapy in BTC, and showing a higher median survival for patients treated with FP+cisplatin treatment in the first line and Gem+/-cisplatin in the second line.

Finally, a number of important limitations should be considered. First, it is a retrospective, nonrandomized study and second, it comes from a single institution. Due to the small number of patients in Gem+/-cisplatin, it was not possible to make a proper statistical analysis: FP+cisplatin vs. Gem+cisplatin excluding the 13 patients from the last group who received only Gem. Moreover, 23 patients from both groups stopped the cisplatin treatment after an average of 3.5 months because of severe nausea and vomiting (10.5% and 10.3%, respectively) even with adequate prophylactic antiemetic treatment. Gastrointestinal adverse events and HFS were the most frequent adverse events for FP+cisplatin based therapy. A notable finding in ABC-02 was a significantly altered liver function tests in the Gem arm, probably explained by the uncontrolled disease progression [6]. In our study we had 13 patients with Gem from the beginning of the study, which probably explains the high rate of liver toxicities in Gem+/-cisplatin group.

Another important aspect which should be considered is the imbalance of baseline characteristics between the two groups: the proportion of patients with extrahepatic cholangiocarcinoma and with curative surgery was higher in the first group than in the second group and this could affect both the RR and OS.

Many clinical trials of single and multidrug regimens have been conducted for BTC in which the reported response rates, toxicity and survival times varied, probably explained by important differences in disease behavior, molecular profiles and sensitivity to therapy [31, 32].

Conclusion

Our results suggest that FP+cisplatin may be as good as Gem/Gem+cisplatin. However, they showed that FP+cisplatin based chemotherapy in the first line and Gem+/-platinum compounds in the second line, provided a

Table VI. Grade 3 or 4 toxicities - first line chemotherapy

	FP +cisplatin (n=57)		Gem+/-cisplatin (n=39)		Fisher exact test (2-sided)
	n	%	n	%	p
1. Hematologic					
Neutropenia	18	31.5	9	33.3	0.489
Leukopenia	7	12.3	7	17.9	0.558
Thrombocytopenia	3	5.3	6	15.4	0.152
Anemia	9	15.8	6	15.4	1.000
2. Hepatic					
Bilirubine > 1.5 x ULN	2	3.5	4	10.3	0.220
ALT > 5 x ULN	2	3.5	6	15.4	0.059
AST > 5 x ULN	3	5.3	5	12.8	0.264
3. Renal					
Creatinine > 1.5 x ULN	1	1.7	2	5.1	0.564
4. Nausea/vomiting	6	10.5	4	10.3	1.000
5. Diarrhoea	3	5.3	1	2.6	0.644
6. Constipation	0	0	1	2.6	0.406
7. Stomatitis	3	5.3	0	0	0.269
8. Hand-foot syndrome	2	3.5	0	0	0.513
9. Fatigue/asthenia	4	7.0	5	12.8	0.479
10. Weight loss	2	3.5	2	5.1	1.000
11. Anorexia	3	5.2	3	7.7	0.684
12. Peripheral oedema	1	1.8	1	2.6	1.00
13. Biliary sepsis	0	0	1	2.6	0.406

Note: Severity was graded according to National Cancer Institute Common Toxicity Criteria (NCI CTCAE), version 3.0. ULN: Upper Limit of Normal.

better survival rate than the former. Therefore, a prospective study comparing Gem+cisplatin to FP+cisplatin would be necessary, checking also the impact of the chemotherapy lines' sequence in the advanced BTC.

Conflicts of interest

None to declare.

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