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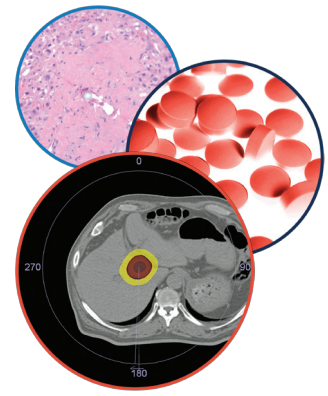

Hepatic Oncology

Identification of active chemotherapy regimens in advanced biliary tract carcinoma: a review of chemotherapy trials in the past two decades

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Practice Points

- The combination of gemcitabine with platinum agents compared with other regimens showed a trend toward improved response rate (RR) (p = 0.047) but no significant difference in progression-free survival (PFS) or overall survival (OS) (p = 0.089 and p = 0.43, respectively).
- No superior outcomes for the combination of 5-fluorouracil (5-FU) with platinum agents in comparison with other regimens in terms of RR, PFS or OS (p = 0.85, 0.08 and 0.82, respectively).
- The regimen of Epirubicin, cisplatin and 5-FU did not demonstrate any statistical significant improvement in RR (p = 0.49), PFS (p = 0.96) or OS (p = 0.14) when compared with the other regimens.
- The global effect of gemcitabine on OS showed a statistical trend (p = 0.014) and a significant improvement in PFS (p = 0.003). However, RR was not significant (p = 0.087) for the global gemcitabine effect.
- Platinum-containing regimens did not reveal any superior outcomes in OS (p = 0.98), PFS (p = 0.72) or RR (p = 0.15) compared with platinum-free regimens.
- There was no statistical differences in OS (p = 0.94) PFS (p = 0.44) or RR (p = 0.79) between regimens containing 5-FU versus combinations without 5-FU.
- No significant difference in RR (p = 0.20), PFS (p = 0.31) or median OS (p = 0.25) was found between regimens with irinotecan versus combinations without irinotecan.
- Gemcitabine in combination with 5-FU showed a trend toward an improved OS when compared with regimens containing gemcitabine or 5-FU in combination with platinum.
- There were no discernable trends in any of the data (RR, PFS or OS) over time.

SUMMARY Biliary tract carcinoma is a rare malignancy. We performed a comprehensive analysis of published prospective clinical trials in advanced biliary tract carcinoma in an attempt to identify active regimens in this setting. We searched PubMed and abstracts presented at the American Society of Clinical Oncology, Gastrointestinal Cancer Symposium, European Society of Medical Oncology and European Cancer Organization conferences for clinical trials in this disease. We found 83 trials. The effect of gemcitabine on overall survival benefit showed a strong trend (p = 0.014) and an improvement in progression-free survival (p = 0.003). Gemcitabine-based regimens containing 5-fluorouracil showed a trend toward an improved overall survival (p = 0.047) relative to platinum agents. Our findings support gemcitabine as the chemotherapy backbone for the treatment of patients with cholangiocarcinoma. Gemcitabine plus 5-fluorouracil combinations warrant further investigations.

KEYWORDS

- biliary tract carcinoma
- chemotherapy
- cholangiocarcinoma
- gallbladder carcinoma
- treatment

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Background

Biliary tract cancers (BTC) are a heterogeneous group of tumors arising from cholangiocytes lining the biliary tree. Subtypes include gallbladder cancers (GBC) as well as intra-hepatic (ICC) and extra-hepatic cholangiocarcinoma (ECC). BTC comprise a rare cancer type with a high mortality rate. Due to the combined reporting of ICC with hepatocellular carcinoma, it is challenging to determine the exact incidence of BTC. Approximately 10–15% of combined primary liver tumors comprise of ICC. In the USA it is estimated that about 33,000 cases of hepatocellular carcinoma and ICC, and approximately 10,500 cases of gallbladder and other biliary cancers will be diagnosed in 2014 [1–4]. Surgery is the only potentially curative treatment modality but even with surgery recurrence rates are high and the 5-year survival is approximately 30–60%. Moreover, most BTC patients are diagnosed with advanced and inoperable disease [5,6]. Patients with GBC are reported to have a worse prognosis than ICC and ECC [7,8]. Historically, gemcitabine has been widely used in pancreaticobiliary tumors based on its proven activity in pancreatic cancer [9]. Other chemotherapy agents have been incorporated in cholangiocarcinoma treatment including 5-FU, platinum agents, epirubicin, combinations of these agents and others. More recently, the combination of gemcitabine and cisplatin became the standard of care in inoperable BTC based on the ABC-02 trial, a randomized Phase III study that showed an increased median progression free survival (PFS) and median overall survival (OS) of 8.5 and 11.7 months, compared with 5 and 8 months, respectively, for single-agent gemcitabine [10]. The efficacy of this combination was also suggested by a meta-analysis of 104 clinical trials, largely Phase II studies [11].

Although there are retrospective data suggesting that approximately 45% of the patients who progress on first-line treatment are eligible for further treatment, there is a scarcity of prospective trials evaluating optimal treatment regimens in the second-line setting. As a result, no consensus on standard second-line treatment has been established [12].

We performed a comprehensive analysis of published prospective clinical trials in BTC in an attempt to identify active regimens both in the first- and the second-line settings. We also performed subgroup analyzes comparing the outcomes of these regimens in GBC compared with non-GBC cases. Finally, we analyzed the response rate and survival over time.

Patients & methods

We obtained the data for this analysis by searching PubMed, for the years 1992–2013, using a combination of the following terms: 'chemotherapy' plus 'biliary tract cancer', 'cholangiocarcinoma' or 'gallbladder cancer'. In addition, we reviewed relevant abstracts presented in American Society of Clinical Oncology, Gastrointestinal Cancer Symposium, European Society of Medical Oncology and European Cancer Organization conferences. Abstract searches were limited to the time period 2008–2013. We excluded trials that used targeted agents due to the diverse mechanism of action of these agents, and trials that treated ten patients or less. The following data from the studies were recorded: study completion date, number of treated patients, first- or second-line treatment, median RR, PFS, and OS. In trials comprising more than one treatment arm, each arm was analyzed separately as a single-arm study. We also preformed a subgroup analysis for the treatment outcomes in GBC versus ICC and ECC.

• Statistical analysis

In each individual treatment arm, the RR, and the median PFS and OS, were obtained and used as the primary outcome variable of interest. We then compared the distributions of those three outcome variables between the different predefined treatment groups. We restricted the analysis to first-line trials and trials in which <25% of patients were on second-line treatment. For each of the three outcome variables (RR, PFS and OS), we made a variety of two-group comparisons using the Wilcoxon rank sum test. Table 1 indicates the 12 regimens utilized for the analysis and Table 2 postulates which combinations of regimens were used for a given specific comparison. Three general types of comparisons were made: specific combination regimen versus all others, global evaluations, and specific pairwise comparisons. Exact tests were used as appropriate. All reported p values are two tailed. In view of the varying degrees of independence and dependence of the groups compared, and considering the number of tests performed here, the multiplicity of tests performed must be taken account of in a balanced way. Thus, to

Table 1. Included chemotherapy regimens, with coupled outcome variables.

Chemotherapy	Outcome	Arms	Minimum	Lower quartile	Median	Upper quartile	Maximum	Ref.
5-FU	OS	10	4.6	5.1	7.7	9.0	14.8	[8,13–21]
ADDIN EN.CITE	PFS	9	1.0	3.3	3.7	4.0	4.7	
	RR	9	0.0	7.0	14.3	32.0	35.0	
5-FU + platinum	OS	13	3.1	8.0	9.5	10.0	12.8	[13,22–31]
ADDIN EN.CITE	PFS	11	1.4	3.3	3.7	4.8	6.5	
	RR	13	0.0	19.0	21.4	30.0	42.9	
ECF	OS	6	4.9	5.8	8.5	9.1	9.9	[32–37]
ADDIN EN.CITE	PFS	5	1.9	4.6	5.1	5.2	5.6	
	RR	6	10.0	10.0	19.1	22.5	40.0	
Gemcitabine	OS	10	5.8	7.5	8.4	11.5	14.0	[10,38–46]
ADDIN EN.CITE	PFS	9	2.5	2.6	4.3	5.6	8.1	
	RR	9	0.0	9.4	17.5	26.1	36.0	
Gemcitabine+platinum	OS	24	5.0	8.7	9.5	10.8	19.9	[8,10,22,47–66]
ADDIN EN.CITE	PFS	23	3.0	4.0	4.8	7.8	11.0	
	RR	21	14.9	21.0	29.0	32.0	50.0	
Gemcitabine + 5-FU	OS	17	4.7	8.9	12.5	14.0	16.0	[20,38,67–81]
ADDIN EN.CITE	PFS	14	2.9	4.6	6.1	7.1	9.0	
	RR	15	9.5	21.4	30.0	31.4	38.0	
Gemcitabine + 5-FU + platinum	OS	2	9.9	9.9	10.0	10.0	10.0	[82]
ADDIN EN.CITE	PFS	0	–	–	–	–	–	
	RR	2	19.0	19.0	21.0	23.0	23.0	
Gemcitabine + pemetrexed	OS	1	6.6	6.6	6.6	6.6	6.6	[83]
	PFS	1	3.8	3.8	3.8	3.8	3.8	
	RR	1	0.0	0.0	0.0	0.0	0.0	
5-FU + etoposide + leucovorin	OS	1	12.0	12.0	12.0	12.0	12.0	[34]
	PFS	1	7.8	7.8	7.8	7.8	7.8	
	RR	1	15.0	15.0	15.0	15.0	15.0	
Gemcitabine + irinotecan	OS	1	7.6	7.6	7.6	7.6	7.6	[84]
	PFS	1	4.3	4.3	4.3	4.3	4.3	
	RR	1	20.5	20.5	20.5	20.5	20.5	
Oxaliplatin + irinotecan	OS	1	9.2	9.2	9.2	9.2	9.2	[85]
	PFS	1	2.7	2.7	2.7	2.7	2.7	
	RR	1	17.9	17.9	17.9	17.9	17.9	
Irinotecan + 5-FU	OS	1	7.0	7.0	7.0	7.0	7.0	[86]
	PFS	1	4.0	4.0	4.0	4.0	4.0	
	RR	1	10.0	10.0	10.0	10.0	10.0	

5-FU: 5-fluorouracil; ECF: Epirubicin, cisplatin and 5-FU; OS: Overall survival; PFS: Progression-free survival; RR: Response rate.

aid in interpretation of the effects tested, only $p < 0.01$ can be deemed statistically significant, while $0.05 < p < 0.01$ indicates a strong statistical trend. The following abbreviations were used: trials (t), arms (a), and patients (n).

Results

Our initial search identified 83 published trials and 15 abstracts presented at scientific meetings. These 98 trials comprised of 109 trial arms treating a total of 4572 patients. Seventeen out of 109 arms were excluded from the analysis, 16 arms used targeted therapy and one had less than ten patients treated on the trial. Thus, 83 trials met inclusion criteria and were included in our analysis, comprising 92 treatment arms and treating 3809 patients. Our search results are summarized in Figure 1. The median RR, PFS and OS for all treatment arms (first and second line) was as follows: RR 21.4% (a = 85), PFS 4.3 months (a = 81) and OS 9.2 months (a = 92).

In a preliminary analysis, we compared distributions of the three outcome variables

Table 2. Comparisons between specific chemotherapy combinations.

Chemotherapy regimens	Trial arms	Gemcitibine + platinum vs others	5-FU + platinum vs others	5-FU + platinum + epiribucin vs others	Global 5-FU	Global platinum effect	Global gemcitibine effect	Global irinotecan effect
5-FU	10	-	-	-	+	-	-	-
5-FU + platinum	13	-	+	-	+	+	-	-
ECF	6	-	-	+	+	+	-	-
Gemcitabine	10	-	-	-	-	-	+	-
Gemcitabine + platinum	24	+	-	-	-	+	+	-
Gemcitabine + 5-FU	17	-	-	-	+	-	+	-
Gemcitabine + 5-FU + platinum	2	-	-	-	+	+	+	-
Gemcitabine + taxol	1	-	-	-	-	-	+	-
5-FU + etoposide + leucovorin	1	-	-	-	+	-	-	-
Gemcitabine + irinotecan	1	-	-	-	-	-	+	+
Oxaliplatin + irinotecan	1	-	-	-	-	-	-	+
Irinotecan + 5-FU	1	-	-	-	+	-	-	+

5-FU: 5-fluorouracil; ECF: Epirubicin, cisplatin and 5-FU.

(RR, PFS and OS) according to whether the trial enrolled patients with first-line chemotherapy only, first line with <25% second-line treatment, or second-line chemotherapy only. Distributions of first line only versus <25% second line, were not significantly different ($p \geq 0.80$). Thus, these two distributions were combined and second line only trials (t = 5) were excluded from further analyses. Accordingly, excluding the second-line only trials, there were 87 treatment arms with 3645 treated patients (Table 1). Chemotherapy regimens were analyzed to determine the most active drug combinations. Subgroups named 5-FU in this analysis comprised fluorouracil, capecitabine or S-1, and platinum agents included were cisplatin, oxaliplatin and carboplatin.

• Specific chemotherapy combinations compared with the other regimens

Gemcitabine in combination with platinum agents

The combination of gemcitabine with cisplatin has become the standard of care treatment for cholangiocarcinoma based on the randomized ABC-02 Phase III trial demonstrating an overall survival benefit for this combination compared with gemcitabine single agent (11.7 vs 8.2 months, $p < 0.001$) [10]. In our analysis a total of 24 treatment arms, treating 1403 patients, evaluated the efficacy of gemcitabine in combination with platinum agents. In ten out of these 24 trials, including the ABC-02 trial, gemcitabine was combined with cisplatin, treating a total of 655 patients [10,22,47–53]. Out of the remaining 14 trials, 12 trials combined gemcitabine with oxaliplatin [8,54–64], treating a total of 683 patients, while the remaining two trials combined gemcitabine with carboplatin, treating a total of 65 patients [65,66]. The pooled analysis demonstrated a median response rate of 29% (a = 21). The median PFS and OS were 4.8 months (a = 23) and 9.5 months (a = 24), respectively (Figure 2). The combination of gemcitabine with platinum agents compared with other regimens showed a trend toward improved RR ($p = 0.047$) but no significant difference in PFS or OS ($p = 0.089$ and $p = 0.43$, respectively).

5-FU in combination with platinum

5-FU in combination with platinum agents has been used with success in several gastrointestinal malignancies including esophageal, gastric and colorectal cancers [87]. In cholangiocarcinoma several trials have evaluated this combination treatment. In our study we identified 13 treatment arms using this combination, treating 421 patients. Four of the 13 trial arms evaluated the efficacy of 5-FU in combination with cisplatin [13,23–24], and two trial arms used 5-FU with oxaliplatin [25,26]. The remaining four trial arms used capecitabine in combination with cisplatin [27,28] (two trial arms) or oxaliplatin [29] (two trial arms). Three of the trials used S-1, two of the trial arms in combination with cisplatin [22,30] and one with oxaliplatin [31]. Pooled analyses showed that the combination of 5-FU compounds with platinum agents had a median RR of 21.4% (a = 13). The median

PFS and OS times were 3.7 and 9.5 months, respectively (Figure 2). Our analysis showed no superior outcomes for the combination of 5-FU with platinum agents in comparison with other regimens in terms of RR, PFS or OS (p = 0.85, 0.08 and 0.82, respectively).

The combination of epirubicin, cisplatin & 5-FU

The chemotherapy regimen combination of epirubicin, cisplatin and 5-FU (ECF) is currently being used as a standard of care treatment for the management of gastroesophageal cancer [88,89]. In order to study the efficacy of this regimen in cholangiocarcinoma, we analyzed trials that used this combination. Six trials in this analysis were identified, treating 206 patients. Four of the six trials used 5-FU [32–35] and the other two used capecitabine [36] or uracil/tegafur [37]. The median RR was 19%. The median PFS and OS were 5.1 and 8.5 months, respectively (Figure 2). ECF did not demonstrate any statistically significant improvement in RR (p = 0.49), PFS (p = 0.96) or OS (p = 0.14) when compared with the other regimens.

• Specific chemotherapy agent effects

Global effect of gemcitabine

Gemcitabine is a nucleoside analog, which has shown efficacy in pancreatic cancer and hence extrapolation of the data led to great interest in many BTC trials [9]. To further investigate the effect of gemcitabine, all regimens containing gemcitabine were compared with regimens that did not use gemcitabine. We identified 55 treatment arms that used gemcitabine. These regimens had a median OS of 9.7 months, median PFS of 5.0 months (a = 48) and RR 26.1% (a = 49). Thirty-two treatment arms in our analysis did not use gemcitabine. These regimens had a median OS of 8.9 months, median PFS of 3.8 months (a = 28) and RR 19.0% (a = 31). The global effect of gemcitabine on OS showed a statistical trend (p = 0.014) and a significant improvement in PFS (p = 0.003). However, RR was not significant (p = 0.087) with respect to the global gemcitabine effect (Figure 3).

The effect of gemcitabine was also tested in two other pair-wise comparisons. A comparison between regimens that used single agent 5-FU [8,13–21] to regimens that used

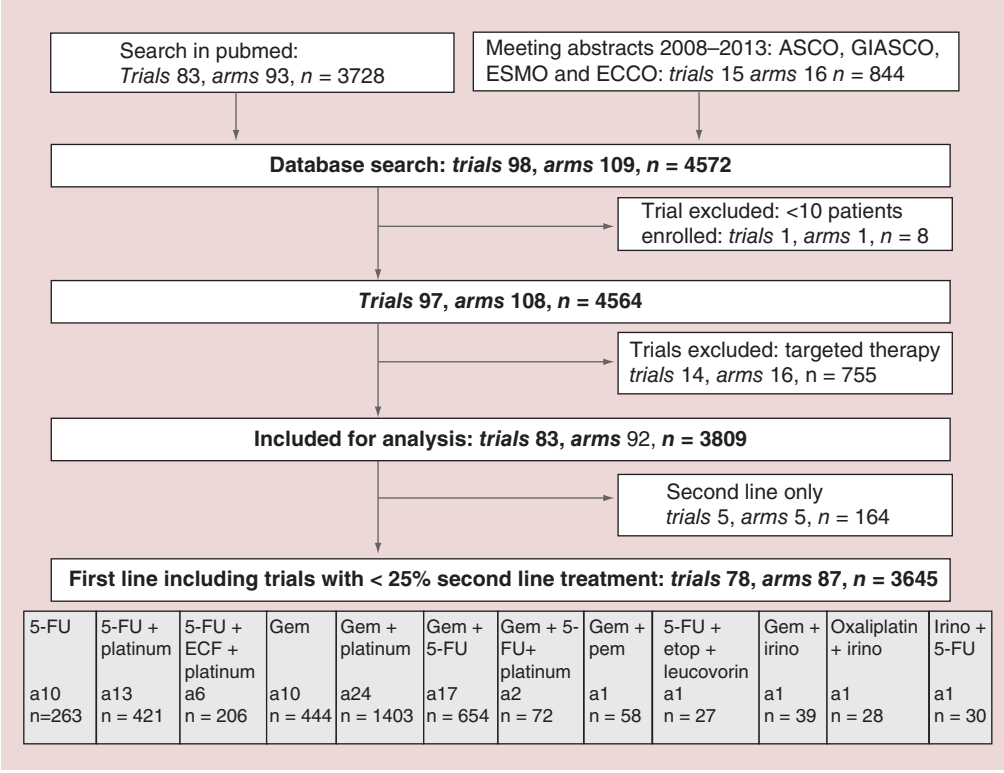

Figure 1. Study selection.

5-FU: 5-fluororuacil; a: number of arms; ECF: Epirubicin, cisplatin and 5-FU; Etop: Etoposide; Gem: Gemcitabine; Irino: Irinotecan; n: Number of treated patients; Pem: Pemetrexed; t: Number of trials.

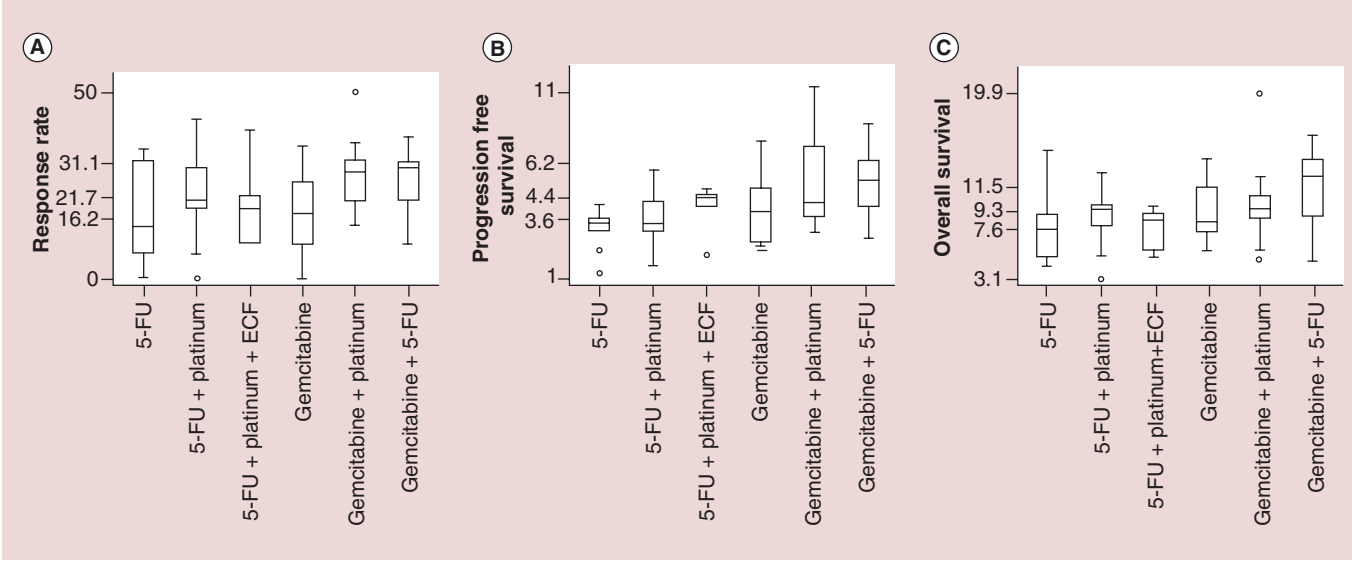

Figure 2. Outcome variables of each of the analyzed studies presented as bubble plots. The five horizontal lines in each figure represent the minimum, the quartiles and maximum of all the data combined. Circle sizes are proportional to the number of patients on each trial. **(A)** Response rate, **(B)** progression free survival and **(C)** overall survival.
5-FU: 5-fluorouracil; ECF: Epirubicin, cisplatin and 5-FU.

5-FU + gemcitabine [20,38,67–81] showed a statistical trend toward improved OS (p = 0.017), and statistically significant improved PFS (p = 0.001) with the combination regimen. However, there was no significant difference in RR (p = 0.17). 5-FU + platinum [13,22–31] versus 5-FU, platinum + gemcitabine [82] was compared, but no difference in RR (p = 0.46), or OS (p = 0.46) was detected (there was insufficient data to test PFS).

Global effect of platinum

In the same manner as above, platinum-containing regimens were compared with platinum-free regimens in an attempt to evaluate the global effect of platinum. This comparison did not reveal any superior outcomes in OS (p = 0.98), PFS (p = 0.72) or RR (p = 0.15).

To further analyze the platinum effect three other pair-wise tests were performed. We found no significant differences between the trials utilizing single agent 5-FU and the 5-FU + platinum trials with respect to any of the three outcome variables (all p > 0.1). The second pair-wise test evaluated gemcitabine single agent [10,38–46] versus gemcitabine in combination with a platinum agent [8,10,22,47–66], to evaluate the effect of platinum given gemcitabine. This comparison indicated a trend toward improved RR when adding platinum to gemcitabine (p = 0.041) but there was no significant difference seen in PFS or OS (p = 0.28 and 0.33, respectively). The third pair-wise comparison was between the combination of gemcitabine and 5-FU with or without platinum agent. No significant difference in RR (p = 0.23), or OS (p = 0.57) was observed (there was insufficient data to test PFS).

5-FU-containing regimens

5-FU-based therapies have been the backbone in many of the randomized Phase II trials evaluating efficacy in BTC. In our analysis 5-FU single agent was used in ten treatment arms, treating 263 patients, resulting in median OS of 7.7 months (a = 10), median PFS 3.7 months (a = 9) and RR 14.3% (a = 9). To evaluate the global 5-FU effect we compared regimens with 5-FU versus combinations without 5-FU, we did not find any statistical differences in OS (p = 0.94), PFS (p = 0.44) or RR (p = 0.79).

The effect of 5-FU was further tested with pair-wise comparisons. Trials treating patients with single agent gemcitabine [10,38–46] were compared with trial arms treating patients with gemcitabine in combination with 5-FU [20,38,67–81]. There was no significant difference in OS (p = 0.13) or PFS (p = 0.08), however, in regards to RR, it was marginally higher in 5-FU + gemcitabine regimens

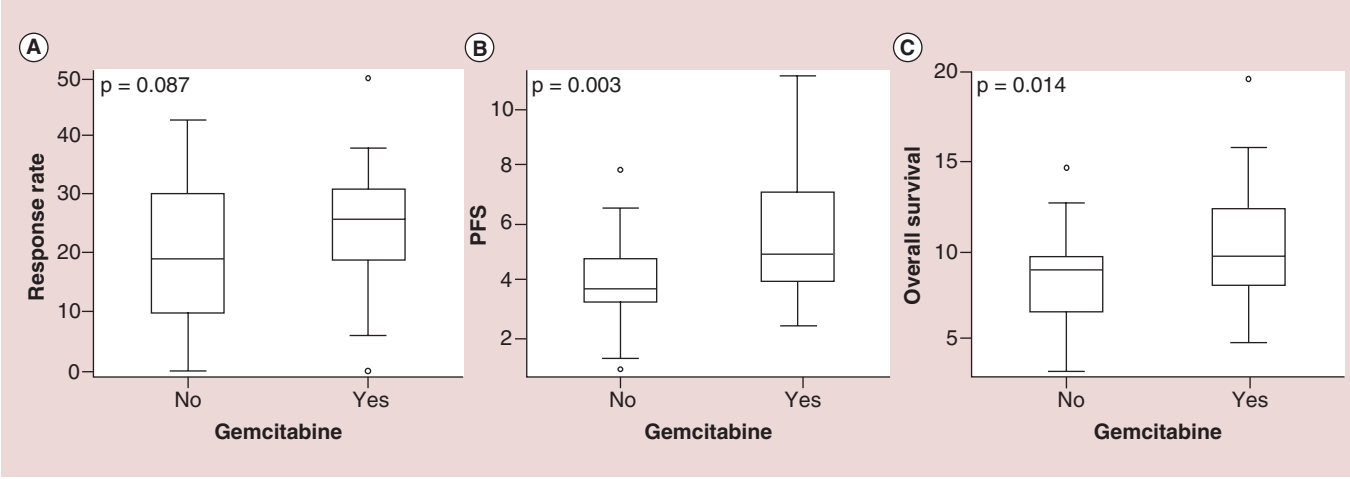

Figure 3. Global effect of gemcitabine plotted by (A) response rate, (B) progression-free survival and (C) overall survival. OS showed a statistical trend (p = 0.014) and there was a significant improvement in PFS (p = 0.003). RR was not significant (p = 0.087). OS: Overall survival: PFS: Progression-free survival; RR: Response rate.

(median 30.0%) compared with gemcitabine alone regimens (median 17.5%) with p = 0.047. In the second pair-wise test we found no statistically significant differences between gemcitabine + platinum regimens compared with gemcitabine + platinum + 5-FU regimens for either OS (p = 0.51) or RR (p = 0.43). PFS was not reported in the two treatment arms utilizing the three-drug regimen gemcitabine + platinum + 5-FU, therefore it was not analyzed.

Global effect of irinotecan

Three trials in our analysis evaluated irinotecan-containing regimens treating 97 patients [84–86]. These trials were compared with all other regimens that did not use irinotecan (Table 1). No significant difference in RR (p = 0.20), PFS (p = 0.31) or median OS (p = 0.25) was found.

• Comparisons between specific chemotherapy combinations

This analysis was performed in an attempt to compare the outcomes of the most frequently used combination regimens in cholangiocarcinoma. These regimens were: 5-FU + platinum agents, gemcitabine + platinum agents, and 5-FU + gemcitabine (Table 1).

5-FU in combination with platinum agents was used in 13 treatment arms, treating 421 patients, and showed a median RR of 21.4%, median PFS of 3.7 (a = 11) months and a median OS of 9.5 months. On the other hand, gemcitabine in combination with platinum compounds was used in 24 treatment arms, treating 1403 patients, and showed a median RR 29%, median PFS of 4.8 months and a median OS of 9.5 months. Comparing regimens containing platinum combined with 5-FU versus gemcitabine demonstrated no significant difference in RR (p = 0.46), or OS (p = 0.59) but a statistical trend (p = 0.041) toward a longer PFS favoring gemcitabine in combination with platinum.

5-FU in combination with platinum [13,22–31] (n = 421 patients, a = 13, median RR 21.4%, median PFS 3.7 months and median OS 9.5 months) was compared with 5-FU in combination with gemcitabine [20,38,67–81] (n = 654, a = 17, median OS 12.5 months, PFS 6.1 months and RR 30%). The outcome of 5-FU with platinum versus gemcitabine showed no difference in RR (p = 0.3), however there was a strong statistical trend (p < 0.05) for both PFS and OS favoring 5-FU in combination with gemcitabine. Comparing regimens containing gemcitabine combined with platinum (a = 24, n = 1403) or 5-FU (a = 17, n = 654) did not show a significant difference in RR or PFS (p = 0.99 and p = 0.49, respectively) but it did show a trend toward an improved OS (median OS 9.5 months vs 12.5 months favoring gemcitabine + 5-FU, p = 0.047). Thus, gemcitabine in combination with 5-FU showed a trend toward an improved OS when compared with regimens containing gemcitabine or 5-FU in combination with platinum.

• Treatment effect over time

In order to study the treatment effect over the past two decades we plotted the RR, PFS and OS for each of the analyzed regimens over the past 18 years (from 1992 to 2010). The median RR was 21.4% (a = 75); the median PFS (a = 70) and OS (a = 81) were 4.4 and 9.4 months, respectively. The number of trial arms differs in this analysis since not all of the trials reported RR or PFS. There were no discernable trends in any of the data over time.

Discussion

Gemcitabine has in recent years been regarded as the main chemotherapeutic agent in the treatment of pancreaticobiliary malignancies [9,10,90,91]. The ABC-02 trial – one of the few Phase III trials in this disease – demonstrated an approximate 30% improvement in median PFS and OS for the combination of gemcitabine and cisplatin compared with gemcitabine alone, thereby establishing a new standard of care in BTC [10]. We performed this analysis in order to identify active regimens in cholangiocarcinoma in both first- and second-line settings. Our analysis evaluating gemcitabine single agent versus gemcitabine in combination with a platinum agent indicated a strong trend toward improved RR when platinum is added to gemcitabine ($p = 0.041$) but this did not translate into benefit in PFS or OS ($p = 0.28$ and 0.33, respectively). Our findings are consistent with those reported in a previous meta-analysis of 104 trials, demonstrating superior RR with gemcitabine combined with platinum [11]. To address the question of whether the effect of this combination is due to the gemcitabine component or the platinum agent component we tested the global effect of each of these agents. The treatment effect was evaluated irrespective of dose and schedule of the agent. While the global effect of gemcitabine showed a strong statistical trend in OS (median OS of 8.9 vs 9.7 months, $p = 0.014$) and a significant improvement in PFS (median PFS of 3.8 vs 5.0 months, $p = 0.003$) favoring gemcitabine-containing regimens, our analyses indicated no significant difference in RR, PFS, or OS ($p = 0.15$, 0.72, 0.98, respectively) between regimens that contained platinum versus the ones that did not. Accordingly, we believe that the clinical effect is mainly due to gemcitabine when combined with platinum agents.

5-FU-based therapy has been shown to improve OS and quality of life compared with best supportive care in patients with advanced pancreatic and BTC [92]. Hence, 5-FU-based therapies have been the backbone of chemotherapy regimens in many of the randomized Phase II trials in BTC. In our pooled analyses we compared regimens with 5-FU versus combinations without 5-FU, but we did not find any statistical differences in RR ($p = 0.79$), PFS ($p = 0.44$) or OS ($p = 0.94$). Comparing 5-FU versus gemcitabine, in combination with platinum demonstrated no significant difference in RR ($p = 0.46$), or OS ($p = 0.59$) but a statistical trend ($p = 0.041$) toward a longer PFS favoring gemcitabine in combination with platinum. Therefore, 5-FU-based chemotherapy regimens are not as active as gemcitabine-based regimens in BTC, according to our analysis. Our findings are consistent with those from a retrospective review of 304 patients with BTC that showed lower risk of death in the patients who received gemcitabine-based regimen versus 5-FU-based regimens [93].

The next question was whether combining these two agents together (gemcitabine + fluoropyrimidine) would be an effective strategy in BTC. We addressed this question by comparing gemcitabine in combination with either platinum- or 5-FU-based regimens. This comparison indicated a strong trend toward an improved OS (median OS 9.5 months vs 12.5 months) favoring gemcitabine combined with 5-FU ($p = 0.047$). Considering the toxicity profiles of these two regimens and the restrictions of using cisplatin in certain patient populations including patients with renal failure, the combination of gemcitabine and 5-FU could be a valid option in unresectable BTC. This analysis is limited by three different fluoropyrimidine agents (fluorouracil, capecitabine and S-1) being merged into one group and that different doses and schedules were utilized. Whether gemcitabine in combination with 5-FU should be considered as a first-line choice in BTC remains to be determined in Phase III clinical trials. A randomized Phase III study comparing gemcitabine and cisplatin with gemcitabine and capecitabine was initiated in Canada but stopped early secondary to poor accrual (clinicaltrials.gov NCT00658593). There are no randomized Phase III trials currently comparing gemcitabine and cisplatin versus gemcitabine in combination with a fluoropyrimidine agent, but such trials are in the planning phase [94].

Although 45% of the patients who progress on first line treatment are eligible for further treatments [12] no consensus on the standard treatment has been established [95] in this setting. This is due to a scarcity of prospective trials in the second-line setting in BTC. We identified only five trials that were exclusively second-line trials, treating a total of 164 patients. Overall, in our pooled analysis cholangiocarcinoma patients who received a second line chemotherapy had a median RR of 6.9%, median PFS of 2.5 months and a median OS of 5.9 months (data not shown). In concordance with our findings, a large retrospective study in a second-line setting found a median PFS of 2.8 months and median OS of 7.5 months [96]. In this study only 25% of the patients with BTC received second-line treatment and in the ABC trial the number was approximately 18% [10,96]. Accordingly, there is a great need for randomized trials in the second-line setting to establish an evidence-based standard of care.

Our analysis has potential limitations. First, although our study includes 83 clinical trials, some prospective studies were not included or full data from abstracts were published after our meta-analysis was completed. Since results of these trials support our findings this limitation should not have a significant impact on our conclusions. Second, comparisons across trials can be difficult due to the heterogeneity of regimens used, deriving from the different platinum or fluoropyrimidine agents, and different doses and schedules. Third, only 25 treatment arms in the analyzed trials specified whether the enrolled patients were diagnosed with ICC or ECC versus GBC neoplasm. Twelve out of these 25 trial arms limited the eligibility criteria to ICC/ECC, and the remaining 13 trial arms treated patients with GBC. These limited data preclude us from performing subgroup analysis. Finally, the trials included in our study were not restricted to randomized trials and the lack of uniformity between the included trials may have affected the results of our pooled analysis.

Our findings suggest that gemcitabine remains the backbone chemotherapy agent for future studies in cholangiocarcinoma. There is a need for randomized clinical trials that compare the current standard of care with other combinations in the first line as well as therapeutic interventions in the second-line setting. Likewise, there is a need for Phase III randomized clinical trials in order to perform more valid subgroup analyses between the different types of BTC. Nonetheless, the main challenge in conducting clinical trials in this disease remains its low incidence. Future efforts should focus on multicenter and cooperative group clinical trials approach in order to overcome this challenge, in addition to identifying new biomarkers predictive of response and exploring novel agents that could improve outcomes.

Future perspective

The increased incidence of cholangiocarcinoma and the unmet needs for treatment in this devastating disease will require future global collaborative efforts in the next decade. These efforts should focus on identifying novel biomarkers that could predict prognosis and treatment efficacy. New treatment modalities, such as immunotherapy, should be also studied and incorporated in the future treatment paradigm if found to be effective.

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