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Combination versus mono-therapy as salvage treatment for advanced biliary tract cancer: A comprehensive meta-analysis of published data

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ABSTRACT

Aim: Gemcitabine-based chemotherapy regimens remain the standard first-line treatment for advanced biliary tract cancers (BTCs) patients with no second-line treatments established yet. The preset meta-analysis aims to comprehensively evaluate the role of second-line treatment for advanced BTCs in terms of response, overall survival and toxicities.

Materials and methods: Eligible studies were identified using Medline, Pubmed, and meeting abstracts. Searches were last updated on April 30, 2018. Eligible studies reported survival and/or response data for refractory BTCs patients receiving second-line therapy. Primary outcomes of interest were objective response rate (ORR), disease controlled rate (DCR), 1-year overall survival (OS), and progression free survival (PFS).

Results: A total of 38 cohorts from 32 studies were eligible for analysis: 23 prospective phase II trials and 9 retrospective studies. In total, data from 1391 patients were reported with median number of patients included in each cohort of 28.5 (range: 9–255). The weighted median PFS and OS for refractory BTCs received second-line therapy were 2.6 months and 6.5 months, respectively. Fluoropyrimidine-based, gemcitabine-based, or Taxanes-based chemotherapy was not superior to single targeted/toxic agent in terms of ORR. In addition, the pooled disease control rate (DCR) and 1-year overall survival (OS) of fluoropyrimidine-based chemotherapy was inferior to single targeted/toxic agent (DCR: 47% versus 60%, RR 0.78, 95%CI: 0.61–1.00, $p = 0.03$; 1-year OS: 15% versus 29.6%, RR 0.90, 95%CI: 0.29-0.87, $p = 0.006$), but not for GEM-based or taxanes-based chemotherapy. In addition, correlation analysis indicates that the best correlations were between median OS and median PFS for all cohorts ($r = 0.57$; $P = 0.003$).

Conclusion: Combined second-line treatment is not superior to single targeted/toxic agent as salvage treatment for advanced BTCs in terms of ORR, DCR and 1-year OS, and fluoropyrimidine-based chemotherapy seems to be inferior to other second-line regimens. With available evidence from published data, we could not clearly recommend a preferred second-line regimen for advanced BTCs. Further prospective randomized studies are needed to confirm our findings and investigate more efficient second-line therapy in this setting.

1. Introduction

Biliary tract cancers (BTCs) are a heterogeneous groups of tumors arising from the epithelial cells of the intrahepatic ducts, extrahepatic bile ducts, gall bladder and ampulla of Vater (Takada et al., 2002). Although BTCs are relatively rare, accounting for 0.7% of all malignant tumors in adults, the incidence has recently been increasing worldwide (Gores, 2003; Matsuda and Marugame, 2007; Randi et al., 2009). Until now, the only curative treatment of BTCs is surgical resection; however, the majority of BTCs (> 65%) are regarded as incurable at initial diagnosis. In addition, most of BTCs often relapse even after curative surgery (Chan and Berlin, 2015). The prognosis of advanced BTCs, including patients with un-resectable locally advanced or metastatic disease, is poor with a 5-year overall survival (OS) of < 10% (Bertuccio et al., 2013; Lamarca et al., 2014). During the past decade, two randomized controlled trials have demonstrated that systemic chemotherapy could improve survival and quality of life compared to best supportive care(Sharma et al., 2010; Glimelius et al., 1996). More recently, the randomized phase III ABC-02 trial indicated that gemcitabine plus cisplatin yielded significantly improved overall survival (OS) as compared with gemcitabine alone (11.7 versus 8.1 months, hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; $P < 0.001$)(Valle et al., 2010). A subsequent phase II study conducted by Okusaka T. et al (Okusaka et al., 2010) also evaluated the same regimes and reported

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very similar results. Based on these published results, gemcitabine plus cisplatin regimen has been globally accepted as the standard first-line chemotherapy for patients with un-resectable or metastatic BTCs.

However, most patients receiving front-line chemotherapy would eventually become refractory to chemotherapy or experience disease progression after a certain period of time. Moreover, about half of patients with progressive disease after first-line chemotherapy maintain a good performance status and are candidates for further therapy. In contrast to first-line treatment, there are no randomized study has been performed to indicate the survival benefit of second-line chemotherapy over best supportive care in patients with advanced BTCs. Despite the lack of high-level evidence, different second-line treatment regimes has been widely used in clinical practice for patients with advanced BTCs (Onesti et al., 2015; Walter et al., 2013). Although these studies have examined the efficacy and safety of second-line treatment in advanced BTCs, but most of these are retrospective studies based on a small sample size and reported controversial results. In addition, there is no head-to-head comparison data available for combination versus single target/toxic agent as second-line therapy in the treatment of advanced BTCs. Whether combined therapy would be superior to mono-therapy remains undetermined. Therefore, we perform a comprehensive meta-analysis of published data to compare treatment outcomes of refractory BTCs patients who received combination therapy or single targeted/toxic agent.

2. Method and materials

2.1. Study design

We developed a protocol that defined inclusion criteria, search strategy, outcomes of interest, and analysis plan. The reporting of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (Moher et al., 2009)

2.2. Procedures

To identify studies for inclusion in our systematic review and meta-analysis, we did a broad search of four databases, including Embase, Pubmed/Medline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, from the date of inception of every database to April, 2018. The search included the following terms: ('biliary tract carcinoma' or 'biliary tract cancer', or 'cholangiocarcinoma', or 'gallbladder') and ('second-line' or 'refractory') and 'survival'. Abstracts of the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology Congress since 2002 (ESMO) and the World Gastrointestinal Congress since 2006 were also searched manually; To be eligible for inclusion in our systematic review and meta-analysis, study populations (referred to hereafter as cohorts) had to meet all the following criteria: (1) patients with advanced biliary cancers and progressive disease after a first-line therapy (any regimens) and who were treated with second-line chemotherapy; (2) patients received systematic therapy without other local therapies (such as radiotherapy, surgery or photodynamic therapies), both prospective and retrospective studies were included; and (3) reported outcomes of interest (ie, tumor control, survival, and complications); We did not restrict our search to language, country, We excluded case reports with fewer than five patients, reviews, notes, letters, errata, and commentaries.

2.3. End-points

The primary end point of this meta-analysis was OS, which was defined as the period from starting second-line therapy until death or last follow-up. Secondary outcome measures included time to progression (TTP)/progression-free survival (PFS), and both of them were defined as the period from starting second-line therapy until progression or last follow-up, objective response rate (ORR), which was defined as rate of partial responses and complete responses, disease control rate (DCR), which was defined as rate of partial responses, complete response and stabilization. Quality-of-life data were also collected if available. Details of the administered first-line chemotherapy regimen were also reviewed.

2.4. Data extraction

Two investigators screened the titles and abstracts of potentially relevant studies. We retrieved the full text of relevant studies for further review by the same two reviewers. A third senior investigator resolved any discrepancies between reviewers. If reviewers suspected an overlap of cohorts in a report, they contacted the corresponding author for clarification; we excluded studies with a clear overlap. The same pair of reviewers extracted study details independently, using a standardized pilot-tested form. A third investigator reviewed all data entries. We extracted the following data: author, study design, study period, median age, first-line chemotherapy regimens, second-line therapy regimens, sample size, and outcomes of interest.

We used the Newcastle-Ottawa quality assessment scale to assess the quality of included non-comparative (uncontrolled) studies (Stang, 2010). This scale was an eight-item instrument that allowed for assessment of patient population and selection, study comparability, follow-up and outcome of interest. We selected items that focused on representativeness of study patients, demonstration that the outcome of interest was not present at the start of the study, adequate assessment of outcome, sufficient length of follow-up to allow outcomes to arise, and adequacy of follow-up.

2.5. Statistical analysis

We pre-specified the analysis plan in the protocol. We analyzed all patients who started second-line therapy (any regimens), regardless of their adherence to treatment. We calculated event rates of outcome (the proportion of patients who developed outcomes of interest) from the included cohorts for both combined therapy and mono-therapy. We pooled log-transformed event rates with DerSimonian and Laird random-effect models (Thorlund et al., 2011) and assessed heterogeneity using the Mantel–Haenszel test (Zintzaras and Ioannidis, 2005). We used the test of interaction proposed by Altman and Bland to compare log-transformed rates of outcomes between different combined chemotherapy regimens and mono-therapy (Altman and Bland, 2003). A statistical test with a p-value less than 0.05 was considered significant. To account for the potential effect of publication bias, we used the Duval and Tweedie non-parametric trim-and-fill method (Duval and Tweedie, 2000). To measure overall heterogeneity across the included cohorts, we calculated the I^2 statistic, with I^2 greater than 50% indicating high heterogeneity. We assessed potential publication bias by visual inspection of the symmetry of funnel plots and with the Egger regression asymmetry test. We did all statistical analyses with open Meta-Analyst software version 4.16.12 (Tufts University, URL http://tuftscaes.org/open_meta/) and SPSS18.0 software (SPSS Inc., Chicago, IL, United States).

3. Results

3.1. Search results

A total of 820 studies were identified from the database search [Pubmed/Medline (n = 542), ASCO (n = 180), ESMO (n = 53) and World Gastrointestinal Congress (n = 45)], of which 76 were duplicates and 670 did not meet the inclusion criteria and were therefore exclude. Of the 74 reports were retrieved for full-text evaluation. A total of 32 trials met the inclusion criteria and were included in this systematic

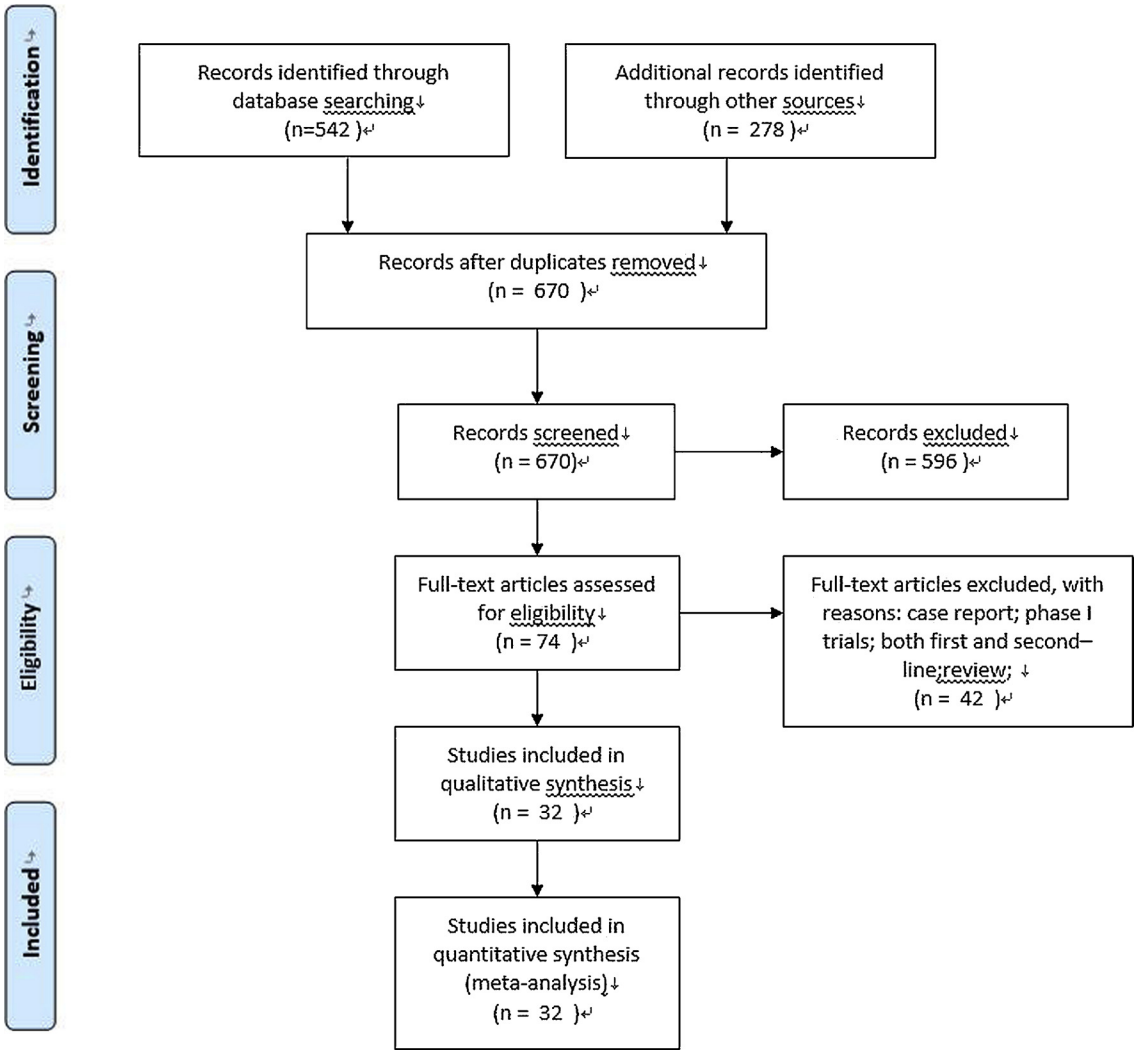

Fig. 1. PRISMA flow diagram.

review (Fig. 1) (Matsuyama et al., 2018; Larsen et al., 2018; Ikeda et al., 2018; Unseld et al., 2017; Kobayashi, 2017; Kim et al., 2017a, b; Jung et al., 2017; Ikeda et al., 2017; Dodagoudar et al., 2016; Cereda et al., 2016; Hwang et al., 2015; Guion-Dusserre et al., 2015; Brieau et al., 2015; He et al., 2014; Sasaki et al., 2013a, b; Yi et al., 2012; Sasaki et al., 2012; Lim et al., 2012; Kobayashi et al., 2012; Katayose et al., 2012; Kameda et al., 2012; Chiorean et al., 2012; Sasaki et al., 2011; Roth et al., 2011; Oh et al., 2011; Buzzoni et al., 2010; Sasaki et al., 2009; Pino et al., 2009; Costello et al., 2009; Paule et al., 2007). We did not find phase III randomized controlled trials or controlled studies that compared combination therapy with mono-therapy directly as salvage treatment for advanced BTCs. Table 1 showed the characteristics of the included studies. Overall, a total of 38 cohorts from 32 studies with 1391 pre-treated advanced BTCs patients were included. The median age was 63 years (range, 52.5–73 years). The median number of patients included in each cohort was 28.5 patients (range: 9–255 patients). The vast majority of patients from included studies (84.3%) received gemcitabine-based chemotherapy as their first-line treatment, and three studies did not report first-line chemotherapy (Table 1). The weighted median OS in the 30 cohorts with survival data available (including retrospective analysis and phase II trials) was 6.5 months (range 4.1–31.0 months) from commencement of second-line therapy. The weighted median PFS in 31 cohorts of refractory BTCs received second-line therapy was 2.6 months (95% CI 1.6–8.0 months) (Table 1).

3.2. Quality of included studies

In general, most of the included studies provided adequate outcome ascertainment, enrolled a representative sample of patients, and had an acceptable length of follow-up. As a result, methodological quality of these studies was fair (Fig. 2). However, comparative evidence was at high risk of bias because we compared data across studies not within them, and selection bias was likely to be present.

3.3. Pooled incidence of primary outcomes

The most frequently assessed second-line regimens in the present meta-analysis were fluoropyrimidine-based combination therapy (n = 13 cohorts), followed by gemcitabine-based combination therapy (n = 8 cohorts), single targeted agent (n = 7 cohorts), single toxic agent (n = 7 cohorts) and taxanes-based combination therapy (n = 3 cohorts), respectively. The pooled ORR incidence of second-line therapy in pre-treated BTCs patients was 9.5% (95%CI: 7.2–12.5%, Fig. 3). We then performed sub-group analysis according to treatment regimens and found that the pooled incidence of ORR for single targeted agent, single toxic agent (mainly fluoropyrimidine alone), fluoropyrimidine-based combination therapy, gemcitabine-based combination therapy, and taxanes-based combination therapy were 8.1%, 6.9%, 8.4%, 12.3% and 8.8% respectively. A total of 1360 BTCs patients were included for DCR analysis, and the pooled incidence of DCR was 50.3%

Table 1
Baseline characteristics of 32 included trials for analysis.

Author	Patient enrolled	Type of study	First-line regimens	Second-line regimens	Median age	ORR, (events/total)	DCR, (events/total)	Median OS	Median PFS
Matsuyama et al. (2018)	27	P	GEM–S-1	GEM + DDP	71	1/27	17/27	6.5	3.3
Larsen et al. (2018)	50	P	GEM-platinum	GEM + CAP + CPT-11 + Bev	66	2/37	30/37	6.4	3.6
Ikeda et al. (2018)	20	P	GEM-based CT	Trametinib	61.5	0/20	13/20	NR	2.5
Kobayashi (2017)	41	P	GEM-based CT	GEM + S-1	65	4/41	19/41	7	2.6
Kim et al. (2017a)	30	P	GEM-based CT	DOC + SPI-1620	64	3/30	14/30	4.78	2.6
Kim et al. (2017b)	255	R	GEM-platinum	FU alone	60	3/255	111/255	6.5	1.8
	66			Fu–platinum	60	5/66	31/66	6.2	2.6
Jung et al. (2017)	40	P	GEM-platinum	CAP + DDP	60	4/40	19/40	6.3	2.3
Ikeda et al. (2017)	26	P	GEM	lenvatinib	64	3/26	22/26	7.4	3.2
Unseld et al. (2017)	13	R	platinum-containing CT	Nab-paclitaxel-based CT	NR	NR	11/13	9.2	7.1
Dodagoudar et al. (2016)	66	P	GEM-platinum	FOLFOX-4	52.5	16/66	39/66	7.6	3.9
Cereda et al. (2016)	29	P	GEM-platinum	CAP + MMC	65	1/29	11/29	8.1	2.3
	28			CAP	66	0/28	7/28	9.5	2.1
Hwang et al. (2015)	30	P	GEM-based CT	mFOLFOX3	63	2/28	14/28	4.4	1.6
Guion-Dusserre et al. (2015)	13	R	GEM-platinum	FOLFIRI + Bev	60	5/13	11/13	20	8
Brieau et al. (2015)	64	R	GEM-platinum	FOLFIRI/XELIRI	NR	7/64	25/64	6.1	3.2
	38	R	GEM-platinum	LV5FU2 plus cisplatin	NR	5/38	23/38	7.1	2.6
	40	R	GEM-platinum	5-FU/CAP	NR	4/40	17/40	5.6	3.9
	21	R	GEM-platinum	FOLFOX/XELOX	NR	2/21	9/21	8.4	3.3
	10	R	GEM-platinum	Sunitinib	NR	1/10	6/10	6.8	4.6
He et al. (2014)	37	P	GEM-platinum	FOLFOX-4	57	8/37	23/37	6.9	3.1
Sasaki et al. (2013a)	60	R	GEM-based CT	GEM + DDP	68.5	1/60	35/60	6.7	3.5
Sasaki et al. (2013b)	13	P	GEM-based CT	Irinotecan	68	1/13	3/13	6.7	1.8
Yi et al. (2012)	56	P	GEM-based CT	Sunitinib	55	5/56	28/56	4.8	1.7
Sasaki et al. (2012)	22	P	GEM-based CT	S-1	71	5/22	11/22	13.5	5.4
Kobayashi et al. (2012)	55	R	GEM-based CT	S-1	69	2/55	21/55	6	2.3
Katayose et al. (2012)	11	R	GEM-based CT	S-1	NR	1/7	4/7	31	5.6
Kameda et al. (2012)	10	R	GEM	GEM + DDP	63	3/10	6/10	6.4	4
Buzzoni et al. (2010)	18	P	NR	Everolimus	60	1/18	10/18	NR	NR
Chiorean et al. (2012)	11	P	NR	DOC + erlotinib	NR	0/11	7/11	5.7	4
Lim et al. (2012)	50	P	GEM-based CT	Fu-based CT	57.3	2/50	11/50	5.6	2.2
Sasaki et al. (2011)	20	P	GEM-based CT	GEM-DDP	68	0/20	14/20	5.9	3.6
Oh et al. (2011)	32	P	5-Fu	GEM	60	2/29	8/29	4.1	1.6
Roth et al. (2011)	9	P	GEM-or FU-based CT	Imatinib	NR	0/9	NR	4.9	2.6
Pino et al. (2009)	35	R	GEM-based CT	CAP and Celecoxib	62	3/35	13/35	4.4	3.97
Costello et al. (2009)	20	P	NR	Bortezomib	NR	1/20	10/20	9.5	1.6
Sasaki et al. (2009)	16	P	GEM	S-1	73	3/16	7/16	8	5.5
Paule et al. (2007)	9	P	GEM-based CT	GEM + L-OHP + Cetuximab	NR	2/9	3/9	7	4

Abbreviations: GEMgemcitabine; DDPcisplatin; CAPcapecitabine; L-OHPoxaliplatin; CPT-11irinotecan; Fufluoropyrimidine; DOCdocetaxel; Bevbevacizumab; 5-FU ; 5-fluorouracil; FOLFOXoxaliplatin + 5-fu/Lv; MMCmitomycin C; ORRobjective response rate; DCRdisease controlled rate; OSoverall survival; PFSprogression-free survival; Rretrospective; Pprospective; CTchemotherapy; NRnot reported.

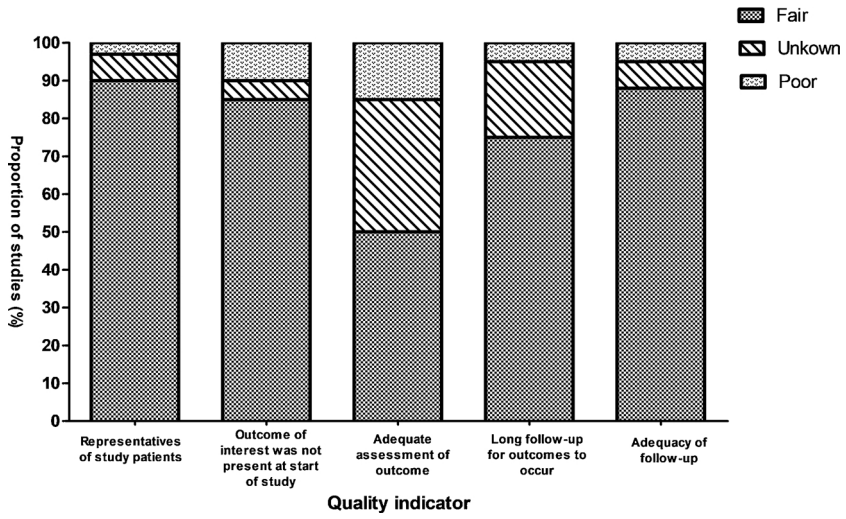

Fig. 2. Selected methodological quality indicator.

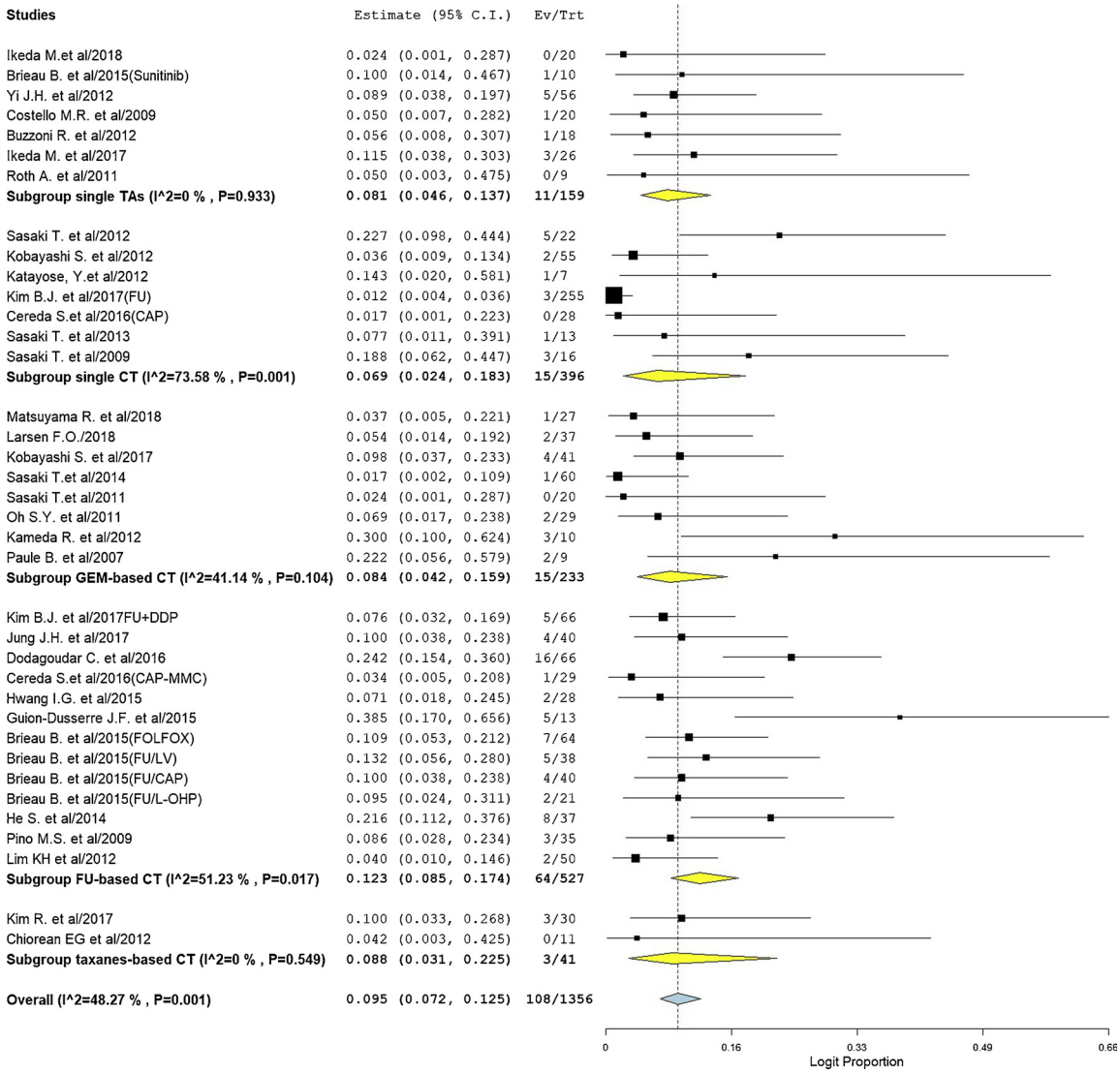

Fig. 3. pooled incidence of ORR for second-line therapy in advanced BTCs.

(95%CI: 45.5–55.1%, Fig. 4). Sub-group analysis based on second-line regimens found that the pooled DCR incidence for single targeted agent (60%), gemcitabine-based combination therapy (56.1%) and taxanes-based combination therapy (63.2%) was higher than that of single toxic agent (mainly fluoropyrimidine alone, 41%) and fluoropyrimidine-based combination therapy (47%). A total of 846 patients from 16 cohorts reported 1-year survival data, and the pooled incidence of 1-year OS in advanced BTCs received second-line therapy was 22.4% (95%CI: 17.6-28%, Fig. 5). Sub-group analysis based on second-line regimens indicated that 1-year OS for single targeted agent (21.1%), single toxic agent (mainly fluoropyrimidine alone, 29.6%), gemcitabine-based combination therapy (26.9%) and taxanes-based combination therapy (23.3%) was higher than that of fluoropyrimidine-based combination therapy (15%).

3.4. Efficacy comparison between combined therapies versus mono-therapy

The pooled analysis showed that fluoropyrimidine-based, gemcitabine-based, or taxanes-based chemotherapy was not superior to single targeted/toxic agent in terms of ORR. However, the pooled DCR and 1-year OS of fluoropyrimidine-based chemotherapy was inferior to single targeted/toxic agent (DCR: 47% versus 60%, RR 0.78, 95%CI: 0.61–1.00, $p = 0.03$; 1-year OS: 15% versus 29.6%, RR 0.90, 95%CI: 0.29-0.87, $p = 0.006$), but not for GEM-based or taxanes-based chemotherapy (Table 2).

3.5. Correlation between OS and PFS/ORR/DCCR

Data from 36 cohorts were available for correlation analysis between median OS and median PFS. There was strongest correlation between median OS and median PFS (r = 0.57), and this correlation was statistically significantly ($p = 0.003$, Supplemental Fig. 1). Data from 35 cohorts were available for correlation analysis between median OS and ORR/DCR. And moderate correlation between median OS and ORR was also observed (r = 0.40), this correlation was statistically significantly (p = 0.0176, Supplemental Fig. 2). No marked correlation was found between median OS and DCR (r = 0.25, $p = 0.15$, Supplemental Fig. 2).

3.6. Publication bias

Assessment of publication bias was not done because data would be unreliable in view of the few studies included for each treatment group and high heterogeneity ($I^2 > 50\%$) in most analyses.

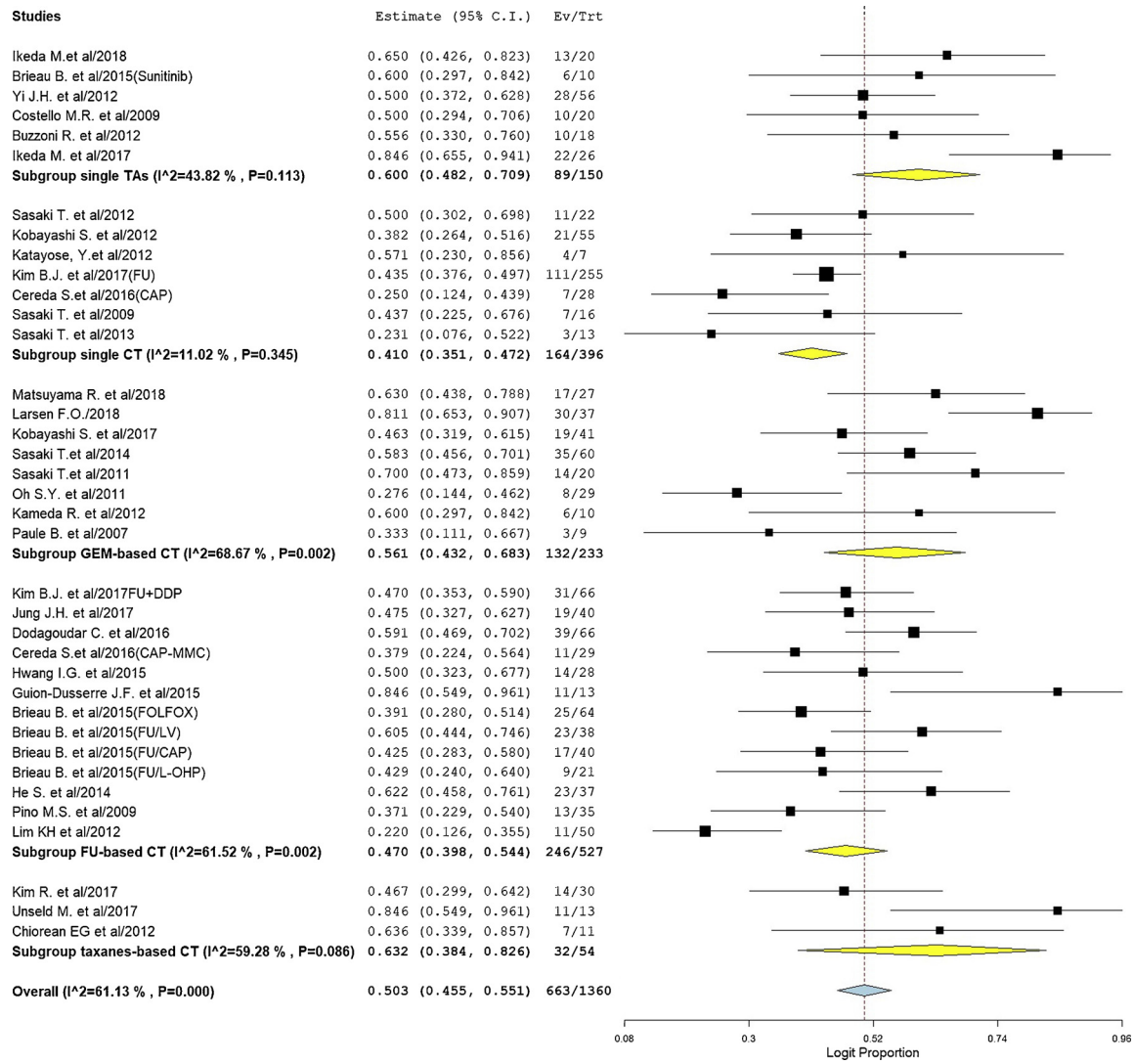

Fig. 4. pooled incidence of DCR for second-line therapy in advanced BTCs.

4. Discussion

Despite initial sensitivity to standard first-line gemcitabine-based chemotherapy in advanced BTCs patients, the majority of these patients would be refractory to chemotherapy, and the prognosis of these patients is very poor. Until now, there is no established treatment for these patients with progressive disease after first-line gemcitabine-based chemotherapy. As a result, there is an urgent need for effective and well-tolerated second-line treatment regimens for previously treated BTCs patients. Indeed, novel targeted/toxic agents alone or combination with chemotherapy have been extensively investigated in the past decade, but most of these are retrospective studies based on a small sample size and reported controversial results (Valle et al., 2017). In addition, there is no available phase III trial to specially compare the efficacy between combination therapy and mono-therapy in previously treated BTCs patients. As a result, we conduct this meta-analysis of published data to investigate the role of second-line therapy in the treatment of advanced BTCs in terms of response, overall survival and toxicities, and compare the potential efficacy differences between combined therapy and mono-therapy.

Prior to the present meta-analysis, (Lamarca et al., 2014) in 2014 performed a systematic review to evaluate the level of evidence for the use of second-line therapy for advanced BTCs patients. A total of 761 patients are included for analysis, and the mean PFS, response rate and disease control rate were 3.2 months (95% CI 2.7–3.7), 7.7% (95% CI 4.6–10.9) and 49.5% (95% CI 41.4–57.7), respectively. In recent years, more studies have been conducted, and we include a total of 1391 patients from 32 trials in the present study. The pooled ORR, DCR, and 1-year OS incidence of second-line therapy in pre-treated BTCs patients is 9.5%, 50.3%, and 22.4%, respectively. The weighted median PFS and OS for refractory BTCs received second-line therapy is 2.6 months and 6.5 months, which seems lower than that in Lamara A. et al's study. The results of present study indicate that BTCs is a highly fatal malignancy and the prognosis for refractory remains very poor.

Fluoropyrimidine-based chemotherapies are widely used in gemcitabine-refractory patients, and this has not been validated in prospective randomized studies. In consistent with this, the most frequently assessed second-line regimens in the present meta-analyses are fluoropyrimidine-based combination therapy (n = 13 cohorts), followed by gemcitabine-based combination therapy (n = 8 cohorts), single targeted agent (n = 7 cohorts), single toxic agent (n = 7 cohorts) and taxanes-based combination therapy (n = 3 cohorts), respectively. Fluoropyrimidine-based, gemcitabine-based, or Taxanes-based chemotherapy is not superior to single targeted/toxic agent in terms of ORR. In addition, the pooled disease control rate (DCR) and 1-year overall survival (OS) of fluoropyrimidine-based chemotherapy is inferior to single targeted/toxic agent (DCR: 47% versus 60%, RR 0.78, 95%CI: 0.61–1.00, $p = 0.03$; 1-year OS: 15% versus 29.6%, RR 0.90,

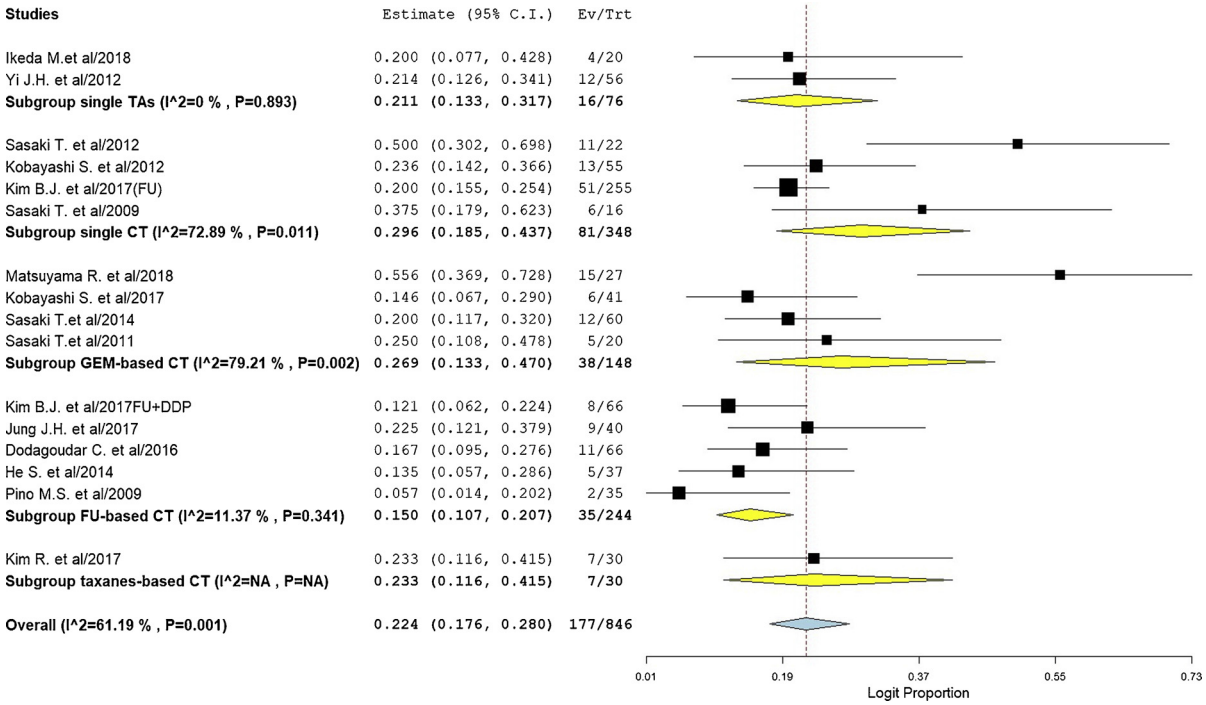

Fig. 5. pooled incidence of 1-year OS for second-line therapy in advanced BTCs.

Table 2
Eficacy comparison between combination versus single agent mono-therapy as salvage therapy in advanced biliary tract cancer in terms of ORR, DCR and 1-year OS.

Regimes	No. of trials	ORR, 95%CI	Combination vs. single TAs (RR, 95%CI)	*P* value	Combination vs. single CT (RR, 95%CI)	*P*, value
Single TA	7	8.1 (4.6-13.7)	Reference	–	1.17(0.37-3.72)	0.39
Single CT(mainly FU alone)	7	6.9(2.4-18.3)	0.85(0.27-2.70)	0.39	Reference	–
GEM-based CT	8	8.4(4.2-15.9)	1.04(0.44-2.45)	0.47	1.21(0.36-4.10)	0.37
Fluoropyrimidine-based CT	13	12.3(8.5-17.4)	1.52(0.79-2.92)	0.10	1.78(0.61-5.23)	0.15
Taxanes-based CT	2	8.8(3.1-22.5)	1.09(0.35-3.37)	0.44	1.27(0.31-5.27)	0.36
Regimes	No. of trials	DCR,95%CI	Combination vs. single TAs (RR, 95%CI)	*P* value	Combination vs. single CT (RR, 95%CI)	*P*, value
Single TA	6	60(48.2-70.9)	Reference	–	1.46(1.15-1.87)	0.001
Single CT (mainly FU alone)	7	41(35.1-47.2)	0.68(0.54-0.87)	0.001	Reference	–
GEM-based CT	8	56.1(43.2-68.3)	0.94(0.69-1.26)	0.33	1.36(1.04-1.80)	0.012
Fluoropyrimidine-based CT	13	47(39.8-54.4)	0.78(0.61-1.00)	0.03	1.14(0.92-1.42)	0.11
Taxanes-based CT	3	63.2(38.4-82.6)	1.05(0.68-1.62)	0.41	1.54(1.02-2.32)	0.02
Regimes	No. of trials	1-year OS, 95%CI	Combination vs. single TAs (RR, 95%CI)	*P* value	Combination vs. single CT (RR, 95%CI)	*P*, value
Single TA	2	21.1(13.3-31.7)	Reference	–	0.71(0.39-1.31)	0.14
Single CT(mainly FU alone)	4	29.6(18.5-43.7)	1.40(0.76-2.58)	0.14	Reference	–
GEM-based CT	4	26.9(13.3-47.0)	1.27(0.59-2.74)	0.27	0.90(0.49-1.67)	0.38
Fluoropyrimidine-based CT	5	15.0(10.7-20.7)	0.70(0.41-1.22)	0.11	0.51 (0.29-0.87)	0.006
Taxanes-based CT	1	23.3(11.6-41.5)	1.10(0.51-2.39)	0.13	0.79(0.36-1.69)	0.27

Abbreviations: ORR, objective response rate; DCR, disease control rate; OS, overall survival; TA, targeted agent; CT, chemotherapy; RR, relative risk; GEM, gemcitabine; FU, fluoropyrimidine.

95%CI: 0.29-0.87, $p = 0.006$), but not for GEM-based or taxanes-based chemotherapy. Based on our findings, fluoropyrimidine-based chemotherapies seem to be less efficient than other second-line regimens in terms of DCR and 1-year OS. In addition, no significant efficacy differences are found between mono-therapy and gemcitabine-based or taxanes-based combined therapy. However, further prospective randomized studies are still needed to confirm our findings and clarify the value of second-line therapy in this setting.

We finally investigate the potential surrogate points for OS in the second-line settings. In consistent with Lamara A. et al's results (Lamarca et al., 2014), the best correlation is observed between median OS and median PFS (r = 0.57, $p = 0.003$). In addition, a statistically significant correlation is found between ORR and median OS (r = 0.40, $p = 0.0176$), while no marked correlation is detected between median OS and DCR (r = 0.25, $p = 0.15$). Based on our findings, PFS appears to be a good surrogate endpoint for OS in second-line setting, althoughOS remains the historical and primary endpoint for studies in advanced BTCs.

There are several limitations need to be mentioned. First and most importantly, the application of formal meta-analytic methods to observational studies has been controversial. One of the most important reasons for this is that the designs and populations of the studies are diverse, and that these differences may influence the pooled estimates. However, when no head-to-head comparison data available for combination therapy versus mono-therapy, a meta-analysis of observational studies is one of the few methods for assessing efficacy and toxicities.

Second, patients in trials have adequate organ and hematological function, which may not be the case in common oncology practice. All of these might cause potential selection bias. Finally, this is a meta-analysis of published data, and lack of individual patient data prevents us from adjusting the treatment effect according to previous treatment and patient variables.

5. Conclusions

With available clinical evidence for advanced BTCs patients, combination therapy is not superior to single targeted/toxic agent as salvage treatment for advanced BTCs in terms of ORR, DCR and 1-year OS, and fluoropyrimidine-based chemotherapy seems to be inferior to other second-line regimens. However, since the overall quantity and quality of data regarding second-line therapy is poor and considering the risk of bias in comparisons between observation studies. The reported results do not allow for definite conclusions. Thus, prospective randomized studies, definitively comparing the survival and treatment toxicity between combined therapy and mono-therapy, are strongly recommended.

Ethics approval and consent to participate

This meta-analysis was approved by the institutional review board, the need for informed patient consent for inclusion was waived.

Consent for publication

All of the authors agree to publish the work in Critical review In oncology and hematology

Conflicts of interest statement

All authors declare that they have no potential conflicts of interests.

Availability of data and materia

All data generated or analyzed during this study are included in this published article.

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JY and JC contributed to the conception and design of the study, the analysis and interpretation of data, the revision of the article as well as final approval of the version to be submitted. JY, and Z.W. participated in the literature screening and data extraction. XH and J.C. offered guidance and provided figures. All authors read and approved the final version of the manuscript.

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Appendix A. Supplementary data

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