Research Paper

EGFR Target Therapy Combined with Gemox for Advanced Biliary Tract Cancers: a Meta-analysis based on RCTs

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Abstract

Background: Controversy exists regarding whether EGFR-targeted therapy combined with GEMOX (gemcitabine and oxaliplatin) provides additional benefits over GEMOX alone for biliary tract cancer patients. Therefore, this meta-analysis of randomized controlled trials (RCTs) was performed to assess the efficacy and safety of the GEMOX + EGFR-targeted regimen, and subgroup analysis was conducted to identify groups that might benefit from targeted therapy.

Methods: The PubMed, Cochrane Library, and ClinicalTrials.gov registries were searched for published studies. Hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) were pooled using a fix-effect model. Risk-ratios (RRs) were used to analyse the objective response rate (ORR) and adverse events.

Results: Four RCTs were assessed. GEMOX + EGFR-targeted therapy significantly improved PFS (HR = 0.80, 95% CI 0.66-0.94, *P* = 0.03) and was associated with a better ORR (RR = 1.52, 95% CI 1.13-2.04, *P* = <0.01), whereas the TKI group achieved a better ORR in subgroup analysis. Patients with cholangiocarcinoma responded well to the GEMOX + EGFR-targeted regimen, leading to a better ORR (RR = 1.78, 95% CI 1.21-2.61, P = <0.01). Unfortunately, PFS benefits were not translated into OS benefits (HR = 0.92, 95% CI 0.75-1.08, *P* = 0.39).

Conclusion: GEMOX + EGFR-targeted therapy is a considerable and tolerable treatment option for patients with advanced BTCs, improving both PFS and ORR but not prolonging patient survival. Patients with cholangiocarcinoma would benefit the most from EGFR-targeted therapy.

Key words: Biliary Tract Cancer, Meta-analysis, Gemcitabine, Oxaliplatin, Target therapy

Introduction

Biliary tract cancers (BTCs) belong to a group of malignancies arising in different parts of the biliary tree and can be divided into intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangio-carcinoma (ECC), gallbladder cancer (GBCA) and ampullary cancer (ampulla of Vater) according to anatomical location. BTC incidence is much lower than that of any other gastrointestinal neoplasia. The number of Americans who received a BTC diagnosis in 2015 was 10,910, and there were 3,700 deaths. Additionally, BTCs have a higher incidence in Asia, particularly in Thailand, Korea, India, and Japan[1]. Although the incidence and mortality from gallbladder cancer has been decreasing[2, 3], the incidence of cholangiocarcinoma has significantly increased in recent years[4]. The five-year survival rate is estimated to be 5% to 30% when considering all patients[5, 6], and the estimated five-year survival

rate varies with stage: 50% for American Joint Committee on Cancer (AJCC) stage I, 30% for stage II, 10% for stage III, and 0% for stage IV[5, 7]. Most patients are unable to receive a complete resection, which is considered the only potentially curative treatment[7, 8]. Therefore, systematic treatment is essential for patients with advanced BTC. G.Q. Zhu performed a network meta-analysis showing that chemotherapy with gemcitabine is the optimal adjuvant treatment, as it has a balanced benefit-toxicity ratio for resected BTC, whereas chemoradiation is more likely to cause toxic effects[9].

Chemotherapy options for BTC patients with unresectable or metastatic disease include gemcitabine-based and fluoropyrimidine-based regimens[1]. The BT22 and ABC 02 studies suggested the potential of gemcitabine and platinum-based regimens as first-line treatments for advanced BTCs[10]. The results of two randomized clinical trials exploring adjuvant chemotherapy, PRODIGE-12/ ACCORD-18, assessed the benefits of adjuvant chemotherapy (gemcitabine and oxaliplatin) and found no significant difference in relapse-free survival compared with observation alone (HR = 0.83, 95% CI 0.58–1.19, P = 0.31). The BilCap clinical trial exploring capecitabine compared with observation alone after surgery showed a benefit from capecitabine in terms of overall survival (OS) (HR = 0.71, 95% CI 0.55–0.92, P < 0.01). Based on these results, capecitabine can be considered for standard chemotherapy following surgery for BTC[11, 12].

KRAS mutations and epidermal growth factor receptor (EGFR) overexpression has been observed in many BTC studies[13-15]. EGFR-TKIs and EGFR-mAbs are two main types of EGFR-targeted drugs. Recently, the combination of EGFR-targeted drugs and GEMOX (gemcitabine and oxaliplatin) regimens has demonstrated various clinical trial outcomes in clinical trials[16-18]. It is likely that although BTCs are histologically similar, they have different aetiologies, and recent genomic footprint results have called into question their biological similarity. According to recent reports, KRAS mutations are observed in intra- and extra-hepatic cholangiocarcinoma more frequently than in gallbladder cancer[19-22], which was observed 4-13% in GBCA, 8.3-42% in ICC and 8.6-24.2% in ECC[23]. Additionally, clinical trials might not have generated convincing, conclusive results because of sample limitations or differences between patient groups[24-26].

Therefore, we conducted a meta-analysis based on randomized controlled trials (RCTs) to investigate the effectiveness and safety of the GEMOX + EGFR-targeted regimen in patients with advanced BTC as well as to identify groups that might benefit from targeted therapy.

Materials and methods

Search strategy and study collection

A wide search of the main computerized databases, including the PubMed, Cochrane Library, and ClinicalTrials.gov registries, was performed with both mesh and free text words. The overall search strategy included the following search terms: "Gemcitabine", "Oxaliplatin", "Gemox", "EGFR-TKIs", "EGFR-mAbs", "EGFR", "Target Therapy", "Biliary Tract Cancers/Carcinomas", "Bile Duct Cancers/Carcinomas", and "clinical trial", with no language or date restrictions. The studies were limited to human subjects and RCTs.

Two of the researchers (Y.Y. and W.G.) evaluated the titles and abstracts of all of the retrieved studies. Both reviewers independently selected trials for inclusion according to prior agreement regarding the study population and intervention. If one of the reviewers determined that an abstract was eligible, then the full text of the article was retrieved and reviewed in detail by all of the reviewers. If disagreements about the inclusion of an article occurred, a third reviewer (H.H.) reviewed the entire article and contributed to a consensus decision. In addition, the reference lists of identified articles were manually checked to include other potentially eligible trials (Fig. 1).

Selection criteria

Well-designed RCTs comparing GEMOX and EGFR-targeted therapy with GEMOX alone were included. The studies were required to clearly report the inclusion and exclusion criteria for patients, the chemotherapy regimens, and the definition and evaluation of prognostic outcomes. The study characteristics and methodological quality of the included trials were then summarized in tables. The risk of bias in the included studies was assessed according to The Cochrane Handbook.

Statistical extraction and analysis

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

We considered sufficient quantitative data as including the necessary descriptive and statistical information to perform a meta-analysis. The study population characteristics, inclusion and exclusion criteria, chemotherapy regimens, adverse event reports and study designs, such as concealment of the sequence of randomization, blinding, application of intention-to-treat analysis, loss of follow-up

description, and whether the trial was multi-centric were separately extracted by two reviewers (Y.Y. and W.G.). The data on the PFS, OS and number of patients who had objective response and disease control according to RECIST 1.0 (Response Evaluation Criteria in Solid Tumors 1.0) were collected by two reviewers (Y.Y. and W.G.) from the full publications and supplementary data downloaded from online.

Four RCTs were identified that included 629 patients, of which 623 were evaluated for PFS, OS and adverse events. We calculated OS from survival curves and from data provided in publications that directly reported HRs for OS, as described by Jayne F Tierney[27]. The number of patients used to analyse the ORR was 612. We further divided patients into cholangiocarcinoma and non-cholangiocarcinoma subgroups. Cholangiocarcinoma was described by anatomical location, including intrahepatic (iCCA), perihilar (pCCA) and distal CCA (dCCA) diagnosed throughout the biliary tree, and was typically classified as intrahepatic and extrahepatic cholangiocarcinoma in RCTs. The non-cholangio-carcinoma group included gallbladder carcinomas and ampulla of Vater carcinomas[1]. Only three publications provided sufficient data to analyse ORR by subgroup.

RRs were used to analyse dichotomous variables, including the ORR and adverse events. HRs for PFS and OS, *P*-values and 95% confidence intervals (95% CIs) were calculated for survival outcomes. The meta-analysis was performed using STATA version 12.0 software (Stata Corporation, College Station, Texas, USA). The studies were considered with a homogeneous and a fixed-effect model, and Mantel–Haenszel's (M-H) method was used to combine and weigh the individual studies. Heterogeneity was evaluated with the Chi^2 and I^2 values: $I^2 < 25\%$ reflects a small level of inconsistency, whereas $I^2 > 50\%$ implies significant inconsistency. For all analyses, $P < 0.05$ was considered statistically significant[28, 29].
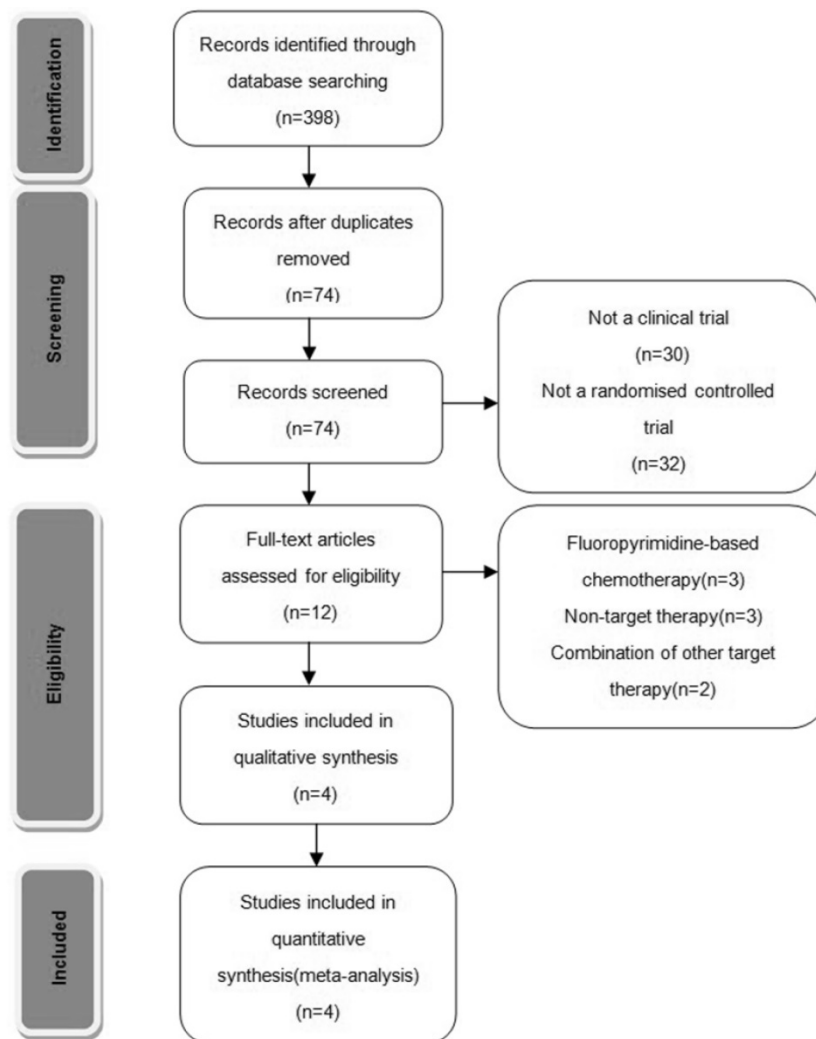

Figure 1. Trails flow diagram.

Table 1: Characteristics of Included Randomized Controlled Trials

Study	Phase	NCT No.	Participant	Male	Median age (G+EGFR vs G)	Disease site (G+EGFR vs G)	Outcome PFS(HR)	OS(HR)	ORR	Intervention Gemox+EGFR	Gemox
Chen.2015	II	NCT01267344	**1.**Advanced BTC **2.**Systemic therapy-naive **3.**Adequate organ functions **4.**ECOG PS 0 or 1	58(47.5%)	61 vs 59	I(44 vs 45); E(9 vs 10); G(9 vs 5)	Y	N	Y	Cetuximab	Gemox
Lee.2012	III	NCT01149122	**1.**Advanced BTC **2.**No adjuvant treatment <6 mo **3.**Adequate organ functions **4.**ECOG PS 0 -2	170(63.4%)	59 vs 61	C(96 vs 84); G(35 vs 47); A(4 vs 2)	Y	Y	Y	Erlotinib	Gemox
Leone.2015	II	NCT01389414	**1.**Unresectable or metastatic biliary tract adenocarcinoma **2.**Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2 **3.**Adequate organ functions **4.**Therapy-naive	32(36.0%)	63.9 vs 64.2	I(21 vs 21); E(21 vs 7); G(12 vs 16)	Y	Y	Y	Panitumumab	Gemox
Malka.2014	II	NCT00552149	**1.**Advanced BTC **2.**Therapy-naive **3.**Adequate organ functions **4.**WHO performance status (WHO PS) of 0 or 1 **5.**Expected life expectancy of more than 3 months	85(56.7%)	61 vs 62	C(62 vs 61); G(11 vs 11); A(1 vs 0)	Y	N	Y	Cetuximab	Gemox

PFS: Progression-free survival; ORR: Object response rate; I/E/G/C/A=intrahepatic/extraheptatic/gallbladder/cholangiocarcinoma/ampulla of vater; G: Gemox regimen; EGFR: EGFR Targeted therapy;

Results

Description of studies

Four RCTs were available for this analysis, and 623 patients were assessed for PFS, OS and adverse events; four patients in the Vecti-BIL trial and two patients in J. S. Chen's study were not included. Sufficient data for analysing ORR were available for 612 patients, as a BINGO trial with six patients in the chemotherapy plus cetuximab group and 11 patients in the chemotherapy alone group were not assessed for disease response. Two publications reported OS directly, whereas another two publications reported only survival curves. Therefore, we calculated OS from the survival curves and data provided in these publications[27]. One study did not report disease response data for original patient sites; therefore, 536 patients, including 411 cholangiocarcinoma patients and 125 non-cholangiocarcinoma patients, were assessed to compare ORR in the cholangiocarcinoma and non-cholangiocarcinoma groups. The study characteristics are reported in Table 1. Enrolled patient descriptions from the four RCTs were well balanced; this information is summarized in Table 2. Table 3 presents the methodological quality of the included trials. All four studies reported acceptable randomization methods. One study did not describe the allocation of concealment details, and one study did not describe the blinding of patients or outcome assessors. All of the analyses were performed with an intention-to-treat basis. The number of patients lost to follow-up was acceptable (< 10%) in all of the studies.

Efficacy

Compared with GEMOX alone, the combination of GEMOX and EGFR-targeted therapy was associated with improved PFS (HR = 0.80, 95% CI 0.66-0.94, P = 0.03), though this did not translate into a larger OS (HR = 0.92, 95% CI 0.75-1.08, P = 0.39). Next, we divided the EGFR-targeting drugs into EGFR-TKI and EGFR-mAb groups and found that heterogeneity between the two groups was not significantly different (P = 0.34 and P = 0.87, respectively) (Fig. 2 and Fig. 3). GEMOX and EGFR-targeted chemotherapy showed a better ORR (RR = 1.52, 95% CI 1.13-2.04, P = 0.006), whereas the EGFR-TKI group achieved a better ORR (Fig. 4).

We divided patients into cholangiocarcinoma and non-cholangiocarcinoma groups and evaluated the ORR for each group (RR = 1.78, 95% CI 1.21-2.61, P = 0.003 and RR = 1.07, 95% CI 0.59-1.98, P = 0.840, respectively) (Fig. 5).

Table 2: Characteristics of Enrolling Patients

	GEMOX +EGFR-targeted	GEMOX
Sex		
Female/Male	139/179(77.65%)	145/166(87.34%)
Primary site		
Non-cholangiocarcinoma/Cholangiocarcinoma	74/254(29.64%)	73/228(32.02%)
ECOG performance status		
Score 2/Score 0-1	10/308(3.25%)	19/292(6.51%)
Disease stage		
Locally advance/ Metastatic	79/239(33.05%)	61/250(24.4%)

Table 3: Assessment of Methodological Quality of Included Studies

Reference	Country	Allocation generation	Allocation concealment	Blinding of patients and assessors	Data analysis	Loss to follow-up (%)	Selective reporting	Other bias
Chen et al.	Taiwan	Computer generated	unclear	Assessor blinded	ITT	3.28	Low risk	/
Lee et al.	Korea	Computer generated	Adequate	Not blinded	ITT	0.75	Low risk	Changed the primary endpoint because >90% deaths were caused by disease
Leone et al.	Italy	Computer generated	Adequate	unclear	ITT	5.62	Low risk	/
Malka et al.	France Germany	Computer generated	Adequate	Not blinded	ITT	2.00	Low risk	/

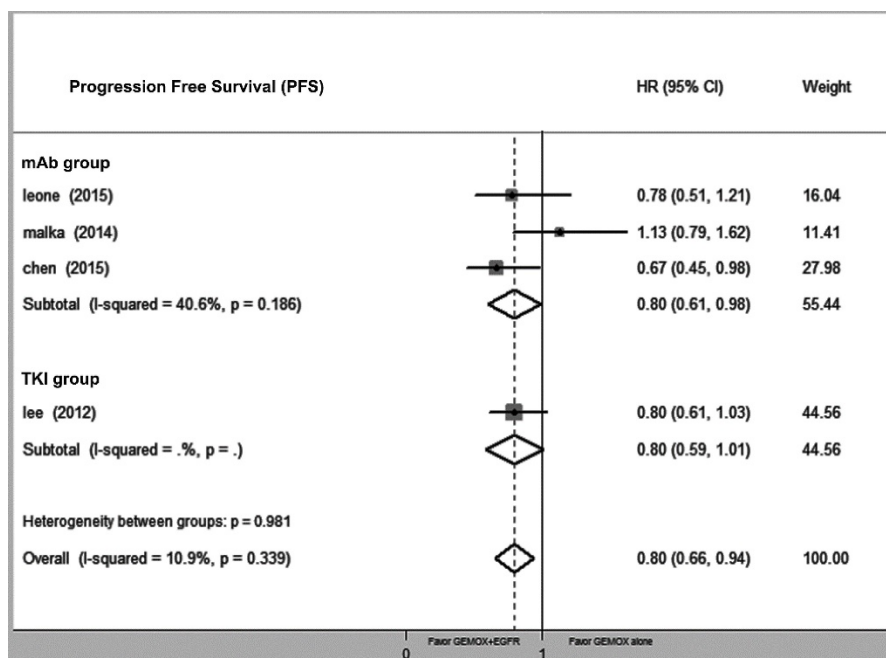Risk of bias was assessed according to the method recommended by the Cochrane

Fig. 2 Forest plot of comparison between Gemox-targeted and GEMOX alone; the outcome was hazard ratio (HR) of progression free survival (PFS).
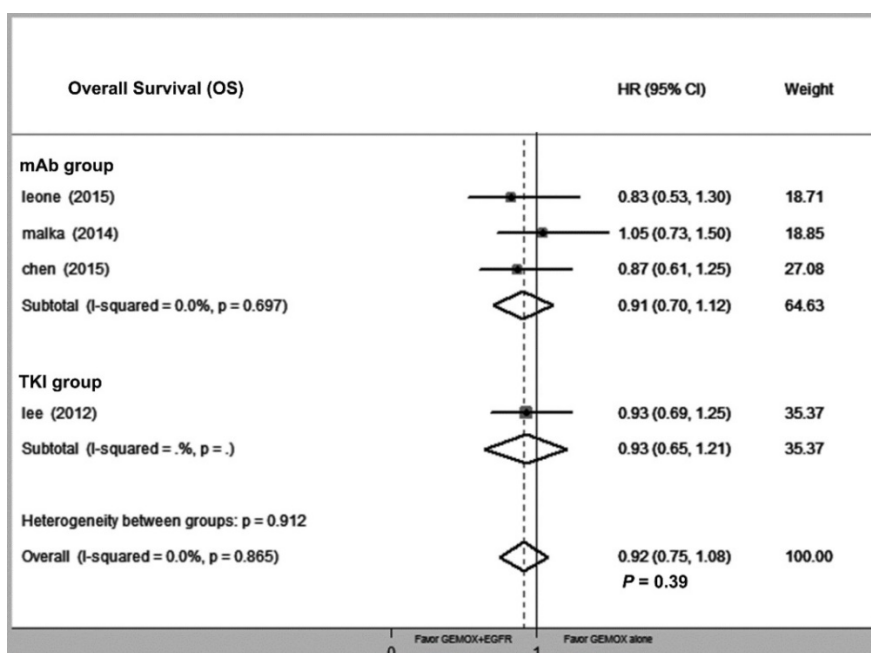

Figure 3. Forest plot of comparison between Gemox-targeted and GEMOX alone; the outcome was hazard ratio (HR) of overall survival (OS).
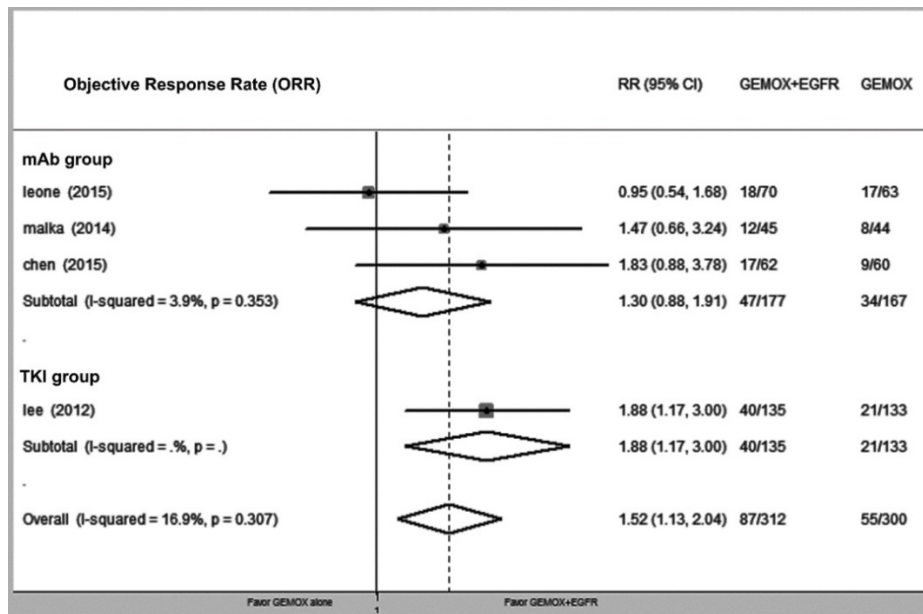
Figure 4. Forest plot of comparison between GEMOX-targeted and GEMOX alone; the outcome was risk ratio (RR) of objective response rate (ORR).
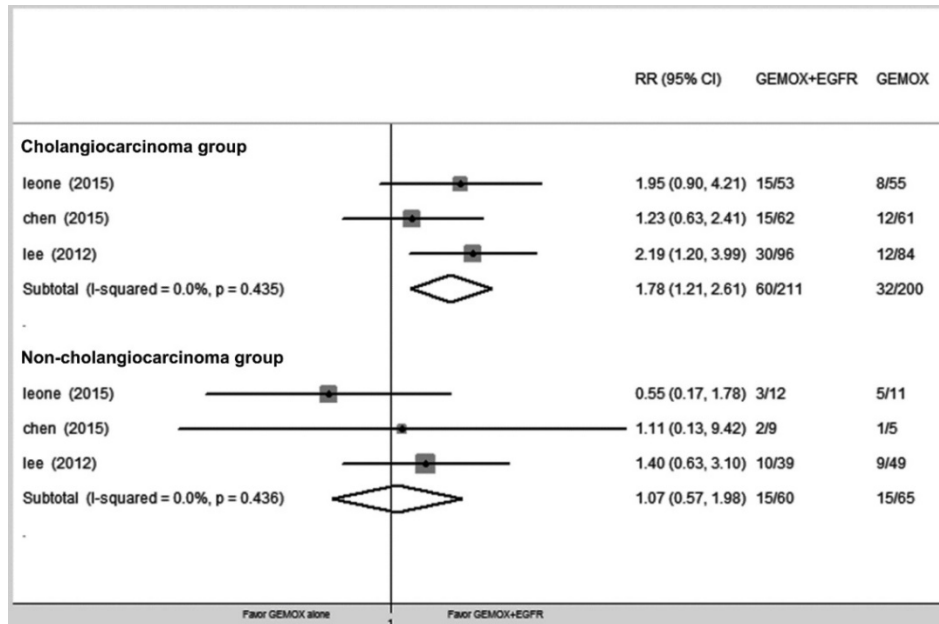

Figure 5. Forest plot of comparison between GEMOX-targeted and Gemox alone in subgroup of cholangiocarcinomas and non-cholangiocarcinomas, risk ratio (RR) of objective response rate (ORR).

Toxicity

We pooled nine types of commonly occurring adverse events from the four RCTs. Comparing patients that received GEMOX chemotherapy, those treated with GEMOX and EGFR-targeted chemotherapy showed higher risks of diarrhoea (RR = 1.54, 95% CI 1.24-1.91, P < 0.01), neutropaenia (RR = 1.30, 95% CI1.01-1.68, P = 0.04) and transaminase increase (RR = 1.15, 95% CI 1.01-1.30, P = 0.04). A skin rash was frequently observed in the GEMOX+EGFR-TKIs group, which was significant compared with the GEMOX alone group (RR = 9.42, 95% CI 6.32-14.05 P < 0.01) (Fig. 6). In addition, we compared the grade 3-4 adverse events that occurred in the GEMOX combined EGFR-target therapy group and the GEMOX alone group and observed no significant difference. All of the above is summarized in Table 4.

Discussion

BTCs are a heterogeneous group of relatively rare tumours that often have extremely poor prognoses. The low incidence of BTCs limits the potential for prospective studies. Furthermore, studies often combine patients with GBCA and

cholangiocarcinoma, which is problematic because the biology of these tumours is different. Adequately powered clinical studies are needed to generate convincing results.

Table 4: Summary of Adverse Events

Adverse event	All grades of adverse events 3-4 grades	
	RR(95%CI)	*P* value RR(95%CI) *P* value
Nausea	1.03 (0.90-1.17)	0.67 0.73 (0.28-1.91) 0.51
Vomiting	1.03 (0.84-1.26)	0.79 0.53 (0.16-1.77) 0.31
Diarrhea	1.54 (1.24-1.91)	0.00 1.32 (0.62-2.78) 0.47
Neutropenia	1.30 (1.01-1.68)	0.04 1.25 (0.79-1.99) 0.35
Thromlocytopenia	1.02 (0.90-1.15)	0.80 1.11 (0.60-2.05) 0.74
Transaminase increase	1.15 (1.01-1.30)	0.04 1.26 (0.69-2.29) 0.46
Skin Rash	9.42 (6.32-14.05)	0.00 4.17 (0.60-28.93) 0.15
Neurophathy	1.01 (0.90-1.14)	0.83 1.56 (0.88-2.76) 0.13
Asthenia	0.98 (0.84-1.15)	0.84 1.28 (0.69-2.36) 0.43
Anorexia	0.99 (0.86-1.14)	0.92 0.87 (0.36-2.09) 0.75

Risk Ratios (RRs) were calculated from the reported events in the population assessable for toxicity (n = 623); CI: confidence interval.

Many meta-analyses and systematic reviews have been conducted to evaluate different interventions. Eckel F. presented a pooled analysis of 104 trials containing 2810 evaluable patients with advanced BTCs and showed that the response rates and tumour control rates were higher for the patient subgroup receiving a combination of gemcitabine and platinum-based agents[30]. Tian-Tian Sun and Heng Liu performed a meta-analysis and systematic review in 2013 and 2014[31, 32] and reported the efficacy and safety of gemcitabine and platinum-based chemo-therapy compared with gemcitabine alone. However, many clinical trials have conflicting outcomes.

Therefore, Lawrence Chen recently conducted a meta-analysis and systematic review of RCTs to evaluate the efficacy of different chemotherapy regimens using the same four RCTs used for our meta-analysis, concluding that combining EGFR-targeted therapy with gemcitabine and platinum-based agents (GP) chemotherapy is an option for treating patients with advanced BTCs[33]. Although the OR and random effect models were applied to analyse RCTs in the previous study, we used the RR and fixed effect models. Furthermore, we conducted a subgroup analysis that revealed potentially different behaviours between cholangio-carcinoma and non-cholangiocarcinoma, and we calculated an OS indicating that drug treatment did not translate into a longer survival time.

Our meta-analysis specifically focused on the GEMOX and EGFR-targeted regimen, which appeared to fail in nearly every RCT but actually reduced progression risk (defined by PFS) by 20%. As different EGFR-targeted drugs inhibit the EGFR pathway via different mechanisms, we divided EGFR-targeted drugs into EGFR-TKI and EGFR-mAb groups and tested heterogeneity between these two groups. The results showed that inhibition of the EGFR pathway in both groups conferred a PFS benefit with tolerable side effects. Additionally, EGFR-TKI drugs might increase ORR, which agrees with other reported clinical data[34]. However, further analysis of OS indicated that the observed PFS did not translate into an increased OS (HR = 0.92, 95% CI 0.75-1.08, *P* = 0.39).
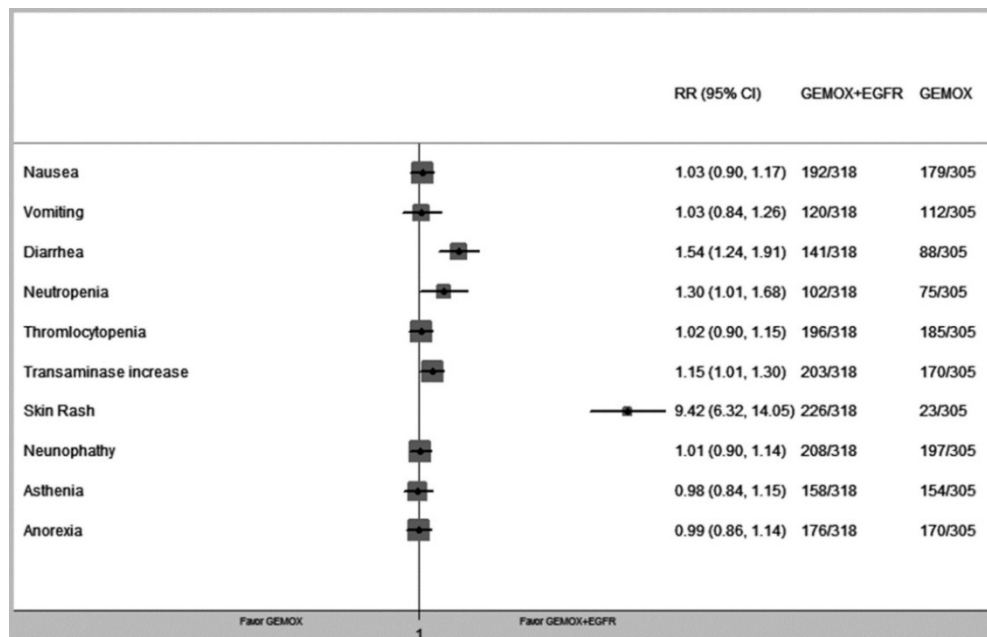

Figure 6. Forest plot of comparison between GEMOX-targeted and Gemox alone in common toxicity.

Analysis of the cholangiocarcinoma and non-cholangiocarcinoma subgroups showed that cholangiocarcinoma exhibited significantly greater benefits from targeted therapy, but only a 6% reduction was observed for non-cholangiocarcinoma, which was not significant. Therefore, patients with cholangiocarcinoma more than patients with gallbladder adenocarcinoma or ampulla of Vater cancer would benefit from targeted therapy. Targeted treatment generated a significant 44% reduction in cholangiocarcinoma risk, but only a 6% reduction in non-cholangiocarcinoma, which was not significant. This result was also supported by recent studies demonstrating that KRAS mutation and EGFR overexpression in BTC, especially in cholangiocarcinoma. Additionally, immunohisto-chemistry studies have shown that EGFR is overexpressed in human cholangiocarcinoma samples. Although the BINGO and TCOG T1210 trial demonstrated that neither KRAS mutations nor EGFR overexpression improved the selection of patients who respond to therapy, the patients were pooled in a mixed analysis. Therefore, this conclusion should be reconsidered in the subgroup selection and when choosing different targeted therapy drugs, which requires more studies and clinical trials. The above findings provide convincing evidence that might offer physicians a meaningful treatment option of EGFR pathway inhibition for groups that might experience a survival benefit.

Furthermore, GP treatments compared with the cisplatin and gemcitabine (GC) regimen, the GEMOX regimen is the first to demonstrate the survival benefit of systemic chemotherapy over best supportive care in BTC patients as well as better compliance with GEMOX than GC in clinical practice. Sharma et al. reported that modified GEMOX improved the PFS and OS compared to the best supportive care or fluorouracil. The median OS times were 4.5, 4.6, and 9.5 months, respectively, for best supportive care, fluorouracil, and modified GEMOX arms (P = 0.039). The corresponding PFS values were 2.8, 3.5, and 8.5 months (P < 0.001)[35]. Additionally, many studies and meta-analyses report a higher rate of adverse events in the group receiving GC. However, the GC regimen appears to provide extra benefits to PFS and OS in recent studies, especially in terms of the outcomes of ABC02 and BT22 for advanced BTC, which demonstrates that this combination improved both the OS and PFS by 30% over gemcitabine alone. The median OS values were 11.7 months and 8.1 months (HR = 0.64, 95% CI 0.52–0.80, P < 0.001), and the median PFS was 8.0 months vs. 5.0 months (HR = 0.63, 95% CI 0.51–0.77, P < 0.001), which favours the GC arm[10]. Therefore, acquiring more data comparing GC or the GEMOX chemotherapy combination with EGFR-TKIs to evaluate the benefit to quality of life and survival would be ideal, even though this has been evaluated in many prior clinical trials (Table 5).

Notably, EGFR-targeted therapy groups exhibited higher rates of adverse events, including significantly increased rates of diarrhoea, neutropaenia and transaminase elevation. However, further analysis comparing grade 3-4 adverse events did not reveal significant differences in either group. Therefore, GEMOX combined with EGFR-targeted therapy is a tolerable choice for advanced BTC patients. Skin rash was also a more common adverse event in the EGFR-targeted therapy group. The correlation between skin rash severity and EGFR-targeted therapy efficacy supports a predictive role for EGFR antagonists in patients with mCRC and NSCLC[36, 37]. Therefore, we calculated the rate for this reaction to occur in the included RCTs and demonstrated a significant difference in the GEMOX+EGFR-targeted therapy group. It would be interesting to explore whether the skin rash might be a predictive factor for BTC patients using EGFR-targeted therapy or be useful in selecting patient subgroups for different therapy regimens.

The limitation of our meta-analysis is that few clinical trials evaluating the benefit of GEMOX and EGFR inhibitors in BTC patients and performing detailed subgroup analyses to identify groups of patients with a benefit in PFS and OS were available. Therefore, we recognized the need for additional clinical trials that can be incorporated into a future meta-analysis.

Table 5: Summary of Relative Ongoing Clinical Trial

NCT No.	Intervention	Status	Country
NCT02170090	Gemcitabine+Cisplatin vs Obervation	Recruiting	Germany
NCT00779454	GEMOX + Panitumumab + Capecitabine	Active, not recruiting	France
NCT01320254	Panitumumab + Cisplatin/Gemcitabine	Unknown (information has not been verified recently)	Denmark
NCT00033462	Erlotinib	Unknown (information has not been verified recently)	Germany
NCT00747097	Gemcitabine + Cetuximab	Completed, no results available	USA
NCT00948935	Gemcitabine/Irinotecan + Panitumumab	Unknown (information has not been verified recently)	Belgium

In conclusion, combination chemotherapy with GEMOX and EGFR-targeted therapy improves PFS with tolerable toxicity in advanced BTCs, but the activity of the drugs does not translate into an increase in OS. Patients with cholangiocarcinoma exhibited a better ORR with EGFR-targeted therapy. Additional randomized studies comparing different platinum therapies with different EGFR-targeted therapy combinations to treat specific original sites malignancies of the biliary tract are warranted. Furthermore, it could be interesting to determine whether a skin rash is a predictive factor for BTC patients using EGFR- targeted drugs.

Abbreviations

EGFR: Epidermal Growth Factor Receptor;
GEMOX: Gemcitabine and Oxaliplatin Regimen;
TKI: Tyrosine Kinase Inhibitor;
mAb: Monoclonal Antibody;
RCT: Randomized Controlled Trial;
CI: Confidence Interval;
HR: Hazard Ratio;
RR: Risk Ratio;
PFS: Progression-Free Survival;
OS: Overall Survival;
ORR: Objective Response Rate;
ITT: Intent to Treat;
GBCA: Gallbladder Cancer;
CCA: Cholangiocarcinoma;
ICC: Intrahepatic Cholangiocarcinoma;
ECC: Extrahepatic Cholangiocarcinoma;
GC: Cisplatin and Gemcitabine;
mCRC: Metastatic Colorectal Cancer;
NSCLC: Non-Small Cell Lung Cancer.

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Compliance with Ethical Standards

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Competing Interests

The authors have declared that no competing interest exists.

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