REVIEW

Adjuvant chemotherapy for resected biliary tract cancers:

A systematic review and meta-analysis

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Adjuvant chemotherapy for cholangiocarcinoma

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Abstract

Introduction: The use of adjuvant treatment (AT) in resected biliary tract cancers (BTC) is still controversial. No efficacy comparison has been performed between chemotherapy (CT) and chemoradiotherapy (CTRT). A systematic review of the available evidence regarding adjuvant chemotherapy (AC) in resected BTC was performed.

Methods: PubMed, EMBASE, Web of Science, SCOPUS and The Cochrane Library databases were searched for relevant articles published. Only studies including at least 50 patients affected by tumors of gallbladder, intrahepatic, perihilar, and distal bile ducts were considered. Data were pooled using a random-effects model. The primary endpoint of the study was overall survival (OS).

Results: Thirty studies were analyzed with a total of 22499 patients, 3967 of whom received AC. Eleven cohorts included Western patients and 19 were Asiatic. Surgeries were classified as R0 with negative margins, R1 with positive microscopic and R2 with positive macroscopic margins. Weighted mean OS difference among experimental (AC) and control arm was 4.3 months (95%CI 0.88-7.79, P=0.014). AC reduced the risk of death by 41% (Hazard ratio [HR] =0.59, 95%CI 0.49-0.71; P<0.001).

Conclusions: AC administration gives an OS benefit in resected BTC. The results of prospective randomized studies are awaited in order to define the standard AT in BTC.

Key words: cholangiocarcinoma, adjuvant chemotherapy, survival, meta-analysis

Introduction

Biliary tract cancers (BTC) represent a heterogeneous group of neoplasms that includes gallbladder cancer and cholangiocarcinoma. Surgery is the only potentially curative treatment. However, despite radical resection, prognosis is poor and relapse frequent. Adjuvant treatment (AT) intended as chemotherapy (CT), radiotherapy (RT) and combination therapies may decrease the relapse rate and improve overall survival (OS) but its role is not clear yet because of the lack of conclusive data coming from randomized studies (1).

Available guidelines (National Comprehensive Cancer Network [NCCN] (2) and European Society of Medical Oncology (3) guidelines (3)) consider multiple different AT options. Fluoropirimidine or gemcitabine based chemotherapy and fluoropyrimidine-based chemoradiation are all suitable therapies for high-risk patients.

The largest available meta-analysis of published studies reported an advantage in OS given by AT in BTC even if only 3 studies used CT alone as AT. The greatest improvement OS happened when CT and chemoradiotherapy (CTRT) were administered especially in patients with node positive and margin positive (R1) disease (1).

Altough combination CTRT and CT are valid treatment alternatives, the use of concomitant RT may bring higher toxicities and a reduced tolerability. Therefore the aim of this study was to analyze the effect of adjuvant chemotherapy (AC), in order to investigate the possible OS advantage for patients undergoing resection for BTC.

Material and methods

Search strategy and selection criteria

Literature searches of PubMed, EMBASE, Web of Science, SCOPUS and The Cochrane Library were performed and all the studies published from the first available item until December 2016 were considered. Searches were limited to human studies and English-language publications. The main keywords used for the PubMed search were ((("gallbladder"[MeSH Terms] OR "gallbladder"[All Fields]) OR biliary [All Fields] OR ("cholangiocarcinoma"[MeSH Terms] OR "cholangiocarcinoma"[All Fields])) AND ("chemotherapy, adjuvant"[MeSH Terms] OR ("chemotherapy"[All Fields] AND "adjuvant"[All Fields]) OR "adjuvant chemotherapy"[All Fields] OR ("adjuvant"[All Fields] AND "chemotherapy"[All Fields])) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms]).

Eligible trials included at least 50 patients with BTC (ampullary tumors only were excluded). AC was defined as mono or polychemotherapy administered after curative-intent surgery. Adjuvant RT or CTRT was permitted only if <20% of patients received it, and data of patients that received adjuvant CT only were provided. No experimental agents were permitted. Studies had to include patients who underwent curative-intent surgery alone (R0-R1) as a comparator group. Curative-intent resections were defined as those in which no macroscopic disease (R2) remained, thus excluding studies that included palliative surgery if palliative surgeries were the majority. Studies in which differentiation between curative and palliative resections was not possible were excluded,

as well as studies involving patients undergoing liver transplantation or neoadjuvant CT(RT).

To avoid inclusion of overlapping series in duplicate publications only the larger or more complete publication was included.

Data analysis

Two authors (MG and FP) independently extracted information using predefined Microsoft word-based forms. The following details were extracted: study period, country, patient number and disease site (intrahepatic versus extrahepatic cholangiocarcinoma versus gallbladder). Where reported, stage, rate of surgeries and type of CT were collected. Efficacy outcomes collected included median and 5-year OS. An additional reviewer (GT) resolved any discrepancies regarding the extraction of data. Also hazard ratios (HR) for survival, calculated from multivariate (preferred) or univariate analysis and associated with receipt or not of adjuvant CT were extracted from articles. Quality of publications was expressed through Nottingham-Ottawa-Scale (NOS) for retrospective and observational studies (4), and with Jadad score for randomized studies (5).

The survival benefit between AT and no AT was expressed as a hazard ratio (HR) and its 95% CI, extracted from multivariate analysis if available. Pooled median OS difference was also calculated. Subgroup analysis and meta-regression was performed to account for year of publication, number of patients (>200 vs < 200), nodal positive disease patients rate, rate of radical surgery, receipt of adjuvant RT, race and subsite (cholangiocarcinoma vs gallbladder). Publication bias was evaluated using Begg's rank correlation test (6), Egger's

regression test (7) and trim and Fill method (8). Data were extracted from the primary publications and combined into a meta-analysis using RevMan 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark) and Comprehensive Meta Analysis software v3.3.3070. Pooled estimates of HRs were computed using the random-effect model (9). Because of expected intra study heterogeneity, studies were weighted by the generic inverse variance approach (10).

Results

A total of 30 studies were eligible for inclusion in the meta-analysis (Fig 1) (11-40). These studies incorporated 22499 patients of whom 3967 (17.6%) received AC (Table 1). Of the included studies, two were prospective series (13, 14), one a randomized study (34) and 27 retrospective patient series (11, 12, 15-33, 35-40). Ten cohorts included Japanese patients (18, 19, 24, 25, 29-32, 34, 37) nine series were from United States of America (14, 15, 17, 20, 22, 23, 27, 28, 33), three from Korea (13, 21, 26) and China (35, 39, 40), two from Thailand (12, 36), one from Taiwan (38) and two were European series (from Germany (11) and Italy (16)). Most surgeries of primary tumors were R0 or R1, with some publications that included few palliative or R2 interventions. Indeed, only four studies reported a R2 resection rate >20%) (12, 32, 34, 38), while palliative surgery was mentioned in a series only (40).

Mean difference in survival and overall risk of death

Data for mean difference in OS were available for n=13 studies. Weighted mean OS difference among experimental (AC) and control arm was 4.3 months (95%CI 0.88-7.79,

P=0.014 according to random effect model). Overall data for OS analysis (HR for OS) was available in n=22 studies. AC reduced the risk of death by 41% (HR=0.59, 95%CI 0.49-0.71; p<0.001). The four studies including a R2 resection rate >20% did not affect the OS analysis, with a resulting HR of 0.61 when these series were not considered. Heterogeneity was high (I^2=82%, P<0.001) so random effect model was used (Fig.2) (9).

Meta-regression analysis

Analysis of survival according to year of publication (2008-2012 and > 2012) did not change significantly the final results. The magnitude of benefit was less in studies with > of 200 patients (HR=0.77, 95%CI 0.65-0.91, P=0.002) compared to those with < 200 patients (HR=0.46, 95%CI 0.35-0.61; P<0.001). Overall, the main effect was not influenced by site (cholangiocarcinoma vs gallbladder carcinoma), nodal status, rate of radical surgeries (R0 and R1) and by race. Instead the magnitude of benefit was inferior in those studies were patients received RT in addition to adjuvant CT (slope 1.5, 95%CI -0.04-3.08, P=0.02). The value of the slope indicates that for each 1% of RT use, the benefit (log HR) decreases, on average, by 1.5 points.

Publication bias

Observation of funnel plot (Fig.3) showed evidence of publication bias (Begg's test p=0.01) (6). Similarly Egger's test was significant (P<0.001) (7). According to the Trim and Fill method the final result according to random effect model is 0,72 (95%CI 0,6-0.85) (8). Under the one-study-removed procedure, the final HR ranged from 0.56 (removing Glazer et al. study (17)) and 0.61 (removing Liu et al. study (40)).

Discussion

This meta-analysis included 30 studies (involving more than 22,499 patients) and assessed the impact of AC for resected biliary tract cancers.

The main analysis reported a 41% reduction in the risk of death that translated in a mean OS benefit of 4 months in an unselected population of both Asiatic and Caucasian patients. According to the meta-regression analysis, the magnitude of benefit was not influenced by: radical surgery, nodal status, subsite, race, year of publication or sample of studies. Moreover, the meta-regression analysis revealed an inferior benefit in OS in patients given adjuvant RT in combination with CT. This means that adjuvant CTRT cannot be viewed as a standard practice, and may be reserved to those patients with gross margin positive disease (R1/2) to reduce local progression. This conclusion is in line with the previous meta-analysis of Horgan et al.,that showed that adjuvant RT seems to benefit only patients with R1 resections with a possible detrimental effect in R0 disease, and AC alone being beneficial in nodal positive disease where it can be considered a possible standard of care in resected biliary tract cancers. Similarly, another meta-analysis of retrospective studies in gallbladder cancer revealed a survival benefit only for node-positive, R1 and stage II or higher disease. This meta-analysis, however, included only 2 studies of AC (41). A further meta-analysis on resected distal cholangiocarcinoma reported similar 5-year survival rate between patients receiving and not receiving AC (42).

The mainstay of treatment for localized cholangiocarcinomas is surgery, with node-positive disease and involved surgical margins being the poorer prognostic factors in both hilar and intrahepatic cancers and a median survival of about 2 years (43, 44) (45) (46) (47).

Both ESMO and NCCN guidelines agree on the lack of evidence-based indication for adjuvant treatment in resected biliary tract cancers. The choice should be driven by a patient-by-patient risk-benefit evaluation (2, 3). Among these different regimens, a meta-analysis reported a superior survival outcome given by gemcitabine over 5-fluorouracil CT and combined CTRT, with a higher 1-year and 5-year OS and a better toxicity profile in terms of haematological and nonhaematological effects (48).

Three randomized phase III studies considering different adjuvant strategies in resected BTC have recently closed patients' accrual or are still ongoing. Results the phase III trial PRODIGE 12-ACCORD 18 (observation versus gemcitabine/oxaliplatin [GEMOX] in resected BTC), showed a non-significant difference in relapse-free survival (RFS) between adjuvant chemotherapy and surveillance (49). The BILCAP study (observation versus adjuvant capecitabine) is no longer recruiting and results are awaited (50) while the ACTICCA-1 study (observation versus gemcitabine/cisplatin) is currently randomizing patients (51).

This meta-analysis has some intrinsic limitations. First, it includes mainly retrospective patient series so that patients with more extended disease and good performance status may have received further therapies after surgery. Secondly, the analysis included 19 Asiatic studies with potentially different response to cytotoxic or different surgical skill. Thirdly, it does not define the preferred regimen to be adopted as the standard of care in these patients, because various regimens have been used in the publications included. Moreover, even studies with small series could have introduced bias and could have slightly enlarged the resulted benefit. Low-powered studies are more likely to provide a

wide range of estimates of the magnitude of an effect, so the effect size observed could be less pronounced or neutral in prospective-randomized studies. For instance, in the recently presented PRODIGE 12-ACCORD 18, an 8-month non-significant benefit in relapse-free survival (RFS) was reported . However, this is the first meta-analysis that has addressed the value of systemic chemotherapy alone as AT in resected BTC. It included a survival analysis with HR as a adequate measure of clinical benefit. And finally, through meta-regression and random effect model, the source of heterogeneity was taken into consideration without finding an explicit variable (except addition of RT) not associated with a survival benefit. Despite this, significant publication bias emerged from Begg's and Egger's test, and different study designs, characteristics of included patients and various regimens adopted as adjuvant therapy could have substantially contributed to observe heterogeneity among publications.

In conclusion, this meta-analysis of 30 studies including more than 20,000 patients showed a considerable benefit coming from AC. Indeed, adjuvant treatment reduced the risk of death by 40% and this translated in an absolute mean OS gain of 4 months in unselected patients with cholangiocarcinoma and gallbladder cancers.

While the PRODIGE 12-ACCORD 18 study failed to show a RFS advantage in patients treated with adjuvant gemcitabine and oxaliplatin, final results of the BILCAP and ACTICCA-1 studies are awaited in order to provide more evidence on this controversial topic.

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