Cetuximab in Pancreatic Cancer Therapy: A Systematic Review and Meta-Analysis

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Keywords

Cetuximab · Pancreatic cancer · Palliative cancer therapy · Targeted therapy · Survival

Abstract

Introduction: The present study evaluated the potential benefit of adding cetuximab to neoadjuvant, adjuvant, or palliative standard therapy for pancreatic cancer. **Methods:** A systematic literature search was performed in MEDLINE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). Only randomised controlled trials (RCTs) investigating the effect of adding cetuximab to standard chemotherapy in pancreatic cancer were included. Evaluated outcomes were overall survival, progression-free survival, objective response, and toxicity. For overall survival and progression-free survival, hazard ratios (HR) with 95% confidence intervals (CI) were chosen as effect measure. For objective response, odds ratios (OR) with 95% CI were used. Analysis was based on a random effects model. **Results:** After screening 568 publications, a total of 4 RCTs with 924 patients were included. In all trials, patients were adequately randomised with balanced intervention and control groups.

There was no significant difference in overall survival (HR 1.04; 95% CI: 0.90–1.19; $p = 0.60$), progression-free survival (HR 1.06; 95% CI: 0.93–1.22; $p = 0.36$), or objective response (OR 0.99; 95% CI: 0.66–1.49; $p = 0.96$) when adding cetuximab to a standard therapy. Toxicity was the same or higher in each of the included trials. According to GRADE, the certainty of the evidence is high. Therefore, adding cetuximab to pancreatic cancer therapy has no clinically relevant benefit. **Conclusion:** In the presence of no survival benefit, increased toxicity, and higher costs, a decreased cost-benefit ratio compared to the standard care must be suggested. Conducting further RCTs in unselected pancreatic cancer populations is unlikely to change this conclusion.

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Introduction

Pancreatic ductal adenocarcinoma is one of the most aggressive malignancies [1] and is typically diagnosed in an advanced state [2, 3], as it is characterised by early locoregional spread and distant metastasis. Gemcitabine used to be the standard first-line therapy for advanced

pancreatic cancer for many years [3]. However, 1-year survival after gemcitabine therapy was reported at only 18–29% [4, 5]. Thus, alternate treatments for this disease are urgently needed. Novel chemotherapy combinations like FOLFIRINOX [6] or gemcitabine plus nab-paclitaxel have significantly improved overall survival for patients with metastatic disease. Unfortunately, except for erlotinib, targeted agents have proved unsuccessful in clinical pancreatic cancer trials to date [7]. Erlotinib with gemcitabine was superior to gemcitabine in a randomised phase III study, but the difference in overall survival was so small that the clinical relevance of this benefit is controversial [8]. Cetuximab, another targeted agent, has been tested in various clinical studies for pancreatic cancer [9–13]. Cetuximab is an immunoglobulin G1 monoclonal antibody that binds the epidermal growth factor receptor (EGFR) with high affinity, which competitively blocks ligand binding, inhibits tyrosine kinases activation, and results in receptor downregulation [14]. In 22–60% of human pancreatic carcinomas, EGFR is overexpressed [15, 16]. While some preclinical research shows positive results [17, 18], the effect of cetuximab in treating pancreatic cancer remains controversial [13]. Older systematic reviews evaluating the effect of cetuximab in pancreatic cancer also show inconsistent results [19, 20]. Further recent RCTs, which have not been considered in previous reviews, are now available [21, 22]. Therefore, a new systematic review is needed. The objective of this study was to systematically evaluate the potential benefits of treatment approaches including cetuximab for patients with pancreatic cancer.

Methods

This systematic review and meta-analysis was conducted according to an a priori defined protocol (PROSPERO CRD42017064450) and is reported according to the PRISMA guidelines [23]. The resources and facilities of the University of Heidelberg were used to conduct this study. There was no additional source of funding.

Systematic Literature Search

The Cochrane CENTRAL, MEDLINE (via PubMed), and Web of Science databases were searched [24] throughout July 2018. A search strategy based on a thesaurus (MeSH or Emtree) in combination with free text words was used. The search strategy for MEDLINE (via PubMed) was as follows:

((cetuximab[tw] OR Erbitux[tw] OR “cetuximab”[Mesh]) AND (pancrea*[tw] OR “Pancreas”[Mesh]))

In addition, reference lists of relevant studies and related systematic reviews were screened manually. References citing trials eligible for inclusion were searched using the Science Citation Index via Web of Science. No language restriction was applied.

Study Selection

Randomised controlled trials (RCTs) investigating any treatment concept including cetuximab for the treatment of any stage of pancreatic cancer in a human adult population and reporting at least one clinically relevant endpoint (i.e., overall survival, progression-free survival, or objective response) were eligible for inclusion.

Following the recommendations of the Cochrane Collaboration [25], two independent reviewers screened the titles, abstracts, and full texts.

Data Extraction

Data extraction was also independently performed by two reviewers for quality assurance purposes [26]. A third reviewer resolved any discrepancies found by the first two reviewers.

The following items were extracted: title, author, year of publication, journal, language, trial duration, trial design, number of treatment groups, total number of patients, evaluable patients, withdrawals, loss to follow-up, funding source, and trial registration or published protocol.

Relevant outcome variables included overall survival, defined as the time period between beginning of randomisation and death for any reason; progression-free survival, defined as the time between randomisation and radiological progress of disease according to the RECIST criteria; objective response, defined as at least partial radiological remission of disease according to the RECIST criteria; and toxicity, as individually reported by the trials.

Critical Appraisal (Bias)

The methodological quality was assessed by the Cochrane Collaboration’s tool for assessing risk of bias [25]. The tool includes six standard domains of bias: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. Each domain was judged to be at low, unclear, or high risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions [25]. Quantitative and qualitative results were merged and the quality of the evidence for each outcome was rated using the GRADE approach [27].

Statistical Analysis

Meta-analyses were performed with Review Manager (RevMan) version 5.3.5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

To measure effects, hazard ratios (HR) with 95% confidence intervals (CI) were used for time-to-event outcomes (overall survival and progression-free survival), and odds ratios (OR) with 95% CI were used for the binary outcome (objective response). If a publication reported no HR or its corresponding standard error but contained appropriate information (e.g., Kaplan-Meier curves), the HR and its standard error were calculated using the methods provided by Tierney et al. [28] and Parmar et al. [29]. HRs were combined using the inverse-variance method, and ORs using the Mantel-Haenszel method. A random effects model was applied because relevant heterogeneity between the effects of the studies was assumed. Statistical heterogeneity was assessed by the I^2 statistics [30]. Potential publication bias could not be evaluated due to the small number of included trials. For the same reason, no subgroup or sensitivity analyses were conducted.

Fig. 1. PRISMA flow chart.

Results

A total of 568 articles were screened for eligibility. Of these, 41 were subject to full text analysis. Thirty-seven trials were excluded due to duplicate publication of the same cohort ($n = 1$), evaluation of a single treatment arm without a control group ($n = 33$), and a lack of information on clinical outcome ($n = 3$) (references available on request). Therefore, 4 RCTs with 924 patients were included in the qualitative and quantitative analysis [10, 21, 22, 31]. A PRISMA flow chart is shown in Figure 1.

All RCTs evaluated cetuximab in a palliative setting. Regarding co-interventions, one trial investigated the combination of gemcitabine and cetuximab [10], one the combination of gemcitabine, cisplatin, and cetuximab [31], one the combination of gemcitabine, capecitabine, radiotherapy, and cetuximab [21], and one the combination of docetaxel, irinotecan, and cetuximab [22]. Two RCTs were conducted in Europe (Italy and the UK) [21, 31] and 2 originated from the USA [10, 22]. All RCTs had two trial arms with equally allocated treatment groups. The sample size varied across the trials (range: 13–743). The trials were published in journals with an impact factor of 3.25–13.28. An overview on the included RCTs is shown in Table 1.

Critical Appraisal (Bias)

Since all trials used an adequate measure of randomisation and allocation, none of them had a high risk of selection bias. Reporting of random sequence generation was precise (i.e., low risk of bias) in all 4 RCTs and for allocation concealment in 3 of the 4 RCTs. One RCT did not provide any information concerning this source of bias [21]. One trial was considered at a high risk of performance and detection bias, as neither participants nor personnel were blinded [10]. One trial reported appropriate blinding measures and was considered low risk [31]. Two trials did not report blinding measures and were at an unclear risk of bias [21, 22]. All trials were at a low risk of attrition bias or reporting bias, and no other biases were present in the 4 RCTs. Overall, 3 of the 4 trials were at a low risk of bias in all reported domains [21, 22, 31].

Quantitative Analysis

A quantitative analysis for overall survival, progression-free survival, and objective response was performed. Three of the 4 RCTs, with a total of 457 patients assigned to both the cetuximab and the non-cetuximab groups, reported overall survival rates. No significant difference in overall survival existed between the cetuximab and non-

Table 1. List of included trials

First author/ year	Origin	Setting	Comparator	Risk of bias						Sample size	Outcomes		
				R	A	B1	B2	IO	SR		OS	PFS	ObR
Cascinu [31], 2008	Italy	palliative	gemcitabine/cisplatin	⊕	⊕	⊕	⊕	⊕	⊕	81	NC	NC	C
Philip [10], 2010	USA	palliative	gemcitabine	⊕	⊕	⊖	⊕	⊕	⊕	743	=	=	=
Khan [21], 2016	UK	palliative	gemcitabine/capecitabine + RT	⊕	?	?	?	⊕	⊕	13	=	C	C
Burtneß [22], 2016	USA	palliative	docetaxel/irinotecan	⊕	⊕	?	?	⊕	⊕	87	NC	=	C

RT, radiotherapy; R, randomization sequence; A, allocation concealment; B1, blinding of participants; B2, blinding of outcome assessment; IO, incomplete outcome data; SR, selective reporting; ⊕, low risk of bias; ⊖, high risk of bias; ?, unclear risk of bias; OS, overall survival; PFS: progression-free survival; ObR, objective response; C, favours cetuximab; NC, favours non-cetuximab; =, no difference.

cetuximab groups (HR 1.04; 95% CI: 0.90–1.19; $p = 0.60$) (Fig. 2a).

In 3 of the 4 RCTs reporting on progression-free survival, 457 patients were treated with cetuximab (with 457 patients in the control group). Progression-free survival was not different between the groups (HR 1.06; 95% CI: 0.93–1.22; $p = 0.36$) (Fig. 2b).

Objective response as defined by RECIST criteria was reported in all 4 RCTs, but in a smaller population of patients (cetuximab group: 418 patients, non-cetuximab group: 423 patients). Compared to the control group, patients treated with cetuximab had no significant benefit in objective response (OR 0.99; 95% CI: 0.66–1.49; $p < 0.96$) (Fig. 2c).

Altogether, cetuximab did not show any effect on the outcomes analysed. Statistical heterogeneity among the included trials could not be detected ($I^2 = 0\%$ for all outcomes). Due to inconsistent reporting of toxicity in the trials, a meta-analysis was not possible. Table 2 shows a summary of reported toxicity, which was the same or higher in the cetuximab group.

Discussion

The objective of this systematic review was to summarise, evaluate, and critically appraise evidence for the potential benefit of cetuximab in the treatment of pancreatic cancer. Cetuximab suggested promising results in preclinical studies when added to gemcitabine in the

treatment of human pancreatic carcinoma xenografts [17, 18]. In this systematic review, 4 RCTs adding cetuximab to standard palliative therapy were included. Cetuximab failed to demonstrate improved patient outcomes in terms of survival or objective response when compared to various chemotherapeutic regimens and/or other biological agents. According to the GRADE approach, the certainty of the evidence is high (Table 3). A quantitative analysis of toxicity was not possible; however, many severe side effects of cetuximab are known: reported grade 3 or 4 adverse events following the use of cetuximab include abdominal pain, neutropenia, thrombocytopenia, diarrhoea, nausea, allergy, and toxic skin reactions [32, 33]. Further, it is obvious that adding a drug to any standard care means higher costs. Therefore, in the presence of no survival benefit, the same or increased toxicity, and higher costs, a decreased cost-benefit ratio compared to the standard care must be suggested.

In the presence of existing synoptic evidence on this topic, it is important to compare those results with the present paper. Three systematic reviews investigating EGFR inhibitors in pancreatic cancer were found [19, 20, 34]. These reviews were published in 2010 and 2013, evaluating only one or two RCTs and not including the newest ones on this topic. Consequently, the present study contains the most comprehensive sample of trials using cetuximab in the treatment of patients with pancreatic cancer. The review of Liu et al. [34] investigated cetuximab in all kinds of advanced cancer and found a general benefit regarding survival; however, not for advanced

Table 2. Toxic effects reported in included trials

First author/ year	Cetuximab	Non-cetuximab
Cascinu [31], 2008	43% of patients with grade III or IV toxic effect; most frequently reported adverse effect was skin toxicity	36% of patients with grade III or IV toxic effects
Philip [10], 2010	48% grade II, 8% grade III, 14% grade IV, and 2% of patients with grade V toxicity; 1% died during treatment; increased frequency of allergic reaction and skin toxicity	11% of patients had grade IV or V toxic effects; 0.3% of patients with grade V toxicity and 0.3% of patients died during treatment
Khan [21], 2016	Well tolerated without grade III or IV toxic effects	Well tolerated
Burtress [22], 2016	56% grade III and 20% grade IV toxicity; most common toxic effect was diarrhoea; 5% of patients with grade V toxicity reported (diarrhoea with sepsis and neutropenia with fever)	57% grade III and 17% grade IV toxicity; most common toxic effects were nausea and diarrhoea; 3% of patients with grade V toxicity reported (neutropenia with fever)

Fig. 2. Forest plots of overall survival (a), progression-free survival (b), and objective response (c).

Table 3. Summary of findings with quality of evidence (GRADE)

Outcomes	Participants (studies), <i>n</i>	Certainty of the evidence (GRADE)	Relative effect (95% confidence interval)
Overall survival	914 (3 RCTs)	⊕⊕⊕⊕ HIGH	HR 1.04 (0.90–1.19)
Progression-free survival	914 (3 RCTs)	⊕⊕⊕⊕ HIGH	HR 1.06 (0.93–1.22)
Objective response	841 (4 RCTs)	⊕⊕⊕⊕ HIGH	OR 0.99 (0.66–1.49)

GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

pancreatic cancer. The review from Tian et al. [20], evaluating the use of EGFR inhibitors in the treatment of pancreatic cancer, shows no improvement in objective response and progression-free survival. The benefit of agents against EGFR on overall survival was shown, but this improvement in overall survival is likely because the authors did not specifically evaluate the effect of cetuximab alone, but also included other agents against EGFR, such as erlotinib. Similarly, Zagouri et al. [19] investigated different molecularly targeted therapies in metastatic pancreatic cancer and found the results promising to further investigate such therapies in pancreatic cancer disease.

Two limitations of the existing literature must be discussed: the heterogeneous control groups and the unselected patient population.

The standard of care in the included RCTs was highly varied. While Philip et al. [10] combined cetuximab with gemcitabine only, other RCTs used a combination of cetuximab with gemcitabine and cisplatin, or gemcitabine and capecitabine [21, 31]. One RCT even involved radiotherapy [21], and one did not use gemcitabine at all, combining cetuximab with docetaxel and irinotecan [22]. As a result, the control group for the meta-analyses is clinically heterogeneous. However, adding cetuximab to any treatment regime did not result in clinical benefit.

One critical point regarding cetuximab trials in pancreatic cancer patients is the fact that all studies were performed in unselected patients. It is well established that cetuximab is not effective in colorectal cancer patients with KRAS or NRAS mutations but very effective in those with RAS wild-type mutations [35]. Since more than 90% of patients with pancreatic cancer harbour mutations in the KRAS gene [36], it is not surprising that cetuximab is

ineffective against this disease. Indeed, a randomised phase II trial investigating the combination of nimotuzumab, a different anti-EGFR monoclonal antibody, with gemcitabine showed a significant advantage in 1-year overall survival of 53.8 versus 15.8% for the combination group in KRAS wild-type patients (HR 0.32, $p = 0.026$), while the difference in KRAS-mutated patients was not statistically significant [37]. Furthermore, KRAS mutations are not the only molecular changes in pancreatic cancer; although pancreatic cancer does not harbour the most genetic alterations of all solid tumours, those that exist are spread over all relevant pathways with mutations in every patient [38]. This is one explanation why the conventional targeted therapy approach is not effective [39], but profiling of all druggable targets and a subsequent holistic analysis is required [40].

In conclusion, further trials investigating cetuximab in an unselected pancreatic cancer population must be viewed with a critical eye. The upper bound of the pooled effect for overall survival excludes a clinically relevant effect. A future RCT would therefore be unlikely to change the effect estimate or could even be unethical in the light of the data presented here. Further research in pancreatic cancer should focus on other treatment regimens than those including cetuximab or should investigate the benefit of cetuximab in the small minority of KRAS wild-type patients, respecting the entirety of all mutations in this dire tumour.

Significant Conclusions

Adding cetuximab to pancreatic cancer therapy has no benefit. Conducting further RCTs in unselected patient populations is discouraged.

Statement of Ethics

Ethical approval was not required as the present work is a meta-analysis.

Disclosure Statement

The authors declare no competing interests according to the ICMJE guidelines that could have inappropriately influenced their work on this article.

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Author Contributions

Tobias Forster: planning of the study, screening of publications, formal analysis, biometric and statistical analysis, original draft, and writing. Felix J. Hüttner, Christoph Springfield, Matthias Löhr, Thilo Hackert, and Markus K. Diener: review and editing. Eva Kalkum: literature search. Matthes Hackbusch: Biometric and statistical analysis. Pascal Probst: planning of the study, screening of publications, formal analysis, biometric and statistical analysis, writing, review, and editing. All authors read and approved the final paper.

Data Availability

All data can be obtained from the corresponding author on reasonable request.

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