Palliative chemotherapy for advanced gallbladder cancer

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Abstract

Introduction

Gallbladder cancer is the most common malignancy of the biliary tract. Given the lack of therapeutic alternatives for advanced stage patients studies have suggested that palliative chemotherapy could benefit these patients.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified two systematic reviews including two studies overall, of which one was a randomized trial. We concluded that palliative chemotherapy may increase survival in advanced gallbladder cancer patients. However, palliative chemotherapy probably increases adverse effects. In addition, it is essential to carry out a new systematic review, since methodological errors were identified in the analysis and there is new evidence that has not been included in the previous reviews.

Problem

Worldwide, gallbladder cancer is the most frequent biliary tract cancer and the sixth most frequent digestive tract malignancy [1]. An estimated 219,000 new cases and 165,000 deaths were reported worldwide for 2018 [1]. Studies demonstrate that gallbladder cancer incidence and mortality rates display a marked geographical heterogeneity, being especially common in developing countries [2]. The highest gallbladder cancer rates are observed in women from southern Chile (27 per 100,000 habitants) followed by regions of northern India (21.5 per 100,000 habitants). The incidence is relatively uniform in western countries and decreasing (1 per 100,000 habitants) [3]. Gallbladder cancer heterogeneity is mainly attributed to cholelithiasis, the most relevant gallbladder cancer risk factor.

As the majority of solid tumors, most gallbladder cancers are adenocarcinomas; on the other hand, more than 50% of patients are diagnosed at advanced stages, with lier, lymph node and/or peritoneal metastases.

Standard of care for localized gallbladder cancer includes surgery. To date, complete surgical resection is the only treatment for gallbladder cancer with curative potential. Adjuvant therapy for patients may include radio or chemotherapy, however their efficacy is still controversial.

On the other hand, in patients with advanced disease, (unresectable, or with distant metastases), local treatments can help to palliate specific symptoms (eg: jaundice), but management is mainly systemic, with chemotherapy. At the moment, no targetable molecular drivers have been identified and, in general terms, the results of treatment are suboptimal compared with other metastatic solid tumors [4]. In this summary, we investigate the effectiveness of palliative chemotherapy in patients with advanced gallbladder cancer, comparing it with the best supportive care.

Key messages

- Palliative chemotherapy may increase survival in advanced gallbladder cancer (certainty of evidence is low).
- Palliative chemotherapy probably increases adverse effects in advanced gallbladder cancer.
- It is essential to carry out a new systematic review, since methodological errors were identified in the analysis and there is new evidence that has not been included in the previous reviews.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We identified two systematic reviews [5], [6] including two studies overall [7], [8], of which one of them was a randomized trial [7]. Finally, this table and the summary, in general, are based on this trial [7] due to the observational study did not increase the certainty of evidence nor did it provide additional relevant information.
What types of patients were included*	Median age of patients was 49 years, and 80.2% were female [7]. Eligibility criteria [7] were**: Patients with a confirmatory biopsy for unresectable or metastatic gallbladder adenocarcinoma, ≥18 year-olds, with a good bone marrow, renal and liver function, >10 g/dL hemoglobin, normal neutrophil counts, > 100,000/uL platelets, <1.8 mg creatinine, liver enzymes (GOT: glutamic-oxalacetic transaminases and GPT: glutamic-pyruvic) <3 times the normal value, or <5 in case of hepatic compromise diffuse, < 3 mg/dL bilirubin, and 0-2 ECOG (Eastern Cooperative Oncology Group). Patients that had undergone adjuvant chemotherapy or radiotherapy were included if they ended treatments at least 6 months prior to enrollment.
What types of interventions were included*	Interventions included: • 5- Fluorouracil (FU) 425 mg/m2 and folinic acid 20 mg/m2 intravenous bolus weekly for 30 weeks (FUFA). • Gemcitabine 900 mg/m2 and oxaliplatin 80 mg/m2 intravenous infusion on day 1 and 8, in 21-day cycles for up to 6 cycles.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

	Both schemes were for 6 cycles unless there was disease progression or unacceptable adverse effects (undefined by systematic reviews). Both interventions were compared with best supportive care (BSC), which were not defined by systematic reviews.
What types of outcomes were measured	The trial reported multiple outcomes, which were grouped by systematic reviews as follows: • Overall survival • Progression-free survival • Response rate • Disease control rate • Vomiting • Sickness • Severe toxicity • Quality of life Mean follow-up: 3 years **.

* Information about primary studies is not extracted directly from primary studies but from identified systematic reviews, unless otherwise stated.

**This information was extracted directly from the primary study.

Summary of findings

The information about the effects of palliative chemotherapy in advanced gallbladder cancer is based on a randomized trial that included 82 patients [7]. Although the trial had two interventions arms (5-fluorouracil (FU) + folinic acid and gemcitabine + oxaliplatin), the data of the patients treated with 5-fluorouracil and folinic acid (FUFA) were not included as it was considered a chemotherapy regimen scheme based on agents not commonly used for this disease.

Therefore, we decided to reuse the conclusions of a network meta-analysis [5]. One trial measured survival and adverse effects in a group of 53 patients [7]. Quality of life was not reported by systematic reviews.

The summary of findings is the following:

- Palliative chemotherapy may increase survival in advanced gallbladder cancer (low certainty of the evidence).
- Quality of life was not measured or reported.
- Palliative chemotherapy probably increases adverse effects in advanced gallbladder cancer (moderate certainty of the evidence).

Palliative chemotherapy for previously untreated advanced gallbladder cancer

Patients Advanced, unresectable or metastatic gallbladder cancer
Intervention Palliative chemotherapy
Comparison Best supportive care

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT palliative chemotherapy	**WITH palliative chemotherapy**		
	Difference: patients per 1000			
Survival (at one year)	111	333	HR 3.44 (2.17 to 5.56)	⨁⨁◯◯[1] Low
	Difference: 222 more (Margin of error: 114 to 369 more)			
Quality of life	The quality of life outcome was not measured or reported by systematic review		--	--
Serious adverse effects**	A network meta-analysis reported serious adverse effects such vomiting (7.7%), myelosuppression (38.5%), neurotoxicity (11%), and transaminitis (15%) in the intervention group.		--	⨁⨁⨁◯[1] Moderate

Margin of error: 95% confidence interval (CI).
HR: Hazard ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT palliative chemotherapy** is based on the risk in the control group of the trials. The risk **WITH palliative chemotherapy** (and its margin of error) is calculated from relative effect (and its margin of error).
** Grade 3 or 4 adverse effects, understood as those that require at least medical assistance or supervision.

[1] The certainty of the evidence was downgraded one level for risk of bias, since the trial was not blinded, and the generation of randomization sequence or its concealment was not clear. In addition, it was decided to decrease an additional level of certainty since the synthesis process of the network meta-analysis has a methodological error that makes its estimation less reliable [See: Balance between benefits and risks, and certainty of the evidence]. For the serious adverse effects outcome, it was decided to decrease only one level since the same effect has been observed in other pathologies.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

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* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

This summary applies to adults with histologically confirmed advanced gallbladder cancer (either unresectable or metastatic), good organ function and 0-2 ECOG (Eastern Cooperative Oncology Group).

This summary does not apply to patients with medical indication of neoadjuvant chemotherapy aiming to reduce tumor size for resection, or to non-adenocarcinomas.

Best supportive care is not specified in reviews. This topic is currently under discussion, as it can be misused [9]. It is necessary to define a standard of supportive care.

About the outcomes included in this summary

Given that gallbladder cancer is commonly associated with poor prognosis we chose 1-year survival as a critical outcome for decision-making. The evidence suggests palliative chemotherapy may improve this outcome. Importantly, this study did not use gemcitabine plus cisplatin, the most widely accepted treatment, which is gemcitabine and cisplatin (following publication of the results of the ABC-02 study that compared it to gemcitabine alone).

Serious adverse effect is another important outcome for making a decision. Unfortunately, this was not adequately reported by the authors. A more comprehensive analysis of the impact of the treatment should include quality of life of patients, however the authors did not report this outcome.

Progression-free survival and event-free survival are not included in this summary. These are surrogate outcomes and not validated outcomes for gallbladder cancer. This was assessed by two systematic reviews [10], [11] which found a poor correlation with mortality/survival or quality of life.

Balance between benefits and risks, and certainty of the evidence

Due to the importance of survival in an oncological disease, the risk/benefit balance of this intervention is usually considered favorable due to the great impact on mortality (even presenting a low certainty of the evidence and a poor presentation of the magnitude of serious adverse effects).

However, in routine clinical practice, it is an individualized decision for each patient, whose key elements for the decision are: the patient's baseline functional status, life expectancy, values, and preferences of the patient and his/her family.

It is important to emphasize the limitations of this summary. It is based on systematic reviews, therefore their methodological issues or lack of information might impact the conclusions presented here (garbage in - garbage out).

The network meta-analysis [5] used to inform this summary, decided to meta-analyse the randomized trial and observational study together, which, under current methodological parameters, is considered incorrect. Following the GRADE working group guidelines, it would be necessary to analyze trials and observational studies separately, estimating the certainty of each group of studies and presenting the conclusions of the set of evidence with greater certainty of evidence [12]. For this reason, the accuracy of the results might be overestimated. Due to all of the above reasons, it was decided to decrease an additional level of certainty of the evidence. Alternatively, we extracted mortality data directly from the randomized trial (RR 0,78; CI 95% 0.58 to 1.04) and found the same absolute difference, but with a wider confidence interval, reinforcing our decision to downgrade the certainty of evidence.

For all of the above, it is essential to carry out a new systematic review that overcomes the limitations of its predecessors.

Resource considerations

Due to the uncertainty of benefits, it is difficult to assess the cost/effectiveness of the intervention. This is likely to vary depending on the characteristics of the patient (eg baseline performance status).

Cost/effectiveness studies are required.

What would patients and their doctors think about this intervention

The opinion of patients/doctors is likely to vary depending on each case. Patients with a good performance status (ECOG) and doctors that prioritize patient survival will likely opt for palliative chemotherapy. In contrast, patients with a poorer functional status and therefore more vulnerable to adverse effects will likely avoid this intervention.

Differences between this summary and other sources

Both systematic reviews agree with the results displayed on this summary, with the exception of the certainty of the evidence (absence of methodologies such as GRADE or similar).

National Comprehensive Cancer Network (NCNN) [13] and European Society of Medical Oncology (ESMO) - Multinational Association of Supportive Care in Cancer (MASCC) [14] guidelines propose that systemic chemotherapy increases advanced biliary tract cancer (including gallbladder cancer) patient survival versus best supportive care.

Could this evidence change in the future?

The conclusions on this summary are likely to change given the certainty of evidence. Regarding serious adverse effects, although this could also change there is greater certainty of evidence

An additional study not included in systematic reviews was identified. However, this is an observational study, and therefore unlikely to change the conclusions on this summary [15].

No systematic reviews or ongoing primary studies were identified on the PROSPERO platform or the WHO International Clinical Trials Registry Platform.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.

An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version** [Chemotherapy versus best supportive care for advanced gallbladder cancer.]

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Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

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