The role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer: a systematic review

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CRD summary
This review assessed the effects of gemcitabine for cholangiocarcinoma and gallbladder cancer. The authors concluded that where surgery is inappropriate, gemcitabine alone or combined with a fluoropyrimidine appears a reasonable option. There was limited evidence from small observational studies that recruited patients with unknown characteristics; a more cautious conclusion may have been more appropriate.

Authors' objectives
To evaluate the effects of gemcitabine in the treatment of patients with cholangiocarcinoma and gallbladder cancer.

Searching
MEDLINE was searched from 1996 to March 2000 for reports in the English language; the search terms were reported. Conference proceedings of the American Society of Clinical Oncology (including the 2004 Gastrointestinal Cancers Symposium) were searched from 1998 to 2004. In addition, CMA Infobase and the National Guideline Clearinghouse were searched for evidence-based guidelines. One additional study (too recent to have been identified by the search) was obtained from a member of the Gastrointestinal Cancer Disease Site Group. The reference lists of selected studies were screened. Studies published as abstracts and full publications were eligible; letters and editorials were not.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and phase II trials were eligible for inclusion. No RCTs were identified.

Specific interventions included in the review
Studies that evaluated gemcitabine, either alone or in combination with other agents, were eligible for inclusion. Comparative studies could compare regimens containing gemcitabine with best supportive care or other treatments. The included studies evaluated gemcitabine monotherapy and gemcitabine plus the following agents: cisplatin, docetaxel, 5-fluorouracil (5-FU) plus leucovorin, oxaliplatin, mitomycin-c, carboplatin and capecitabine (details of treatment regimens were reported).

Participants included in the review
Studies in patients with cholangiocarcinoma and gallbladder cancer were eligible for inclusion. None of the included studies separated patients with cholangiocarcinoma from those with gallbladder cancer.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. The primary review outcomes were overall response rates (complete plus partial response), survival, quality of life and adverse effects. None of the included studies assessed quality of life.

How were decisions on the relevance of primary studies made?
Two reviewers selected studies.

Assessment of study quality
The authors did not state that they assessed validity.
**Data extraction**

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, the number of patients used in the evaluation of response and toxicity, the response rate, median survival, 1-year survival, and the number with specified adverse effects were extracted, where possible.

**Methods of synthesis**

How were the studies combined?
The studies were grouped according to the interventions (monotherapy or combination therapy) and combined in a narrative.

How were differences between studies investigated?
Differences between the studies were apparent from the description of individual studies and from inspection of the tables.

**Results of the review**

Thirteen single-arm phase II studies (n=420) were included.

**Gemcitabine monotherapy** (3 studies, n=79; sample size: 23 to 30).

The response rates ranged from 30% (2 studies) to 36% (1 study). None of the patients experienced a complete response. Median survival ranged from 30 to 56 weeks, while 1-year survival ranged from 16 to 57%.

One study reported no gastrointestinal toxicity or grade 3 or 4 haematological toxicity, while another reported no grade 4 toxicity. The most commonly reported grade 3 to 4 adverse effects were nausea (13%), neutropenia (3.3% and either 13% or 4% in a second study, it was not clear which), anaemia (4%), flu-like symptoms (4%), haemolytic uraemic syndrome (4%) and anorexia (3.3%).

**Gemcitabine plus cisplatin** (3 studies, n=85; sample size: 11 to 44).

The response rates ranged from 36.6 to 50%. Complete response rates ranged from 9 to 27%. Median survival ranged from 20 to 45.2 weeks, while 1-year survival was 18.6% in the only study reporting this outcome.

A total of four patients died during treatment (cerebral ischaemia, unknown cause, renal toxicity and disease progression). The most common adverse effects were grade 3 and 4 thrombocytopenia (18%, 16.6% and 2%), anaemia (36.6% and 14%), neutropenia (0%, 23% and 33.2%), fever (9%), asthenia (9%) and granulocytopenia (9%).

**Gemcitabine plus 5-FU/leucovorin** (2 studies, n=72; sample size: 30 and 42).

The response rates were 9.5% and 21.4%. None of the patients achieved a complete response. Median survival was 38.8 and 18.8 weeks, while 1-year survival rates were 14% and 20%.

The most common adverse effects were grade 3 and 4 infection (31%), nausea and vomiting (19% and 7%), fatigue (17%), leukopenia (14%) and thrombocytopenia (14% and 10%).

**Gemcitabine plus capecitabine** (1 study, n=45).

The response rate was 31% and 4% achieved a complete response. Median survival was 56 weeks and 1-year survival was 49%.

The most common grade 3 and 4 adverse effects were neutropenia (34%), thrombocytopenia (11%), hand-foot rash (9%), and infection and fatigue (both 4%).

**Gemcitabine plus other agents** (docetaxel, oxaliplatin, mitomycin-c and carboplatin; 1 study of each intervention; sample size: 15 to 56).
The response rates ranged from 9.3% with docetaxel to 35.5% with oxaliplatin. Median survival ranged from 26.8% with mitomycin-c to 61.6% with oxaliplatin. One-year survival ranged from 23% with mitomycin-c to 57% with oxaliplatin. Median survival and 1-year survival were not reported for the carboplatin combination regimen.

The most common adverse effects were grade 3 and 4 alopecia (65%) and nausea and vomiting (18.6%) with doxetaxel, neutropenia (14%) and thrombocytopenia (9%) with oxaliplatin, leukopenia (17% and thrombocytopenia (13%) with mitomycin-c. Adverse effects with the carboplatin combination included nausea and vomiting, increase in liver enzymes, proteinuria, haematuria, oedema and fatigue, but incidences were not reported.

Authors’ conclusions
For patients not suitable for surgery, gemcitabine alone or in combination with a fluoropyrimidine (such as 5-FU or capecitabine) appears a reasonable option, but requires further confirmation.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention and study design. The search strategy included attempts to locate unpublished studies, thus reducing the possibility of publication bias, but no attempts were made to reduce language bias. Two reviewers selected studies but it was unclear whether they performed the selection process independently. In addition, the methods used to extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. Since study validity was not assessed, the results from these studies and any synthesis may not be reliable.

No information on the characteristics and performance status of the participants was presented, thus the generalisability of the results could not be judged. Given the diversity of the interventions in the individual studies, a narrative synthesis was appropriate. Potential reasons for the variable response rates between studies were not discussed. The review was weakened by the lack of complete reporting of review methods. Evidence was based on small uncontrolled observational studies that recruited participants whose characteristics were unknown, hence the population that these results apply to cannot be judged. In view of the limited evidence, a more cautious conclusion may have been appropriate.

Implications of the review for practice and research
Practice: The authors stated that, for appropriate patients, surgery should remain the first treatment of choice. For patients not suitable for surgery who are willing and able to tolerate chemotherapy, gemcitabine alone or in combination with a fluoropyrimidine (such as 5-FU or capecitabine) appears a reasonable option in comparison with best supportive care. However, the authors noted that this recommendation has not been confirmed in an RCT.

Research: The authors stated that patients should be encouraged to enrol in RCTs assessing promising new treatments such as gemcitabine, either alone or in combination with fluoropyrimidine, and other treatments with proven response rates. Future trials should assess efficacy, adverse effects and quality of life.

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