Use of gemcitabine in non-small cell lung cancer
Ellis P, Mackay J A, Evans W K, Lung Cancer Disease Site Group

CRD summary
The authors concluded that sufficient evidence was only available for the use of cisplatin-gemcitabine, which could be recommended as first-line treatment for locally advanced or metastatic non-small-cell lung cancer. Given the limitations of the review, the authors' conclusions should be treated with some caution.

Authors' objectives
To investigate the role of gemcitabine, alone or in combination, in the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC).

Searching
MEDLINE (1966 to June 2002), Cancerlit (1975 to June 2000) and the Cochrane Library (Issue 2, 2002) were searched for English language articles; the search terms were reported. The National Cancer Institute clinical trials database, conference proceedings of the American Society of Clinical Oncology (ASCO; 1998 to 2001), bibliographies of relevant articles and reviews, CMA Infobase and the National Guideline Clearinghouse were also searched. Only studies that were published in full or as an ASCO abstract were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) or phase II trials (of second-line chemotherapy only) were eligible for inclusion.

Specific interventions included in the review
Studies of gemcitabine as first-line or second-line chemotherapy, alone or in combination with other chemotherapy agents, compared with best supportive care (BSC) or another chemotherapy regimen, were eligible for inclusion. The included studies used various combinations of gemcitabine, platinum, cisplatin, carboplatin mitomycin, ifosfamide, vinblastine, vinorelbine, epirubicin, vindesine, lonidamine, paclitaxel, docetaxel and taxane, with no 2 studies evaluating the same regimens.

Participants included in the review
Studies of patients with advanced stage NSCLC were eligible for inclusion. Most studies recruited a higher proportion of patients at stage IV than stage IIIa or b.

Outcomes assessed in the review
Studies reporting response rate or survival data were eligible for inclusion. The outcomes reported included response rates, time to disease progression, overall survival, median survival, 1-year survival, progression-free survival and adverse events.

How were decisions on the relevance of primary studies made?
Two reviewers selected articles for the review. It was not reported whether this was conducted independently.

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.
Methods of synthesis
How were the studies combined?
The studies were grouped by study design and intervention, and combined in a narrative.

How were differences between studies investigated?
Differences between the studies were discussed in the text and study details were tabulated.

Results of the review
Forty-three studies (n approximately 8,101) were included: 30 RCTs (n approximately 7,516) and 13 non-randomised phase II trials (n=585).

First-line chemotherapy.

Single-agent gemcitabine (4 RCTs): one RCT reported no difference in median survival or 1-year survival between gemcitabine and BSC; the other RCTs reported no difference between gemcitabine and cisplatin in relation to response rates, time to disease progression, median survival or 1-year survival, but gemcitabine caused fewer adverse events.

Gemcitabine-platinum doublets (13 RCTs): the response rates to gemcitabine-platinum ranged from 22 to 67%.

Gemcitabine-cisplatin doublets (10 RCTs): compared with cisplatin alone or in other combinations, or gemcitabine alone, gemcitabine-cisplatin produced significantly higher response rates in 3 large RCTs and response rates tended to be higher in 3 smaller RCTs, but the significance level was not reported for these studies. There was no significant difference in response rate in the remaining 4 RCTs. Gemcitabine-cisplatin doublets produced longer progression-free survival (1 RCT), longer median survival (1 RCT) and higher 1-year survival (1 RCT) compared with cisplatin alone.

Compared with newer chemotherapy agents (3 RCTs), gemcitabine-cisplatin showed no difference in objective response rates (3 RCTs), progression-free survival (2 RCT), median survival (3 RCTs) or 1-year survival (3 RCTs). Gemcitabine-cisplatin generally resulted in fewer cases of neutropenia (1 RCT), febrile neutropenia (2 RCT) and alopecia (1 RCT), but caused more thrombocytopenia (2 RCTs), anaemia (1 RCT) and renal toxicity (1 RCT).

Gemcitabine-carboplatin doublets (3 RCTs): 2 inadequately powered RCTs compared gemcitabine-carboplatin with gemcitabine-cisplatin. One reported similar response rates and the other a higher response rate and median survival rate for gemcitabine-cisplatin. The third RCT reported no difference in response rate between gemcitabine-carboplatin and mitomycin, cisplatin and ifosfamide or vinblastine combinations.

Gemcitabine triplet regimens (7 RCTs): cisplatin-gemcitabine-vinorelbine produced response rates ranging from 44 to 57%, and a median survival time of approximately 12 months (3 RCTs). Cisplatin-gemcitabine-vinorelbine was superior to cisplatin-epirubicin-vindesine-lonidamine in relation to quality of life, response rate, median survival (1 RCT). The response rate and median survival for cisplatin-gemcitabine-vinorelbine was similar to that for cisplatin-gemcitabine (1 RCT). Similar response rate, median survival and 1-year survival were reported for carboplatin-gemcitabine followed by paclitaxel and cisplatin-vinorelbine followed by docetaxel (1 RCT). There were no differences in response rate, progression-free survival or overall survival between carboplatin-paclitaxel with gemcitabine or vinorelbine, and gemcitabine with either paclitaxel or vinorelbine (1 RCT). A higher response rate and longer median survival was reported for carboplatin-paclitaxel when gemcitabine was added (1 RCT). Cisplatin-gemcitabine-vinorelbine (2 RCTs), carboplatin-paclitaxel-vinorelbine (1 RCT) and gemcitabine-paclitaxel (1 RCT) caused more febrile neutropenia than other regimens. Carboplatin-paclitaxel-gemcitabine caused more thrombocytopenia and neutropenia than carboplatin-paclitaxel-vinorelbine (1 RCT).

Non-platinum-containing regimens (4 RCTs): there was no significant difference in response rate between gemcitabine-vinorelbine compared with vinorelbine alone, although median survival was longer with gemcitabine-vinorelbine (1 RCT). Gemcitabine-taxane had similar response rates and survival to combinations with platinum-taxane (3 RCTs).

Second-line chemotherapy (13 phase II studies).
The use of gemcitabine as a second-line therapy resulted in response rates ranging from 5 to 20%, and median survival times ranging from 3.9 to 7.8 months (4 studies). When combined with docetaxel (4 studies), paclitaxel (2 studies) or vinorelbine (3 studies), the response rates ranged from 3 to 33% and median survival times ranged from 5.5 to 11 months.

Authors' conclusions
There was only sufficient evidence to recommend the use of cisplatin-gemcitabine as one of several first-line chemotherapy regimens for patients with locally advanced or metastatic NSCLC.

CRD commentary
The review question was clear in terms of the participants, interventions, outcomes and study design. Several relevant sources were searched, but only English language studies were included, which might have introduced language bias into the review. The authors did not test for publication bias. Although two reviewers selected studies, it was not clear whether this was conducted independently; it was also not clear whether the data extraction was conducted in duplicate. Therefore, the potential for error and bias cannot be ruled out. Study quality was not assessed, thus the quality of the evidence provided was unclear. The decision to combine the studies in a narrative was appropriate given the degree of clinical heterogeneity present between the studies. Given these limitations, the authors' conclusions should be treated with some caution.

Implications of the review for practice and research
Practice: The authors stated that cisplatin-gemcitabine can be recommended as one of several first-line chemotherapy regimens for patients with locally advanced or metastatic NSCLC. They also stated that there is insufficient evidence to recommend routinely adding a third drug to gemcitabine-platinum combinations, substituting carboplatin for cisplatin when combined with gemcitabine, recommending gemcitabine combined with taxane as a first-line therapy, or using gemcitabine as a second-line therapy.

Research: The authors did not state any implications for further research.

Funding
Cancer Care Ontario; Ontario Ministry of Health and Long-term Care.

Bibliographic details

Original Paper URL
https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/lung-ebs/

Other publications of related interest

Database of Abstracts of Reviews of Effects (DARE)
Produced by the Centre for Reviews and Dissemination
Copyright © 2020 University of York
Indexing Status
Subject indexing assigned by CRD

MeSH
Adult; Antineoplastic Combined Chemotherapy Protocols; Carcinoma, Non-Small-Cell Lung /drug therapy; Cisplatin /administration & dosage; Deoxycytidine /administration & dosage /therapeutic use

AccessionNumber
12005008527

Date bibliographic record published
31/10/2006

Date abstract record published
31/10/2006

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.