Docetaxel in advanced gastric cancer: review of the main clinical trials

CRD summary
This review assessed the effectiveness of docetaxel, either as a single agent or in combination with other widely used cancer drugs, in the treatment of advanced gastric cancer. The authors concluded that firm conclusions about the effectiveness of docetaxel cannot be drawn until the results of further phase III studies are available. On the basis of the limited evidence reviewed and a number of potential biases in the review process, this statement appears reliable.

Authors' objectives
To assess the effectiveness of docetaxel, either as a single agent or in combination with widely used other cancer drugs, in the treatment of advanced gastric cancer.

Searching
MEDLINE, EMBASE and Cancerlit were searched from January 1966 to February 2003 without any language restrictions; the keywords were reported. In addition, conference proceedings, textbooks, and the references of all retrieved articles were handsearched. The ‘novelties’ from the 38th American Society of Clinical Oncology (ASCO) and 28th European Society for Medical Oncology (ESMO) meetings in 2002 were also obtained. Abstracts and letters were included if they contained sufficient methodological information and results.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and uncontrolled clinical trials were eligible for inclusion. Case reports were excluded.

Specific interventions included in the review
Studies that included docetaxel, used either alone or in combination (including sequential therapy) with widely used other cancer drugs, were eligible for inclusion. The specific chemotherapeutic drugs assessed were docetaxel, PELF (a combination of cisplatin, fluorouracil, epirubicin, stereoisomer of leucovorin and glutathione), 5-fluorouracil (either alone or in combination with leucovorin), irinotecan, epirubicin and cisplatin. The majority of the studies used a 3-weekly dosing cycle, with the minority using weekly cycles.

Participants included in the review
Studies that included either chemotherapy naive or pre-treated patients with advanced gastric cancer were eligible for inclusion.

Outcomes assessed in the review
Studies that do not report clinical outcomes were excluded. The specific outcomes assessed were the overall response rate, median survival and toxicity.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

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. Data were extracted on the number of patients, the line of therapy, dosage and treatment schedule, the overall response rate, median response duration, median time to progression, median survival and toxicities (where the data were reported).

Methods of synthesis
How were the studies combined?
The studies were grouped according to whether a single-, two- or three-agent regimen was used, and were combined in a narrative discussion. However, the authors also discussed trials for which there were no tabulated data.

How were differences between studies investigated?
Differences between the studies were discussed according to differences in regimens, dosing cycles and dose, and participants.

Results of the review
The total number of included studies was unclear. It appears that 1 RCT and 21 uncontrolled trials were included (the total number of participants was 818: 83 in the RCT and 735 in the uncontrolled studies).

Single-agent regimens (8 studies, 321 patients eligible, 261 available).

The response rates varied from 17 to 24% with a mean of 19.1% (95% confidence interval, CI: 14.3, 23.8). The most common toxicities observed were non-cumulative neutropenia (36 to 95%), with leucopenic fever (5 to 46%) and grade 1 to 3 hypersensitivity reactions (24%) (based on 4 studies with 149 patients). Alopecia and fluid retention were also observed in the majority of patients. There were no treatment-related deaths.

Two-drug regimens (8 studies, 286 patients).

The addition of fluorouracil to docetaxel showed response rates of 22% and 86% (based on 2 studies with 26 and 14 patients, respectively). These two studies were based on different patient populations and modalities of drug administration (continuous versus bolus infusion). The response rates for the docetaxel-cisplatin combination were 56%, 37% and 36% in three phase II trials, and 35% in a phase III trial. Grade 3 to 4 neutropenia was reported for between 12 and 81% of the patients (based on 6 studies).

Three-drug regimens (6 studies, 211 patients).

The addition of cisplatin and fluorouracil to docetaxel did not increase the number of toxicities observed. Grade 3 to 4 neutropenia was reported in between 50 and 81% of the patients. RCTs comparing docetaxel-cisplatin-fluorouracil with cisplatin-fluorouracil or epirubicin-cisplatin-fluorouracil are ongoing.

Authors’ conclusions
Phase III studies are required before firm conclusions can be drawn about docetaxel and its role in clinical practice.

CRD commentary
The review question was clearly defined in terms of the interventions, participants and study designs. An adequate number of sources were searched for potentially relevant studies and efforts were made to minimise language and publication bias. However, the review methods were unclear, and it is not known whether any efforts were made to minimise reviewer error and bias in the study selection and data extraction processes. Furthermore, the quality of the included studies was not assessed; therefore, it is not possible to comment on how study quality might have affected the results of the review.

There was inadequate information on the included studies. The duration of follow-up was not reported, so it is not possible to judge whether this was long enough to adequately assess response. The definitions used for ‘response’ in the individual studies were not reported, making it difficult to interpret the results. In addition, not all of the patients were...
evaluated, but no reasons for drop-outs were reported. The authors grouped the studies according to intervention and appropriately combined the studies in a narrative discussion. Some differences between the studies were discussed. The authors highlighted that firm conclusions regarding the effectiveness of docetaxel cannot be drawn until the results of further phase III studies are available. On the basis of the evidence reviewed and a number of potential biases in the review process, this statement appears correct.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further phase III studies are necessary to draw any firm conclusions about the extensive use of docetaxel in clinical practice.

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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.