Chemotherapy for recurrent, metastatic, or persistent cervical cancer: a systematic review

Hirte HW, Strychowsky JE, Oliver T, Fung-Kee-Fung M, Elit L, Oza AM

CRD summary
This review concluded that cisplatin plus topotecan should be offered as a treatment option to appropriate patients with recurrent, metastatic or persistent cervical cancer; further research was required. There were several considerations with the included studies, but the authors' conclusions appeared to reflect the evidence available and their recommendations for further research seem appropriate.

Authors' objectives
To investigate the effectiveness of chemotherapy for recurrent, metastatic and persistent cervical cancer.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials were searched to February 2006. Canadian Medical Association Infobase and National Guidelines Clearinghouse were searched. Only publications in English were eligible. Search terms were reported. Conference proceedings of the American Society of Clinical Oncology (1995 to 2005) and the European Society of Medical Oncology (2002 to 2005) were searched for new or ongoing trials. References from retrieved and recent review articles were searched manually.

Study selection
Randomised controlled trials (RCTs), practice guidelines, systematic reviews and meta-analyses that compared one chemotherapy regimen with another or no treatment in women with recurrent, metastatic or persistent cervical cancer were eligible for inclusion. Eligible studies were required to report one of the following outcomes: response rate, survival, toxicity, or quality of life. Studies of women with a range of disease stages were eligible if results were given separately for the relevant population. Studies that evaluated radiotherapy in combination with chemotherapy were not eligible for inclusion.

Included studies were conducted in USA, Europe, Russia, Belgium, South Africa, Mexico and Denmark. Studies compared single-agent cisplatin with combination cisplatin-based chemotherapy, cisplatin-based chemotherapy with other chemotherapeutic regimens, carboplatin with other chemotherapy and non-platinum containing agents. Platinum doses ranged between 20 and 400mg/m$^2$. Some patients received prior chemotherapy, chemotherapy as a radiosensitizer, radiotherapy or surgery. The site of disease was reported as distant, in the pelvis, or both. Quality of life was assessed using various different assessment tools.

The authors stated that the evidence was selected and reviewed by members of the Program in Evidence-Based Care (PEBC) gynaecology Cancer Disease Site Group (DSG) and two methodologists; no further information was given.

Assessment of study quality
The authors did not state how they assessed validity, but reported on blinding, method of randomisation, statistical power, comparability of participants and intention-to-treat analysis.

Data extraction
The authors did not state how data were extracted. The number (%) of patients who experienced adverse events (toxicity), complete response, partial response or complete plus partial response were extracted. Median survival and median progression-free survival (in months) were also extracted, along with hazard ratios with their 95% confidence intervals (CIs), where this data were reported. Quality of life data were extracted in descriptive form.

Methods of synthesis
Data were presented as a narrative synthesis and in tables by outcome and comparison type. Meta-analysis was planned and undertaken, but not presented due to clinical heterogeneity.
Results of the review
Fifteen RCTs (n=2,538) were included in the review. Sample sizes ranged between 20 and 438 patients. The quality of the RCTs was deemed to be adequate although none of the studies were blinded, only seven studies reported methods of randomisation and only four trials were sufficiently powered. Baseline characteristics of participants were comparable between groups. Nine studies used intention to treat analysis. Three RCTs were terminated early.

Significant improvements were reported in patients who received combination cisplatin-based chemotherapy compared with single-agent cisplatin for overall response (complete response plus partial response) (four of 15 RCTs), median overall survival (one of 13 RCTs) and median progression-free survival (three of eight RCTs). Cisplatin in combination with topotecan showed the greatest median overall survival benefits (HR 0.76, 95% CI 0.59 to 0.98, p=0.017). Fifteen treatment-related deaths were reported in five RCTs; most had received combination cisplatin-based chemotherapy.

Greater haematologic toxicity was reported in patients who received combination therapy compared to single agent cisplatin (six of seven RCTs). Results for non-haematologic toxicity were also reported in the review.

There were no significant differences between the two treatment groups in quality of life scores (two RCTs). Four RCTs showed that the greatest benefit in median survival was observed in patients who had not previously been treated with cisplatin as part of chemoradiotherapy.

Authors' conclusions
Cisplatin in combination with topotecan should be offered as a treatment option to appropriate patients who may be willing to maximise the response and survival benefits associated with combination chemotherapy. Patients should be aware that prior chemoradiotherapy with cisplatin may reduce the benefits and that toxicity was greater. Further research was needed to investigate the treatment options.

CRD commentary
The review question and inclusion criteria were clear, and were supported by a comprehensive search of the literature for published and unpublished publications. Only articles published in English were searched, hence language bias may have been introduced. The authors reported that the quality of included studies was adequate, but only limited data were reported by studies and it was unclear how the validity assessment process was performed. In addition, the process for study selection and data extraction was unclear, thus reviewer error and bias could not be ruled out. Due to clinical and methodological heterogeneity, the authors’ decision not to pool the results was appropriate; such heterogeneity should be taken into account when considering the generalisability of the results. Further limitations included the small number of studies for treatment comparisons and the small study populations. Despite the above considerations, the authors’ conclusions appeared to reflect the evidence available and their recommendations for further research seem appropriate.

Implications of the review for practice and research
Practice: The authors stated that there was concern that as more patients underwent cisplatin chemoradiotherapy, the median survival benefit with first-line combination cisplatin-based chemotherapy may reduce.

Research: The authors stated that further RCTs were required to investigate the effects of single and combination platinum and non-platinum chemotherapy regimens, particularly in patients with prior chemoradiotherapy. Further RCTs were required to determine the generalisability of survival benefit to patient populations with a greater rate of prior chemoradiotherapy with cisplatin.

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