Neoadjuvant chemotherapy followed by radiotherapy should not be a standard approach for locally advanced cervical cancer

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Authors' objectives
To investigate the role of neoadjuvant chemotherapy followed by radiotherapy in locally advanced cervical cancer, in terms of survival.

Searching
MEDLINE and CANCERLINE were searched from 1970 to 1996. In addition, the bibliographies of included articles were checked for potentially useful references. Only English language articles were retrieved.

Study selection
Study designs of evaluations included in the review
Randomised Phase II and III trials were included in the review, with results reported for survival, local control or toxicity. Abstracts were included.

Specific interventions included in the review
Treatment with various combinations and doses of the following chemotherapeutic agents: ifosfamide, cisplatin, carboplatin, mitomycin, bleomycin, mesna, vinblastine, vincristine, methotrexate, epirubicin, cyclophosphamide, chlorambucil.

The treatments varied in terms of the numbers of cycles of drugs and the interval between cycles, and included 2 to 4 cycles with a 3-week interval between cycles, and 2 cycles with a 2-week interval.

The interventions also included combinations of the following radiotherapy treatments: pelvic radiotherapy (40, 50, 40 to 55 Gy), and intracavitary brachytherapy (25 to 40 Gy, 30 Gy, 30 to 35 Gy, 40 Gy to point A, 3,320 cGy), and external-beam parametrical boost (10 Gy, 15 to 20 Gy). Patients in the control arm were treated using conventional radiotherapy alone.

Participants included in the review
There were no predetermined criteria for participant inclusion. Women with Stage II, IIb, III, IIIb, IV, IVa and IVb cervical cancers were included in the review.

Outcomes assessed in the review
The outcomes included in the review were survival rate, response rates (complete and partial), percentage failure rate (local failure, distant metastases and both failure rates combined) and toxicity levels.

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

Assessment of study quality
The authors do not state that they assessed quality.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken, where the trials were separated into Phase II and Phase III studies. The response rate, treatment failure rate and the safety of the therapies were discussed.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Twenty-two studies with 1,375 patients were included in the review: 13 Phase II trials (460 patients) and 9 Phase III trials (915 patients).

Phase II trials: a reduction in tumour size was reported in two thirds of those patients using the neoadjuvant PVB scheme (cisplatin, vinblastine and bleomycin at 21-day intervals). Most trials used radiotherapy following 3 courses or 3 weeks of induction chemotherapy. Others administered surgery plus pelvic irradiation for good responders, or radiotherapy alone for poor responders. Most of these studies used cisplatin-based combinations. The complete response rate to chemotherapy was 0 to 50%, and the overall response rate was 23 to 100%. Cisplatin, in combination with vincristine and bleomycin, was the most popular regimen.

Phase III trials: the 9 randomised controlled trials used 8 different chemotherapy regimens, all containing cisplatin alone or cisplatin-based combinations. The dose intensities for cisplatin were similar, i.e. range 50 to 80 mg/m2, with 2 to 4 cycles of chemotherapy given before irradiation. Generally, the interval between each cycle was 3 weeks, although there were some variation among institutions; radiotherapy generally consisted of external pelvic irradiation (40 to 50 Gy), followed by intracavitary radiotherapy (30 to 40 Gy to point A) with or without an external parametrical boost. Eight trials reported the response rates to chemotherapy; these ranged from 35 to 73%. Seven of them showed complete response rates of less than 10%. The complete response rates for combined chemotherapy and radiotherapy were greater than 60% in 5 studies.

Treatment failure (5 trials): pelvic relapse was the most common site of failure, either in the radiotherapy alone or the chemoradiation arm. Two trials reported an increased total recurrence rate in the combined chemotherapy and radiotherapy arm.

Survival (8 randomised controlled trials): no trials showed any significant benefit of neoadjuvant chemotherapy on survival. Results from 2 trials suggested reduced survival in the combined treatment arms.

Most studies reported that prior use of induction chemotherapy was tolerable without any prominent enhancement of toxicity. The most toxic effects observed were mild to moderate and included nausea, vomiting, alopecia, hyperthermia, peripheral neurotoxicity and anaemia. Other more severe effects included myelosuppression, acute pulmonary toxicity and high haematological toxicity.

Authors' conclusions
A variety of multi-agent induction regimens have been used, the majority of which were cisplatin-based combinations. Most of the Phase II trials investigating novel schedules support further investigation of this approach, although eight of the nine Phase III randomised trials failed to demonstrate any benefit of neoadjuvant chemotherapy in terms of loco-regional control and/or survival. Moreover, the largest randomised trial reported disappointing local failure and survival figures in the combined treatment arm.

CRD commentary
This review featured an adequate search of the published literature. However, relevant articles may have been missed by limiting the search to English language articles and only searching for published articles in two databases. In addition, it would be difficult for others to repeat the literature search as no search terms were provided. No predefined inclusion criteria for patient populations or treatment regimes were given, and it was unclear how decisions on the
relevance of primary studies were made or how the data were extracted from the included studies. The definitions of the outcomes assessed were also unclear, and there appeared to be no assessment of study quality or heterogeneity. The authors' conclusions appear to be justified given the variation in the results of the included studies and the treatment regimens used.

**Implications of the review for practice and research**
The authors state that 'based on these results, induction chemotherapy followed by radiotherapy should not be a standard treatment for advanced cervical cancer'.

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