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Review

Radiotherapy with concurrent cisplatin-based doublet or weekly cisplatin for cervical cancer: A systematic review and meta-analysis

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HIGHLIGHTS

- Weekly cisplatin + radiotherapy is the standard treatment for locally advanced cervical cancer.
- We report a meta-analysis comparing weekly cisplatin- vs. cisplatin combinations associated to radiotherapy in cervical cancer.
- Platinum-based combinations increase PFS and OS with respect to weekly cisplatin when associated to radiotherapy and could become a new standard of care.

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ABSTRACT

Background. Treatment with weekly cisplatin (CDDP) plus radiotherapy (RT) is the standard regimen for stage IB to stage IVA cervical carcinoma (CC). We performed a systematic review and meta-analysis of published studies to evaluate whether CDDP-based doublet therapy improves survival compared to weekly CDDP plus RT in patients with CC.

Materials and methods. We conducted a systematic search for randomized and nonrandomized studies in PubMed, EMBASE, Web of Science, Scopus, and the Cochrane Register of Controlled Trials. We then carried out a meta-analysis by using the fixed- or random-effects models. The primary endpoints were overall survival (OS) and progression-free survival (PFS), reported as odds ratios (ORs) and 95% confidence intervals (CIs).

Results. Four randomized trials and 4 retrospective studies that included a total of 1500 patients matched our selection criteria. Meta-analysis showed that for locally advanced CC, concurrent RT and with CDDP-based doublet chemotherapy significantly improved the OS (OR, 0.65; 95% CI, 0.51–0.81; $p = 0.0002$), PFS (OR, 0.71; 95% CI, 0.55–0.91; $p = 0.006$), and rate of locoregional relapse (OR, 0.64; 95% CI, 0.47–0.89; $p = 0.008$), compared to RT with concurrent weekly CDDP alone.

Conclusions. In patients with CC, platinum-based doublet chemotherapy plus concurrent RT was associated with improvements in the OS and PFS of 35% and 30% patients, respectively, compared to RT plus weekly CDDP. Therefore, platinum-based combination therapy plus RT should be the preferred treatment over weekly CDDP plus RT for stage IB–IVA CC.

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Introduction

Cervical cancer (CC) is highly sensitive to radiotherapy (RT) and chemotherapy (CT), and the standard treatment is platinum-based CT combined with RT (CTRT). Two prospective studies demonstrated that concurrent administration of cisplatin (CDDP)-containing CT and RT is the preferred treatment for bulky stage I and advanced stage CC [1,2]. A third study suggested that patients who require adjuvant RT for lymph node metastasis or involved surgical margins also benefit from concurrent CTRT over RT alone [3]. RT is also the primary treatment for locally advanced CC (stage IIB–IVA). Results from clinical trials conducted in the late 1990s indicate that patients with stage IB or higher CC should receive concurrent platinum-based CTRT, except in cases where there are medical contraindications.

The addition of CDDP-therapy to RT improved the outcomes in nearly all trials. One trial compared hydroxyurea (HU), the previous clinical standard, to concurrent weekly CDDP alone or CDDP plus 5-fluorouracil (5-FU) plus HU [4]. Another trial compared HU to CDDP plus 5-FU [5]. These studies showed that the risk of relapse reduced by 43–45% (Gynecologic Oncology Group [GOG] 120) and by 21% (GOG 85), respectively. In particular, CTRT with the combination of CDDP and 5-FU resulted in better progression-free survival (PFS) and overall survival (OS) with a lower rate of pelvic relapse (25% vs. 30%) and with a similar rate of distant metastases compared to HU plus RT in the GOG 85 study [5]. Conversely, Rose et al. in the GOG 120 study found that patients treated with CDDP, 5-FU, and HU plus RT had lower rates of locoregional and distant metastases compared to patients treated with single agent HU plus RT with long-term follow-up [7]. In another randomized study, pelvic RT plus CDDP and 5-FU reduced the risk of relapse and death by 50% compared to pelvic plus para-aortic RT alone in patients with locally advanced disease without para-aortic lymph node involvement [6]. In addition, the risk of locoregional and distant relapse reduced by 60% and 50%, respectively.

A phase III trial that examined RT plus concurrent CDDP and gemcitabine followed by 2 adjuvant cycles of CDDP plus gemcitabine compared to RT plus 6 weekly CDDP cycles was published in 2011 [8]. Two of the primary endpoints, PFS and OS, increased in the combination chemotherapy arm (PFS: hazard ratio [HR], 0.68; 95% CI, 0.49–0.95; $p = 0.0227$; OS: HR, 0.68; 95% CI, 0.49–0.95; $p = 0.0224$). Approximately 100% of the patients completed the CTRT phase, but only 76.5% of the patients in the experimental arm completed the second cycle of adjuvant CT. This occurred even though the incidence of late toxicities, but not acute toxicities, was similar in the 2 arms.

Adopting platinum-based multi-agent CT during the RT phase of treatment could significantly improve locoregional and distant disease control. This combination strategy will likely lead to increased cytotoxicity and radiosensitization compared to CDDP as a single agent.

We performed a meta-analysis of data from published literature to confirm this hypothesis and to evaluate whether CDDP-based CTRT can improve OS and PFS compared to single agent weekly CDDP plus RT, which is currently the standard of care for locally advanced CC.

Materials and methods

The results of this meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9].

Search strategy

The databases of PubMed, EMBASE, Scopus, the Cochrane Library of Controlled Trials, and Web of Science were searched by using the following Medical Subject Heading terms: “uterine cervical neoplasms”, “cervix uteri”, “chemoradiotherapy”, “radiotherapy”, “radiation”, “electromagnetic radiation”, and “cisplatin”. These terms were combined with the following additional key words: “cancer”, “cervical cancer”, “carcinoma”, “cervical carcinoma”, “chemoradiation”, and “radiochemotherapy”. Only studies in English were considered. The search included literature published from 1990 to 9 February 2014. The computer search was supplemented with manual searches for references of the included studies and for related citations. To select studies for inclusion in the analysis, we first reviewed article titles and abstracts, and then obtained the full text to verify eligibility. Two independent investigators (FP and DL) evaluated each study. Any disagreements between the reviewers were resolved by a third investigator (SB). Data were extracted from the selected studies and entered into a table designed in advance that included the characteristics of interest.

Inclusion and exclusion criteria

Studies were included in the analysis if: (1) they were randomized controlled trials or retrospective studies that compared polychemotherapy plus RT plus versus weekly CDDP plus RT with or without brachytherapy; (2) there was no evidence of distant metastasis or para-aortic lymph node involvement before treatment (stage I to IVA); and (3) the long-term OS and PFS (or relapse-free survival [RFS]) were assessed as outcomes to measure the effect of the treatment. If studies were duplicates, the study with the most up-to-date results was included. Studies were excluded if patients received experimental drugs or other unapproved molecular agents. Adjuvant (or neoadjuvant) CT was not permitted; conversely primary debulking surgery that revealed high-risk features in surgical specimens that required subsequent adjuvant CTRT was.

The Jadad scale was used to evaluate the quality of the randomized controlled trials included in the primary outcome analysis. The Newcastle-Ottawa Quality Assessment Scale was used to assess observational studies [10]. This scoring system evaluates studies on the basis of the selection of patients in the exposed and non-exposed groups, the comparability of the 2 groups, and the outcomes of the single studies. On the basis of these criteria, studies are scored between 0 and 9 stars. Six stars or greater was considered to be sufficiently high-quality studies.

Statistical analysis

OS and PFS (or RFS) were the primary endpoints, and the locoregional relapse rate (LRR), rate of distant metastasis, and occurrence of severe (G3