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The efficacy of concurrent weekly carboplatin with radiotherapy in the treatment of cervical cancer: A meta-analysis

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HIGHLIGHTS

- A shortage of tumor response and a trend toward inferior survival were observed in Car-RT compared with Cis-RT.
- The estimated complete response rate, 3-year PFS and OS in Car-RT were acceptable.
- Car-RT had a low level of toxic effects.
- Carboplatin can be an alternative in patients for whom cisplatin is inappropriate.

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ABSTRACT

Objectives. We aimed to evaluate whether carboplatin has a comparable efficacy with cisplatin as part of weekly concurrent chemoradiotherapy for cervical cancer (Car-RT vs. *Cis*-RT).

Methods. A literature search was conducted and both prospective and retrospective studies that evaluated the efficacy of Car-RT for cervical cancer were included. The primary endpoints were complete response (CR) rate, progression-free survival (PFS)/disease-free survival (DFS), overall survival (OS), reported as odds ratios (ORs) and 95% confidence intervals (CIs). The estimated CR rate and survival of patients treated with Car-RT were pooled. Acute toxicity was also summarized.

Results. Twelve studies consisting of 1698 patients were eligible for meta-analysis. A lower CR rate (OR, 0.53; 95% CI, 0.34–0.82, $I^2 = 0\%$) and a trend toward poorer 3-year PFS/DFS (OR, 0.71; 95% CI, 0.49–1.02, $I^2 = 0\%$) and 3-year OS (OR, 0.70; 95% CI, 0.46–1.05, $I^2 = 36\%$) were found in Car-RT compared with Cis-RT. For the Car-RT groups, the pooled overall CR rate was 81% (95% CI 0.74–0.89). The pooled 3-year PFS/DFS rate was 64% (95% CI 0.52–0.78). The pooled 3-year OS rate was 73% (95% CI 0.62–0.87). Acute toxic events ≥ grade 3 were infrequent in the Car-RT groups.

Conclusions. Car-RT showed a poorer tumor response and a trend toward inferior survival compared with Cis-RT in the treatment of cervical cancer. However, this evidence was limited by the imbalance among studies. Due to the encouraging efficacy and low toxicity, carboplatin is a suitable concurrent agent for patients with contraindications to cisplatin.

1. Introduction

Cervical cancer is one of the most commonly diagnosed female malignancies worldwide [1]. With the help of the HPV vaccine and the popularization of early screening, the morbidity and mortality of patients with cervical cancer have begun to decrease in developed countries [1–3]. However, in regions with poor health service, cervical cancer is still one of the biggest threats to women [1, 2].

Currently, cisplatin-based concurrent chemoradiation is the standard care for locally advanced cervical cancer [4–7]. Due to the relatively low toxicity, weekly cisplatin as a single concurrent agent plus radiation (Cis-RT) is the preferred regimen [4, 8]. However, the potential nephrotoxicity, ototoxicity and highly emetic effects of cisplatin limit its use to special populations. The requirement for sufficient hydration also reduces its use, especially in high-capacity hospitals. For now, no alternative to cisplatin for use in this weekly schedule has been recognized.

Carboplatin, a platinum analog, has a biochemical activity and antitumor spectrum similar to cisplatin [9]. Carboplatin is easier to administer as it is associated with reduced emesis and nephrotoxicity but an increased risk of myelosuppression [9, 10]. Carboplatin has been found

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to be non-inferior to cisplatin for metastatic and recurrent cervical cancer when combined with paclitaxel [11, 12], and some physicians prefer to use carboplatin because of its ease of administration and tolerability [12]. However, the role of concurrent weekly carboplatin plus RT (Car-RT) in treatment for a curative intent remains unknown. Thus, we performed this meta-analysis of published studies to systematically evaluate this regimen.

2. Methods

2.1. Search strategy

PubMed, EMBASE, Web of Science and The Cochrane Library were searched using the following keywords: "uterine cervical cancer [Mesh]"and "carboplatin". Only "human studies" published in English were considered. The last search was updated on April 1, 2018. Conference abstracts about unpublished studies were also reviewed. The references of the relevant studies were further examined to find other potential eligible studies.

2.2. Eligibility criteria

Studies were included in the meta-analysis if: (1) they evaluated the efficacy of Car-RT for cervical cancer with or without comparison with cisplatin; (2) at least one outcome (CR, PFS, DFS or OS) was assessed. Studies were excluded if: (1) they were conducted in an adjuvant (or neoadjuvant) setting; (2) they used carboplatin-based double or multiple concurrent agents; (3) they included patients with recurrent disease or evidence of distant metastasis before treatment (stage IVB); (4) they included <20 patients. The studies excluded from the meta-analysis but that had available toxicity data were also recorded and were included in the descriptive summary.

2.3. Quality control

The Newcastle-Ottawa Quality Assessment Scale for Cohort Studies was used to evaluate the selected studies [13]. Scores of six or higher indicated high-quality studies. For those with a single-arm design, the scale was adjusted so that the total score was between 0 and 6. Scores of 4 or higher indicated that a study was qualified.

2.4. Data extraction

The following data were extracted from the included studies: author's name, publication year, study design, number of patients treated by carboplatin or cisplatin, age of the patients, disease stage, dose and schedule of chemotherapy and radiation, rate of complete response, rate of toxicity events ≥ grade 3, and the 1-, 2-, 3-year PFS/DFS/OS rates. Furthermore, to make our results comparative, we took advantage of the survival data from other published studies in which cervical cancer patients were treated with Cis-RT. The relevant survival data were also extracted. Two investigators extracted the data independently, and any discrepancies were discussed and resolved by them.

2.5. Statistical analysis

First, traditional pair-wise meta-analyses were performed to compare the outcome between Car-RT and Cis-RT. The primary endpoints were CR, PFS, DFS and OS. Due to the limited number of available studies, we analyzed disease progression by combining PFS and DFS. Since most studies were retrospective and only mentioned the absolute number of events, CR, PFS/DFS and OS were calculated as binary data. The odds ratios (ORs) with 95% CIs were used as a summary statistic for all endpoints. If the number of events was not directly reported, it was derived from the survivor function graphs or from the survival rates. The 1-year, 2-year, and 3-year PFS/DFS and OS were assessed. The pooled ORs were calculated using a fixed-effects model with the Mantel-Haenszel method [14] or a random-effects model with the DerSimonian-Laird method [15] depending on the heterogeneity of the studies. Heterogeneity was evaluated by Cochran's Q-test and the I^2 statistic [16]. A p value < 0.10 for the Q-test or an $I^2 > 50\%$ suggests marked heterogeneity among studies, in which case a random-effects model was chosen. Otherwise, a fixed-effects model was used. For the meta-analysis of the carboplatin-specific groups, the 1-year, 2-year, and 3-year PFS/DFS and OS rates and the CR rates were pooled after natural logarithmic transformation using the random-effects model with the DerSimonian-Laird method, and the results were expressed as the incidence of an event with a 95% CI. The Launch Open Meta Analyst tool was used for quantitative data synthesis [17]. Acute toxicities ≥ grade 3 in the Car-RT groups were recorded, and the averages of the toxic event rates were calculated and described briefly due to their inappropriateness for inclusion in this meta-analysis.

3. Results

3.1. Literature search and study characteristics

We identified a total of 1037 studies in the initial search. Fig. 1 outlines the selection process and the reasons for study exclusion. No randomized control trial met the inclusion criteria. Finally, six prospective trials [18–23] and six retrospective studies [24–29] were included in this meta-analysis. Five studies compared weekly carboplatin and cisplatin as part of concurrent chemoradiotherapy [18, 19, 24–26]. The data obtained in the study by Valdiviezo [25] were derived from a conference abstract, which was included after an assessment of its eligibility. The studies by Veerasarn [20] and Au-Yeung [26] contained two or three control arms, and only the Car-RT and/or Cis-RT arms were included here. The study by Micheletti used continuous infusion of low-dose carboplatin combined with RT [30]. Given that this treatment setting was quite different from those in the other included studies and that only 11 patients were treated, this study was excluded. Dubay's study [31] used a 3-week concurrent schedule in addition to an adjuvant chemotherapy setting, and thus this study was also excluded. Furthermore, Corn's study [32] was not included in the meta-analysis because some of the patients studied had recurrent disease, but its toxicity data were available for a descriptive analysis. Diaz's study [33] was also excluded, but its toxicity data were summarized. Finally, 12 studies consisting of 1698 patients were entered into the final meta-analysis (Table 1, details of quality assessment in Table S1).

3.2. Comparison of Car-RT and Cis-RT

The CR rate of patients treated with Car-RT and Cis-RT was reported in three studies. All the comparisons were retrospective in nature. In all, 521 cases were included. The meta-analysis showed that Car-RT was associated with a lower CR rate compared with Cis-RT (OR, 0.53; 95% CI, 0.34–0.82; $I^2 = 0\%$; Fig. 2).

Four studies were available for comparison of the PFS/DFS and OS between patients treated with Car-RT and those treated with Cis-RT. Tharavichitkul's study [18] was prospective but not randomized, and Nam's study [19] was a prospective cohort that was compared with a historical group after they were matched according to their clinical characteristics. The remaining two studies [24, 26] were both retrospective. In all, 824 cases were evaluated. The meta-analysis of the 1-year, 2-year, and 3-year PFS/DFS and OS rates did not find any marked heterogeneity among the studies, and thus a fixed-effects model was selected to pool the results. According to the meta-analysis, Car-RT demonstrated a trend toward a lower PFS/DFS compared with Cis-RT, although the difference was not statistically significant. The ORs of the 1-year, 2-year,

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