Review

A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer

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HIGHLIGHTS
• Platinum-taxane combinations are active agents in advanced cervical cancer.
• Which of cisplatin or carboplatin is the better platinum agent when combined with paclitaxel is a matter of debate.
• We report a review of cisplatin- vs carboplatin-taxane studies that confirms similar outcome for the two doublets.

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ABSTRACT

Introduction. The prognosis of advanced/recurrent cervical cancer patients is generally poor with 1-year survival ranging between 15 and 20%. Cisplatin (CDDP) based treatments are considered the most effective regimens; unfortunately toxicity is an issue in a population in which the treatment remains palliative in the finality. Carboplatin (CBDCA), with its more favorable non toxicity profile and the convenience of outpatient administration, may be a suitable alternative to CDDP in combination regimens.

Materials and methods. We performed a systematic review of the literature comparing CDDP and CBDCA based chemotherapy for advanced cervical cancer (recurrent, persistent or metastatic disease). Only studies that met the following criteria were considered for the present review: 1) patients treated with CDDP/paclitaxel or CBDCA/paclitaxel combinations as first line chemotherapy for metastatic disease; 2) one or more of the following data available: overall response rate (RR), progression free survival (PFS) or time to progression (TTP); overall survival (OS); 3) single-arm retrospective or prospective study; and 4) at least 20 patients enrolled.

Results. 17 eligible studies comprehensive of 1181 patients were included in the final analysis. The objective RR was 48.5% for CBDCA and 49.3% for CDDP-based chemotherapy. Median PFS for CDDP and CBDCA-based treatments was 6.9 months and 5 months respectively (p = 0.03); the corresponding figures for median OS were 12.87 and 10 months respectively (p = 0.17).

Discussion. Our study indicates that CBDCA may represent an attractive and valid alternative to the more toxic and equally effective CDDP in the treatment of advanced or recurrent cervical cancer.

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Introduction

Cervical cancer is still a leading cause of cancer-related death in women, accounting for 14% of all deaths due to gynecologic cancers worldwide [1]. Although several advances in screening, diagnostic and treatment modalities have been made, the overall prognosis of cervical cancer has not changed dramatically, and the mortality still approaches 50%. The treatment of choice of cervical cancer is represented by radiotherapy or surgery for early stage disease and concurrent chemoradiation for advanced stage patients. Chemotherapy remains an option for metastatic patients (FIGO stage IVB) or persistent/recurrent disease after primary treatment not suitable for curative surgery or radiotherapy. The prognosis of advanced/recurrent patients generally remains poor with 1-year survival ranging between 15 and 20% [2]. Single agent cisplatin (CDDP) is considered the most active agent in the treatment of advanced/recurrent disease [3], and the combination of CDDP-paclitaxel (P) has been reported to be better to CDDP monotherapy in terms of response rate (RR), progression free survival (PFS) but not overall survival (OS) [4]. The recently closed GOG 204 moreover reported CDDP-P as the most active combination in the treatment of advanced or recurrent cervical cancer [5] thus confirming the treatment as the new standard of care in advanced cervical carcinoma. Unfortunately, the toxicity of the treatment and the discomfort of the schedule, with P given as 24-hour infusion in order to minimize neurologic toxicity, make the combination hardly to propose in a setting of disease where, despite the improved clinical outcomes, all treatments remain palliative in the finality. In this context, CBDA, with its more favorable toxicity profile and the convenience of the outpatient administration, may be a suitable substitute of CDDP in combination regimens. In ovarian cancer, CBDA has been reported to be equally effective than CDDP but better tolerated [6,7]. Recently a randomized JCOG phase III trial on stage IVB, persistent or recurrent cervical cancer reported that CBDA-P is equally effective with respect to CDDP-P in terms of PFS and OS, the latter being more efficacious in chemo naive patients [8]. We performed a systematic review of the literature comparing CDDP and CBDA paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer in order to describe the activity and outcomes associated with both doublets.

Methods

Literature search

PubMed, EMBASE, Web of Science and The Cochrane Library were systematically searched in March 2013, to identify relevant publications. Keywords included in the search were “uterine cervical neoplasm [Mesh]”, “cisplatin or carboplatin”, “paclitaxel” and “recurrent or relapsed or advanced or metastatic”. The literature search was limited to “human studies” in “English” language. We also reviewed conference abstracts to identify unpublished papers. All potentially relevant studies were retrieved, and their references were checked to see if there were further eligible studies.

Study selection

To summarize the effectiveness of CDDP and CBDA + paclitaxel-based chemotherapy, only studies that met all of the following criteria were considered eligible to be included in the present review: 1) patients with advanced cervical cancer (recurrent, persistent or metastatic disease); 2) treated with CDDP/paclitaxel or CBDA/paclitaxel combinations as first line chemotherapy for metastatic disease; 3) one or more of the following information available: overall RR (the amount of complete response and partial response), PFS or TTP (time to progression), OS; 4) single-arm retrospective or prospective study, which means that the platinum/paclitaxel arms of randomized controlled trials were also eligible, and 5) at least 20 patients enrolled. Studies were excluded if they included less than 20 patients, if included patients treated after 1st line chemotherapy, and if they did not report outcome data for platinum-paclitaxel combinations.

For the comparison of CDDP/paclitaxel and CBDA/paclitaxel, only randomized controlled trials were included, with the above mentioned criteria 1–3 remaining unchanged.

When the same population was studied in more than one publication, only one with the most relevant data was included in this review. Two investigators (DL and FP) independently reviewed the “potentially eligible” studies and then cross-checked their results. Disagreements between them were resolved by consensus after discussion with a third expert (SB) for final decision.

Data extraction

The following data were extracted independently by two investigators from included studies: first author’s name, year of publication, study design, number of patients treated by platinum/ paclitaxel combinations, age (median) of patients, regimen type and dose, stage, rate of previous chemo-radiation, rate of objective response, PFS or TTP, OS and hazard ratio (HR) for the comparison of PFS/TTP and OS of CDDP/ paclitaxel-treated patients with that of patients receiving CBDA/ paclitaxel. When available, data on the first line chemotherapy only were abstracted, if more pretreated patients were included. We also extracted RR and OS according to previous (or not) treatment with CDDP with or without radiotherapy. The HRs of CBDA/ paclitaxel for PFS, TTP and OS in comparison with their counterparts treated with CDDP/ paclitaxel, and the results about potential predictive factors for CBDA and CDDP-based treatment were summarized descriptively due to insufficient data for a formal meta-analysis.

Statistical analysis

The objective RRs (for both CDDP and CBDA combinations) were meta-analyzed by using the Comprehensive Meta Analysis software v.2.2.64 July 27th 2012 with the random or fixed-effects model [9]. The statistical heterogeneity among studies was assessed by the Cochran’s Q-test and the I2 statistic. A p value <0.10 for the Q-test or an I2 >50% was suggestive of substantial between study heterogeneity and so a random effect model was chosen. The PFS/TTP and OS with both CDDP/paclitaxel and CBDA/paclitaxel combinations, the comparison of them in randomized trials and the results for RR according to
exposure to CDDP during the primary treatment were summarized descriptively due to the inappropriateness for meta-analysis. The weighted median PFS and OS were calculated. The median PFS and OS values of the two groups were compared through a T-test for two samples [10]. Main grades (G) 3–4 toxicities were recorded and compared between the 2 arms. Egger’s funnel plots were initially planned to be employed but eventually not used to assess the possibility of publication bias, due to either the limited number of studies included for meta-analysis or the significant heterogeneity among studies.

Results

Literature search and study characteristics

The flow of study selection is reported in Fig. 1. Initially, 860 references were identified (PubMed: n = 138, Web of Science: n = 262, Cochrane register of Controlled trials: n = 26, EMBASE: n = 434). After careful selection, a total of 17 eligible studies comprehensive of 1181 patients were included in the final analysis (7 for CBDCA/paclitaxel analysis, 9 for CDDP/paclitaxel analysis and 1 for both analyses) [4,5,8,11–19,22–25,27]. Table 1 summarizes the key characteristics of the included studies. Table 2 reported principal risk factors potentially impacting the effectiveness of chemotherapy in the studied populations: the two arms appear well balanced according to the analyzed factors.

For CBDCA/paclitaxel analysis (n = 473 patients) 2 studies were single arm phase II CBDCA/paclitaxel trials and one was a phase III trial comparing CBDCA/P with CDDP/P. In addition, there were five retrospective patient series. The sample sizes of included studies ranged from 21 to 154 patients. The median ages of patients in these studies were similar and ranged from 45 to 54 years. In all except 1 trial [16] where CBDCA-based triplet (CBDCA/P/ifosfamide) constituted the treatment arm, CBDCA-based doublets were the main treatments (all containing CBDCA + P). CBDCA/P combinations were given as first-line therapy to cervical cancer in all studies except in two [8,25] where treatment after the second recurrence was permitted. Also in the retrospective series of Torfs et al. the inclusion was independent of prior therapy lines [18]. The average rate of patients exposed to CDDP-based chemoradiation or chemotherapy for initial treatment at presentation was 61%.

For CDDP/paclitaxel analysis (n = 711 patients) 4 studies were the CDDP + P treatment arms of randomized trials (3 phase III and 1 phase II), 5 were single arm phase II trials and 1 was a prospective series. The sample sizes of included studies ranged from 34 to 130. The median ages of patients ranged from 47 to 56 years. In all except 5 trials, where CDDP-based triplets (CDDP/P/ifosfamide) represented the treatment arms, CDDP + P doublets were the schedules adopted. In all trials except the Kitagawa et al. phase III trial [8], CDDP/paclitaxel-based treatment was the first line therapy for advanced or recurrent disease after primary radiotherapy ± chemotherapy ± surgery. In these studies, the mean proportion of patients exposed to CDDP-based chemoradiation or chemotherapy for initial treatment at presentation was 31%.

Objective RR

Objective RRs were reported in all 18 studies, ranging from 33% to 67.9% for CBDCA/paclitaxel studies and from 29.1% to 67% for CDDP/paclitaxel studies. The combined objective RR estimated by the random-effects model was 48.5% (95% CI 37.9%–59.3%; P for heterogeneity = 0.0001; I² = 75%) for CBDCA and 49.3% (95% CI 41.1%–
Table 1

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<th>Author(s)</th>
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<th>N° pts</th>
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<th>RR %</th>
<th>PFS/TTP</th>
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<td>2nd CBDCA (AUC 5 q 21) + P (175 q 21)</td>
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N° = number; Pts = patients; CDDP = cisplatin; CBDCA = carboplatin; P = paclitaxel; AUC = area under the curve; Doc = docetaxel; IFO = ifosfamide; RR = response rate; TTP = time to progression; PFS = progression-free survival; OS = overall survival; recurr = recurrent; persist = persistent; M + =metastatic; dd = dose dense; w = weekly; NR = not reported; ° = first line only; # = CCDP + P arm; °° = dose escalation to 170 mg/m² in 6 patients; * = first line only; ** = first line only; °°° = 2 patients treated with a weekly regimen.

For CBDCA/paclitaxel combinations average weighted rates were 57.5%; P for heterogeneity = <0.0001; I² = 77.7% for CDDP-based chemotherapy (Figs. 2 and 3). After exclusion of studies that used a triple combination the results were slightly better for CBDCA-combinations (50.3% vs 43%) but this is probably related to the greater number of patients exposed to chemotherapy in CBDCA-doublets arms (median: 55% vs 24%).

### Progression free survival or TTP and OS

Among CBDCA-based trials PFS was reported in 7 trials ranging from 2.9 to 7 months; the median weighted PFS was 5 months. Overall survival was available in all except one trial ranging from 8.4 to 21 months; the median weighted OS was 10 months.

For CDDP-based trials PFS was reported in nine (TTP was the outcome measure in 3 trials) trials and the medians ranged from 4.8 to 8.3 months; the median weighted PFS was 6.9 months. Overall survival was available in all except one trial, with a range from 9 to 39 months; the median weighted OS was 12.87 months.

The difference between median PFS of CBDCA and CDDP-based treatments was significant (p = 0.03); on the contrary median OS differences were not significant according to T-test. These results are probably related to the inferior exposure to CDDP-based treatment in CDDP arms (median chemotherapy exposure: 24 vs 56.5% in CBDP and CBDCA arms respectively).

### Subgroup analysis according to previous CDDP exposure

The RRs for patients previously treated with CDDP-based chemoradiation were 42.3% and 43.9% in CBDCA (n = 5 trials with information available) and CDDP arms respectively (n = 4 trials with information available) (p = 0.54).

In the same way, the RRs for patients not previously treated with CDDP-based therapy were 68.3% and 59.1% for CBDCA-based chemotherapy (n = 4 trials with data available) and CDDP-based chemotherapy (n = 4 trials with data available) respectively (p = 0.73).

A systematic survival analysis according to CDDP exposure was not possible because only 1 trial reported analysis of OS according to it. In the Moore trial [27], CBDCA/P seems to fare better if there was no previous CDDP exposure (OS: 19 vs 10 months, p = 0.007), but this analysis included only 14 patients treated with CDDP/P among the overall population. In one retrospective study [24], TTP was better in patients not previously treated with CDDP (5.9 vs 2.9 months, p not reported).

### Comparison of CBDCA/paclitaxel with CDDP/paclitaxel combinations

Among the randomized controlled trials we identified, only Kitagawa et al. [8] directly compared CBDCA/P and CDDP/P. The objective RRs were similar (63% vs 60%, respectively) and no difference in OS (HR 0.99, 90% CI, 0.79–1.25) was observed. However, among women not previously treated with CDDP, CBDCA/P resulted in a worse OS compared to CDDP/P (13 versus 23 months, HR 1.57; 95% CI 1.06–2.32). Among women previously treated with CDDP (n = 127), CBDCA/P resulted non inferior to CDDP/P in terms of OS (19 versus 16 months, HR 0.69; 95% CI 0.47–1.02). The authors concluded that the 2 treatments were equally effective and that CBDCA/P presented a more favorable toxicity profile especially in terms of grade 4 neutropenia (45% vs 75%), febrile neutropenia (7.1% vs 16%), grades 2–4 renal toxicity (4.8% vs 9.6%), and grades 2–4 nausea vomiting (23% vs 36.8% for CBDCA and CDDP-based treatments respectively).

### Toxicity

Main hematological and non-hematological toxicities (G3–4 events) analyzed were anemia, neutropenia, febrile neutropenia, thrombocytopenia, fatigue, vomiting, neurotoxicity, diarrhea and stomatitis. For CDDP + paclitaxel combinations average weighted rates were...
as follow: anemia 39.5%, febrile neutropenia 7.6%, thrombocytopenia 21.6%, neutropenia 51.1%, fatigue 7%, vomiting 17.9%, neurotoxicity ranging from 20 to 30% and OS of 7 months [20], has been considered as the most effective single agent for cervical cancer treatment. Even in the absence of a direct comparison, other platinum analogs were considered less active than CDDP after the publication of a phase II GOG trial reporting 15% RR for CBDCA and 11% for ifosfamide [21]. The combination of CDDP-P became the preferred treatment for advanced cervical cancer after the publication of 2 phase II trials reporting RR in the range of 45–50% [22,23] and following a phase III trial demonstrating increased RR and PFS (but not OS) for the combination with respect to CDDP single agent [4]. More recently [5] CDDP-P has emerged as the winner arm of the GOG 204 trial comparing CDDP-P vs CDDP-based doublets with Topotecan, Gemcitabine and Vinorelbine in the treatment of advanced cervical cancer. Unfortunately, the toxicity of the combination is not scanty especially in terms of myelo- and neurotoxicity (grades 3–4 neutropenia 78.2%; febrile neutropenia 12.9%; grades 3–4 neurotoxicity 3%, grades 3–4 vomiting 19.8%) and, given the palliative intent of systemic chemotherapy in this setting, therapeutically equivalent options, with more favorable toxicity profile are a challenge. Carboplatin may represent an acceptable alternative to CDDP: it can be delivered in an outpatient setting and, in a different way to CDDP, the dose is calculated according to renal function, which may be impaired in cervical cancer patients. Moreover, the reduced nephro and neurotoxicity of CBDCA allow the administration of P in 3 h rather than in 24 h without massive hydration, and also the platelet-sparing activity of P can reduce the myelotoxicity of CBDCA, which is often increased in this population due to prior pelvic irradiation on bone

Factors predictive of survival of platinum-paclitaxel combinations

Some authors explored clinical variables independently associated with better OS. Mabuchi et al. [17] reported that site of recurrence (irradiated vs not irradiated field; p = 0.0098) and chemotherapy regimen (CBDCA/P; p = 0.0214) were independent prognostic factors for predicting response to chemotherapy.

Among the CDDP-paclitaxel trials Monk et al. [5] analyzed the variables associated with better OS and reported that platinum free interval >24 months, PS 0, recurrence outside the irradiated field and Hispanic origin were associated with better OS (HR 0.598 and 0.577). Mountzious et al. [14] showed that PS (0 vs 1), age at diagnosis as a continuous variable and treatment regimen (CDDP/P/ifosfamide) maintained predictive significance for PFS and OS.

Discussion

The experience with substituting CBDCA for CDDP is limited in advanced or recurrent uterine cervical cancer, and our systematic

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<th>p-Value</th>
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Fig. 2. Pooled analysis of response rate carboplatin + paclitaxel studies.
marrow reserve. Several retrospective and prospective phase II trials have addressed the effectiveness of CBDDA-P combination in advanced cervical cancer [24–28] reporting RRs between 40 and 78%, median PFS ranging between 3 and 6 months and median OS between 9.6 and 13 months. As far as toxicity the authors in general conclude that CBDDA-P is a well tolerated outpatient regimen with hematological toxicity (especially thrombocytopenia) being the most significant toxicity of the combination. The only trial directly comparing CBDDA-P vs CDDP-P in advanced and recurrent cervical cancer patients did not reveal any difference in terms of RR, PFS and OS between treatments, although CDDP seemed to be more active in patients not previously treated with chemotherapy [8] and the authors concluded that the 2 treatments were equally effective with CBDDA-P presenting a more favorable toxicity profile. Our analysis confirmed the equivalence of treatments in terms of objective RRs and OS with a slight 2-month PFS advantage for CDDP-P combination. We were unable to discover any difference in terms of RRs between treatments in patients previously treated or not with platinum; moreover a systematic survival analysis according to previous CDDP exposure was not possible because only 1 trial reported analysis of OS according to it. Otherwise, our study confirms that previous platinum-exposure, in combination or not to radiotherapy, significantly reduces responses to subsequent platinum based chemotherapy, regardless of CDDP or CBDDA. Several explanations have been suggested to clarify the differences in responses; previous radiotherapy and/or chemotherapy may select radio and chemo-resistant clones; the severe radio-induced blood vessel disruption may lead to lower perfusion of the relapsed cancer and, therefore, reduced concentration of cytotoxic agents within the tumor; hypoxia resulting from poor blood supply may lower the proliferating fraction of cancer and reduce the potential cytotoxic effects of chemotherapeutic agents.

Pertinent limitations of our study include the retrospective and not randomized nature of this pooled analysis, the absence of cost data, detailed toxicity data, and quality of life data and the potential imbalances in relevant clinical characteristics that may also affect clinical outcome of cervical cancer patients such as different previous platinum exposure and platinum-free interval. However, with a satisfactory number of trials included in the analysis, this is the first systematic review to establish substantial similarity in the outcome and activity with CDDP and CBDDCA doublets as first line chemotherapy in advanced cervical cancer.

Keeping in mind the palliative aim of chemotherapy treatment in recurrent cervical cancer, and considering the overall dismal prognosis of the patients, an effective and low-toxic regimen is needed. The results of our analysis seem to indicate that CBDDCA may represent an attractive and valid alternative to the more toxic and equally effective CDDP in the treatment of advanced or recurrent cervical cancer.

Conflict of interest statement
The authors declare no conflict of interest.

References

Study name | Statistics for each study | Event rate | 95% CI | p-Value |
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<td>0.670</td>
<td>0.522</td>
<td>0.791</td>
<td>2.234</td>
</tr>
</tbody>
</table>

Fig. 3. Pooled analysis of response rate cisplatin + paclitaxel studies.

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