First-Line Paclitaxel and Carboplatin in Persistent/Recurrent or Advanced Cervical Cancer

A Retrospective Analysis of Patients Treated at Brazilian National Cancer Institute

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Objective: Cervical cancer represents the third most commonly diagnosed cancer and the fourth cause of cancer death in women worldwide. In the palliative scenario, the combination of paclitaxel and cisplatin is widely used. Carboplatin is also an active agent in cervical cancer, and its association with paclitaxel could represent a well-tolerated, less toxic, and effective therapeutic option. The objective of this study was to evaluate response rate, progression-free survival, overall survival, and toxicity of carboplatin and paclitaxel in first palliative line for cervical cancer.

Methods: A retrospective search of database at Brazilian National Cancer Institute was performed, and all patients with persistent/recurrent and advanced cervical cancer treated with paclitaxel and carboplatin in first palliative line, between August 2008 and January 2010, were included.

Results: A total of 153 women were enrolled. Objective responses were documented in 34.6% (5.2% of complete responses and 29.4% of partial responses). With a median follow-up of 27.8 months, the median progression-free survival was 5.2 months, and the median overall survival was 10.63 months. The most common toxicity was myelosuppression: grades 3 and 4 anemia, neutropenia, and thrombocytopenia observed in 43.0%, 17.8%, and 9.2% of the cases, respectively. Neurotoxicity was presented by 30.7% of the patients. Renal toxicity was detected in 21.9% of the patients, but only 4.0% were grade 3, and none were grade 4.

Conclusions: This retrospective study has demonstrated that paclitaxel-carboplatin is an active and well-tolerated regimen for the treatment of advanced cervical cancer.

Key Words: Cervical cancer, Carboplatin, Paclitaxel, Palliative chemotherapy

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Cervical cancer represents the third most commonly diagnosed cancer and the fourth cause of cancer death in women worldwide.[1] In 2008, across the world, 530,000 new cases were diagnosed with 275,000 deaths, and this number is expected to increase to 410,000 by 2030.[2,3] Developing countries carry the biggest burden with approximately 76% of cervical cancer.[4]

In Brazil, it was estimated that there were 17,540 new cases of invasive cervical cancer for 2012, a rate of 17 cases per 100,000 Brazilian women.[5] Most patients present with locally advanced disease (ie, IIB, III, and IVA), and the majority of them relapse, especially in stages III and IVA where the 5-year overall survival (OS) varies from 40% to 15%, respectively.[6]

In this palliative scenario, cisplatin is widely studied and is the most active single agent, with response rates (RRs) of 18% to 50% with doses ranging from 50 to 100 mg/m^2 intravenously every 3 weeks,[7] compared with an RR of 28% in a phase II study using carboplatin[8] and around 11% to 22% with irinotecan, ifosfamide, paclitaxel, vinorelbine, topotecan, or bevacizumab used as monotherapy.[9–12]

The comparison between cisplatin as single agent with the combination of paclitaxel plus cisplatin (T + P) in patients with squamous cell cervical cancer in GOG (Gynecologic Oncology Group) 169 study has resulted in a higher RR (19% vs 36%, $P = 0.002$) and longer median progression-free survival (PFS) (2.8 vs 4.8 months, $P < 0.001$) with no significant difference in quality-of-life scores; however, median OS was similar in both arms.[13] The paclitaxel regimen was given over 24 hours, requiring either an infusion pump or inpatient hospital stay, in order to reduce neurologic toxicity.

The first phase III trial that demonstrated a survival advantage for combination chemotherapy over cisplatin alone in first palliative line has compared cisplatin to its combination with topotecan in GOG 179. Patients receiving cisplatin plus topotecan had statistically superior outcomes to those receiving cisplatin alone, with a median OS of 9.4 versus 6.5 months ($P = 0.017$), a median PFS of 4.6 versus 2.9 months ($P = 0.014$), and RR of 27% versus 13%, respectively. Indeed, a significant increase in the toxicity was presented (1% of grades 3 and 4 neutropenia with cisplatin monotherapy against 70% with combined therapy).[14]

An additional phase III trial, GOG 204, was performed to define the best cisplatin doublet among women with advanced or relapsed cervical cancer, including patients with squamous, adenocarcinoma, or adenosquamous cell carcinoma (SCC). Four doublets, the reference arm T + P and the 3 comparator arms cisplatin plus vinorelbine, cisplatin plus gemcitabine, and cisplatin plus topotecan, were evaluated; neither of the arms incorporated carboplatin. This study was discontinued in the planned interim analysis for futility. None of the tested regimens was superior; nevertheless, the trend in RR, PFS, and OS has favored T + P.[15]

Therefore, in advanced and persistent/recurrent cervical cancer not amenable to curative therapy, the combination of T + P is a worldwide current first choice for systemic treatment.

Although carboplatin is an active agent in cervical cancer,[16] and available results point equivalence between the T + P and paclitaxel plus carboplatin (T + C) schemes in ovarian cancer–GOG 158,[17] information is still limited in reference to cervical tumors. Moreover, the combination of T + C could represent a well-tolerated option for outpatients, with less neurotoxicity and nephrotoxicity.[18] Recently, the Japan Clinical Oncology Group has presented the results of the first randomized phase III trial, showing significant noninferiority between T + C and T + P in advanced, persistent, or recurrent cervical cancer in terms of OS, with less adverse events. This study showed PFS and OS of 18.3 and 6.9 months for T + P and 17.5 and 6.21 months for T + C, respectively.[19] At Brazilian National Cancer Institute (INCA), the combination of T + C has been routinely selected as first palliative line treatment to patients with cervical cancer since 2008 because of the convenient outpatient schedule compared with 24-hour infusion in the T + P combination and the more favorable toxicity profile versus the formerly used schema using cisplatin and topotecan. In this article, we provide a review of the institutional experience with T + C emphasizing RR, survival, and toxicity.

MATERIAL AND METHODS

Patient Selection and Data Collection

This study was approved by the Ethics in Human Research Committee of INCA, Rio de Janeiro, Brazil, and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

To evaluate RR, PFS, OS, and toxicity, an analysis of all cervical cancer patients treated with T + C in first palliative line at INCA, between August 2008 and January 2010, was performed. Patients were identified through internal database. Clinical data including demographics, stage, histology, previous therapies, and the toxicity related with T + C therapy were retrospectively collected by medical records review. The clinical stage at initial diagnosis was assigned based on the International Federation of Gynecology and Obstetrics. All patients treated with the T + C protocol had performance status 0–2 and hepatic, renal, and hematologic functions appropriated for the proposed treatment. Patients who were not initially diagnosed as at stage IVB received previously radiotherapy alone or chemoradiation (including patients who underwent primary surgery and received radiotherapy or chemoradiation as adjuvant or as treatment for pelvic recurrence). Response to treatment was assessed using clinical and, especially, radiological criteria as follows: complete response (CR), partial response (PR), progressive disease, and stable disease. The radiological evaluation was based on the Response Evaluation Criteria in Solid Tumors, version 1.0,[20] with a frequency determined by the assistant physician. The National Cancer Institute Common Toxicity Criteria, version 3.0,[21] was used for characterizing adverse events every cycle. Exclusion criteria included small cell carcinomas and any prior cytotoxic treatment, except when used in the radiosensitization setting.

Treatment

The chemotherapy regimen consisted of paclitaxel 175 mg/m^2 over 3 hours plus carboplatin at an area over the curve of 5 mg/mL per minute over 1 hour, both intravenously on day 1, every 3 weeks. Treatment doses were decreased in the beginning at physicians' discretion or on the scheduled day of retreatment, as well as delayed, according to the presented

TABLE 1. Patient characteristics

	n	%
Age, y		
Median	48.0	
Range	21–81	
Histology		
Squamous cell carcinoma	114	74.5
Adenocarcinoma	31	20.3
Others*	8	5.2
FIGO stage		
IA, IB1, and IIA	15	9.8
IB2, IIB, III, and IVA	106	69.3
IVB	32	20.9
Prior radiotherapy only†	20	13.1
Prior chemoradiation†	99	64.7
Site of recurrence/persistence‡		
Pelvic	52	34.0
Distant	37	24.2
Both	64	41.8
No. cycles		
Median	6	
Range	1–8	
Total		153

*Adenosquamous, undifferentiated carcinoma.

†Including patients who underwent primary surgery and received radiotherapy or chemoradiation as adjuvant or as treatment for pelvic recurrence.

‡Before the first palliative line.

FIGO, International Federation of Gynecology and Obstetrics.

toxicities. As it was a retrospective study, there was not a fixed pattern of dose level reduction. The regimen was to be administered until prohibitive toxicity, progression, or for a maximum of 8 cycles for responders. The carboplatin dose in milligrams was calculated using the Calvert formula[22] and the premedication for paclitaxel administration followed local standard. Glomerular filtration rate was estimated using the Cockcroft formula.[23] History, physical examination, and laboratory evaluations were obtained before each treatment cycle.

Statistical Analysis

Overall survival was estimated from the time of the first treatment day until death or, for living patients, the last available follow-up, and PFS was measured from the date of the first palliative chemotherapy infusion to either first progression or death or the date of last contact for patients who are alive and progression-free, in both cases using the Kaplan-Meier method. Associations among characteristics including prior radiotherapy, prior chemotherapy, site of disease recurrence, the platinum-free interval (PFI), and RR were compared using Pearson χ^2 test. $P<0.05$ was considered statistically significant. All analyses were performed with the SPSS software, version 18.0.

RESULTS

A total of 153 women with advanced or persistent/recurrent disease were enrolled in the study. Patient characteristics are listed in Table 1. The median age at the time of initial diagnosis was 48 years (range, 21–81 years), and the most frequent histology was SCC (74.5%), followed by adenocarcinoma (20.3%).

Thirty-two patients (20.9%) were diagnosed as stage IVB (advanced disease). Overall, 99 women (64.7%) received chemotherapy with cisplatin as a sensitizer plus radiation as former treatment for cervical cancer, as well as 20 patients (13.1%) received prior isolated radiotherapy, which means that 77.8% of the group was previously treated with radiation therapy. For these patients, radiotherapy was performed with curative intent. Following external beam radiotherapy, 105 patients (68.8%) received intracavitary brachytherapy.

There were 52 patients (34.0%) who had persistent or recurrent cervical cancer limited to the pelvis and 101 patients (66.0%) with distant disease (64 of 101 women with pelvic and distant disease and the remainder with only distant recurrence).

The median number of chemotherapy cycles delivered was 6 (range, 1–8). Reasons for not completing 6 cycles were disease progression in 81%, unacceptable toxicity in 5.2%, and other causes in 13.8%.

Objective RR was documented in 34.6% (95% confidence interval [CI], 27.1–42.1); 5.2% (95% CI, 1.7–8.7) achieved CR, and 29.4% (95% CI, 23.1–35.7) had PR (Table 2). Seven patients (95% CI, 1.3–7.9) did not perform radiological evaluation because of clinical progression or loss of follow-up. Comparing patients who had received prior chemoradiotherapy versus those who had not received it, objective responses were 24 (25.5%) of 94 patients and 29 (55.8%) of 52 patients, respectively ($P < 0.001$). Objective responses among patients with isolated pelvic recurrence or disease persistence after chemoradiotherapy or radiotherapy alone were 12 (24.0%) of 50 patients versus 41 (42.7%) of 96 patients with distant metastasis with or without pelvic disease ($P = 0.026$). Patients with a PFI of 12 months or greater experienced more responses (17/44 [38.6%]) than the patients who had received platinum-containing chemotherapy within 12 months before enrollment (7/49 [14.3%]), $P = 0.007$.

With a median follow-up of 27.8 months (95% CI, 25.1–30.4 months), the median PFS was 5.2 months (95% CI, 3.8–6.5 months), and the median OS was 10.63 months (95% CI, 8.6–12.6 months). A subgroup analysis in patients

TABLE 2. Objective response

	n	%	95% CI
Responders	53	34.6	27.1–42.1
CR	8	5.2	1.7–8.7
PR	45	29.4	23.1–35.7
Stable disease	22	14.4	8.9–19.9
Progressive disease	71	46.4	38.6–54.2
Radiological evaluation not available	7	4.6	1.3–7.9

TABLE 3. Prevalence and grade of adverse effects (%)*

	Grade				
Adverse Effect	**0**	**1**	**2**	**3**	**4**
Anemia	7.3	20.5	29.1	29.8	13.2
Neutropenia	61.6	7.9	12.6	13.2	4.6
Febrile neutropenia	95.2	NA	NA	3.4	1.4
Thrombocytopenia	53.0	31.1	6.6	6.6	2.6
Nausea	45.9	30.4	19.6	4.1	0.0
Vomiting	70.8	19.4	7.6	2.1	0.0
Constipation	75.0	13.6	11.4	0.0	0.0
Diarrhea	87.0	8.2	3.4	1.4	0.0
Mucositis	79.9	14.8	5.4	0.0	0.0
Muscle pain	72.8	18.4	8.2	0.7	0.0
Fatigue	60.6	21.8	16.9	0.7	0.0
Peripheral neuropathy	69.1	23.5	6.7	0.7	0.0
Joint pain	91.1	6.1	2.8	0.0	0.0
Renal	78.0	12.0	6.0	4.0	0.0
Hypersensitivity reaction	94.0	2.0	2.0	1.3	0.7

*Considering valid information.
NA, Not applicable.

who did not receive prior chemotherapy indicated that median PFS was 7.16 months (95% CI, 5.28–9.04 months) versus 3.83 months (95% CI, 2.91–4.75 months) for the subgroup previously treated with platinum-containing chemotherapy as radiosensitizer, $P = 0.018$, and OS of 12.56 months (95% CI, 6.45–18.67 months) versus 8.8 months (95% CI, 5.48–12.11 months), $P = 0.033$, respectively.

The toxicities are summarized in Table 3. Considering possible bias of retrospective assessment, taking into account that for laboratory data less than 2% of results were missing and a lack of less than 8% for the selected clinical adverse events, the most common toxicity was myelosuppression: grades 3 and 4 anemia was observed in 43.0% of the patients, and grades 3 and 4 neutropenia and thrombocytopenia were identified in 17.8% and 9.2% of the cases, respectively. Peripheral neuropathy was presented by 30.9% of the patients, 23.5% of them diagnosed with neurotoxicity grade 1. Renal dysfunction, based on laboratory test results indicating increased levels of creatinine in blood samples, was detected in 22.0% of the patients, but only 4.0% had renal toxicity grade 3, and none of them grade 4. It is important to consider that some patients could have developed ureteral obstruction during chemotherapy, resulting in renal dysfunction.

DISCUSSION

To date and to our knowledge, this study represents the first analysis of response, survival, and toxicity in a cohort of Brazilian cervical cancer patients treated with T + C in first palliative line. The retrospective nature of this study raises the possibility of bias once some clinical details were not identified on the medical chart reviews.

Patients with advanced or recurrent cervical cancer have poor prognosis (1-year OS around 20%),[13] and generally, those women are managed with palliative chemotherapy aiming symptoms control, quality of life, and, when feasible, prolongation of life. Cisplatin is the most active and widely used drug in the treatment of cervical carcinoma; until now, the patients have been treated with a platinum-based chemotherapy. Although increase in OS has not been shown, the GOG 169 trial acclaimed T + P as the reference regimen for the treatment of advanced cervical cancer, as combined therapy presents higher RR and longer PFS compared with monotherapy.[13] The new standard was confirmed in the GOG 204 trial that directly compared 4 platinum-based doublets. The trial was stopped early at a planned interim analysis for futility once no differences in terms of RR, OS, and PFS were reported regarding the 4 regimens, including cisplatin plus topotecan, which had demonstrated in GOG 179 trial a statistically significant improvement in OS over the single-agent cisplatin.[14]

An important goal in palliative care is to use the less toxic regimen that provides better efficacy. As the single-agent carboplatin has a more favorable nonhematologic toxicity profile compared with cisplatin, a regimen of carboplatin plus paclitaxel seems to be reasonable, especially in a population that have received pelvic radiotherapy as primary treatment limiting bone marrow function or for patients with renal dysfunction secondary to postrenal obstructions, commonly seen in cervical cancer, restraining or forbidding the use of known nephrotoxic drugs such as cisplatin. In addition, neither hospitalization nor outpatient pump for 24-hour infusion favors the combination of T + C. Therefore, T + C arrangement has been used as the standard treatment, but until recently, prospective data from phase III trials evaluating effectiveness and toxicity of this combination were not available.

The indirect comparison between the results of this retrospective study and the published data of the prospective GOG 169 and 204 trials,[13,15] considering the arm using T + P, showed only slight differences, probably related to the diversity in clinical data, the inclusion of patients with characteristics known to negatively affect prognosis in the setting of recurrent cervical cancer, for example, performance status 2 in GOG 169, histology, and the retrospective nature of the present study. All patients had SCC of the cervix in the GOG 169 trial, 81% of patients in the GOG 204, and 74.5% in this retrospective trial.

The results for RR, CR, and PR in our analysis were 34.6%, 5.2%, and 29.4%, quite similar to 36%, 15%, and 21% in the T + P arm in GOG 169 study and 30%, 3%, and 27% in the GOG 204, respectively.

In this study, similarly with preceding reports,[24] the majority of patients (77.8%) were previously treated with pelvic radiation, and more than half of patients (64.7%) also received concurrent cisplatin. In the current trial, primary treatment with chemotherapy and radiotherapy and having target lesions only inside of the prior irradiated field appeared to be negatively prognostic for objective RR. Patients formerly treated with concurrent cisplatin and radiotherapy had statistically significant lower RRs than cisplatin-naive patients (25.5% vs 55.8%) and shorter PFS (3.83 vs 7.16 months) and OS (8.8 vs 12.56 months).

The GOG 179 study also reported higher RRs in patients not previously treated with platinum therapy (20% vs 8% in the cisplatin arm and 39% vs 15% in the cisplatin-topotecan arm). Taken together, the results of GOG 179 study and the results presented here suggest that recurrent cervical cancer following concurrent chemoradiation is more likely to be platinum-resistant. Adequate drug distribution may be limited for recurrences in previously irradiated tissues because of secondary fibrosis and compromised blood supply related to microvascular disruption. Concomitant chemoradiation is the standard of care in early cervical cancer; therefore, this issue requires careful attention regarding emerging palliative treatments in this patient group.

In addition, in our data set, lower responses were significantly observed in patients with prior platinum administration within the past 12 months (14.3% vs 38.6%). In the GOG 204,[15] former chemoradiotherapy is associated with an increased risk of death, and PFI has been reported as a prognostic factor for second platinum therapy.[25]

The toxicities were predictable based on the regimen. Hematologic toxicities were higher in our revision compared with T + P arm in GOG 169 and 204, except for neutropenia—grades 3 and 4 anemia, neutropenia, and thrombocytopenia were 43.0%, 17.8%, and 9.2%, respectively, in our analysis, versus 27.9%, 66.6%, and 3.9% in GOG 169 and 16.8%, 78.2%, and 6.9% in GOG 204. In both analyses, the majority of patients have received prior radiotherapy, what could have limited the bone marrow function and contributed to the chemotoxicity. One possible explanation for the lower percentage of neutropenia in this retrospective trial can be the higher frequency of laboratory evaluation in prospective studies. All grades of peripheral neuropathy were less common in our analysis, accounting for 30.9%, most commonly mild in intensity, weakly different from GOG 169, which showed 35.7% of the patients with neurotoxicity.

The median PFS was 4.8 months and median OS was 9.7 months for the T + P arm in GOG 169 trial, 5.82 and 12.87 months in GOG 204, and 5.2 and 10.63 months for this retrospective cohort, respectively.[13,15] These results, not remarkably different, suggest that the use of T + C may provide equivalent outcomes to the demonstrated effects with T + P.

The first direct comparison with standardized doses and assessment of response to delineate the role of T + C combination was presented only few months ago at the 2012 American Society of Clinical Oncology Annual Meeting. The randomized study of T + C versus T + P in advanced, persistent, or recurrent cervical cancer showed significant noninferiority of T + C in terms of OS. Interestingly, the phase III trial of T + C versus T + P has evidenced better results ever described regarding PFS and OS—18.3 and 6.9 months for T + P and 17.5 and 6.21 months for T + C, respectively—and probably these differences can be explained by patient selection.[19] Apparently less toxic and feasible, T + C can be recommended, from now on, as the new reference therapy.

Although retrospective, as expected, this study has demonstrated that T + C is a promisingly active, reasonably tolerated, and feasible regimen in the outpatient setting, for first palliative line treatment of advanced cervical cancer, even in patients previously treated with chemoradiation.

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