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Carboplatin and low-dose paclitaxel. An effective regimen in older and comorbid patients with advanced cervical cancer. A phase II study.

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Summary

Objective: To investigate the efficacy and safety of low-dose weekly paclitaxel and carboplatin in elderly and/or any age comorbid patients with FIGO Stage IVB, recurrent or persistent cervical cancer. *Materials and Methods:* Thirty patients were accrued. Eligibility criteria included older than 65 years, or any age with uncontrolled diabetes and/or blood hypertension and other comorbid conditions. Treatment consisted of six 28-day cycles of carboplatin at AUC of 5 at day 1, and low-dose paclitaxel at 50 mg/m^2 at days 1, 8, and 15 infused in two hours. Metabolic response was evaluated by [18F]-FDG uptake (PET-CT) and toxicity with the NCI CTC v2. *Results:* From January 2012 to January 2015 a total of 30 patients were included in the study. The median number of chemotherapy cycles administered was five (1-6). Three (10%) had complete response and nine (30%) partial response for an overall response rate of 48%. One patient (4%) had stable disease and 17 (56%) showed progressive disease. At a median follow-up time of 12.5 (1-37) months, the median progression-free survival (PFS) and overall survival (OS) were 7.7 and 14.3 months, respectively. Grade 4 toxicities were anemia in three patients (10%), grade 3 neutropenia and vomiting occurred in one (3%), and one (3%) respectively. All other toxicities were grades 1 and 2. A substantial proportion of patients had grade zero toxicity**.** *Conclusion:* This study shows that this 28-day regimen of low-dose carboplatin and paclitaxel is effective and safe in an elderly and/or comorbid population of advanced cervical cancer.

Key words: Advanced cervical cancer; First-line chemotherapy; Low-dose paclitaxel; Carboplatin; Aged; Comorbid.

Introduction

Advanced cervical cancer remains a deadly disease that comprises women presenting with FIGO Stage IVB at diagnosis and approximately 30% of early and locally advanced disease who progress or relapse after curative surgery or chemoradiation [1]. Even with modern chemotherapy, incorporating bevacizumab, the median survival remains below 18 months [2]. A frequently underestimated issue is the fact that as the lifespan increases worldwide, the number of elderly patients with cancer is on the rise [3]. Elderly cervical cancer patients may show shorter survivals as compared with younger patients, which could be accounted by different biological behavior of tumors, higher stages at presentation, and reluctance to undergo aggressive treatment, mostly because of associated morbidity such as uncontrolled diabetes mellitus and blood hypertension [4-8]. Older age is by itself associated with decreased glomerular filtration rate [9] and for both, diabetes and blood hypertension end-stage renal failure is not uncommon after several years of uncontrolled disease. Despite creatinine levels remain within the normal, subclinical and progressive dysfunction of the kidneys are a well-described process [10, 11]; hence, the delivery of standard doses of common cytotoxic drugs could be compromised. Thus, it has been stated that many oncologists empirically dose-reduce older patients, often without much data to guide them [12], and dose reduction may also be needed for patients with comorbidities [13]. Several commonly used cytotoxic chemotherapy regimens have been evaluated for older patients and those with impaired organ function. Yet there is variability in regards to which traditional anticancer chemotherapy agents requires dose reductions in these populations [13].

The regimen of carboplatin paclitaxel has been widely studied in gynecological cancers. In ovarian cancer, the recommended schedule comprises 175mg/m^2 of paclitaxel in a three-hour intravenous infusion plus carboplatin at an area under the curve (AUC) of 6 mg/ml/min both at day 1, repeated every three weeks for six cycles [14]. For advanced cervical cancer, the standard regimen is similar (JCOG-0505 study), but carboplatin is dosed at AUC of 5, this regimen showed non-inferiority over the standard

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cisplatin-paclitaxel, but induces grade 3-4 neutropenia in 76.2% of patients and grade 2 renal toxicity in 4.8% [15]. In routine practice it is common to see elderly and/or comorbid advanced cervical patients in whom the standard carboplatin paclitaxel could be expected to cause increased toxicity, however, there is no information in literature on how to dose these patients.

Here the authors report the results of a phase II study using a schedule of carboplatin at AUC 5 at day 1, and weekly paclitaxel at 50 mg/m^2 days 1, 8, 15 every 28 days for elderly and/or comorbid patients.

Materials and Methods

Eligible patients had a histological diagnosis of invasive cervical carcinoma with recurrent or persistent disease to primary treatment, or untreated Stage IVB. All patients were required to have measurable disease defined as lesions which could be measured in at least two dimensions by physical examination or by means of medical imaging techniques, and no previous systemic chemotherapy other than that used as a radiosensitizer. In addition, patients had to be older than 65 years or any age, but having uncontrolled diabetes mellitus and/or blood hypertension as defined by fasting glucose >130 mg/dL and blood pressure >140/90 despite treatment [16, 17], and/or other morbidities. These morbidity criteria were subjectively considered by investigators to decide not to offer the standard carboplatin paclitaxel regimen [15]; including but not limited to: obstructive uropathy with or without abnormal creatinine and recto or vesicovaginal fistulae. Patients also had a status performance 0-3 and bone marrow, hepatic, and renal function as follows: leucocyte, platelets, and hemoglobin counts equal or above 2,000 mm^3, 100,000 mm^3, and 8 gr/dL respectively; total bilirubin, aspartate aminotransferase, and alanine aminotransferase < 2.5 (the upper normal limit) and creatinine levels up to 3 mg/dL or calculated (Cockcroft-Gault) creatinine clearance equal or higher than 30 mL/min. Patients were excluded from study participation if they had an active infection (except HIV infection), were pregnant, had a second neoplasia diagnosed in the previous five-years or suffered from a myocardial infarction in the previous six months.

Treatment consisted of six 28-day cycles of carboplatin at AUC of 5 administered at day 1, and paclitaxel at 50 mg/m^2 at days 1, 8, and 15 infused in two hours. Premedication for paclitaxel included dexamethasone 8 mg, ondansetron 8 mg, ranitidine 50 mg, and chlorpheniramine 10 mg, all four intravenously. Doses were not reduced but treatment was held when neutrophils and platelets were less than 1,500 mm^3 and 100,000 mm^3 respectively. Treatment was discontinued in cases of a progressive disease, unacceptable toxicity, or patient's refusal or non-adherence with the treatment plan.

All patients underwent a clinical and laboratory examination, as well as PET-CT before treatment protocol to evaluate metabolic response. Complete metabolic response (CMR) was defined as complete resolution of [18F]-FDG uptake within the tumor volume so that it was indistinguishable from surrounding normal tissue; partial metabolic response (PMR) as a reduction of a minimum of 15 ± 25% in tumor [18F]-FDG SUV after one cycle or more than 25% after more than one cycle; metabolic stable disease (MSD) as an increase in tumor [18F]-SUV of less than 25% or a decrease of less than 15%, and no visible increase in extent of [18F]-FDG uptake (20% in the longest dimension), and progressive metabolic disease (PMD) as increase in tumor [18F]-SUV greater than 25% within the tumor region defined on the baseline scan and visible increase in the extent of tumor [18F]-tumor uptake (20% in the longest dimension) or the appearance of new [18F]-SUV uptake in metastatic lesions [18]. PET-CT were taken at cycles 3 and 6. Efficacy and toxicity were evaluated in all patients who received at least one application of treatment. Toxicity was evaluated with the NCI CTC version 2 criteria.

This is a single-center, Simon's two-stage optimal design study [19] under the null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, ten patients will be accrued. If there is one or no responses in these ten patients, the study was to be interrupted. Otherwise, 19 additional patients will be accrued for a total of 30. The null hypothesis was be rejected if six or more responses were observed in the total sample. This design yields a type I error rate of 0.05 and 80% power when the true response rate is 30%. The primary objectives were to determine the overall response rate, progression-free survival (PFS), overall survival (OS), and toxicity. Responses were analyzed with descriptive statistics and survival curves constructed with the Kaplan and Meier method. PFS and OS were assessed from the date of signed consent to the first documentation of progression or death for PFS and to death for OS. This protocol was approved by the institutional review board of the Instituto Nacional de Cancerología México, and written informed consent was obtained from all patients prior to enrollment.

Table 1. — *Main patient demographics and tumor characteristics*

Variable	Number (30)	%
Age (years)	Median:54 (26-91)	100%
Older (>65)	1	3.0
Older plus morbidity	6	20.0
Morbidity (<65)	23	76.6
EGOG		
1	12	40.0
2	15	50.0
3	3	10.0
Plasma Creatinine		
Normal	21	70.0
Elevated	9	30.0
Stage (FIGO)		
IVB	5	16.6
Recurrent	9	30.0
Progressive	16	53.3
Previous Treatment		
None	5	16.6
Chemoradiation	25	83.3
Histology		
Squamous	23	76.6
Adenocarcinoma	5	16.6
Adenosquamous	2	6.6

Table 2. — *Comorbidities by patient.*

Patient	Comorbidities	Age	ECOG	Serum Cr/Cr Clear.
1	Diabetes, rectovaginal fistula, colostomy	59	2	0.61/80
2	Cachexia, deep venous thrombosis, bilateral hydronephrosis	36	3	0.66/100
3	Rectovaginal fistula, colostomy, right hydronephrosis, left renal hypotrophy	53	2	1.59/30
4	Aged, obesity, hypertension	73	1	0.80/60
5	Cachexia	47	2	0.63/80
6	Bilateral obstructive uropathy, hypertension	46	2	0.67/70
7	Aged, diabetes, hypertension	67	1	0.59/84
8	Bilateral obstructive uropathy, unilateral hydronephrosis	58	3	0.85/70
9	Bilateral obstructive uropathy, right hydronephrosis, left renal hypotrophy	47	2	1.36/44
10	Bilateral obstructive uropathy, bilateral hydronephrosis	33	1	1.28/33
11	Bilateral obstructive uropathy, bilateral hydronephrosis	37	2	1.39/38
12	Aged, hypertension	91	1	0.80/35
13	Bilateral obstructive uropathy	48	1	0.94/62
14	Radiation proctitis	59	1	0.87/45
15	Aged, hypertension, bilateral obstructive uropathy	68	2	1.2/36
16	Pulmonary fibrosis, hypertension, unilateral obstructive uropathy	63	3	1.52/30
17	Deep venous thrombosis, radiation proctitis, bilateral hydronephrosis	34	2	0.80/90
18	Bilateral hydronephrosis	44	2	1.3/40
19	Aged, hypertension, radiation proctitis	69	2	0.88/52
20	HIV infection	60	1	0.53/90
21	Hypertension, brain aneurysm	55	1	0.88/55
22	Recto and vesico-vaginal fistula, radiation proctitis	26	1	0.44/90
23	Aged	78	1	0.64/48
24	Bilateral obstructive uropathy	50	1	1.0/56
25	Bilateral obstructive uropathy, hypertension	46	2	0.67/70
26*	Bilateral obstructive uropathy	29	2	1.56/49
27*	Diabetes, hypertension, bilateral obstructive uropathy	49	2	2.5/30
28*	Left obstructive uropathy	46	1	0.69/80
29*	Aged, diabetes, hypertension	80	2	1.0/40
30*	Diabetes, hypertension, unilateral obstructive uropathy	62	2	1.69/40

**These patients abandoned treatment before the third cycle of therapy and were registered as progressive disease. Serum creatinine (mg/mL). Creatinine clearance (mL/min).*

Results

From January 2012 to January 2015 a total of 30 patients were included in the study. The overall clinical characteristics of patients are shown in Table 1. Most patients had squamous histology (76%) and presented with a recurrent or persistent disease to primary radiation or chemoradiation (83.3%). The mean age was 54 years (26-91). Table 2 lists morbidities of the study population. The most frequent morbidity was uni- or bilateral obstructive uropathy with or without hydronephrosis or renal dysfunction (60%). Ten (33%) had creatinine elevation (> 1.2 mg/ml) and seven (23.3%) had a calculated creatinine depuration below 60 mL/min with normal serum creatinine. The mean and median creatinine clearance for the 30 patients were 57.53 and 53.5 mL/minute (30-100) respectively. Uncontrolled blood hypertension with or without uncontrolled diabetes was registered in 13 patients (43.3%): eight with blood hypertension only, four with both, and one patient diabetes alone. Three (10%) of patients had fistulae; a single patient had age as the sole inclusion criteria; another was included because of cachexia and another one for HIV infection.

All patients were evaluated for toxicity. A total of 137 cycles were delivered (median 5, range 1-6). Treatment was well-tolerated and no dose reductions were registered. As shown in Table 3, the only grade 4 toxicity observed was anemia in three patients (10%) whereas grade 3 toxicities were observed in four patients: two (6%) anemia, one (3%) neutropenia, and one (3%) vomiting. All other toxicities were grades 1 and 2. A substantial proportion of patients had grade zero toxicity. No toxic deaths were registered.

Efficacy was evaluated in the intention-to-treat. Five abandoned treatment before the third cycle of chemotherapy and were registered as progressive disease. Three (10%) had complete response and nine (30%) partial response for an overall response rate of 40%. One patient (3%) had stable disease and 17 (56%) showed progressive disease. At a median follow-up time of 12.5 (1-37) months, the PFS was 7.7 months and the median OS was 14.3 months (Figure 1) for the whole population (30 patients).

Table 3. — *Toxicity per patient.*

Toxicity	G 0 (%)	G1(%)	G2(%)	G3(%)	G4(%)
Anemia	3 (10)	8 (27)	14 (47)	2 (7)	3 (10)
Neutropenia	17 (57)	3 (10)	9 (30)	1 (3)	0
Nausea	10 (33)	14 (47)	6 (20)	0	0
Vomiting	23 (77)	2 (7)	4 (13)	1 (3)	0
Diarrhea	22 (73)	6 (20)	2 (7)	0	0
Neuropathy	13 (43)	11 (37)	6 (20)	0	0
Renal	29 (97)	0	1 (3)	0	0

Decimals are rounded.

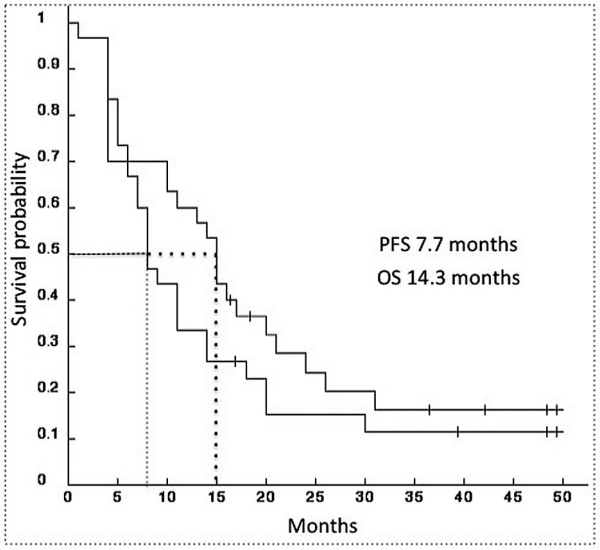

Figure 1. — PFS and OS. In the intention-to-treat analysis, at a median follow-up time of 12.5 (1-37) months, median PFS and OS were 7.7 and 14.3 months, respectively.

Discussion

The results of this phase II study demonstrate that the use of a lower-dose regimen of carboplatin at AUC of 5 day 1 with paclitaxel at 50mg/m^2 days 1, 8, and 15 in cycles of 28-day is well-tolerated with minimal grade 4 and 3 toxicity and yields an overall response rate and median survival of 40% and 14.3 months, respectively. These results approach to those seen in the cisplatin-paclitaxel arm of GOG-204 (29.1% and 12.9 months) and GOG-240 studies (45% and 12.8 months, respectively [2, 20]. Taken into account the population here treated (older/or any age with comorbidities), these results seem encouraging.

It has been reported that only 36% of patients enrolled in cancer clinical trials are older that 65 years [21]. On the other hand, it is commonly observed that clinical trials most often are limited to patients with good performance status. For instances, the GOG-204 and GOG-240 limited inclusion to GOG performance status of 0-1 [2, 20] whereas in the JCOG-0505 study, less than 2% had an ECOG of 2 [15]. These data clearly indicate the fact that there is high need for research in aged/comorbid cervical cancer patients as dose and regimens encountered safe or tolerable in "usual" clinical trials may not apply for them. In this sense, the population here treated is unique as more that 50% were ECOG 2 and 3 and one-third had abnormal creatinine levels. On these basis the present findings that a low-dose weekly paclitaxel with carboplatin at AUC of 5 is not only very well tolerated but effective, seems remarkable.

Despite a number of clinical trials have been performed in advanced cervical cancer testing the combination of carboplatin paclitaxel at different dose and schedules, none of them has used the regimen administered in this study. The most similar are the studies using cycles of 28 days. Secord *et al.* reported a study [22] where both drugs were administered weekly (carboplatin AUC 2 and paclitaxel 80mg/m^2) in 28-day cycles. The response rate among 15 cervical cancer patients was 20%, but grade 3 or 4 hematological toxicity was frequent; 7 % grade 3 anemia, 21% grade 3 or 4 neutropenia, and 7% grade 3 or 4 thrombocytopenia. Mabuchi *et al.* retrospectively reviewed a series of seven patients treated with carboplatin AUC 5 and paclitaxel 175mg/m^2, every 28-days and reported grade 3/4 hematological toxicities in three out of seven patients (42.8%) and an uncommonly high response rate of 71% [23]. A third study reported 25 patients receiving carboplatin AUC 5-6 and paclitaxel 155-175 mg/m^2, repeated every 28 days [24]. Authors reported an overall response rate (ORR) of 40% (20% CR and 20% PR) and an median survival of 21 months; nevertheless, this regimen induced 32% of grade 3/4 anemia and 32% of grade 3/4 neutropenia. Despite these results cannot be compared with the present due to the different populations studies, it seems that ORR are somehow similar (20%, 71% and 40%) [22-24] in comparison to 40% in the present study. Nevertheless, the toxicity observed in this study despite the authors treated an elderly/comorbid population, is clearly lower as compared to any of these 28-day regimens, as they only observed grade 4 anemia in 10%, grade 3 anemia, and neutropenia in 6% and 3%, respectively. These can be explained by the lower dose-intensity of the present regimen.

The present study has the limitation of high variability in comorbid conditions of studied patients and that the nature of the one-arm design. In addition, this study is limited by the lack of use of a comprehensive geriatric assessment (CGA) tool, which is an urgent issue to address, as an ageing population, and the rising incidence of gynecological cancer indicate that oncologists will be treating a population with a substantial number of older, potentially frailer patients [25]. Despite these caveats, the present results are clearly encouraging taking into account the median survival of 14.3 months achieved in this population with significant comorbidities. However, the lack of similar studies performed in such populations impedes the authors to comment on the clinical relevance of their findings. Nevertheless, they can infer that if otherwise untreated, the

survival of these patients could have been shorter if untreated. In fact, the recently published guidelines of resource-stratified global recommendations on the management and palliative care of women diagnosed with invasive cervical cancer [26], regardless of the setting, recommends palliative care in patients unfit for receiving chemotherapy. Thus, a non-toxic and well-tolerated regimen as the reported here could be an option for unfit patients. Nevertheless, this cannot be taken as a recommendation but to encourage further clinical testing of this regimen in the setting of older and/or comorbid advanced cervical cancer patients.

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