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Platinum rechallenge in second-line treatment for endometrial carcinoma

R. Pereira Souza[1*], G. Pinheiro Soares[3*], L. Valente Lage[3], G. Baiocchi[2], A.A.B.A. da Costa[1], M. del Pilar Eestevez Diz[3]

[1]Medical Oncology Department, [2]Gynecologic Oncology Department, A.C. Camargo Cancer Center, São Paulo
[3]Medical Oncology Department - Instituto do Câncer do Estado de São Paulo, São Paulo (Brazil)

Summary

Objectives: Metastatic endometrial carcinoma (EC) has a poor prognosis. Systemic treatment (hormone therapy or chemotherapy) has been used in first line, however, the best therapy as second-line therapy is not known. The aim of this study is to evaluate the role of platinum-based chemotherapy rechallenge in second-line treatment for EC. *Materials and Methods:* Retrospective review of patients with recurrent EC who were treated with second-line systemic therapy from April 2007 to April 2015 at two cancer centers. Clinical data included: age, histology, tumor grade, tumor stage at diagnosis, site of disease progression, ECOG performance status, adjuvant chemotherapy, first- and second-line chemotherapy for recurrent disease and comorbidities. *Results:* A total of 84 patients were evaluated. Median age was 66.2 years; most patients had endometrioid histology (67.9%) and grade 2 tumors (45.8%). Twenty-nine patients (34.5%) were treated with platinum rechallenge at second line. Median overall survival (OS) was 9.7 months (7.1-12.3 months; 95% CI). Longer OS was observed in platinum rechallenge group compared to non-re-exposed (13.8 months *vs.* 7.9 months, $p = 0.005$). Only platinum rechallenge was significantly associated to a better OS on multivariate analysis (HR 0.43 [95%CI 0.21-0.87, $p = 0.019$]). Platinum rechallenge was also associated with a higher progression-free survival (PFS) (4.9 months *vs.* 3.4 months, $p = 0.008$). *Conclusions:* The present findings suggest a longer OS and PFS for patients treated with platinum rechallenge at second-line treatment for EC and add more evidence for adoption of this strategy in a scenario where there is little evidence of effective treatments.

Key words: Endometrial carcinoma; Second-line therapy.

Introduction

Endometrial cancer (EC) is the most common gynecologic malignant tumor in developed countries [1] and is one of the most frequent in less developed ones, wherein cervical cancer is the first in incidence [2]. The majority of women with EC are diagnosed in early stage disease [3] and therefore they have favorable prognosis (five-year survival of approximately 95%). However, 8% of patients with EC have metastatic disease at the moment of diagnosis and others present recurrence after curative-intent treatment [4]

Metastatic disease has a poor prognosis and, most of times, represents an incurable condition. Survival is generally inferior to 12 months [5-7] and less than 20% is alive beyond five years [4]. Systemic treatment which includes hormone therapy or chemotherapy has been used in first-line [8], although no randomized trial compared these strategies with best supportive care.

Among active cytotoxic drugs against EC, carboplatin-paclitaxel (TC) combination has become the standard of care regime in first line setting [8]. According to preliminary data of a non-inferiority study (GOG 209), TC (carboplatin AUC 6, paclitaxel 175mg/m^2 every three weeks for seven cycles) revealed to be non-inferior in comparison to TAP (paclitaxel 160 mg/m^2 D2, doxorubicin 45 mg/m^2 D1, and cisplatin 50 mg/m^2 D1 every three weeks for seven cycles), considered as standard chemotherapy [9]. The difference in overall survival (OS) was not statistically significant (TC 36.5 *vs.* TAP 40.3 months) and both arms had similar response rate (51%) and progression-free (PFS) (14 months). In terms of toxicity, however, TC demonstrated to be better tolerated [8].

In contrast to high quality evidence-based data for first-line treatment, there are no randomized clinical trials (except for one) evaluating chemotherapy in further lines, but only few phase II single-arm and retrospective studies [10]. The exception is a phase III trial comparing ixabepilone to paclitaxel or doxorubicin as second-line therapy. The trial was prematurely closed after interim analysis demonstrated worse survival outcome in experimental arm (ixabepilone arm 10.9 months *vs*. control arm 12.3 months) [11]. Thus, the best therapy as second line has not been established yet and current decision-making in daily clinical practice is generally based on choosing a drug with activity against EC in first line setting (e.g. doxorubicin) to which patient has not been previously exposed. However, most data in this setting show no clear clinical benefit and disappointing response rates (<15%) with single agents. In the other hand,

*Contributed equally.

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Table 1. — *Clinical characteristics for all patients and according to second-line treatment.*

Characteristics	All patients Freq. (%)	Platinum rechallenge Freq. (%)	Other regimes Freq. (%)	*p*-value*
Total patients	84 (100)	29 (100)	55 (100)	
Age (years)				
< 65	38 (45.2)	14 (48.3)	24 (43.6)	0.685
≥ 65	46 (54.8)	15 (51.7)	31 (56.4)	
Histology				
Non-endometrioid	26(32.1)	8 (27.6)	18 (34.6)	0.516
Endometrioid	55(67.9)	21 (72.4)	34 (65.4)	
Grade				
1	23 (31.9)	9 (34.6)	14 (30.4)	0.577
2	33 (45.8)	13 (50.0)	20 (43.5)	
3	16 (22.2)	4 (15.4)	12 (26.1)	
Initial FIGO Stage				
I-III	50 (61.7)	14 (50.0)	36 (67.9)	0.100
IV	31 (38.3)	14 (50.0)	17 (32.1)	
Pelvic recurrence/progression				
No	62 (73.8)	20 (76.9)	42 (89.4)	0.155
Yes	11 (13.1)	6 (23.1)	5 (10.6)	
ECOG Performance				
0-1	36 (49.3)	12 (48.0)	24 (50.0)	0.871
≥ 2	37 (50.7)	13 (52.0)	24 (50.0)	
Obesity				
No	78 (92.9)	28 (96.6)	50 (90.9)	0.340
Yes	6 (7.1)	1 (7.1)	5 (9.1)	
Diabetes Mellitus				
No	64 (76.2)	23 (79.3)	41 (74.5)	0.626
Yes	20 (23.8)	6 (20.7)	14 (25.5)	
Hypertension				
No	35 (41.7)	14 (48.3)	21 (38.2)	0.372
Yes	49 (58.3)	15 (51.7)	34 (61.8)	
Dyslipidemia				
No	78 (92.9)	26 (89.7)	52 (94.5)	0.408
Yes	6 (7.1)	3 (10.3)	3 (5.5)	
Previous neoplasm				
No	77 (91.7)	25 (86.2)	52 (94.5)	0.189
Yes	7 (8.3)	4 (13.8)	3 (5.5)	
Treatment free interval (months)				
< 6	40 (48.2)	4 (13.8)	36 (66.7)	< 0.001
≥ 6	43 (51.8)	25 (86.2)	18 (33.3)	
Treatment free interval (months)				
< 12	60 (72.3)	15 (51.7)	45 (83.3)	0.002
> 12	23 (27.7)	14 (48.3)	9 (16.7)	

**Calculated with Qui-square test or Fisher's exact test when necessary.*

a retrospective study suggests that platinum-based combination may improve survival and this improvement is directly related to the interval between the first and second platinum exposure [12]. Due to limited data regarding this issue, the aim of this study is to evaluate the role of platinum-based chemotherapy rechallenge in second-line treatment for EC.

Materials and Methods

The authors performed a retrospective review of the medical records of patients with recurrent EC who were treated with second-line systemic therapy for recurrent disease from April 2007 to April 2015 at two cancer centers in São Paulo – Brazil: A.C.Camargo Cancer Center and Instituto do Câncer do Estado de São Paulo (ICESP). The inclusion criteria were: patients older than 18 years with histologically-confirmed endometrial carcinoma and who received at least one dose of systemic treatment as second-line therapy. The authors excluded patients with history of others malignant tumors, or who underwent neoadjuvant chemotherapy or endocrine therapy in first-line, or whose medical records were considered incompleted. For patients who received adjuvant chemotherapy for locally advanced disease, treatment at first recurrence was considered first-line treatment for recurrent disease and treatment received after progression to first-line treatment was considered second-line treatment.

Clinical data collected included: age at beginning of second-line treatment, histology, tumor grade, tumor stage at diagnosis,

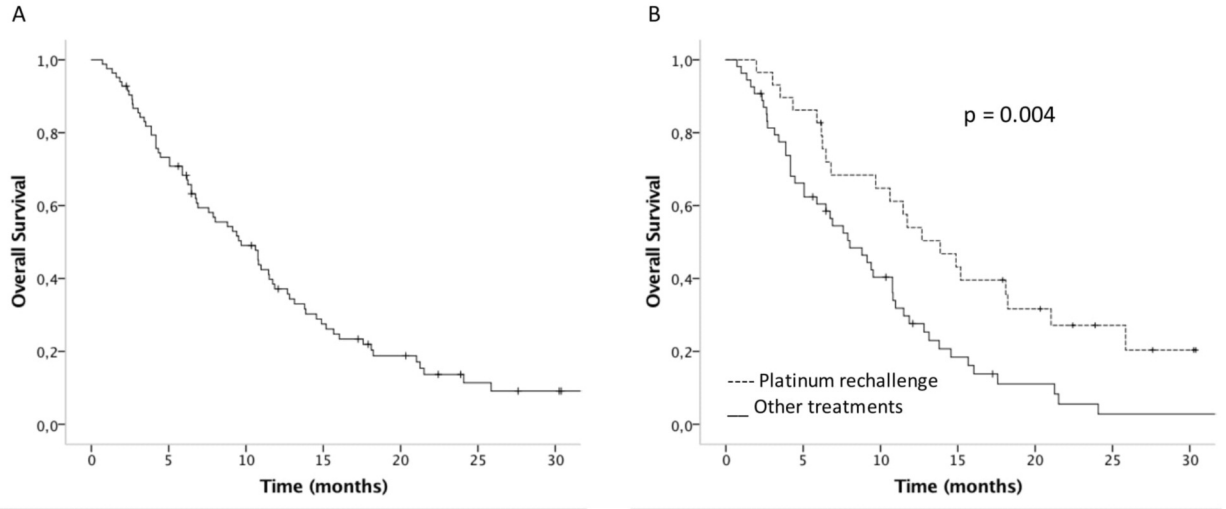

Figure 1. — A) Overall survival for the role cohort of second-line treated endometrial cancer patients. B) Overall survival according to platinum rechallenge. *p*-value calculated with the Log-Rank Test.

Table 2. — *Univariate cox regression for overall survival.*

Variable	HR (95%CI)	*p*-value
Age (years)		
< 65	1	0.489
≥ 65	1.19 (0.73 - 1.93)	
Histology		
Non-endometrioid	1	0.491
Endometrioid	0.83 (0.50 – 1.40)	
Grade		
1	1	0.577
2-3	1.70 (0.94 – 3.07)	
Initial FIGO Stage		
I-III	1	0.260
IV	0.95 (0.58 – 1.57)	
Pelvic recurrence/progression		
No	1	0.098
Yes	1.66 (0.91 – 3.02)	
ECOG performance		
0-1	1	0.136
≥ 2	1.49 (0.88 – 2.50)	
Adjuvant chemotherapy		
No	1	0.260
Yes	1.46 (0.76 – 2.83)	
Treatment free interval (months)		
< 6	1	0.005
≥ 6	0.49 (0.30 – 0.81)	
Platinum rechallenge		
No	1	0.005
Yes	0.47 (0.28-0.80)	

Table 3. — *Multivariate cox regression analysis for overall survival*.

Variable	HR (95%CI)	*p*-value
Platinum rechallenge		
No	1	0.019
Yes	0.43 (0.21 - 0.87)	
ECOG Performance		
0-1	1	0.271
2-3	1.39 (0.77 – 2.49)	
Pelvic recurrence		
No	1	0.001
Yes	3.54 (1.67 – 7.50)	
Treatment free interval (months)		
< 6	1	0.142
≥ 6	0.62 (0.32 – 1.18)	
Grade		
1	1	0.102
2-3	1.96 (0.89 – 3.43)	

**51 events for 61 patients included in the final model.*

site of disease progression before second-line therapy, ECOG performance status at beginning of second-line treatment, previous neoplasm, adjuvant chemotherapy, first line chemotherapy for recurrent disease, second-line chemotherapy for recurrent disease, and the presence of the following comorbidities: obesity, diabetes, hypertension, and dyslipidemia. Dates for diagnosis, recurrent disease, begining and ending of systemic treatment at adjuvant, firs-line and second-line setting, and last follow-up were recorded. Response to second-line chemotherapy was considered as recorded by the medical evaluation on medical charts. Response was categorized as a ‘‘response’’ in the case of a complete response or partial response and ‘‘no response’’ if there was stable disease or disease progression. PFS was defined as the interval between the dates of beginning of second line therapy and disease progression or death by any cause. Overall survival (OS) was defined as the interval between the dates of beginning of second-line therapy and death by any cause. Treatment-free interval (TFI) was considered the interval between the date of the last chemotherapy infusion in the first line treatment and the date of disease progression before the second-line treatment. This study was approved by the ethics committee of both institutions.

The database was generated in SPSS, version 21.0. The association between categorical variables was analyzed by Chi-Square or Fischer’s Exact Test. Survival curves were constructed by Kaplan-Meier life table analysis. Multivariate analysis was performed by Cox regression. All variables with a *p*-value < 0.20 in the univariate

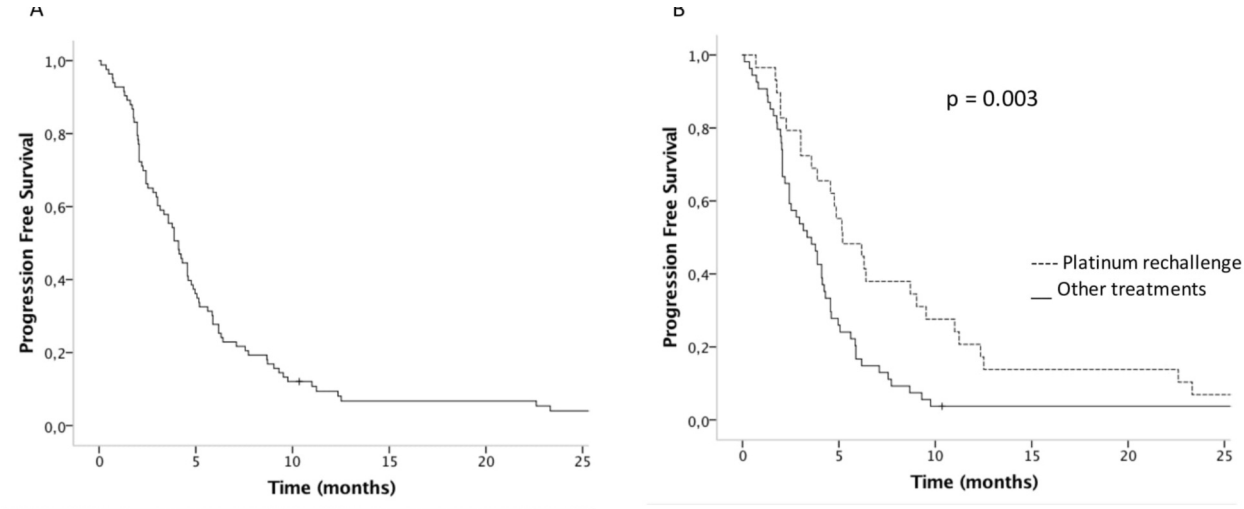

Figure 2. — A) Progression-free survival for the role cohort of second-line treated endometrial cancer patients. B) Progression-free survival according to platinum rechallenge. *p*-value calculated with the Log-Rank Test.

Table 4. — *Univariate cox regression for progression-free survival*.

Variable	HR (95%CI)	*p*-value
Age (years)		
< 65	1	0.495
≥ 65	1.17 (0.75 – 1.84)	
Histology		
Non-endometrioid	1	0.556
Endometrioid	1.16 (0.71 – 1.90)	
Grade		
1	1	0.435
2-3	1.23 (0.73 – 2.07)	
Initial FIGO Stage		
I-III	1	0.506
IV	0.85 (0.54 – 1.36)	
Pelvic recurrence/progression		
No	1	0.089
Yes	1.59 (0.93 – 2.71)	
ECOG Performance		
0-1	1	0.033
≥ 2	1.70 (1.04 – 2.77)	
Adjuvant chemotherapy		
No	1	0.088
Yes	1.72 (0.92 – 3.02)	
Treatment free interval (months)		
< 6	1	0.005
≥ 6	0.49 (0.30 – 0.81)	
Platinum rechallenge		
No	1	0.010
Yes	0.55 (0.35 – 0.87)	

analysis were entered into the multivariate analysis. For all tests, an alpha error of up to 5% ($p < 0.05$) was considered significant.

Results

A total of 84 patients fulfilled the criteria for this analysis and were evaluated. The clinical and pathological characteristics are summarized in Table 1. Median age was 66.2 years; most patients had endometrioid histology (67.9%) and grade 2 tumors (45.8%). Fourteen patients (16.6%) were treated with adjuvant chemotherapy. Most patients (86.9%) received TC at first-line. Among patients not treated with TC at first-line, one patient received TAP, two patients received carboplatin monotherapy, two patients received doxorubicin monotherapy, three patients received paclitaxel monotherapy, and three patients received hormone therapy at first-line treatment. Median TFI to second line was 6.2 months.

Twenty-nine (34.5%) patients were treated with platinum rechallenge at second-line. Patients treated with platinum rechallenge at second-line had a longer TFI than patients treated with other systemic therapies with 13.8% of patients with TFI < 6 months for patients treated with platinum rechallenge *vs.* 66.7% with TFI < 6 months for patient not rechallenged with platinum therapy ($p < 0.001$). All other characteristics were similar in the two groups (Table 1).

With a median follow-up of 27.6 months (20.7–34.5 months) 69 out of 84 patients had died. Median OS for all patients was 9.7 months (7.1-12.3 months; 95%CI) (Figure 1A). Patients who were re-exposed to platinum had higher OS than non re-exposed patients, 13.8 months *vs.* 7.9 months ($p = 0.005$) (Figure 1B).

On univariate analysis platinum rechallenge, TFI > 6 months, pelvic recurrence, histologic grade 1 and ECOG performance status ≥ 2 were related to OS with a *p*-value < 0.20 and entered the multivariate model (Table 2). In the multivariate Cox regression model, platinum rechallenge was significantly associated to a better OS with a HR 0.43 (95%CI 0.21-0.87, $p = 0.019$) and pelvic recurrence was associated to a worse overall survival HR 3.54 (95%CI 1.67-7.50, $p = 0.001$) (Table 3). TFI > 6 months

Table 5. — *Multivariate cox regression analysis for progression free survival.*

Variable	HR (95%CI)	*p*-value
Platinum rechallenge		
No	1	0.005
Yes	0.36 (0.17 - 0.74)	
ECOG Performance		
0-1	1	0.006
2-3	2.46 (1.30 – 4.67)	
Pelvic recurrence		
No	1	0.008
Yes	2.81 (1.30 – 6.07)	
Treatment free interval (months)		
< 6	1	0.130
≥ 6	0.62 (0.34 - 1.15)	
Adjuvant chemotherapy		
No	1	0.132
Yes	1.73 (0.85 - 3.54)	

** 50 Events for 53 patients included in the final model.*

was not related to a better OS in the multivariate model with a HR 0.62 (95%CI 0.32-1.18, $p = 0.142$). Among the group of patients who were platinum re-exposed, PFI > 6 months was also not associated to OS (HR 1.88, 95%CI 0.43-8.10, $p = 0.400$).

Median PFS was 4.1 months (3.4-4.8 months) (Figure 2A). PRe was associated with a higher PFS, with median PFS of 4.9 months *vs.* 3.4 months for non re-exposed ($p = 0.008$) (Figure 2B).

On univariate analysis platinum rechallenge, TFI > 6 months, ECOG performance status ≥ 2 and use of adjuvant chemotherapy were related to progression survival with a *p*-value < 0.20 and entered the multivariate model (Table 4). In the multivariate cox regression model platinum rechallenge was significantly associated to a better PFS with a HR 0.36 (95%CI 0.17-0.74, $p = 0.005$) and ECOG ≥ 2 was associated to a worse PFS with a HR 2.46 (95%Ci 1.30-4.67, $p = 0.006$) as well as pelvic recurrence with a HR 2.81 (95%CI 1.30-6.07, $p = 0.008$) (Table 5). TFI > 6 months was not related to a better PFS in the multivariate model with a HR 0.62 (95%CI 0.34-1.15 p = 0.130).

Response rate

Seventy-six out of 84 patients had data on response evaluation. Response rate in these patients was 16.7%. Patients who were rechallenged with platinum therapy had a RR of 25.9% vs 14.3% to those not rechallenged with platinum therapy (p = 0.210). Patients rechallenged with platinum in combination to paclitaxel had a RR of 42.9% versus 13.1% for patients treated with other therapies (p = 0.010). All these patients rechallenged with platinum and paclitaxel had received the same regime with both drugs as first line chemotherapy.

Response rates according to each systemic therapy used in second line are shown in Table 6. Doxorubicin was the most frequently used second line therapy accounting for 41.7% of patients. Patients who were treated with doxorubicin had a RR of 11.1%.

Table 6. — *Response rates to second line treatment according to each treatment used.*

Second-line chemotherapy	Patients (%)	Response rate (%)
Carboplatin plus paclitaxel	19 (22.6)	7/17 (41.2)
Cisplatin plus doxorubicin	7 (8.3)	1/7 (14.3)
Carboplatin plus gemcitabine	2 (2.4)	0/2 (0.0)
Cisplatin	2 (2.4)	0/2 (0.0)
Carboplatin	2 (2.4)	0/2 (0.0)
Doxorubicin	30 (35.7)	3/27 (11.1)
Paclitaxel	5 (6.0)	2/5 (40.0)
Liposomal doxorubicin	5 (6.0)	0/5 (0.0)
Vinorelbine	2 (2.4)	0/2 (0.0)
Gemcitabine	1 (1.2)	-
Ifosfamide	1 (1.2)	0/1 (0.0)
Topotecan	1 (1.2)	-
Endocrine therapy	7 (8.3)	1/6 (16.7)

Patients who had a TFI > 6 months had a RR of 23.1% *vs.* 13.9% for patients who had a TFI < 6 months ($p = 0.308$). RR to platinum rechallenge was independent of TFI > 6 months, with RR of 25.0% for patients rechallenged with platinum therapy and a TFI < 6 months and 26.1% for patients rechallenged with platinum therapy and a TFI > 6 months ($p = 0.963$).

Discussion

Recurrent EC has a poor prognosis with an expected median OS around 12 months [5-7]. Carboplatin and paclitaxel is the standard first line chemotherapy [9]. There is no standard second-line therapy for EC, and this is an unmet need in drug development, with previous phase II trials showing response rates of less than 15% [10] and only few targeted agents showing modest activity in early phase trials[13-17]. Even if immunotherapy with anti-PD-1 drugs gives us hope with impressive response rates of 53% in non-colon cancers with mismatch repair deficiency [18], these tumors account for only about 24% to 35% of ECs [19, 20] and response in unselected patients is as low as 15% [21].

In this context of study, evaluated platinum rechallenge as a strategy for second-line palliative treatment in a retrospective cohort from two tertiary cancer centers in Brazil. The authors found a longer OS and PFS for patients treated with platinum rechallenge compared to patients treated with other strategies of systemic treatment. They also found a higher response rate for patients who were treated with platinum and paclitaxel as the platinum rechallenge combination. Notably TFI was not significantly related to survival or response to treatment, irrespective of the type of systemic treatment used, and doxorubicin showed a low response rate as second line agent.

One large ancillary analysis from GOG first line trials evaluated subsequent treatment in 586 patients [22]. This analysis compared platinum based *vs.* non platinum based

therapy for second-line treatment. There was no difference according to platinum treatment and the factor with greatest impact on prognosis at second-line treatment was TFI.

This study differs from the present study in the type of chemotherapy used in first and second lines. In the GOG study, only 25% patients received paclitaxel as the combination agent at first-line, while in the present study, 86.9% received paclitaxel with platinum at first-line. The GOG study does not specify non-platinum treatments used as second line, but considering the years of late 90's and early 2000s when they where run, paclitaxel may have been a predominant chemotherapy used as second line. In the GOG study, 36% of patients had their adjuvant platinum chemotherapy considered as the first line treatment, while in the present study all patients had one treatment line for recurrent or metastatic disease. These two different aspects make patients in the GOG study less heavily pretreated when they arrived at second line therapy, notably 75% not having received paclitaxel yet. This would bias the response towards a higher response for non-platinum therapy, and could explain the finding of no benefit of platinum rechallenge.

Another small retrospective study including 40 patients who were treated with different second-line treatments had 24 patients re-exposed to platinum [23]. The study showed no statistically significant benefit for platinum rechallenge compared to other second line treatments, but the number of patients was small and, even if not statistically significant, response rate was 38.0% for platinum rechallenge versus 6.2% for other therapies.

One retrospective study from 30 institutions in Japan examined 279 patients, all treated with platinum rechallenge [12]. Response to platinum rechallenge was related to platinum-free interval. Patients with platinum-free interval of < 6 months, 6-11 months, 12-24 months, and > 24 months had response rates of 25%, 38%, 61%, and 65%, respectively. In this study 80% of patients had their first platinum treatment as adjuvant treatment for locally advanced disease. The present authors did not show an impact of TFI in response to second-line treatment, but they had a smaller number of patients compared to the Japanese study, and among patients treated with platinum rechallenge, only 13.8% had a TFI < 6 months what hampers a conclusion regarding TFI impact in our study.

Patients retreated with platinum and taxane had higher response rates than patients treated with other drugs. Early trials of paclitaxel as second line agent in a time patients did not receive paclitaxel as first line showed response rates as high as 25% to 37% [24, 25]. The present results suggest rechallenge with the paclitaxel and platinum combination is a more effective treatment than retreatment with platinum monotherapy or other combinations, even nowadays when paclitaxel is routinely used as first-line therapy.

Doxorubicin was the most frequent used second-line chemotherapy, accounting for 35.7% of patients. Response rate to doxorubicin was 11%. One retrospective study showed no response among 17 patients treated with antracycline at second-line [26]. The only phase III trial for second-line treatment used doxorubicin as the control arm [27]. Paclitaxel was another option for treatment in the control arm. Response rate in the control arm was 15.7%, and even if there is no data on the response rate specifically to doxorubicin, 80% of patients in the control arm received doxorubicin. The present results corroborate modest activity of doxorubicin as second-line treatment.

The present study has limitations related to its retrospective design. Selection bias can be noted by the difference in TFI between patient treated with platinum rechallenge and patients not treated with platinum therapy at second-line, all other characteristics were similar between the two groups. This difference could drive the benefit of platinum rechallenge once more as patients in this group had TFI > 6 months. Despite this difference TFI entered the model in multivariate analysis for OS and PFS together with platinum rechallenge and in both models platinum rechallenge remained independently related to both OS and PFS, while TFI was not independently related to OS or PFS. The retrospective nature of the study makes response rate more difficult to be evaluated, but the main benefit of platinum rechallenge was noted in OS, an objective endpoint irrespective of the retrospective nature of the study.

In conclusion the present study shows a longer OS and PFS for patients treated with platinum rechallenge at second-line treatment for recurrent EC and brings more evidence for adoption of this strategy in a scenario where there is little evidence of effective treatments.

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Corresponding Author:
A.A.B.A. DA COSTA, M.D., PhD
A.C. Camargo Cancer Center
Rua Professor Antonio Prudente 211
Liberdade, São Paulo, SP (Brazil)
ZIP code: 01509-900
e-mail: alebalieiro@uol.com.br