Medical Oncology (2018) 35:20
https://doi.org/10.1007/s12032-018-1086-7

ORIGINAL PAPER

Efficacy of doxorubicin after progression on carboplatin and paclitaxel in advanced or recurrent endometrial cancer: a retrospective analysis of patients treated at the Brazilian National Cancer Institute (INCA)

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Received: 3 January 2018 / Accepted: 11 January 2018 / Published online: 31 January 2018

Abstract
The treatment of endometrial cancer (EC) is challenging. There is no standard of care for patients who progressed after carboplatin and paclitaxel (CT) and all available drugs show a small response and poor long-term survival in this scenario. The objective of this study was to evaluate the efficacy and toxicity profile of palliative doxorubicin after progression to CT therapy in advanced or recurrent EC. A retrospective review of the Brazilian National Cancer Institute database between 2009 and 2013 was performed, and all patients with recurrent and advanced EC treated with palliative doxorubicin after progression on CT were included. Progression-free survival (PFS), overall survival (OS), objective response rates as well as toxicity were evaluated. A total of 33 patients were enrolled, with a median age of 65.7 years. Objective responses were documented in 12.1% (3.0% of complete responses and 9.1% of partial responses). The median PFS was 4.4 months, and the median OS was 8.1 months for patients exposed to doxorubicin. The most common adverse event was anemia observed in 60.6% of patients. This retrospective study suggests that doxorubicin has a modest activity in patients with advanced or recurrent EC after treatment with CT.

Keywords Endometrial cancer · Doxorubicin · Palliative chemotherapy

Introduction

Endometrial cancer (EC) represents the most commonly diagnosed gynecological cancer in developed countries [1]. In the USA, the American Cancer Society expects more than 60,000 new cases in 2017 [2]. In Brazil, it was estimated 6950 new cases of EC for 2017, a rate of 6.74 cases per 100,000 Brazilian women [3].

EC is usually diagnosed in early stage leading to a high chance of cure with a 5-year survival rate of 83–85% [4, 5]. On the other hand, advanced disease at diagnosis is not common and has a 5-year overall survival (OS) of only 17% [4]. Hysterectomy and bilateral salpingo-oophorectomy is the main treatment and, in spite of all the controversy regarding lymphadenectomy, this procedure is required to make an adequate staging and tailor adjuvant therapy [6].

Historically, external radiotherapy and/or brachytherapy are given after primary surgery for high–intermediate-risk tumors, reserving chemotherapy for those with FIGO stage III–IV [7]. In the past decades, chemotherapy with platinum doublets, usually carboplatin and paclitaxel (CT), has replaced radiotherapy as the preferred option for high-risk early-stage disease [8], even in the absence of studies showing a clear survival benefit for this approach, and also for stage III–IV. This makes the options for treatment at relapse or progression limited since the most active drugs were used in the adjuvant or first palliative line setting.

After failure to initial chemotherapy, treatment options include surgery in very restrict cases, hormonal therapy for those indolent and oligosymptomatic tumors expressing hormonal receptors and second-line chemotherapy [5]. Retreatment with platinum compounds is an option, but platinum sensitivity is not clear as in ovarian cancer [9–11]. An alternative for those who relapse in a short period after platinum (less than 6–12 months) is usually second-line

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chemotherapy. Several chemotherapeutic agents have been evaluated, with variable response rates, including cisplatin, oxaliplatin, docetaxel, gemcitabine, ifosfamide, ixabepilone and liposomal doxorubicin [4]. The use of doxorubicin in second-line therapy has no documented clinical benefit [4, 11].

At the Brazilian National Cancer Institute (INCA), the use of doxorubicin has been routinely used as palliative treatment for patients with EC who progressed after CT. This study provides a review of the institutional experience emphasizing treatment response, survival and toxicity.

Materials 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 was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

In order to evaluate response rates (RR), progression-free survival (PFS), OS and toxicity, an analysis of all EC patients treated with doxorubicin after progression on CT at INCA, between 2009 and 2013, was performed. Patients were identified through internal database. Clinical data including demographics, stage, histology, previous therapies and the toxicity related to 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 (FIGO) 2009. All patients treated with doxorubicin had performance status 0–2, appropriate hepatic, renal and hematologic functions for the proposed treatment. Patients not initially diagnosed as IVB stage underwent primary surgery and received adjuvant radiotherapy and/or chemotherapy with CT according to institutional guidelines. Response to treatment was assessed using clinical and especially radiological criteria as follows—complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD). The frequency of radiological evaluation was determined by the treating physician. The RR were obtained from the medical records and were reviewed by radiologist in order to confirm response based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The adverse events were recorded at every cycle using version 4.03 of the Common Terminology Criteria for Adverse Events (CTCAE).

Tumors with endometrioid, serous or clear cell histologies of any grade and stage were included. Mixed tumors with endometrioid and serous component were grouped as serous histology since their behavior is similar to this more aggressive histology. Carcinosarcomas were not included in this analysis. Patients should have progressed on CT as adjuvant or palliative treatment. Retreatment with CT was allowed if patients were treated in adjuvant setting and the platinum-free interval was longer than 6 months.

Treatment

The chemotherapy regimen consisted of doxorubicin 60 mg/m^2 in bolus intravenously on day 1, every 3 weeks. Dose reductions and treatment delays were determined by the treating physician. The regimen was administered until limiting toxicity, disease progression or for a maximum of six cycles whichever came first. Clinical history, physical examination and laboratory evaluations were obtained prior to each treatment cycle.

Statistical analysis

OS was defined as the time from first doxorubicin infusion to death from any cause or the date of the last follow-up visit. PFS was defined as the time from the first doxorubicin infusion to the first documented progression, death or the date of last contact with patients who were alive and progression free. The Kaplan–Meier method was used to estimate OS and PFS. SPSS software, version 18.0, was used to perform all analyses.

Results

A total of 33 women with advanced or recurrent EC were enrolled in the study, and the main patients' characteristics are summarized in Table 1. The median age at the time of initial diagnosis was 65.7 years (range, 52.1–79.5), and most patients had PS 1 (48.5%). The most prevalent race was brown (57.6%).

The stage distribution at diagnosis was: stage IB—12.1% ($n = 4$); II—15.2% ($n = 5$); IIIB—18.2% ($n = 6$); IIIC—27.2% ($n = 9$); IVA—6.1% ($n = 2$); IVB—18.2% ($n = 6$) and data were missing for 1 patient (3.0%). The most frequent histologic sub-types were serous, 39.4% ($n = 13$); endometrioid, 33.3% ($n = 11$); mixed cell type, 18.2% ($n = 6$); clear cell, 3.0% ($n = 1$); and undifferentiated sub-types, 6.1% ($n = 2$). Eleven patients (33.3%) had adjuvant radiotherapy/brachytherapy. Distant metastasis occurred in 42.4% ($n = 14$) of patients, followed by pelvic recurrence in 9.1% ($n = 3$) of patients. Forty-nine percent ($n = 16$) of patients had both distant and local metastases (Table 1). Twenty-one (63.6%) patients received CT in the adjuvant setting; 13 (61.9%) were treatment free for more than 6 months and were re-challenged with the platinum doublet as the primary palliative treatment, and doxorubicin was given as a second-line palliative therapy. The median number of doxorubicin cycles was 4 (range, 1–6).

Table 1 Patients and tumor characteristics

Characteristics	$n = 33$	%
Age at diagnosis, years		
Median	65.7	
Range	52.1–79.5	
Race		
Brown	19	57.6
Black	7	21.2
White	7	21.2
Performance status		
0	9	27.3
1	16	48.5
2	1	3.0
Missing	7	21.2
FIGO stage		
IB	4	12.1
II	5	15.2
IIIB	6	18.2
IIIC	9	27.3
IVA	2	6.1
IVB	6	18.2
Missing	1	3.0
Histologic sub-type		
Endometrioid	11	33.3
Serous	13	39.4
Mixed cell type	6	18.2
Clear cell	1	3.0
Undifferentiated	2	6.1
Site of recurrence		
Pelvis	3	9.1
Distant	14	42.4
Both	16	48.5

Table 2 Tumor response after doxorubicin

	$n = 33$	%
Objective response	4	12.1
Complete response	1	3.0
Partial response	3	9.1
Stable disease	7	21.2
Progressive disease	19	57.6
Not evaluated	3	9.1

Objective response rate (ORR) was documented in 12.1% ($n = 4$) with CR 3.0% ($n = 1$) and PR 9.1% ($n = 3$) as shown in Table 2. Three patients did not perform radiological evaluation due to clinical progression and/or loss of follow-up.

The median PFS was 4.4 months (95% CI, 2.8–6.0) and the median OS was 8.1 months (95% CI, 4.6–11.6) as shown in Fig. 1.

The frequency and severity of toxicities are summarized in Table 3. Considering possible bias of retrospective assessment, the most frequent were hematological and gastrointestinal adverse events. Predominant grade 3 and 4 toxicities were neutropenia (24.3%) and anemia (15.2%).

Discussion

Doxorubicin, since approved for medical use in the USA in 1974, has been used in many hematological and solid cancers such as lymphomas, breast and gynecological cancers. It is on the World Health Organization's list of essential medicines, among the most effective and safe medicines needed in a health system [12]. The main side effects are anemia, nausea, vomiting, stomatitis, and cardiac toxicity that limit its use.

Treatment of recurrent EC after platinum and paclitaxel exposure is challenging. There is no standard of care in this scenario and in many institutes, as well as in ours, single-agent doxorubicin remains the first option of treatment, and this strategy is supported by the National Comprehensive Cancer Network (NCCN) guidelines [13]. Other options include (in selected scenarios) repeat platinum and taxane doublets (specially in those with more than 12 months of progression-free survival), hormonal therapy (for hormone receptor-positive tumors), radiotherapy and salvage surgery. One trial in second-line therapy for recurrent EC compared ixabepilone to doxorubicin or paclitaxel (control group). There was no difference regarding OS (10.9 and 12.3 months) and ORR (15% in both arms) with different toxicity profile [14].

Based on The Comprehensive Genomic Atlas (TCGA) for EC, which subclassified this tumor in four molecular groups (POLE, MSI, copy number low and copy number high), there are distinct pathway abnormalities in each specific histologic sub-type [15]. PI3K-AKT-mTOR dysfunction and mutations in FGFR receptors are commonly seen in endometrioid histology, while P53 alterations in serous like carcinomas. This knowledge had been used to perform studies targeting these pathways; however, until now none of them showed striking results. The most promising studies used agents to inhibit mTOR (temsirolimus and everolimus); however, they showed only minimal activity. In phase II studies, everolimus showed ORR of 9% with PFS and OS of 2.8 and 8.1 months, respectively [16], while temsirolimus showed ORR of 14% and PFS of 7.3 months [17]. Others tried to block angiogenesis. Bevacizumab showed modest activity in recurrent pretreated EC (ORR of 13.5%) [18]; however, based on these findings, temsirolimus and bevacizumab were put in the roll of drugs for EC treatment in the NCCN guideline.

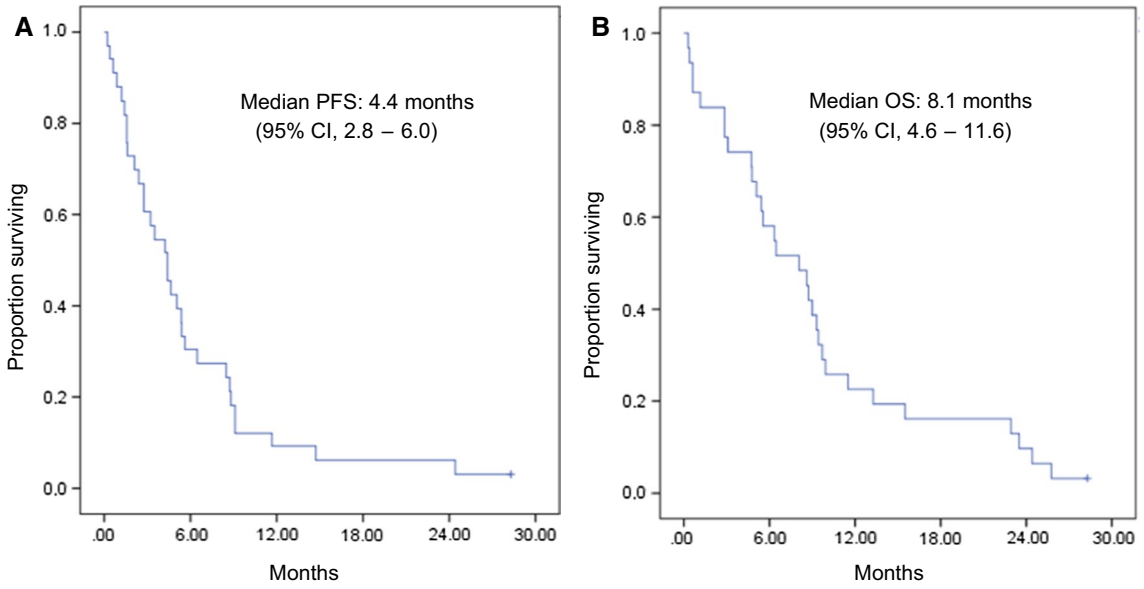

Fig. 1 Survival among EC patients treated with palliative doxorubicin. **a** PFS; **b** OS

Table 3 Treatment-related adverse events in patients treated with doxorubicin (%)

Adverse effect	Grade			
	1	2	3	4
Anorexia	9.1	6.1	0	0
Dyspepsia	12.1	12.1	6.1	0
Diarrhea	12.1	3.0	6.1	0
Vomiting	9.1	3.0	6.1	0
Constipation	18.2	3.0	0	0
Oral mucositis	6.1	6.1	0	0
Myalgia	0.0	12.1	0	0
Fatigue	3.0	9.1	6.1	0
Anemia	33.3	12.1	15.2	0
Neutropenia	6.1	0	9.1	15.2
Thrombocytopenia	6.1	0	3.0	0
Febrile neutropenia	0.0	0	3.0	6.1
Left ventricular systolic dysfunction	0	0	3.0	0

Immunotherapy represents an encouraging treatment for EC. The multicohort phase Ib KEYNOTE-028 study was designed to evaluate the safety and efficacy of pembrolizumab, in patients with PD-L1-positive advanced solid tumors who had experienced progression after standard therapy. The results from the EC cohort were recently reported. Fifteen (62.5%) of the 24 patients enrolled had received at least two previous lines of therapy for advanced disease. Three patients (13.0%) achieved confirmed PR and three additional patients (13.0%) had SD, with a median duration of 24.6 weeks [19].

This retrospective analysis showed limited efficacy of doxorubicin as second-line therapy, and it is in line with previous reports. In the experience of Memorial Sloan Kettering Center, doxorubicin after platinum and taxane combination showed an OS of 5.8 months and PFS of 2.1 months compared to 8.1 and 4.4 months in our analysis. A Gynecologic Oncology Group study tested liposomal doxorubicin in 42 pretreated patients and showed an ORR and a median OS of 9.5% and 8.2 months, respectively [20]. Another report also showed low ORR (21%) in 19 patients treated with liposomal doxorubicin [21] (14 had prior chemotherapy). The comparison between the results of this retrospective study and the published data of the prospective trials shows that patients with advanced or recurrent EC have poor prognosis after first-line chemotherapy for metastatic disease. In low-resource regions where clinical trials are not available, discussion must include early best supportive care since there are no proven treatment options that improve survival and quality of life [11].

This study has some limitations as its retrospective nature raises the possibility of bias once some clinical details were not identified on the medical chart reviews, but it was possible to show similar findings to the international literature.

In summary, doxorubicin after carboplatin and paclitaxel doublet showed minimal clinical activity in this retrospective single-institution analysis, which is in line with previous reports. Clearly, efficient treatment for patients in second-line treatment is an unmet need and studies are urgent since

even more patients receive chemotherapy in the adjuvant setting.

Compliance with ethical standards

Conflicts of interest All the authors declare that they have no conflict of interests.

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