MEDDOCS Open Access Publisher

Journal of Gynecology Case Reports

Open Access | Research Article

Management of Recurrent Endometrial Cancer Once Lifetime Cumulative Dose of Doxorubicin Has Been Reached: Is There a Role for Switching to Pegylated Liposomal Doxorubicin?

Sadie Longo[1]*; Paulina J Haight[2]; Logan A Chrislip[3]; Molly Morton[2]; Laura M Chambers[2]; Kristin L Bixel[4]

[1]Department of Obstetrics and Gynecology, The Ohio State University Wexner Medical Center, James Hospital and Solove Research Institute, Columbus, OH, USA.

[2]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, The Ohio State University Wexner Medical Center, James Hospital and Solove Research Institute, Columbus, OH, USA.

[3]Department of Obstetrics and Gynecology, TriHealth, Cincinnati, OH, USA.

[4]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Stanford Medical Center, Stanford, CA, USA.

***Corresponding Author(s): Sadie Longo**

Department of Obstetrics and Gynecology, The Ohio State University Wexner Medical Center, James Hospital and Solove Research Institute, 395 W. 12th Ave, 5th Floor Columbus, OH 43210, USA.

Email: sadie.longo@osumc.edu

Received: Oct 01, 2025

Accepted: Oct 30, 2025

Published Online: Nov 06, 2025

Journal: Journal of Gynecology Case Reports

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Endometrial cancer; Doxorubicin; Pegylated-liposomal doxorubicin.

Abstract

Objective: We sought to describe single-institution practice patterns and outcomes of next-line therapy for patients with recurrent endometrial cancer who have reached the lifetime cumulative dose of doxorubicin.

Methods: A retrospective, single-institution review of endometrial cancer patients treated with doxorubicin for recurrent disease from 2014-2022 was performed. Demographics, clinicopathologic factors, and outcomes were recorded. Descriptive statistics were performed to describe treatment patterns and cancer-related outcomes.

Results: A total of 27 patients with recurrent endometrial cancer were treated with doxorubicin. The Objective Response Rate (ORR) was 41% and the Clinical Benefit Rate (CBR) was 52%. 12 patients died or transitioned to hospice while actively receiving doxorubicin. 5 patients progressed on doxorubicin and went on to receive additional treatments. Lifetime cumulative dose (550 mg/m2) of doxorubicin was reached in 8 patients. Of those, 3 were transitioned to Pegylated Liposomal Doxorubicin (PLD), 2 were transitioned to alternate treatment lines, and 3 underwent treatment holiday. Those patients transitioned to PLD received a median of 6 cycles, with a median Progression-Free Survival (PFS) of 5 months (range 4-15 months), and one patient had a complete response. No patients receiving PLD after doxorubicin had grade 3 or higher toxicity. Of the patients that received alternative treatment or holiday, outcomes were variable with median PFS 11 months (range 3-53 months).

Conclusion: For patients with recurrent endometrial cancer who receive the lifetime cumulative dose of doxorubicin and are having clinical benefit, both transition to PLD and treatment holiday are reasonable treatment options.

Cite this article: Longo S, Haight PJ, Chrislip LA, Morton M, Chambers LM, et al. Management of Recurrent Endometrial Cancer Once Lifetime Cumulative Dose of Doxorubicin Has Been Reached: Is There a Role for Switching to Pegylated Liposomal Doxorubicin?. J Gynecol Case Rep. 2025; 4(2): 1022.

Introduction

Endometrial Cancer (EC) is the most common gynecologic malignancy in the United States, with an estimated 69,120 cases projected for the year 2025 [1]. Surgery is the mainstay of treatment and may be curative for those patients with low-risk, early-stage disease. However, those with high-risk clinicopathologic and molecular features or advanced-stage disease are at higher risk of recurrence [2]. Mortality has continued to rise over the last decade, and those patients with advanced-stage or recurrent disease have poor estimated 5-year overall survival rate of less than 20% [1].

The treatment landscape of endometrial cancer is rapidly evolving. Platinum-based chemotherapy has long been established as the recommended first-line therapy for endometrial cancer, however unprecedented improvement in oncologic outcomes have been seen when immunotherapy is added in the frontline setting [3]. For those with progression on prior therapy, the FDA has approved immunotherapy alone for mismatch repair deficient (MMRd) tumors, or in combination with lenvatinib (MMR proficient tumors) [3, 4]. Hormonal therapy may be considered, especially for patients with low-grade, hormonally sensitive tumors []. Additionally, antibody-drug conjugates targeting HER2 have shown promising response rates in recurrent endometrial cancer [6]. However, for those who progress despite these advances, treatment is limited to cytotoxic chemotherapy, especially for those who have limited access or are ineligible for clinical trials.

Doxorubicin is an anthracycline derived from *Streptomyces peucetius* that has shown activity in metastatic endometrial cancer [7-9]. Its use has been limited to the recurrent setting since carboplatin and paclitaxel demonstrated non-inferiority and a more favorable toxicity profile as compared to doxorubicin/cisplatin/paclitaxel in Gynecologic Oncology Group (GOG) Study 209 [7]. Small, retrospective case series have argued that doxorubicin is only minimally active in the second-line treatment of endometrial cancer [11-12]. Prospective, randomized data have reported an overall response rate (ORR) of approximately 25% to Doxorubicin [10]. Median Progression-Free Survival (PFS) and overall survival (OS) have been reported to be 3.8 and 9.0-11.4 months, respectively, for patients with metastatic/recurrent endometrial cancer undergoing treatment with doxorubicin alone [10,11]. For those who respond, duration of treatment is limited by the lifetime cumulative dose (550 mg/m2) given significant risk of cardiac toxicity (15%) once this threshold has been reached, namely left ventricular dysfunction and heart failure [12]. The cumulative lifetime dose for those with pre-existing cardiac risk factors including hypertension, diabetes, and obesity is lower (450 mg/m^2) given increased risk for treatment-related cardiac events [12]. After approximately 7-8 cycles of doxorubicin, a decision must be made for transition to alternative therapy versus treatment holiday. Currently, there is little data regarding best practice following achievement of lifetime cumulative dose of doxorubicin in patients with recurrent EC and whether transition to Pegylated Liposomal Doxorubicin (PLD) would be associated with continued clinical benefit. PLD has a longer half-life and slower plasma clearance than doxorubicin, and these alterations in pharmacokinetics and tissue distribution significantly reduce the risk of cardiotoxicity while maintaining antitumor effect [13]. We aim to report on our experience regarding the feasibility of this approach, as patients with recurrent EC who have reached the lifetime cumulative dose of doxorubicin encompass a unique population, often with limited data-supported treatment options.

The objective of this observational study was to describe the treatment strategies and oncologic outcomes for patients receiving doxorubicin for recurrent endometrial cancer at a single comprehensive cancer center.

Methods

The Institutional Review Board and the Comprehensive Cancer Center Clinical Scientific Review Committee at The Ohio State University approved this study (IRB No. 2023C0164). A retrospective review was performed of all patients who were treated with doxorubicin for recurrent endometrial cancer between January 1, 2014, and December 31, 2022. Patients with a diagnosis of sarcoma were excluded.

Patient demographics and clinicopathologic factors including age, BMI, stage at diagnosis, histology/grade, adjuvant treatment, and molecular immunohistochemical information (where appropriate) were abstracted from medical records. Treatment information related to doxorubicin was abstracted from patient charts as reported/documented by the treating physician, including number of cycles, grade/number of toxicities experienced, dose reduction/delay/discontinuation, and cumulative lifetime dose achievement. Oncologic outcomes including best response to treatment, survival, and subsequent treatment lines were also recorded. PFS was defined as the time from start of doxorubicin until documented recurrence or death; patients who did not recur were censored at their last physician encounter.

Demographics, clinicopathologic factors, and treatment outcomes were analyzed for the study cohort. Descriptive analysis was performed. Statistical analysis was performed using JMP software version 17 (SAS Institute Inc., Cary, NC, 1989-2023).

Results

Twenty-seven eligible patients with recurrent EC treated with doxorubicin were included in the analysis. Demographic and clinicopathologic characteristics of the cohort are listed in Table 1. The median age of the cohort was 61 years (range 42-71), and most patients identified as white (n=26, 96%). Endometrioid (n=11, 40.7%), carcinosarcoma (n= 9, 33.3%), and serous (n=3, 11.1%) histologies were the most common. Twenty-four (89%) patients underwent surgery at time of diagnosis and were treated with adjuvant chemotherapy for high-risk disease. The median number of systemic therapy lines prior to doxorubicin treatment was 1 (range 1-3). ORR to doxorubicin was 41% (n=1 CR, n=10 PR) (Table 2). The Clinical Benefit Rate (CBR) was 52% (n=14). Twelve patients died/transitioned to hospice while actively receiving doxorubicin therapy (n=2 had stable disease at the time of discontinuation, n=2 had Partial Response (PR), n=4 had imaging evidence of disease progression, while n=4 did not have an evaluable response). Seven patients progressed on doxorubicin and went on to receive additional treatment: bevacizumab (n=1), everolimus/letrozole (n=2), paclitaxel (n=1), PLD/bevacizumab (n=1) carboplatin/paclitaxel (n=1), and clinical trial (n=1); three of these patients also received radiation therapy.

Most patients (93%) experienced toxicity while receiving doxorubicin. Nine (33%) patients experienced a documented grade 3 or greater toxicity, the most common of which were gastrointestinal (44%) and hematologic (33%). Dose delay/reduction occurred for 9(33%) patients due to treatment toxic-

ity. Additionally, grade 5 toxicity was observed in 2(7%) patients (respiratory failure, neutropenic fever).

The maximum lifetime dose of doxorubicin was achieved for 8(30%) patients (Table 3). Of those, 3 were transitioned to PLD, 2 were transitioned to alternative treatment (1 gemcitabine/cisplatin, 1 clinical trial), and 3 underwent treatment holiday. The patients that were transitioned to PLD received a median of 6 cycles (range 6-16) and the median PFS was 5 months (range 4-15 months). One patient also received concurrent Stereotactic Body Radiation Therapy (SBRT) to a lung nodule and achieved a durable Complete Response (CR). She received a total of 16 cycles of PLD, which was ultimately discontinued when CR was achieved. She is alive without evidence of disease for now 30 months after transition from doxorubicin to PLD. No patients receiving PLD after doxorubicin experienced toxicity of grade 3 or higher, and no patients required dose reduction or delay for toxicity. Importantly, no cardiac toxicity was observed.

For those patients who transitioned to alternative treatment or holiday, outcomes were variable. One patient that transitioned to gemcitabine and cisplatin progressed after 3 cycles of treatment. One patient that transitioned to clinical trial discontinued after 3 months due to toxicity, though had a PFS of 22 months. Of the patients that went on treatment holiday, one had CR and two had PR to doxorubicin. The patient with CR died of other disease 53 months after discontinuation of treatment. The other two patients had a PFS of 11 and 15 months.

Table 2: Treatment outcomes and adverse effects of patients receiving doxorubicin.

Outcome associated w/ Adriamycin	n(%)
ORR	11(40.74)
CBR	14(51.85)
G3-5 toxicity	8(29.63)
Dose reduction/discontinuation	10(37.04)
Lifetime dose reached	8(29.63)

Table 1: Patient demographics and clinicopathologic data.

Patient factor	Median	Range
Age	61	[42-71]
BMI	31	[20.1-56.8]
	N = 27	%
Race		
African American / Black	1	3.7
Other	0	0
White	26	96.3
Surgical management		
Yes	24	88.9
No	3	11.1
Histology		
Carcinosarcoma	9	33.3
Clear cell	1	3.7
Dedifferentiated/undifferentiated	2	7.4
Endometrioid	11	40.7
Mixed	1	3.7
Serous	3	11.1
Grade 3	21	77.8
2	5	18.5
1	1	3.7
Stage		
Early	4	14.8
Advanced	23	85.2
NACT	4	7.4
Adjuvant therapy		
Chemotherapy	8	29.6
Chemotherapy + RT	16	59.3
Chemotherapy + IO	2	7.4
IO + RT	1	3.7
Number of lines of therapy prior to Doxorubicin		
Mean (SD)	1.63	
Median [range]	1	[1-2]

Table 3: Treatment outcomes for patients who achieved maximum dose of doxorubicin.

Patient	Response to Doxorubicin	Number of Cycles	Next Line Therapy	Number of Cycles	PFS*	Notable Side Effects
1	PR	8	Treatment holiday		15	
2	PR	8	Treatment holiday		11	
3	CR	8	Treatment holiday		53	
4	SD	7	Other (gemcitabine/cisplatin)	3	8	diarrhea (G1), fatigue (G1), dyspnea (G2) nausea (G1), constipation (G1), anemia (G1)
5	PR	9	Other (clinical trial)	3	10	Mucositis (G1), maculo-papular rash (G1), decreased performance status (G3), diarrhea (G1), nausea (G1)
6	PR	6	PLD	6	10	nausea (G1), dyspnea (G1), diarrhea (G1), anemia (G1)
7	PR	9	PLD	6	12	PPE (G1), mucositis (G1), anorexia (G1)
8	PR	7	PLD	16	20	rash (G1), neutropenia (G2), mucositis (G1)

*PFS defined as time from start date of DOXORUBICIN, until progressive disease or death of any cause.

Discussion

Doxorubicin is a moderately active regimen for metastatic/recurrent EC, often utilized after the exhaustion of other more effective and less toxic treatment options (platinum-based chemotherapy, immunotherapy, other targeted therapies and/or clinical trials) [9-11]. While pretreated patients experience reasonable response rates (25%) to doxorubicin, the duration of treatment can be limited by the increased risk of cardiac toxicity once the maximum lifetime dose has been achieved [10-12]. In our experience, doxorubicin is often utilized later in the treatment paradigm, and data for subsequent treatment are limited once the 550 mg/m2 threshold has been reached. At this juncture, some providers opt to transition to PLD under the

premise of similar mechanism for disease control at decreased toxicity risk related to the pharmacokinetics of the drug [13]. Alternatively, others transition to alternative treatment vs treatment holiday, although there is a paucity of data to describe any of these approaches. Here, we demonstrate in a small case series that transition to PLD following doxorubicin is safe and feasible, with a median of 6 cycles given prior to discontinuation for disease progression. No patients receiving PLD after lifetime dose of doxorubicin experienced dose delay or discontinuation for toxicity. Thus, this may be a reasonable option for some patients. Treatment holiday remains another reasonable alternative especially for those patients with PR/CR to doxorubicin.

Patients tolerated PLD well, with limited toxicity, similar to those previously reported [14]. Patients in this study experienced grade 1 nausea, dyspnea, diarrhea, anemia, rash, PPE, mucositis, and anorexia. One patient underwent PLD dose reduction secondary to neutropenia. No patients in this study on PLD experienced grade 3 or 4 toxicity. Oncologic outcomes for this small cohort of patients were favorable, including a durable complete response.

The most worrisome potential side effect of PLD is cardiac toxicity, especially for patients who have previously received doxorubicin. Previous studies have shown that patients receiving prolonged course of PLD do not experience clinically significant cardiac toxicity [14, 15]. Yost et al described toxicity profiles of 18 who received from 10-31 cycles of PLD. No patients exhibited signs or symptoms of cardiac disease, and only 2 patients had a decrease in left ventricular ejection fraction by 10-16% [14]. The patients in this study received an average of 6 cycles of PLD, with no patients experiencing cardiac toxicity.

There were only two patients who went on to receive alternative therapy (one cytotoxic chemotherapy, one clinical trial), and response/survival were variable. There were 3 patients who transitioned to treatment holiday after PR/CR to doxorubicin. Interestingly, response and survival outcomes were similar to those transitioned to PLD. One patient on treatment holiday never recurred but died of other cause 53 months after treatment. The two patients with PR on doxorubicin that then underwent treatment holiday had PFS between 11-15 months. Of course, disease biology likely plays a role in the response and survival seen in those patients transitioned to PLD or treatment holiday, as this is the population that had either PR or CR to initial treatment with doxorubicin. But our data suggests that transition to PLD or treatment holiday are both very reasonable options for the pretreated EC patient following achievement of lifetime cumulative dose of doxorubicin. One must consider the cumulative toxicities of chemotherapy and the values of the patient with regard to this decision.

There are several limitations associated with this study, including those associated with any retrospective study. There is potential for biases due to difficulties retrieving complete and accurate information relating to specific treatment plans, response to therapy, and grading/severity of toxicities. This study is also limited by the small sample size and that the majority of the patients were treated prior to widespread use of immunotherapy. Of this group, only 8 patients achieved cumulative lifetime dose. This small sample size makes it difficult to draw definitive conclusions. However, given the rarity of this event, reporting the experience is valuable.

There have been several advancements in EC treatment over the last few years. With improvements in oncologic outcomes seen with the introduction of immunotherapy and ADCs into the management of recurrent endometrial cancer, the utilization of doxorubicin and PLD will likely become more limited. However, for those heavily pretreated patients who do not respond to or are ineligible for other treatments, doxorubicin and PLD may be appropriate treatment options. This data, though limited, adds to the previous literature showing safety of transitioning to PLD and/or treatment holiday after receiving lifetime cumulative dose of doxorubicin.

Conclusion

Doxorubicin is a reasonable option for recurrent endometrial cancer for patients who progress on other treatment. For patients who receive maximum doses of doxorubicin, transition to pegylated liposomal doxorubicin should be considered in appropriate patients.

Author declarations

Credit author statement

SL – data curation, formal analysis, investigation, project administration, software, writing – original draft; PH – conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, resources, validation, visualization, writing – review & editing; LC – data curation; MM – conceptualization, writing – review & editing; LC – conceptualization, writing – review & editing; KB – conceptualization, methodology, visualization, writing – review & editing.

Conflict of interest statement

each of the authors report no conflicts of interest related to the content of this manuscript.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

References

1. SEER*Explorer: an interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. Data source(s): SEER Incidence Data, November 2024 Submission (1975–2022), SEER 21 registries. 2025.

2. Riedinger CJ, Patterson JM, Backes FJ, et al. The contemporary presentation and diagnosis of endometrial cancer recurrence: when, where, and how? Gynecol Oncol. 2022; 167: 174-180.

3. O'Malley DM, Bariani GM, Cassier PA, et al. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. J Clin Oncol. 2022; 40: 752-761.

4. Makker V, Colombo N, Herraez AC, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med. 2022; 386: 437-448.

5. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, Soper JT, Given FT. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol. 1999; 17: 1736-1744.

6. Meric-Bernstam F, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol. 2024; 42: 47-58.

7. Miller DS, Filiaci VL, Mannel RS, et al. Carboplatin and paclitaxel for advanced endometrial cancer: final overall survival and adverse event analysis of a phase III trial (NRG Oncology/GOG 0209). J Clin Oncol. 2020; 38: 3841-3850.

8. Makker V, Hensley M, Zhou Q, et al. Treatment of advanced or recurrent endometrial carcinoma with doxorubicin in patients progressing after paclitaxel/carboplatin: Memorial Sloan Kettering Cancer Center experience from 1995–2009. Int J Gynecol Cancer. 2013; 23: 929-934.

9. Rawat PS, Jaiswal A, Khurana A, et al. Doxorubicin-induced cardiotoxicity: an update on the molecular mechanism and novel therapeutic strategies for effective management. Biomed Pharmacol. 2021; 139: 111708.

10. Thigpen JT, Blessing JA, DiSaia PJ, et al. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 1994; 12: 1408-1414.

11. Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, Burger RA, Liao S. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2004; 22: 3902-3908.

12. Barrett-Lee PJ, Dixon JM, Farrell C, Jones A, Leonard R, Murray N, Palmieri C, Plummer CJ, Stanley A, Verrill MW. Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk. Ann Oncol. 2009; 20: 816-827.

13. Rafiyath SM, Rasul M, Lee B, et al. Comparison of safety and toxicity of liposomal doxorubicin versus conventional anthracyclines: a meta-analysis. 2012; 1: 10.

14. Yost S, Konal JL, Hoekstra AV. Prolonged use of pegylated liposomal doxorubicin in gynecologic malignancies. Gynecol Oncol Rep. 2019; 29: 89-93.

15. Safra T, Muggia F, Jeffers S, Tsao-Wei DD, Groshen S, Lyass O, Henderson R, Berry G, Gabizon A. Pegylated liposomal doxorubicin (Doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m². Ann Oncol. 2000; 11: 1029-1033.