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Evaluation of Pegylated Liposomal Doxorubicin Dose on the Adverse Drug Event Profile and Outcomes in Treatment of Recurrent Endometrial Cancer

Justin M. Julius, Pharm.D.¹, Janos L. Tanyi, M.D., Ph.D.², Graciela M. Nogueras-Gonzalez, M.P.H.³, Jack L. Watkins, Pharm.D.¹, Robert L. Coleman, M.D.⁴, Judith K. Wolf, M.D.⁵, and Judith A. Smith, Pharm.D.^{1,4,6,*}

¹Division of Pharmacy, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

²Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas

³Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

⁴Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

⁵MD Anderson – Banner, Phoenix, AZ

⁶Department of Obstetrics, Gynecology and Reproductive Sciences, The University of Texas Health Sciences Center, Houston, Texas

Abstract

Objective—To determine factors which may increase the likelihood of adverse drug events (ADEs) in recurrent endometrial cancer patients treated with pegylated liposomal doxorubicin (PLD) as well as this agent's impact on clinical outcomes.

Methods—The treatment records of endometrial cancer patients who received PLD at The University of Texas, M.D. Anderson Cancer Center from 1996 to 2006 were reviewed. Patient demographics, PLD dose, ADEs, use of supportive care interventions, disease progression and survival were extracted. Logistical regression analysis was used to identify factors which were associated with higher incidence of ADEs and which influenced survival.

Results—A total of 60 recurrent endometrial cancer patients were identified who experienced 122 ADEs. The most commonly reported ADEs were nausea (18.9%), palmar-plantar erythrodysesthesia (PPE) (16.4%), muscle weakness (12.3%), mucositis (10.7%), and peripheral neuropathy (9.8%). Seventeen patients (28%) required a dose reduction due to ADEs. However, only five (8.3%) patients discontinued therapy because of toxicity. Cooling mechanisms were used in 19 patients to prevent PPE, although nine of these patients still experienced PPE. Treatment

*Corresponding Author: Judith A. Smith, Pharm.D., BCOP, CPHQ, FCCP, FISOPP, Associate Professor & Director of Pharmacology Research, UT MD Anderson Cancer Center, Department Gynecologic Oncology & Reproductive Medicine, CPB6.3244, 1155 Herman Pressler, Unit 1362, Houston, Texas 77230, Tele: 713-500-6408, FAX: 713-500-5474, jasmith@mdanderson.org.

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AUTHOR CONTRIBUTIONS

Conception and design: Judith K. Wolf, Judith A. Smith, Robert Coleman

Collection and assembly of data: Justin M. Julius, Janos L. Tanyi, Judith A. Smith, Lafit R. Mora

Data analysis and interpretation: Justin M. Julius, Judith A. Smith, Judith K. Wolf, Graciela M. Nogueras-Gonzalez, Robert Coleman, Jack Watkins

Manuscript writing: Justin M. Julius, Judith A. Smith, Judith K. Wolf, Robert Coleman, Jack Watkins

with six or more cycles of PLD was associated with increased incidence of neutropenia ($p=0.045$), peripheral neuropathy ($p=0.004$), and PPE ($p<0.001$). No differences in PFS or TTP was found between the doses of PLD, however there was an assessable trend toward increased survival with doses of 40mg/m^2 .

Conclusions—While there was no association with dose level and ADEs, more cycles received increased the incidence of toxicities, including PPE and neuropathy. There was no association between different doses of PLD and PFS or TTP.

Keywords

Doxil; endometrial cancer; adverse effects; dose intensity

Introduction

Endometrial adenocarcinoma is the most commonly diagnosed gynecologic malignancy in the United States and is estimated to result in the death of 8010 women in 2012.[1] Patients often present in early stages with disease confined to the uterus due to presenting symptom of abnormal vaginal bleeding in a typically post menopausal population. Usually these patients are managed surgically with total abdominal hysterectomy with bilateral salpingo oophorectomy (TAH-BSO).[2] Recurrent disease can be managed with surgery or radiation but often relies on the use of systemic chemotherapy. Several studies to date have evaluated single agent cisplatin, carboplatin, paclitaxel, and doxorubicin with response rates ranging from 13 to 36%.[3]

Combination regimens of these agents have been shown to provide superior response rates, progression-free and, in some studies, overall survival, but at the expense of significantly greater toxicity.[4] These toxicities are often challenging for this patient population who are typically of advanced age and have other co-morbid conditions.[5] Pegylated liposomal doxorubicin (PLD) is a nanoparticle reformulation of doxorubicin, which has been associated with reduced drug-related toxicities, particularly cardiotoxicity.[6] PLD has only been evaluated in a small population of patients with endometrial cancer, predominately recurrent, prior anthracycline-exposed patients. A study by Muggia and colleagues reported a response rate of 9.5% (95% confidence interval, 2.7% to 22.6%) and relatively short time to progression (TTP) of three months in 42 patients.[7] Other studies have had very limited endometrial cancer patient enrollment and have been focused on use in ovarian cancer.[8]

The safety of PLD in patients with gynecologic malignancy has been established both over the short term as well as with prolonged treatment.[9] Uyar and colleagues evaluated the safety of PLD in 22 patients, including one with endometrial cancer, with therapy beyond six cycles and concluded that cardiac dysfunction does not appear to be a dose limiting toxicity. Rather, it was the dermatologic and hematologic toxicity that was more common in this study and resulted in more significant impact on continuation of therapy.[10]

With limited prospective data to support the use of PLD in treatment of endometrial cancer, this study attempts to further determine the impact of dose of PLD on the overall treatment outcomes and incidence of common ADEs.

Methods

Patient population

This was a retrospective review of medical records of patients who had received PLD as treatment of recurrent endometrial cancers between January 1, 1996, and June 30, 2006 at The University of Texas M. D. Anderson Cancer Center (UTMDACC), Gynecologic

Oncology Center. The protocol was reviewed and approved by The UTMDACC Institutional Review Board (IRB). All medical charts included in this study were from patients that had received PLD as single agent at initial doses of 50 mg/m² (FDA approved label dose) or reduced doses of 40 mg/m² (standard single-agent dose in current clinical practice), 35 mg/m², or 30 mg/m² for the treatment of recurrent endometrial cancer. Patients were not chemotherapy naïve, all had received at least one prior chemotherapy regimen prior to being initiated on PLD regimen.

Data Collection

Data extracted from the medical records included patient demographics, co-morbid conditions, chemotherapy history, reported ADEs, body mass index (BMI) at the start of therapy, CA-125 levels throughout therapy, duration of PLD treatment, radiographic evidence of response to therapy, reasons for discontinuation of treatment, and survival. For patients experiencing ADEs, data was recorded for time of onset, duration, and the treatment used to mitigate symptoms including cooling mechanisms for PPE. Criteria set forth by Gordon and colleagues was used in determining platinum-sensitive and -resistant disease. [11] Greater than 50% increase in the sum of the products of the bi-dimensional (two greatest perpendicular) diameters of all measurable lesions was deemed progressive disease. In cases of carcinomatosis, progression was determined based on clinical judgment and correlative changes in CA-125.

National Cancer Institute Common Toxicity Criteria (NCI-CTC v3.0) were used to evaluate incidence and severity of ADEs. The relationship between PLD dose and eight toxicities were evaluated including: nausea, vomiting, mucositis, neutropenia, myocardial toxicity, muscle weakness and pain, and peripheral neuropathy. In addition the correlation between platinum sensitivity and the incidence of PPE was evaluated. An association between toxicities evaluated, preexisting co-morbidities and patient characteristics such as BMI, age and race of the patient, as well as the season at the start of the treatment was also explored. Co-morbidities were organized into organ system groups in order to evaluate the relationship between the incidence of ADEs and different system related co-morbidities.

Statistical Analysis

The Cox proportional hazards regression model was employed to explore the effect of PLD dose on progression free survival (PFS). Time to progression was calculated as the interval between the date of the first cycle and the date of the last documented cycle for those patients with disease progression. In addition to the PFS analysis, a time-to-progression (TTP) analysis was also performed.

The secondary objectives of this study included: 1) explore the impact of PLD dose on response, 2) explore the impact of PLD dose on the incidence of PPE, and 3) to explore the impact of using cooling mechanisms on the incidence and grade of PPE. The Pearson's chi-square or Fisher's exact test were used to evaluate the association between PLD dose and the incidence of disease progression. These were also used to evaluate the relationship between the incidence of PPE and PLD dose and between the incidence of PPE and the use of cooling mechanisms. Finally, the Pearson's chi-square or Fisher's exact test were also used to explore the relationship between PPE and platinum sensitivity; each of 8 toxicities, or pre-existing co-morbidities, independently.

To explore the relationship between PLD dose and each of 8 toxicities evaluated a test for trend across ordered groups was completed. Summary statistics were used to describe CA125 response in the first 6 cycles, first cycle dose, and the reported reasons for dose reduction.

Results

Demographic and clinical patient characteristics are presented in Table 1. Mean patient age was characteristic of patients with endometrial cancer occurring in the seventh decade of life. Mean BMI was overweight, bordering on obese at 29.8 kg/m². This patient population was predominately non-Hispanic white. PLD dose ranged from 30–50 mg/m² with the majority of patients receiving the common standard clinical single agent dose of 40mg/m² as first cycle dose. Twenty-nine percent of patients required dose reduction during treatment with PLD and the majority of PLD discontinuation was due to disease progression 75% versus toxicity.

Median overall survival was 6.2 months in this population. Survival was not impacted by dose of PLD used on first cycle (Figure 1). There was also no difference in survival seen when the model was adjusted by platinum sensitivity status of the disease. The median survival for platinum resistant disease was 7.1 months compared to 6.2 months in patients with platinum sensitive disease (p=0.42). The median PFS for PLD doses of 30 mg/m²(N=7), 35 mg/m²(N=10), and 40 mg/m²(N=41) was 6.0, 3.3, and 7.0 months, respectively, which was not statistically significant between groups. There was also no difference in PFS when the models were adjusted by platinum disease.

A total of 122 ADEs were reported (Table 2). The most commonly reported ADEs were nausea (18.9%), PPE (16.4%), muscle weakness (12.3%), disease progression (12.3%), mucositis (10.7%), and peripheral neuropathy (9.8%). A significantly different trend across the doses of PLD in the first cycle was associated with incidence of neutropenia (p=0.013).

Table 3 shows the association of adverse events with development of PPE. Patients who experienced peripheral neuropathy were more likely to also experience PPE (p=0.014). This was the only toxicity evaluated which associated with PPE incidence. Use of cooling mechanisms was not associated with incidence of PPE.

Association of ADEs with number of PLD cycles received is shown in Table 4. Administration of six cycles or greater of PLD was associated with increased incidence of neutropenia (p=0.045), peripheral neuropathy (p=0.004) and PPE (p<0.001). The only incident of myocardial toxicity (grade 3) was documented from two-dimensional transthoracic echocardiogram in a patient who received greater than six cycles. All other ADEs assessed trended toward increased incidence with greater than six cycles.

Discussion

This retrospective review of recurrent endometrial cancer patients receiving PLD showed varying doses did not significantly impact ADEs rates other than neutropenia and did not have an effect on overall survival, PFS, or TTP. Treatment beyond six cycles with PLD was associated with higher incidence of ADEs suggestive of a threshold of cumulative exposure. Only incidence of peripheral neuropathy was associated with incidence of PPE, suggesting that incidence of PPE cannot be predicted based on presence of toxicities other than peripheral neuropathy. This study shows similar ADEs and progression free survival findings to a previous report in the ovarian cancer population receiving PLD. [9]

No differences were seen based on the first cycle dose of PLD with regards to OS, PFS, or TTP. This was limited by small sample size in the 30 mg/m² and 50 mg/m² treatment groups as well as the heterogeneity in the number of prior chemotherapy agents and/or cycles of chemotherapy. Overall, there was not a statistically significant difference on the time to progression or overall survival based on dose level. This confirmed data from previous studies indicating that there is no loss of efficacy at this dose compared to the FDA

approved label dose of 50 mg/m². [9, 12–14] Clinically this is an important finding because it confirms that implementing dose reductions based on toxicity and/or organ dysfunction is unlikely to impact overall PLD efficacy in the recurrent endometrial cancer setting. In this study, platinum resistance did not influence TTP or PFS, however, this association was not powered to detect a differences in clinical outcome observed in many other published reports. [12–13]

In general, PLD appeared to be well tolerated in this patient population. Only 8% of patients discontinued therapy due to toxicities however, 29% of patients had required some level of dosage reduction due to toxicity. The most commonly reported ADEs were similar to those seen in studies of PLD in other gynecologic malignancies. [9, 15] Neutropenia was the only toxicity observed in this study to have varying incidence across the starting doses evaluated.

The occurrence of PPE is 31 % in our and 13–49 % in different studies. [16–18] Of the variety of factors analyzed for association with PPE, only peripheral neuropathy showed a positive association with PPE incidence. This could be contributed to be difficulty of distinguishing between pain due to neuropathy that often begins in finger/toes and pain associated with PPE that also most often is in the hands/feet region. Of interest, the use of cooling mechanisms was only documented in approximately one-third of the patients despite current recommendations for patients to put hands and feet on ice during drug administration to prevent or at least decrease incidence of PPE. In patients not using the recommended cooling mechanisms, PPE developed in only 16.2 % (11 patients). However in the 19 patients that did use the recommended cooling mechanisms, 47% (9 patients) did develop PPE, while not statistically significant it does bring into question the benefit of the current recommendations to use cooling recommendations. The effect of cooling mechanism was evaluated by only study, which theorized that cooling causes vasoconstrictions and decrease the extravasation of the drug. [19] Only twenty patients were followed in that study and even inside of this small patient group, different PLD doses were applied which can easily modify the outcome of the study. [19] There was not an association seen with acute toxicities such as nausea which were predictive of PPE. This suggests methodology to predict this ADE is insufficient. Based on this data, PPE is still an ADEs without known risk factors and remains difficult to treat in patients receiving PLD. Other investigators have examine the potential of PLD dose reduction or delay, avoidance of sunlight, use of pyridoxine, and minimizing trauma to the skin decrease the severity of PPE. [20,21]

Prolonged use of PLD was associated with increased risk of developing neutropenia, peripheral neuropathy, and PPE. This illustrates the need to continually assess toxicity in patients. Patients with recurrent endometrial cancer are more likely to have had prior pelvic radiation, older age, and are female all of which are risk factors for neutropenia. Skin exams and assessment of neuropathy should remain a part of each clinical visit regardless of prior tolerances of PLD. Prophylactic use of colony stimulating factors or empiric dose reduction may be appropriate in those patients receiving greater than six cycles of therapy in the palliative setting, in patients with a history of chemotherapy-induced neutropenia, or those patients that have already received multiple prior regimens.

There are several limitations associated with this study including those with any retrospective study. There are often difficulties with retrieval of all information as it relates to treatment plan, response to therapy, and severity of toxicities observed. This study was also limited by a relatively small patient sample size and lack of dose diversity with majority of patients receiving 35 to 40 mg/m². Another limitation of the study was the heterogeneity in the number of prior chemotherapy agents and/or cycles of chemotherapy patients had received prior to receiving PLD which may have influenced propensity for PLD-toxicity in this study. Despite these limitations, this is one of the first studies to demonstrate benefit of

PLD in recurrent endometrial cancer as well as that dose level did not significantly influence efficacy. This study confirmed cumulative dose/cycles did increase risk of toxicity with PLD, which is common with most cytotoxic agents.

PLD remains a viable option for patients with recurrent or progressive endometrial cancer. This study showed survival data which is similar to that seen for other regimens in this setting. The impact on clinical outcomes (PFS, TTP) were not influenced by dose administered in this study, however, there was a trend toward improved outcomes in patients receiving 40 mg/m². The ADE profile of PLD includes nausea, mucositis, peripheral neuropathy, neutropenia, muscle pain/weakness, and PPE. Neutropenia, peripheral neuropathy, and PPE appear to be associated with chronic PLD use. PPE remains difficult to predict and avoid and may have higher incidence in patients receiving cooling mechanism as preventative strategies. In the future, additional studies are needed to determine efficacy of the combination of PLD with carboplatin in patients with platinum-sensitive recurrent endometrial cancer as well as prospectively determine if cooling mechanisms prevent or increase incidence of PPE with PLD administration.

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Figure 1. Overall Survival by PLD Starting Dose

Cox Proportional Hazards Regression Analysis of Overall Survival. Median overall survival was 6.0, 3.2, and 7.0 months for PLD starting doses of 30 mg/m²(N=7), 35 mg/m²(N=10), and 40 mg/m²(N=41), respectively

Table 1**Patient Demographics**

Characteristic	Mean (SD)	Median (range)
Age (years)	66.8 (9.6)	67.0 (34–87)
BMI	29.8 (8.2)	28.2 (19.8–49.6)
Number of prior chemotherapy regimens	2 (2)	3 (1–5)
CA-125 response		
Cycle 1	922.4 (2782.0)	140.8 (3.5–18,356.0)
Cycle 2	1048.1 (2848.1)	191.7 (8.4–16954.0)
Cycle 3	656.9 (1365.8)	159.3 (7.0–6960.0)
Cycle 4	420.9 (499.1)	233.7 (11.4–1742.8)
Cycle 5	250.6 (270.3)	198.5 (10.6–980.0)
Cycle 6	390.6 (528.2)	203.8 (9.6–1959.0)
Cycles of PLD	4.72 (4.23)	3.0 (1–25)
Mean Dose per cycle (mg)	63 (5.3)	64 (50–75)
Mean cumulative dose (mg)	306 (277.7)	225 (55 – 1627)
Characteristic	Number (%)	
Ethnicity		
White	44 (73.3%)	
Hispanic	6 (10.0%)	
African American	10 (16.7%)	
Comorbidities		
Diabetes	9 (15%)	
Hypertension	36 (60%)	
Other Cardiovascular	16 (26.6%)	
Cycle 1 PLD dose		
30 mg/m ²	7 (11.7%)	
35 mg/m ²	10 (16.7%)	
40 mg/m ²	42 (70.0%)	
50 mg/m ²	1 (1.7%)	
Reason PLD discontinued		
Disease progression	45 (75.0%)	
Toxicity	5 (8.3%)	
Lost to follow-up	4 (6.7%)	
Not reported	2 (3.3%)	
End of treatment planned	2 (3.3%)	
High cumulative dose	1 (1.7%)	
Chemotherapy break	1 (1.7%)	

Abbreviations: SD, standard deviation; BMI, body mass index; PLD, pegylated liposomal doxorubicin. Data are number (%) of patients, unless otherwise indicated.

Table 2

Adverse Events by PLD Starting Dose

Toxicity	No. of patients by cycle 1 PLD dose (%)				P
	30 mg/m ²	35 mg/m ²	40 mg/m ²	50 mg/m ²	
Disease progression	3 (42.9)	3 (30.0)	8 (19.0)	1 (100.0)	0.555
Nausea	3 (42.9)	4 (40.0)	15 (35.7)	1 (100.0)	0.879
Vomiting	1 (14.3)	0 (0.0)	7 (16.7)	0 (0.0)	0.640
Mucositis	1 (14.3)	1 (10.0)	11 (26.2)	0 (0.0)	0.465
Neutropenia	0 (0.0)	0 (0.0)	7 (16.7)	1 (100.0)	0.013
Myocardial toxicity	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0.400
Muscle weakness	2 (28.6)	3 (30.0)	10 (23.8)	0 (0.0)	0.555
Muscle pain	1 (14.3)	0 (0.0)	5 (11.9)	1 (100.0)	0.174
Peripheral neuropathy	1 (14.3)	3 (30.0)	7 (16.7)	1 (100.0)	0.551
PPE	1 (14.3)	4 (40.0)	14 (33.3)	1 (100.0)	0.318

Abbreviation: PPE, palmar-plantar erythrodysesthesia. Adverse events were similar across the doses observed with the exception of neutropenia which was more common at higher dose levels.

Table 3

Association of Adverse Events and Other Factors with Incidence of PPE

Evaluated variables	Patients w PPE (n=20)	Patients w/o PPE (n=40)	P
No cooling mechanisms	11 (55.0)	30 (75.0)	0.146
Platinum sensitive	3 (15.0)	16 (40.0)	0.123
Preexisting comorbidity	19 (95.0)	37 (92.5)	0.999
Nausea	10 (50.0)	13 (32.5)	0.261
Vomiting	17 (85.0)	35 (87.5)	0.999
Mucositis	7 (35.0)	6 (15.0)	0.101
Neutropenia	4 (20.0)	4 (10.0)	0.422
Myocardial toxicity	1 (5.0)	0 (0.0)	0.333
Muscle weakness	5 (25.0)	10 (25.0)	0.999
Muscle pain	4 (20.0)	3 (7.5)	0.208
Peripheral neuropathy	8 (40.0)	4 (10.0)	0.014
Race			
White	15 (75.0)	29 (72.5)	0.743
Hispanic	1 (5.0)	5 (12.5)	
African-American	4 (20.0)	6 (15.0)	

Abbreviations: SD, standard deviation; BMI, body mass index. Data are number (%) of patients, unless otherwise indicated. Use of cooling mechanisms was not associated with a decreased incidence of PPE. PPE was more common in patients who also experienced peripheral neuropathy associated with PLD use.

Table 4

Association of Adverse Events with Number of PLD cycles

Variable	<6 cycles (n=42)	6 cycles (n=18)	P
Nausea	14 (33.3)	9 (50.0)	0.257
Vomiting	5 (11.9)	6 (16.7)	0.686
Mucositis	7 (16.7)	6 (33.3)	0.181
Neutropenia	3 (7.1)	5 (27.8)	0.045
Myocardial toxicity	0 (0.0)	1 (5.6)	0.300
Muscle weakness	9 (21.4)	6 (33.3)	0.347
Muscle pain	3 (7.1)	4 (22.2)	0.182
Peripheral neuropathy	4 (9.5)	8 (44.4)	0.004
PPE	6 (14.3)	14 (77.8)	< 0.001

Abbreviation: PPE, palmar-plantar erythrodysesthesia. Data are number (%) of patients, unless otherwise indicated. While ADEs were more common in later cycles, due to limited sample size only neutropenia, peripheral neuropathy, and PPE were shown to be associated with cumulative dose exposure to PLD.