Gynecologic Oncology Reports 29 (2019) 89–93

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case series

Prolonged use of pegylated liposomal doxorubicin in gynecologic malignancies

S. Yost[a], J.L. Konal[b], A.V. Hoekstra[b,c,*]

[a] Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI, USA
[b] Department of Obstetrics and Gynecology, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI, USA
[c] Division of Gynecologic Oncology, West Michigan Cancer Center, Kalamazoo, MI, USA

ARTICLE INFO

Keywords:
Pegylated liposomal doxorubicin
Cardiac toxicity
Palliative
Prolonged

ABSTRACT

Pegylated liposomal doxorubicin (PLD) is a palliative treatment option for patients with recurrent gynecologic malignancies. It has an appealing toxicity profile and responses can be prolonged. There is no consensus as to the level of cardiac toxicity. Current label warnings, National Comprehensive Cancer Network (NCCN) guidelines, and extrapolation of prescribing guidelines from doxorubicin, may limit PLD's use in patients with baseline cardiac comorbidities, limit the lifetime dosing of an effective palliative treatment, or lead to over-use of unnecessary cardiac testing. This case series describes the experience of 18 patients using prolonged courses of PLD for gynecologic malignancies with no cardiac toxicity.

1. Introduction

Advanced stage gynecologic malignancies are clinical challenges when they recur. At the time of recurrence, treatment for advanced stage uterine, ovarian, fallopian tube and primary peritoneal cancers is generally palliative. Often patients and physicians are challenged with balancing quality and quantity of life. Several chemotherapeutic agents are useful in minimizing toxicity while prolonging quality life. Pegylated liposomal doxorubicin (PLD) is one of these second line palliative therapies for women with gynecologic malignancies.

PLD, an anthracycline chemotherapy derived from doxorubicin, is the first FDA-approved cancer nanomedicine (Barenholz, 2012). It is often very well tolerated, allowing patients to continue treatment without significant adverse effects. Its response rate is high in both uterine cancer and ovarian/fallopian tube/primary peritoneal disease relative to the response rates of alternative drugs, making it an appealing choice among second line agents. Dosing is most commonly 40 mg/m^2 every 4 weeks, reduced from the original use of PLD at 50 mg/m^2 due to equal efficacy at both doses and better toleration (Rose et al., 2001).

The most common side effects of PLD are dermatologic (plantar palmar erythrodysesthesia, mucositis), but one of the primary warnings is for potential cardiac toxicity. PLD's parent drug, doxorubicin, is associated with a sharp increase in congestive heart failure as cumulative lifetime dose increases, reaching up to 26% of patients even when cumulative doses is within the recommended lifetime dose of 450-550 mg/m^2 (Kushnir et al., 2015; Theodoulou and Hudis, 2004). The liposomal preparation of PLD decreases the risk of cardiac toxicity, but there is no consensus on the objective cardiac risk reduction of PLD compared to doxorubicin, the recommended maximum lifetime dose of PLD, or standard recommendations for cardiac monitoring. The package insert of PLD and other standard sources of prescribing information for physicians describe the cardiac risks. The National Comprehensive Cancer Network recommends universal cardiac evaluation with ECHO or MUGA scan for a baseline, followed by repeat testing at the physician's discretion. The literature, another source of guidance for prescribing physicians, describes a much less significant level of cardiac risk. There are several reports of small numbers of patients who received more than the 500 mg/m^2 of PLD with no significant cardiac ramifications (Blank et al., 2017; Grenader et al., 2010; Rabinovich et al., 2015; Safra et al., 2000; Uyar et al., 2004). There are additional reports indicating routine monitoring is futile due to high level of safety of even prolonged courses of PLD (Gill et al., 2013; Kesterson et al., 2010; Skubitz et al., 2017). In this manuscript we report on the clinical course of 18 patients with gynecologic malignancies who were treated with 10 or more cycles of PLD with median cumulative dose of 865 mg, ranging from 660 mg to 2794 mg, with no symptomatic cardiac toxicity. Perhaps the accumulation of data documenting patient toxicity profiles will support prolonged use in patients enjoying a response to treatment, as well as supporting discussions with

* Corresponding author at: 200 North Park Street, Kalamazoo, MI 49007-3731, 1-269-382-2500, 1-269-384-8617, USA.
E-mail address: ahoekstra@wmcc.org (A.V. Hoekstra).

https://doi.org/10.1016/j.gore.2019.07.012
Received 23 May 2019; Received in revised form 21 July 2019; Accepted 27 July 2019
Available online 07 August 2019

patients to reflect true cardiac risk.

2. Methods

We performed a retrospective single institution review of patients undergoing treatment with PLD between January 2009 and January 2019 who received at least 10 cycles. Patient medical records were reviewed to identify characteristics of the patients, disease characteristics, treatments, outcomes, complications, and monitoring for cardiac complications in particular. Patient demographics, treatment details, cardiac function/testing, and PLD toxicities were collected for each patient. Toxicities were graded according to NCI common toxicity criteria. Medical records were reviewed to identify signs and symptoms of heart disease including: jugular venous distention, new murmur, peripheral or pulmonary edema, new arrhythmia, dyspnea not explained by other condition, orthopnea, and chest pain. An attempt was made to identify cause of death for each deceased patient. Patients whose death was directly related to their cancer are noted as such; other causes of death were categorized as either cardiac-related or non-cardiac. Local IRB approval was obtained prior to initiation of this study. Informed consents were obtained from patients still undergoing therapy, or from next of kin if deceased.

3. Results

At our institution, 156 patients were treated with PLD between January 2009 and January 2019 for recurrent uterine, ovarian, fallopian tube or primary peritoneal cancer. Of these, 18 patients received at least 10 cycles of PLD. Table 1 shows the clinical and pathologic characteristics of these patients. The majority (12/18) were diagnosed with ovarian or primary peritoneal carcinoma, all with serous histology except for 1 patient with endometrioid. Another 5 patients were diagnosed with uterine cancer of various histologic subtypes: 1 carcinosarcoma, 2 serous, 1 mixed endometroid and clear cell, and 1 unspecified adenocarcinoma. Finally, there was 1 patient with carcinoma of unknown primary with serous histology. Most were diagnosed at advanced stage, 10 at stage III (55.6%) and 7 at stage IV (38.9%), with a single exception at stage IIC. Median age at diagnosis was 60 years, with a range from 43 to 79 years. The most common initial treatment modality (14/18, 77.8%) was primary surgery followed by chemotherapy; 2 (11.1%) patients received neoadjuvant chemotherapy, and 2 (11.1%) others received chemotherapy alone. All patients received initial chemotherapy with platinum and taxane based regimens. The time to recurrence after completion of this treatment had a median of 12 months, with a range of 1–99 months. At the time of writing, 4 patients remain alive. The remaining 14 patients died of disease, 2 patients for whom PLD was their most recent treatment choice. No patients died of cardiac-related causes.

The PLD-treated patients included in this study received a median cumulative dose of 865 mg, with a range of 660 mg – 2794 mg (Table 2). The range of the number of cycles patients underwent was 10–31. The 2 patients with the greatest number of cycles both had an

Table 2
PLD treatment.

Patient	PLD cycles	Cumulative PLD dose (mg)	PLD line of treatment	PFS (months)	Reason for discontinuation
1[a]	31	2794	2	37	Death
2[b]	25	1740	2	27	Progression
3	18	1326	3	16	Progression
4	15	1204	3	14	Progression
5	14	1000	3	14	Progression
6	13	956	4	12	Progression
7	13	916	2	12	Progression
8	12	992	4	66	Progression
9	12	804	4	12	Progression
10	12	816	2	14	Chemo holiday with stable disease
11	12	904	3	12	Progression
12	11	682	4	11	Progression
13	11	754	3	11	Progression
14	11	826	3	11	Death
15	10	660	2	12	Progression
16	10	716	2	10	Progression
17	10	680	3	10	Progression
18	10	720	3	10	Progression

[a] Patient 1 received 19 cycles of PLD and was given a chemo holiday with stable disease. She received an additional 12 cycles after progression 9.4 months later.

[b] Patient 2 received 10 cycles of PLD and was given a chemo holiday with stable disease. She received an additional 15 cycles after progression 5.1 months later.

Table 1
Clinical and pathological characteristics of patients receiving at least 10 cycles of PLD.

Patient	Age at dx	Primary tumor location	Tumor histology	Stage	Grade	Primary treatment	Time to recurrence (months)	Mortality status	Cause of death
1	43	Uterus	Carcinosarcoma	IV	3	NAC + ICS	28	Deceased	ARDS,aspiration
2	79	Unknown	Serous	IV	3	CT	1	Deceased	Non-cardiac
3	69	Ovary	Serous	IIIB	3	PCS	9	Alive	NA
4	61	Ovary	Serous	IIC	3	PCS	30	Deceased	Non-cardiac
5	55	Uterus	Serous	IIIC1	3	PCS	13	Deceased	Cancer
6	45	Ovary	Endometrioid	IV	2	NAC + ICS	99	Deceased	Cancer
7	63	Ovary	Serous	IIIC	3	PCS	2	Deceased	Cancer
8	53	Ovary	Serous	IIIA	3	PCS	72	Deceased	Cancer
9	72	Uterus	Adenocarcinoma, unspecified	IV	?	CT	11	Deceased	Cancer
10	57	Uterus	Serous	IVB	3	PCS	5	Alive	NA
11	75	Ovary	Serous	IIIC	2	PCS	13	Deceased	Non-cardiac
12	59	Ovary	Serous	IIIC	3	PCS	15	Deceased	Non-cardiac
13	57	Ovary	Serous	IV	3	PCS	28	Deceased	Non-cardiac
14	49	Primary Peritoneal	Serous	IIIC	3	PCS	26	Deceased	Non-cardiac
15	64	Ovary	Serous	IIIC	3	PCS	2	Deceased	Non-cardiac
16	53	Ovary	Serous	IIIC	3	PCS	3	Deceased	Non-cardiac
17	61	Ovary	Serous	IIIC	3	PCS	6	Alive	NA
18	65	Uterus	Mixed endometrioid and clear cell	IVB	3	PCS	1	Alive	NA

NAC + ICS = Neoadjuvant chemotherapy with interval cytoreductive surgery.
CT = Chemotherapy.
PCS = Primary cytoreductive surgery; all patients treated with PCS received platinum/taxane chemotherapy after.

Table 3
PLD toxicities[a].

Patient	Grade 1: Number (%)	Grade 2: Number (%)
Dermatitis	9 (50%)	2 (11%)
Neuropathy	1 (6%)	0
Nausea	3 (17%)	0
Esophagitis	0	1 (6%)
Mucositis	0	1 (6%)
Cough	1 (6%)	0
Fatigue	1 (6%)	0

[a] No patients experienced grade 3 or 4 toxicities.

interval chemotherapy holiday due to stable disease then resumed PLD. PLD was given as the second line of chemotherapy for 6 patients, third line for 8 patients, and fourth line for 4 patients. The median time from diagnosis to initiation of PLD treatment was 26 months, with a range of 8–126 months. For 15 patients (83.3%) PLD was discontinued due to progression of disease; 1 patient progressed while on chemo holiday and opted for alternate therapy. The remaining 2 patients passed away of progressive disease-related issues while on PLD.

Toxicities experienced by this cohort of patients are the most commonly reported and dose limiting toxicities in similar studies (Table 3). The most common was dermatitis; 50% of patients had grade 1 and another 11% developed grade 2. Other toxicities included grade 1 nausea in 17% of patients; grade 1 neuropathy, grade 2 esophagitis, grade 1 cough, grade 2 mucositis, and grade 1 fatigue each occurring in 6% of patients. No patients experienced grade 3 or 4 toxicities.

The cardiac history and monitoring of each patient is outlined in Table 4. Prior to beginning treatment with PLD only 1 patient had any history of cardiac disease, with atrial fibrillation well controlled on atenolol. Six (6/18) patients had an available LVEF measurement prior to beginning treatment with PLD. Half (9/18) of the patients had interval LVEF monitoring prior to completion of PLD treatment after a varying number of cycles. Of the 6 patients who had multiple LVEF measurements, 3 had stable LVEF, 1 saw an increase of 5%, and 2 had a decrease in LVEF (by 10% and 16%). The median duration from last cycle of PLD to last LVEF measurement was 16.2 months, with a range of 0.2–54.7 months. No patient had a recorded LVEF of < 55% before, during, or after PLD treatment. There were 3 patients in the study population who had no LVEF measurements available. No patient exhibited any clinical signs or symptoms of heart disease at any point during or after PLD treatment.

4. Discussion

PLD is a second line agent for uterine and ovarian/fallopian tube/primary peritoneal cancer with a relatively high level of efficacy. Ovarian cancer treatment is palliative only once it recurs, and when platinum resistant the response rates of all second line therapies are low. Recurrence of uterine cancer outside the pelvis is also palliative for most women, with even fewer chemotherapy options, each with low response rates. The response rate of PLD reported in the literature is up to 29% (Campos et al., 2001) in ovarian/fallopian tube/primary peritoneal cancers with up to 49% of patients with stable disease (Rose et al., 2001). There is less data about efficacy of PLD in uterine cancer, with series showing response rates of 9.5–21% (Escobar et al., 2003; Muggia et al., 2002). If a patient with one of these diseases has a response to PLD, this and other series show the response could be prolonged. In this series, median PFS was 12 months, with a range of 10–66 months. Median overall survival of women with a prolonged response to PLD was 57.2 months, with a range of 21.8–223.3 months. Limitations of lifetime doses of PLD based on unsubstantiated cardiac risks may shorten overall survival time for select patients with recurrent ovarian/fallopian tube/primary peritoneal and uterine cancers.

The quality of life for patients on PLD is generally good, with low rates of Grade 3/4 toxicities. Patients with incurable disease often prioritize quality of life to a greater degree than those with hopes of cure. While the most commonly reported symptoms are dermatologic, patients in this series reported few side effects overall. Their perceived quality of life allowed continued treatment in circumstances under which any toxicity at all may have led them to decline active treatment in favor of palliative care alone. There were no Grade 3 or 4 toxicities in our study population. Grade 1 and 2 toxicities were limited to dermatologic, including palmar-plantar erythrodysesthesia (PPE) or rash, and nausea. While response rates may be improved with doublet therapy, the risk and toxicity of doublets is higher. This was shown by the AURELIA trial, where doublet therapy using second line chemotherapy

Table 4
Cardiac monitoring.

Patient	History of heart disease	Baseline LVEF	Interval LVEF (PLD cycles completed)	Post-PLD LVEF (test used)	PLD cycles completed at last LVEF (total cycles)	Time from final PLD cycle to last LVEF (months)*	Clinical signs or symptoms of heart disease**
1	No	60%[a]	65% (19)[a]	55–60%[a]	31 (31)	0.2	No
2	No	60%[a]	65% (24)[a]	65%[a]	25 (25)	16.7	No
3	No	?	60% (12)[b]	?	12 (18)	–	No
4	No	?	–	?	NA	–	No
5	No	?	60% (13)[a]	?	13 (14)	–	No
6	No	61%[b]	61% (6)[b]	55–60%[a]	13 (13)	0.7	No
7	No	?	–	58%[b]	13 (13)	0.7	No
8	No	?	66% (10)[b] and 70% (16)[b]	66%[b]	22 (22)	57.4	No
9	No	70%[b]	70% (7)[b]	60%[a]	12 (12)	20.7	No
10	Yes***	?	65% (10)[a]	?	10 (12)	–	No
11	No	?	–	55%[a]	12 (12)	15.8	No
12	No	?	–	72%[b]	11 (11)	27.0	No
13	No	60–65%[a]	–	–	0 (11)	–	No
14	No	?	–	70%[a]	11 (11)	1.7	No
15	No	76%[b]	–	60%[a]	10 (10)	54.7	No
16	No	?	–	–	NA	–	No
17	No	?	60% (9)[a]	–	9 (10)	–	No
18	No	?	–	–	NA	–	No

* In this column indicates that no LVEF measurements were taken after completion of PLD.
** At any point during or after PLD treatment.
*** Atrial fibrillation well controlled on atenolol.
[a] Measured by TTE.
[b] Measured by MUGA.

with bevucizumab resulted in improved PFS by 3.3 months, at the cost of an increase in adverse events from 40.3% to 57%. Interestingly, there was no increase in heart failure when bevucizumab was added to standard second line single agent chemotherapy, but there was an increase in PPE (Pujade-Lauraine et al., 2013). Treatment with single-agent PLD offers minimal side effects while offering potentially prolonged responses.

The most concerning potential side effect of doxorubicin and PLD is often cited as congestive heart failure. Doxorubicin works through several mechanisms of action, primarily inhibition of DNA topoisomerase II which induces DNA double strand breaks. Doxorubicin also binds to mitochondrial cardiolipin and intracellular iron, creating oxygen free radicals. Doxorubicin-induced oxidative stress and oxygen free radicals in turn lead to cardiomyocyte damage. Cardiac tissue is more sensitive to oxidative stress because of their metabolic differences and mitochondrial density compared to tumor cells. Cardiomyocytes have non-chelated intracellular iron which also increases the production of oxygen free radicals by doxorubicin. High doses of the drug increases the toxicity to both cardiac tissue and tumor. PLD is one of the first FDA approved and most frequently used nanomedicines, formulated to specifically target tumor tissue. Doxorubicin is loaded into small liposomes that are selectively released through fenestrations of blood vessels in tumor tissue. The liposomal preparation allows sparing of doxorubicin effect on healthy tissue including cardiomyocytes. Lower plasma concentration of doxorubicin is also seen with PLD due to slow release into blood and tissue because of the liposome. Pegylation, coating the liposome with a hydrophilic protective coating, allows a prolonged time of the drug in circulation due to its ability to evade immunologic elimination. Both lower plasma levels and improved ability to target tumor tissue allow for the sparing of cardiac toxicity with PLD (Gabizon et al., 2016).

The degree to which the cardiac risk is reduced with PLD is not well established. Theodoulou and Hudis (Theodoulou and Hudis, 2004) state that use of PLD vs. conventional doxorubicin reduced incidence of cardiotoxicity by 5-fold even in doses $\geq 500\ mg/m^2$. This benefit was also seen in patients with a high risk for cardiotoxicity, such as those over 65 or a history of cardiac disease. There are multiple case series reporting outcomes for over 100 patients undergoing treatment with prolonged courses of PLD ($> 450\ mg/m^2$). In these case series, there were no patients with any clinical evidence of cardiac toxicity, and only one reported to have > 10% change in ejection fraction without any symptoms of heart failure (Rabinovich et al., 2015; Safra et al., 2000; Uyar et al., 2004; Gill et al., 2013; Kesterson et al., 2010). Our data on an additional 18 women with cumulative PLD doses ranging from 660 mg–2794 mg and no symptoms of cardiotoxicity, support these findings. This significantly challenges the validity of a maximum recommended lifetime dose of PLD for palliative use.

Cardiac monitoring with MUGA or echocardiography (ECHO) is frequently utilized during the course of PLD treatment, however the need for such measurements is not well established. The NCCN recommends a baseline ECHO with repeat testing at the physician's discretion. There are several studies that support the need for cardiac surveillance on a selective basis. Gill et al. (Gill et al., 2013) propose that only patients with cumulative doses of PLD $\geq 1000\ ng/m^2$ should be monitored. Alternatively, Kushnir et al. (Kushnir et al., 2015) proposed that monitoring only select patients at increased risk for cardiac disease was much more cost-effective without adversely affecting clinical outcomes. The patients we present underwent testing depending on the practice patterns of the treating physician, cardiac risk factors, and total dose of PLD given.

Treatment with PLD is palliative, making informed consent vital to the discussion of treatment. The theoretical risks of treatment-related heart failure must be weighed against risk of death from disease. Virtually all patients with recurrent ovarian cancer will die of their disease or other life-limiting comorbidities. Over 80% of patients with uterine cancer recurrences outside the pelvis will face the same prognosis. Quality of life throughout the duration of palliative treatment must be a major factor in discussion of goals of treatment and is considered a distinguishable benefit of PLD. With appropriate counseling, patient and physicians together may decide whether the quality of life and potential quantity of life benefits are worth taking the evidently limited risk of developing heart failure.

The strength of this study is in the number of patients who met the inclusion criteria during the study period. This provides strength for the assertions of the authors and builds on much of the recently published data describing the safety of this treatment from a cardiac standpoint. A weakness of this report is its retrospective nature, which limits the standardization of treatment among patients. There was also no standard protocol for cardiac monitoring during the time period of the study. The study period is long and multiple providers cared for these patients, although one provider treated over 90% of them. The experience of the other 138 patients who underwent treatment with < 10 cycles of PLD was not described, but the treating physicians had no anecdotal evidence for discontinuation of treatment due to clinical symptoms of CHF. The patients treated with at least 10 cycles of PLD who died during the period of the study and data collection did not have autopsies to assess cardiac function peri-mortem. Quality of life data was retrieved from retrospective studies. Future prospective studies using QOL questionnaires may more objectively measure toxicity.

In conclusion, for patients with advanced recurrent gynecologic malignancies, PLD can be an effective drug for prolonged palliative use. The collective experience of these patients show that the quality of life impact does not include cardiac toxicity. This is useful for providers when considering prolonged PLD as a palliative treatment option for patients with clinical benefit from the drug.

Author contribution

Dr. Anna Hoekstra participated in the literature review, care of the patients, writing and editing the manuscript. Dr. Sam Yost performed the literature review, data collection and analysis, writing of the manuscript. Dr. Jessica Konal participated in literature review, writing and editing the manuscript.

Declaration of Competing Interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript. This project underwent review and approval by the local institutional review board. Informed consent has been obtained from patients and/or families of deceased patients for completion of this study.

References

Barenholz, Y.C., 2012. Doxil ® — The first FDA-approved nano-drug: lessons learned. J. Control. Release 160 (2), 117–134. https://doi.org/10.1016/j.jconrel.2012.03.020.

Blank, N., Laskov, I., Kessous, R., Kogan, L., Lau, S., Sebag, I.A., ... Rudski, L., 2017. Absence of cardiotoxicity with prolonged treatment and large accumulating doses of pegylated liposomal doxorubicin. Cancer Chemother. Pharmacol. 80 (4), 737–743. https://doi.org/10.1007/s00280-017-3412-8.

Campos, S.M., Penson, R.T., Mays, A.R., Berkowitz, R.S., Fuller, A.F., Goodman, A., ... Seiden, M.V., 2001. The clinical utility of liposomal doxorubicin in recurrent ovarian cancer. Gynecol. Oncol. 81 (2), 206–212. https://doi.org/10.1006/gyno.2000.5980.

Escobar, P.F., Markman, M., Zanotti, K., Webster, K., Belinson, J., 2003. Phase 2 trial of pegylated liposomal doxorubicin in advanced endometrial cancer. J. Cancer Res. Clin. Oncol. 129 (11), 651–654. https://doi.org/10.1007/s00432-003-0497-8.

Gabizon, A.A., Patil, Y., La-Beck, N.M., 2016. New insights and evolving role of pegylated liposomal doxorubicin in cancer therapy. Drug Resist. Updat. 29 (2016), 90–106. https://doi.org/10.1016/j.drup.2016.10.003.

Gill, S.E., Savage, K., Wysham, W.Z., Blackhurst, D.W., Winter, W.E., Puls, L.E., 2013. Continuing routine cardiac surveillance in long-term use of pegylated liposomal doxorubicin: is it necessary? Gynecol. Oncol. 129 (3), 544–547. https://doi.org/10.1016/j.ygyno.2013.03.012.

Grenader, T., Goldberg, A., Gabizon, A., 2010. Monitoring long-term treatment with pegylated liposomal doxorubicin: how important is intensive cardiac follow-up? Anti-Cancer Drugs 21 (9), 868–871. https://doi.org/10.1097/CAD.0b013e32833dc3c4.

Kesterson, J.P., Odunsi, K., Lele, S., 2010. High cumulative doses of pegylated liposomal doxorubicin are not associated with cardiac toxicity in patients with gynecologic malignancies. Chemotherapy 56 (2), 108–111. https://doi.org/10.1159/000312644.

Kushnir, C.L., Angarita, A.M., Havrilesky, L.J., Thompson, S., Spahlinger, D., Sinno, A.K., ... Fader, A.N., 2015. Selective cardiac surveillance in patients with gynecologic cancer undergoing treatment with pegylated liposomal doxorubicin (PLD). Gynecol. Oncol. 137 (3), 503–507. https://doi.org/10.1016/j.ygyno.2015.02.020.

Muggia, F.M., Blessing, J.A., Sorosky, J., Reid, G.C., 2002. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a gynecologic oncology group study. J. Clin. Oncol. 20 (9), 2360–2364. https://doi.org/10.1200/JCO.2002.08.171.

Pujade-Lauraine, E., Hilpert, F., Weber, B., Reuss, A., Poveda, A., Kristensen, G., ... Ray-Coquard, I., 2013. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J. Clin. Oncol. 32 (13), 1302–1308. https://doi.org/10.1200/JCO.2013.51.4489.

Rabinovich, A., Ramanakumar, A.V., Lau, S., Gotlieb, W.H., 2015. Prolonged pegylated liposomal doxorubicin treatment for recurrent pelvic cancers: a feasibility study. Acta Obstet. Gynecol. Scand. 94 (7), 776–780. https://doi.org/10.1111/aogs.12642.

Rose, P.G., Hawthorne Maxson, J., Fusco, N., Mossbruger, K., Rodriguez, M., 2001. Liposomal doxorubicin in ovarian, peritoneal, and tubal carcinoma: a retrospective comparative study of single-agent dosages. Gynecol. Oncol. 82 (2), 323–328. https://doi.org/10.1006/gyno.2001.6272.

Safra, T., Muggia, F., Jeffers, S., Tsao-Wei, D.D., Groshen, S., Lyass, O., ... Gabizon, A., 2000. Original article patients reaching or exceeding cumulative doses of 500 mg/m2. Ann. Oncol. 11, 1029–1033. https://doi.org/10.1023/A:1008365716693.

Skubitz, K.M., Blaes, A.H., Konety, S.H., Francis, G.S., 2017. Cardiac safety profile of patients receiving high cumulative doses of pegylated-liposomal doxorubicin: use of left ventricular ejection fraction is of unproven value. Cancer Chemother. Pharmacol. 80 (4), 787–798. https://doi.org/10.1007/s00280-017-3420-8.

Theodoulou, M., Hudis, C., 2004. Cardiac profiles of liposomal anthracyclines: greater cardiac safety versus conventional doxorubicin? Cancer 100 (10), 2052–2063. https://doi.org/10.1002/cncr.20207.

Uyar, D., Kulp, B., Peterson, G., Zanotti, K., Markman, M., Belinson, J., 2004. Cardiac safety profile of prolonged (≥6 cycles) pegylated liposomal doxorubicin administration in patients with gynecologic malignancies. Gynecol. Oncol. 94 (1), 147–151. https://doi.org/10.1016/j.ygyno.2004.03.024.