ORIGINAL ARTICLE

Pegylated liposomal doxorubicin (CAELYX®) in patients with advanced ovarian cancer: results of a German multicenter observational study

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Abstract

Purpose Pegylated liposomal doxorubicin (PLD, CAE-LYX®) has demonstrated activity in several phase-III trials and has been approved for the therapy of relapsed ovarian cancer after platinum treatment. Aim of this observational study was to analyze the efficacy and toxicity profile of PLD under routine clinical conditions and without the general restrictions of defined inclusion and exclusion criteria of clinical trials.

Methods Between 2003 and 2005, a total of 190 patients with relapsed ovarian cancer were enrolled. 183 patients were available for evaluation; dose-intensity, modifications, treatment duration, toxicities and response were systematically analyzed.

Results The median patient age was 62 years (range 23–86 years). 45.4% of the patients received PLD as second-line therapy and a median of four courses per patient were administered. The median dose of PLD was 40 mg/m^2, most frequently used every 4 weeks (68.8%). Grade 3 Leucopenia (1.6%) and grade 3 and 4 thrombocytopenia (0.5%) were the most frequent hematological toxicities. The most frequent non-hematological toxicities were skin toxicity, pain and nausea, which were observed in 38.8, 41 and 45.9% of the patients, respectively. Twenty-seven percent of the patients showed a response to therapy with 6.9% achieving complete remission and 20.1% achieving partial remission. 37.7% achieved a stable disease. The median duration of response for all patients was 4.8 months (range 0–51.8 months). Median progression-free interval and overall survival were 5.8 months (95% CI 5.1–6.6 months) and 16.6 months (95% CI 13.9–22.6 months), respectively.

Conclusions PLD is safe and effective in patients with relapsed ovarian cancer, even after numerous previous treatment regimens. A dose of 40 mg/m^2 every 28 days seems to be an effective and well-tolerated therapeutic option in advanced ovarian cancer with a low incidence of hematological toxicities and acceptable non-hematological toxicities.

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Abbreviations

BfArM	German Federal Institute for Drugs and Medical Devices
CI	Confidence interval
CR	Complete remission
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
nd	Not determined
NOGGO	North-Eastern German Society of Gynecological Oncology
PD	Progressive disease
PLD	Pegylated liposomal doxorubicin
PPE	Palmar-plantar erythrodysesthesia
PR	Partial remission
SAE	Serious adverse events
SD	Stable disease

Introduction

Standard primary therapy for advanced ovarian cancer consists of radical surgery with the goal of maximal tumor resection and combination chemotherapy with paclitaxel and carboplatin [1, 2]. Despite radical primary surgery with the goal of maximal tumor resection and initial high response rate to chemotherapy with carboplatin and paclitaxel, many patients relapse and die due to tumor progression. The aim of treatment for patients with recurrent ovarian cancer is a prolongation of survival with maintenance or improvement of quality of life, as a cure is generally not achievable. Various cytotoxic agents are active in recurrent ovarian cancer, including anthracyclines, which have a proven anti-tumor activity in various malignant solid tumors [3, 4]. However, the hematologic and cardiac toxicity of anthracyclines is clinically important and often dose limiting [3–5]. Thus, pegylated liposomal doxorubicin (PLD) was developed to improve the toxicity profile without compromising its activity against malignant tumor cells.

PLD is a stealth formulation of doxorubicin in which a polyethylene glycol layer surrounds a doxorubicin-containing liposome. These modifications significantly alter the pharmacokinetic and pharmacodynamic properties of the drug resulting in an increased bioavailability and increased half-life of this agent. In comparison to conventional doxorubicin, PLD causes significantly less hematological and cardiac side-effects as well as alopecia, while skin toxicities are observed more frequently [5, 6]. PLD has demonstrated activity in recurrent ovarian cancer in various phase-III trials, in both platinum-resistant and platinum-sensitive patients [7, 8].

In the European Union, in the United States and in many other western countries, PLD at a dose of 50 mg/m^2 every 28 days has been approved for the treatment of recurrent ovarian cancer in women who have failed platinum-based therapy.

Primary objective of this multicenter observational study was to analyze the toxicity profile and the efficacy of PLD in daily clinical practice without the general restrictions of predefined inclusion and exclusion criteria of clinical trials. A special focus was put on the application and modification of the approved dosage of PLD by physicians under routine conditions.

Patients and methods

Study design

This study was conducted as multicenter observation study in Germany. According to national guidelines it was registered and approved by the German Federal Institute for Drugs and Medical Devices (BfArM), the German Federal Association of Panel Doctors and the Association of Health Insurances (represented by the Federal BKK Organization). This study was initiated by ESSEX Pharma Germany, all statistical analyses and their interpretation as well as the preparation of the manuscript were completely independent and performed by the authors only.

Patient eligibility and treatment

Patients with recurrent ovarian cancer were treated with PLD for a maximum of 12 cycles.

Disease recurrence was determined clinically (physical examination, ultrasound, CT or MRI). No restrictions were made with regard to prior therapies, co-morbidities or concomitant medications. No further inclusion or exclusion criteria were defined and the indication for a treatment with PLD as well as the eligibility of patients for this study was judged by the investigators of each participating institution. Demographic data, previous cytostatic therapies and concomitant diseases as well as the applied dosage and application intervals of PLD were analyzed.

Toxicity determinations

Toxicities were determined according to the classification of the National Cancer Institute "Common Terminology Criteria for Adverse Events" (CTCAE) in the version of 1994 at the end of each cycle. Safety was assessed by the

analysis of toxicity parameters (occurrence of adverse events, serious adverse events (SAE) and deaths).

Response

Response was assessed by evaluation of clinical response parameters according to best clinical practice. In patients with bi-dimensionally measurable disease, response was determined by physical examination and ultrasound, CT or MRI. Generally, response evaluation was not based on CA-125 determination. Neither the type of diagnostic test nor the time of its application was predefined by the protocol. Response evaluation was routinely performed at the third and sixth cycle of chemotherapy and documented as "best response to therapy" for every patient. Progressive disease was also documented. "Time to response" was defined as the interval between the first cycle of PLD and achievement of best response.

Statistical analysis

All analyses were conducted in an exploratory fashion. Data are presented as raw numbers, rates, or medians and ranges, according to the underlying distribution. Binomial-exact 95% confidence intervals (CI) are presented. Toxicity and clinical response rates were also evaluated descriptively. For continuous variables, the mean, standard deviation, median, minimum and maximum are provided. Subgroup analyses of patients with platinum-sensitive or platinum-resistant disease could not be performed because the interval between last cycle of platinum-based chemotherapy and date of relapse had not been uniformly documented. Progression-free survival and overall survival were modeled by the non-parametric Kaplan–Meier method.

Results

Patient characteristics

Between May 2003 and November 2005, 190 patients with ovarian cancer were enrolled from 42 German institutions. 183 patients were assessable for response and safety analysis. Data of seven patients who received PLD as first-line therapy was not included in the analyses due to violation of the predefined protocol, since PLD is only approved for the treatment of recurrent ovarian cancer after failure of platinum-based chemotherapy. The characteristics of evaluable patients are provided in Table 1. Patients had a median age of 62 years (range 23–86 years). 73.8% of the patients had FIGO stage of III or IV disease at initial diagnosis and 97.3% had had debulking surgery as initial treatment.

Table 1 Patient Characteristics

No. of patients	190
Assessable for toxicity	183
Assessable for clinical response	183
Median age in years (range)	62 (23–86)
FIGO Status at initial diagnosis	
FIGO I	13 (7.1%)
FIGO II	18 (9.8%)
FIGO III	110 (60.1%)
FIGO IV	25 (13.7%)
Unknown	17 (9.3%)
Grading at initial diagnosis	
G1	9 (4.9%)
G2	78 (42.6%)
G3	70 (38.3%)
Unknown	26 (14.2%)
Histology at initial diagnosis	
Serous-papillary carcinoma	55 (30.1%)
Others	128 (69.9%)
ECOG-Performance Score before therapy	
0	48 (26.2%)
1	91 (49.7%)
2	31 (16.9%)
3	8 (4.4%)
unknown	5 (2.7%)
Therapeutically situation	
Second line	83 (45.4%)
Third line	64 (35.0%)
Fourth line	33 (18.0%)
>Fourth line	3 (1.6%)
Previous therapies	
Surgery	178 (97.3%)
1st Chemotherapy	149 (81.4%)
2nd Chemotherapy	95 (51.9%)
3rd Chemotherapy	35 (19.1%)
Irradiation	18 (9.8%)
Hormone therapy	12 (6.6%)
Immunotherapy	4 (2.2%)
Others	18 (9.8%)

Therapy

A total of 1,065 cycles of PLD chemotherapy were administered with a median of four courses per patient (range 1–12 courses). 21.3% of the patients received six courses. Table 2 provides an overview of the treatment parameters. The administration of PLD given in a 4 weeks interval was the most frequently used schedule and was applied in 68.8% of the patients. A biweekly regimen was applied in 21.6% and a 3-week interval in 9.7% of the patients. In seven patients the dose schedule could not be documented,

Table 2 Treatment

Total courses (patients)	1,065 (183)
Courses, median (range)	4 (1–12)
Patients with >1 course of therapy	176
(2-weekly scheme), n (%)	38 (21.6%)
(3-weekly scheme), n (%)	17 (9.7%)
(4-weekly scheme), n (%)	121 (68.8%)
PLD dose (all treatment schedules), median (range)	40 mg/m^2 (15–53)
PLD dose (2-weekly scheme)	20 mg/m^2 (15–40)
PLD dose (3-weekly scheme)	50 mg/m^2 (25–50)
PLD dose (4-weekly scheme)	40 mg/m^2 (20–53)
Therapy schedule, median (range)	4 weeks (2–4)
Treatment delay, courses/patients	95 (8.9%)/55 (30.1%)
Dose reduction, courses/patients	36 (3.4%)/28 (15.3%)
Supportive therapy, patients	172 (94.0%)

as only one course of PLD had been administered. The median PLD dose applied correlated with the applied therapy schedule. In the biweekly schedule a median PLD dose of 20 mg/m^2 (range 15–40 mg/m^2) was administered, whereas in the monthly scheme the median PLD dose was 40 mg/m^2 (range 20–53 mg/m^2). The median PLD dose of the 3-weekly regimen was 50 mg/m^2 (range 25–50 mg/m^2). A treatment delay was defined as any delay of >7 days after the scheduled application of a course of chemotherapy. According to this definition, 8.9% treatment delays occurred. Reasons for delay were organizational aspects (30.5%), followed by non-hematological toxicities (27.4%) and patient's preference (16.8%).

The main reason for therapy discontinuation was progressive disease followed by patient's preference and adverse events. These were observed in 90, 26 and 23 patients, respectively. A planned therapy discontinuation was documented for 26.8% of the patients.

In 36 courses (3.4% of total courses) PLD was given at a reduced dose. Non-hematological toxicities were the reasons most frequently specified for dose reduction (50.0%) followed by patient's preference (13.9%) and hematological side-effects (5.6%). 172 patients (90.5%) received prophylactic antiemetic treatment, and pyridoxine was given in 10 patients.

Toxicity

183 patients were assessable for toxicity. No unexpected toxicities occurred. Non-hematological toxicities were observed more often than hematological toxicities: Grade 3/4 non-hematological toxicities were observed about six times more often than hematological toxicities. Most of the grade 3/4-toxicities occurred in less than 1% of all courses.

Non-hematological toxicity

Analysis of toxicities per patient and per course revealed 592 non-hematological toxic events in 183 patients and 1,580 non-hematological toxic events in 1,065 courses. More than 50% were grade 1 toxicities. Nausea and skin toxicity were the most commonly observed non-hematological toxicities. Nausea with grade 1, 2 and 3 occurred in 55 (30.1%), 21 (11.5%) and 2 (1.1%) patients, respectively. Grade 1, 2 and 3 skin toxicity was observed in 38 (20.8%), 25 (13.7%) and 7 (3.8%) patients, respectively. Overall 13.4% of the patients were affected by grade 3/4 toxicities (Table 3). No cardiac toxicity was reported during or after PLD treatment.

Hematological toxicity

Hematological toxicities occurred significantly less frequent than non-hematological toxicities. Based on patients, 299 hematological events and based on courses, 897 hematological events were observed. The majority were grade 1 toxicities. Hematological side-effects were generally not associated with severe complications. Anemia was the most frequent hematological side-effect. Grade 4 toxicity was only noted in form of thrombocytopenia in 0.5% of the patients. Table 4 lists all grade 3 and 4 toxicities.

Serious adverse events

Altogether 29 reported toxicities in 23 patients were considered as SAE (1 patient had 3 SAE, 4 patients had 2 SAE). The most frequent SAE was hospitalization due to toxicity (31.0%). Forty-nine percent of the SAE were classified as possibly or probably related to the therapy with PLD by the responsible investigators. Four patients died during therapy, all deaths were classified as unrelated to PLD treatment.

Response and survival

A summary of best responses is provided in Table 5. Forty-three patients (27%) achieved a clinical response to therapy with 6.9% complete remission (CR) and 20.1% partial remission (PR). Stable disease (SD) was observed in 60 patients (37.7%) and 56 patients (30.6%) developed progress during chemotherapy.

If PLD was given as second-line treatment, the response rate was 28.9% (CR = 8.4%, PR = 20.5%), whereas the response rate in patients with more than two previous chemotherapy regimens was lower (19.0%, CR = 5.0%, PR = 14.0%, $p = 0.085$). However, statistical significance was not reached. The median time to best response was 3.7 months (range 0.03–30.3 months/95% CI 3.9–5.0).

Table 3 List of non-hematological toxicities (% of 1,065 courses/% of 183 patients)

Toxicity	All grades		NCI grade 1		NCI grade 2		NCI grade 3		NCI grade 4		NCI grade unknown	
	Courses (%) (n = 1,065)	Patients (%) (n = 183)	Courses (%) (n = 1,065)	Patients (%) (n = 183)	Courses (%) (n = 1,065)	Patients (%) (n = 183)	Courses (%) (n = 1,065)	Patients (%) (n = 183)	Courses (%) (n = 1,065)	Patients (%) (n = 183)	Courses (%) (n = 1,065)	Patients (%) (n = 183)
Allergic reaction	0.2	1.1	0.1	0.5	0.0	0.0	0.1	0.5	0.0	0.0	0.0	0.0
Alopecia	17.9	26.8	10.5	13.7	4.0	4.9	1.1	2.2	0.0	0.0	2.3	6.0
Diarrhea	11.0	22.4	5.8	9.8	2.6	6.0	0.8	1.1	0.0	0.0	1.8	5.5
Infection	1.1	4.4	0.4	1.1	0.7	2.7	0.0	0.0	0.1	0.5	0.0	0.0
Nausea	22.3	45.9	16.5	30.1	3.9	11.5	0.2	1.1	0.0	0.0	1.6	3.3
Obstipation	14.1	32.2	10.0	21.9	2.3	6.0	0.1	0.5	0.2	0.5	1.4	3.3
Skin toxicity	23.9	40.4	16.4	20.8	5.1	13.7	1.0	3.8	0.0	0.0	1.3	2.2
Thrombosis	0.1	0.5	0.0	0.0	0.0	0.0	0.1	0.5	0.0	0.0	0.0	0.0
Stomatitis	11.5	27.9	7.7	15.8	2.3	8.2	0.1	0.5	0.0	0.0	1.5	3.3
Vomiting	9.9	27.9	6.1	15.8	1.7	5.5	0.4	2.2	0.0	0.0	1.7	4.4
Sum	112.0	229.5	73.1	129.5	22.6	58.5	3.9	12.4	0.3	1.0	11.6	28.0

Kaplan–Meier Analysis of median progression-free interval and overall survival of all patients showed 5.8 months (95% CI 5.1–6.6) and 16.6 months (95% CI 13.9–22.6), respectively (Fig. 1). For patients with complete or partial response to PLD-therapy, the median progression-free interval was 8.1 months (95% CI 6.1–11.6), whereas patients with SD as best clinical response had a progression-free interval of 6.4 months (95% CI 5.5–9.9).

Discussion

PLD has demonstrated efficacy in the treatment of relapsed ovarian cancer [7, 9]. Despite this well-documented experience from clinical phase-III studies there is only limited information about the use of PLD in clinical routine without the 'restriction' of inclusion and exclusion criteria of a controlled phase-III trial.

An observational study represents a trial in which the principal investigators do not influence the use of a specific approved intervention. Therefore, the local investigators do not treat the individual patient according to a detailed study protocol. Instead, routine clinical practice is applied and the patients are observed by the local investigator. Thus, observational studies are prone to bias, but can nonetheless be useful to generate hypotheses and evaluate clinical reality after a new drug has been approved. To our knowledge, this is the first report of a multicenter observation trial of PLD in recurrent ovarian cancer.

Based on various randomized phase-III trials, PLD was approved for patients with recurrent ovarian cancer after first-line platinum based chemotherapy [7, 8, 10]. The approved dose of PLD is 50 mg/m^2 every 4 weeks. In the present study, physicians most frequently used PLD with 40 mg/m^2 every 4 weeks.

Observational studies aim to describe the clinical reality. Thus, we can not explain, why a dose reduction of 20% was preferred. In several non-randomized studies, authors concluded that 40 mg/m^2 every 28 days was equally effective to the higher dose with significantly lower rates of palmar-plantar erythrodysesthesia (PPE), mucositis and other toxicities [9, 11]. For instance, Rose et al. [12] performed a retrospective analysis in patients with recurrent ovarian cancer that were treated with PLD at different dosages. In the cohort of patients treated with an initial dose of 40 mg/m^2 PLD every 28 days instead of the approved dose of 50 mg/m^2, fewer treatment delays and a lower rate of PPE were observed. In this analysis, no significant differences in response were observed between both dose levels. In general, the toxicity profile of PLD given at the approved dose level usually consists of PPE and stomatitis. Previous studies report a rate of PPE between 30 and 50% [7] with grade 3 and 4 of 20–32%.

Table 4 List of hematological toxicities of grade 3/4 (% of 1065 courses/% of 183 patients)

Toxicity	All grades		NCI grade 3		NCI grade 4	
	Courses (%) ($n = 1,065$)	Patients (%) ($n = 183$)	Courses (%) ($n = 1,065$)	Patients (%) ($n = 183$)	Courses (%) ($n = 1,065$)	Patients (%) ($n = 183$)
Anemia	33.2	60.1	0.2	0.5	0.0	0.0
Leukopenia	22.1	45.4	0.4	1.6	0.0	0.0
Neutropenia	24.0	41.0	0.1	0.5	0.0	0.0
Thrombocytopenia	4.8	16.4	0.2	0.5	0.1	0.5
Sum	84.1	162.9	0.9	3.1	0.1	0.5

Table 5 Best response during therapy

Clinical response	Number of patients	% patients ($n = 159$)
CR	11	6.9
PR	32	20.1
SD	60	37.7
PD	56	35.2
Sum	159	
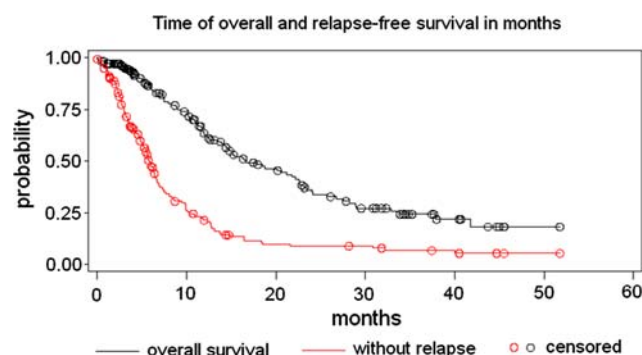
Fig. 1 Progression-free survival (*red*) and overall survival (*black*) in months, 183 patients

In the present observational study, skin toxicity was reported in 40.4% of the patients, in which no differentiation was made between PPE and other skin toxicities. Even in the available results of published phase-III trials, a detailed differentiation between PPE and other skin toxicities was not performed despite the fact that there are various different chemotherapy induced skin toxicities [7, 8, 10, 13]. Thus, future trials should give more attention to this relevant topic to identify possible risk factors as well as adequate therapies for skin toxicities. Of note, only 3.8% of the patients in our study developed grade 3 or 4 skin toxicity. Ten patients received pyridoxine despite the lack of evidence for its efficacy to prevent or treat PPE [14]. It is important to note that despite the promising results with reduced dose of PLD there is no prospective randomized study comparing 40 and 50 mg/m² of PLD every 28 days in relapsed ovarian cancer.

More than 20% of the patients in our study were treated with a biweekly schedule, again despite the fact that currently no randomized study has shown equal efficacy. However, the North-Eastern German Society of Gynecological Oncology (NOGGO) could previously demonstrate that PLD given at a dose of 20 mg/m² every two weeks is feasible and well tolerated in heavily pre-treated patients with relapsed ovarian cancer [15, 16]. In this cohort, only 3 out of 64 patients developed grade 3/4 PPE. In this first study with a biweekly schedule, 13 of the 64 included patients received PLD as a second-line therapy. Another phase-II study with PLD as second-line treatment could confirm the feasibility and efficacy of the biweekly schedule [16]. The lower dose applied in most of the patients in our observational study might also explain the significantly lower incidence and severity of hematological and non-hematological toxicities. Another reason might be that—in contrast to controlled phase-III trials—side-effects are possibly under-reported in observational trials.

Nevertheless, the outcome parameter reported, including response rate, progression-free survival and overall survival are in the range of previously published phase-III studies. Due to the indirect cross-trial comparison and the mixture of patients with different PLD regimens, no final conclusion can be made about the efficacy of these dose modifications.

Despite these limitations, PLD given at a monthly dose of 40 mg/m², which is lower than the recommended 50 mg/m², seems to be an effective and well-tolerated option in advanced ovarian cancer, minimizing toxicities but maintaining clinical benefit for pre-treated patients. Thus, a randomized study comparing both dose schedules is highly desirable.

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