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ORIGINAL ARTICLE

Factors affecting the pharmacokinetics of pegylated liposomal doxorubicin in patients

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Abstract
Purpose There is significant inter-patient variability in the pharmacokinetics of pegylated liposomal doxorubicin (PLD). Identification of factors affecting the pharmacokinetics of PLD would enable personalization of therapy. We previously reported that age, gender, body composition, and monocytes affect the clearance of other liposomal agents. Therefore, we evaluated how these factors affect the pharmacokinetics of PLD.
Methods Pharmacokinetic studies of PLD were performed as part of phase I and II studies in 70 patients with solid tumors or Kaposi's sarcoma. The effects of monocyte count, age, gender, and body composition on PLD clearance were examined.
Results There was a 15.3-fold variability in PLD clearance. Body surface area-based dosing did not significantly reduce the variability in PLD clearance. The mean ± SD clearance for patients <60 years old and ≥60 years old were 54.6 ± 28.5 and 23.3 ± 10.8 mL/h/m^2, respectively

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($P < 0.0001$), and for female and male patients were 23.7 ± 18.8 and 55.6 ± 26.8 mL/h/m^2, respectively ($P < 0.0001$). A reduction in pre-cycle monocyte count was associated with a greater reduction in PLD clearance.

Conclusions Age, gender, and monocyte counts appear to correlate with PLD clearance. Further investigation of the association between these factors, PLD pharmacokinetics, and clinical outcomes (efficacy and toxicity) is warranted. These effects on the pharmacokinetics of PLD may be an approach for personalizing PLD therapy and may affect other pegylated liposomes and nanoparticle agents.

Keywords Doxil · Liposomal · Pharmacokinetics · Variability · Monocytes · Reticuloendothelial system · Doxorubicin

Introduction

Nanoparticle-associated anticancer agents, such as PLD, may provide increased tumor delivery and antitumor activity as well as reduced toxicity as compared with traditional small molecule anticancer agents [1]. Pegylated liposomal doxorubicin (PLD, Doxil®) is approved worldwide for the treatment of recurrent ovarian cancer, advanced breast cancer (except for the US), AIDS-related Kaposi's sarcoma, and multiple myeloma [2, 3]. However, there is significant inter-patient variability in the clearance of PLD and it is currently difficult to predict which patient will have a high or low clearance of PLD. In addition, the factors that affect the pharmacokinetics of PLD are unclear. The main clearance pathway of non-pegylated and pegylated liposomes is via the reticuloendothelial system (RES), which include monocytes, macrophages, and dendritic cells located primarily in the liver, spleen, and bone marrow [4, 5]. Studies suggest that monocytes and macrophages engulf nanoparticle-associated drugs, such as PLD, as a mechanism of clearance [4, 6, 7]. Thus, factors which affect RES activity could affect PLD clearance, toxicity, and response.

One proposed method for individualizing PLD dosing is by using body surface area (BSA). However, it has been shown that this approach still results in large inter-patient variability in drug exposure for most chemotherapeutic agents [8, 9] and possibly also for PLD [10]. Furthermore, the clearance of PLD decreases significantly from cycle 1 to cycle 3 [11]. Yet, the factors associated with the variability and decrease in clearance have not been identified. A decrease in clearance of PLD has clinical significance since a longer PLD half-life has been found to be associated with a greater risk of skin toxicity [12], and drugs such as taxanes, which retard clearance of PLD, increase the incidence and severity of skin toxicity [13].

In order to improve response and minimize toxicity with PLD therapy, it is imperative that factors associated with intra- and inter-patient variability in the pharmacokinetics and pharmacodynamics of PLD are identified. Since the RES is involved in the clearance and tumor delivery of carrier-mediated agents, patient factors that affect RES function may be associated with the variability in the pharmacokinetics and pharmacodynamics of PLD. These factors may include age and gender since there is a decline in immune function associated with aging, which may also affect the RES [14, 15]. In addition, gender may be an important factor since male and female sex hormones may have immune suppressive or immune stimulatory effects [16]. Therefore, we evaluated the relevance of BSA dosing for PLD and how age, gender, body composition, and monocyte count affect the pharmacokinetic disposition of PLD.

Materials and methods

Patients, dosage, and administration

Pharmacokinetic studies of PLD were conducted as part of three phase I and II studies in patients with solid tumors (22 and 12 patients, respectively) and in patients with acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma (36 patients). Detailed study methods are published elsewhere [11, 17]. Briefly, inclusion criteria included patients >18 years of age with histologically or cytologically confirmed solid tumors or Kaposi's sarcoma that were refractory to at least one conventional therapy or for whom no standard therapy existed. All patients had adequate organ function. Exclusion criteria included patients with a prior cumulative exposure to doxorubicin >400 mg/m^2. The studies were approved by the institutional review board, and written informed consent was obtained from all patients prior to study entry.

In study 1 (22 patients with solid tumors) and study 2 (36 patients with AIDS-related Kaposi's sarcoma), PLD was administered at doses of 10–60 mg/m^2 IV every 28 days. In study 3 (12 patients with solid tumors), subjects were randomized to one of two treatment arms: PLD administered IV every 28 days at 30, 60, and 45 mg/m^2 (six patients) on cycles 1, 2, and 3, respectively, or PLD administered IV every 28 days at 60, 30, and 45 mg/m^2 (six patients) on cycles 1, 2, and 3, respectively.

Sample collection, processing, analytical studies, and pharmacokinetic analysis

The complete methods for sample collection, preparation, and analysis have been published in detail elsewhere [11, 17]. Briefly, pharmacokinetic studies were performed for cycle 1 only for studies 1 and 2. Blood samples were collected at

baseline, and at 0.5, 1, 4, 8, 24, and 96 h, and 7, 10, 21, 22, 25, and 28 days after administration of PLD. In study 3, pharmacokinetic studies were performed for cycles 1, 2, and 3. Blood samples were collected at baseline, and at 1, 24, and 72–96 h, and 7, 14, 21, and 28 days after administration of PLD. Plasma levels of sum total doxorubicin (encapsulated and released) were determined by high-pressure liquid chromatography (HPLC) with fluorescence detection. The clearance of sum total doxorubicin, mL/h/m^2 and mL/h, was calculated for each patient by non-compartmental methods using standard equations in WinNonlin.

In study 3, absolute monocyte count was obtained up to 1 week prior to the administration of PLD for each of the first 3 cycles of therapy. Changes in monocyte count from cycle 1 to cycle 3 of PLD therapy were determined by taking the difference between the two laboratory values and categorized as a decrease, no change, or increase in monocyte count. Monocyte counts were not available for studies 1 and 2.

Criteria by Baker et.al. were used to determine whether BSA dosing was associated with a reduction in inter-patient variability in PLD clearance. These criteria are as follows: (1) a linear regression coefficient between BSA and PLD clearance (mL/h) with $R^2 \geq 0.25$; (2) $P < 0.01$ for R^2; and (3) a relative reduction in variability of clearance ≥15% [18]. The ratio of actual body weight to ideal body weight (ABW/IBW) and body mass index (BMI) was calculated using standard equations, as a measure of body composition [9].

Statistical analysis

Pre-cycle monocyte count, age, gender, and ABW/IBW were compared with PLD clearance. Comparisons were made using analysis of variance (ANOVA), and statistical significance was determined using Wilcoxon and Kruskal–Wallis tests; adjustments were made for multiple comparisons. The statistical analysis was performed using SAS software (Cary, NC).

Results

Patient characteristics

Detailed patient characteristics and pharmacokinetic parameters are published elsewhere [11, 17] and briefly summarized here in Table 1. The mean ± standard deviation (SD) age of patients with Kaposi's sarcoma was significantly lower than solid tumor patients, 39.9 ± 5.3 and 62 ± 11.5, respectively ($P < 0.0001$). The mean ± SD ABW/IBW ratios in patients with Kaposi's sarcoma were also significantly lower than in solid tumor patients, 0.99 ± 0.17 and 1.24 ± 0.28, respectively ($P < 0.0001$). There was a 15.3-fold variability in PLD clearance (range 8.8–135.0 mL/h/m^2) for all patients and a 10-fold variability in PLD clearance (range 8.8–92.6 mL/h/m^2) for solid tumor patients, respectively. The mean ± SD PLD clearance in all patients and in solid tumor patients were 46.1 ± 28.6 and 28.0 ± 18.1 mL/h/m^2, respectively.

Evaluation of body surface area dosing

The linear regression coefficient between BSA and PLD clearance (mL/h) on cycle 1 was $R^2 = 0.25$. The relative reduction in variability of clearance was 8.6%. The criteria by Baker et.al, used to determine whether BSA dosing was associated with a reduction in inter-patient variability in PLD clearance, were not met. Thus, BSA dosing does not result in significant reduction in inter-patient variability in PLD clearance.

Table 1 Summary of gender, body composition, age characteristics, and PLD clearance of the study groups

	Gender	ABW/IBW Mean ± SD Median (range)	BMI Mean ± SD Median (range)	BSA (m^2) Mean ± SD Median (range)	Age (years) Mean ± SD Median (range)	PLD clearance (mL/h/m^2) Mean ± SD Median (range)
Kaposi's sarcoma patients	36 males	0.99 ± 0.17* 0.98 (0.66–1.32)	22.02 ± 3.86 21.97 (14.75–29.16)	1.91 ± 0.17 1.90 (1.46–2.30)	39.9 ± 5.3† 41 (28–50)	63.1 ± 26.2§ 58.8 (24.7–135.0)
Solid tumor patients	13 males 21 females	1.24 ± 0.28* 1.22 (0.60–1.87)	26.17 ± 4.92 25.29 (13.85–34.61)	1.74 ± 0.19 1.72 (1.36–2.42)	62 ± 11.5† 62.5 (33–77)	28.0 ± 18.1§ 21.1 (8.8–92.6)
All patients	49 males 21 females	1.11 ± 0.26 1.05 (0.60–1.87)	24.04 ± 4.85 23.38 (13.85–34.61)	1.83 ± 0.20 1.81 (1.36–2.42)	50.6 ± 14.2 46 (28–77)	46.1 ± 28.6 42.2 (8.8–135.0)

SD standard deviation, *ABW* actual body weight, *IBW* ideal body weight, *BMI* body mass index, and *BSA* body surface area

* $P < 0.0001$; † $P < 0.0001$; § $P < 0.0001$

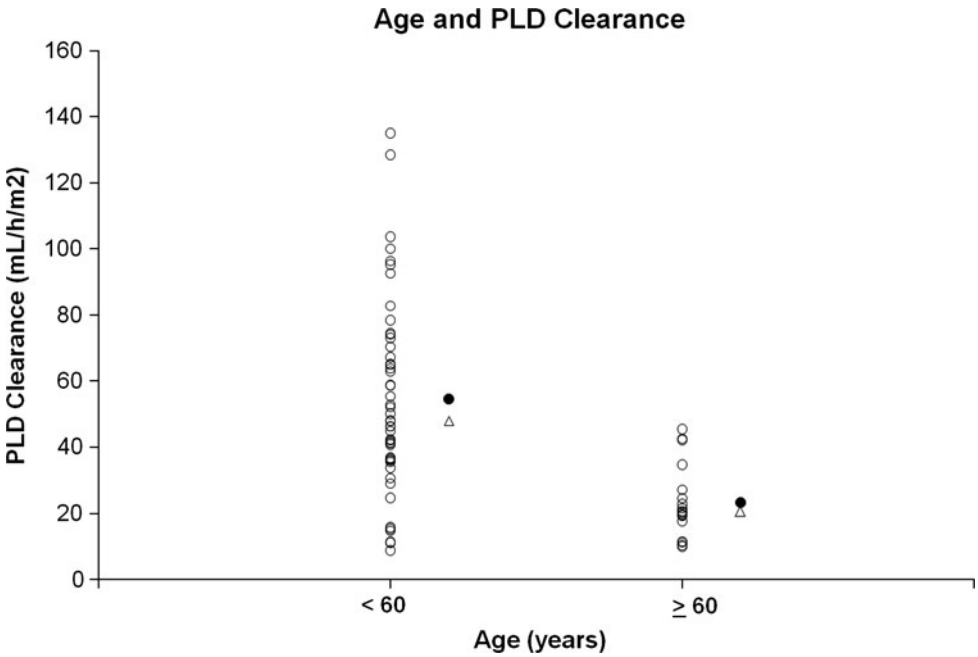

Fig. 1 The relationship between age and PLD clearance. *Open circles* represent individual patient data, *closed circles* represent the mean, and *triangles* represent the median. Patients ≥60 years old had significantly lower clearance than patients <60 years old ($P < 0.0001$)

Table 2 Summary of age and gender relationship with PLD clearance

	PLD clearance (mL/h/m^2) Mean ± SD Median (range)							
	Age <60 years old	Age ≥60 years old	Males	Females	Males <60 years old	Males ≥60 years old	Females <60 years old	Females ≥60 years old
Kaposi's sarcoma patients	63.1 ± 26.2* 58.8 (24.7–135.0) $n = 36$	–	63.1 ± 26.2†† 58.8 (24.7–135.0) $n = 36$	–	63.1 ± 26.2 58.8 (24.7–135.0) $n = 36$	–	–	–
Solid tumor patients	34.1 ± 23.5* 33.8 (8.8–92.6) $n = 15$	23.3 ± 10.8 20.6 (10.0–45.5) $n = 19$	34.9 ± 15.0**,†† 34.8 (10.4–65.1) $n = 13$	23.7 ± 18.8** 19.5 (8.8–92.6) $n = 21$	43.8 ± 13.5§§ 41.2 (29.1–65.1) $n = 6$	27.4 ± 12.5 22.8 (10.4–42.6) $n = 7$	27.6 ± 27.1 15.3 (8.8–92.6) $n = 9$	20.8 ± 9.4§§ 20.4 (10.0–45.5) $n = 12$
All patients	54.6 ± 28.5† 48.1 (8.8–135.0) $n = 51$	23.3 ± 10.8† 20.6 (10.0–45.5) $n = 19$	55.6 ± 26.8§ 48.1 (10.4–135.0) $n = 49$	23.7 ± 18.8§ 19.5 (8.8–92.6) $n = 21$	60.3 ± 25.6***,†††,§§§ 54.1 (24.7–135.0) $n = 42$	27.4 ± 12.5*** 22.8 (10.4–42.6) $n = 7$	27.6 ± 27.1††† 15.3 (8.8–92.6) $n = 9$	20.8 ± 9.4§§§ 20.4 (10.0–45.5) $n = 12$

SD standard deviation and n = number of patients

* $P < 0.0001$; † $P < 0.0001$; § $P < 0.0001$; ** $P = 0.016$; †† $P < 0.0001$; §§ $P = 0.00075$; *** $P = 0.0002$; ††† $P = 0.0004$; §§§ $P < 0.0001$

Factors affecting PLD clearance

The mean ± SD PLD clearance on cycle 1 in all patients that were <60 years old and ≥60 years old were 54.6 ± 28.5 and 23.3 ± 10.8 mL/h/m^2, respectively ($P < 0.0001$) (Fig. 1). All patients with Kaposi's sarcoma were males less than 60 years old and their mean ± SD PLD clearance was 63.1 ± 26.2 mL/h/m^2, which was higher than solid tumor male patients <60 years old clearance of 43.8 mL/h/m^2 ($P = 0.016$) and solid tumor male patients ≥60 years old clearance of 27.4 mL/h/m^2 ($P < 0.001$) (Table 1). The mean ± SD PLD clearance for cycle 1 in solid tumor patients that were <60 years old and ≥60 years old were 34.1 ± 23.5 and 23.3 ± 10.8 mL/h/m^2, respectively ($P = 0.34$) (Table 2). There was no significant relationship between PLD clearance on cycle 1 and body composition as measure by ABW/IBW or BMI ($r^2 = 0.22$ and 0.13, respectively).

Overall, the PLD clearance in female patients (23.7 ± 18.8 mL/h/m^2) was lower than in male patients

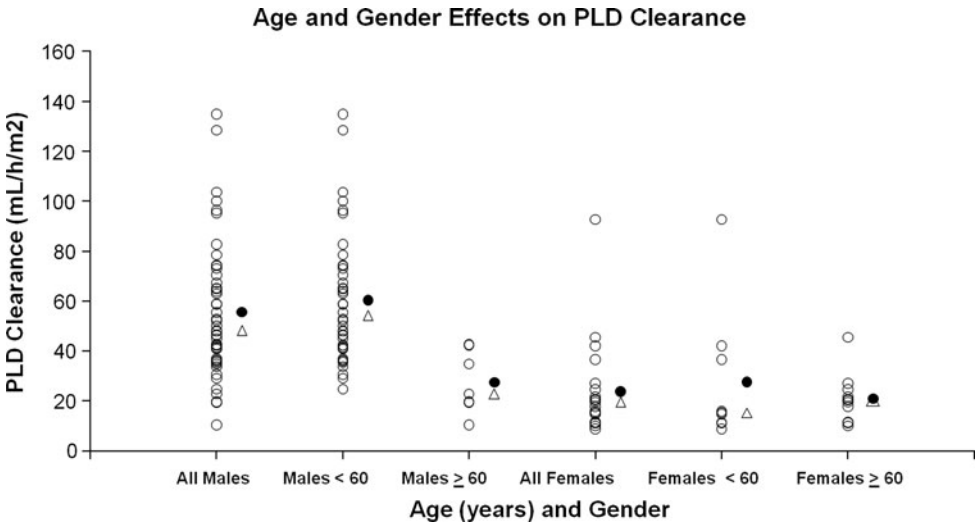

Fig. 2 The effects of age and gender on PLD clearance. *Open circles* represent individual patient data, *closed circles* represent the mean, and *triangles* represent the median. Female patients had significantly lower clearance than male patients ($P < 0.0001$). Male patients <60 years old had significantly higher clearance than male patients ≥60 years old, female patients <60 years old, and female patients ≥60 years old ($P < 0.001$ for all three pair-wise comparisons)

(55.6 ± 26.8 mL/h/m^2) ($P < 0.0001$) (Table 2; Fig. 2). In solid tumor patients, the PLD clearance in female patients (23.7 ± 18.8 mL/h/m^2) was also lower than in male patients (34.9 ± 15.0 mL/h/m^2) ($P = 0.016$). Further analysis by age revealed that mean ± SD PLD clearance in male patients >60 years old (27.4 ± 12.5 mL/h/m^2), female patients >60 years old (20.8 ± 9.4 mL/h/m^2), and female patients <60 years old (27.6 ± 27.1 mL/h/m^2) were similar (Table 1; Fig. 2). Male patients <60 years old had significantly higher clearance than the other three groups, mean ± SD PLD clearance 60.3 ± 25.6 mL/h/m^2 ($P < 0.001$ for all three pair-wise comparisons) (Table 2). When patients with Kaposi's sarcoma were excluded, solid tumor male patients <60 years old still had a higher clearance than female patients ≥60 years old ($P = 0.00075$) but there was no significant difference between solid tumor male patients <60 years old and male patients ≥60 years old or female patients <60 years old.

In study 3 (12 patients), pharmacokinetic studies were performed on cycles 1, 2, and 3. In addition, monocyte count was evaluated up to 1 week prior to PLD administration for each cycle (pre-cycle monocyte count). As previously reported, the mean ± SD PLD clearance on cycles 1 and 3 was 23.7 ± 7.7 mL/h and 16.4 ± 5.4 mL/h, respectively ($P < 0.0001$) [11]. We evaluated the association between pre-cycle monocyte count and changes in PLD clearance from cycle 1 to cycle 3 of therapy. Patients with a reduction as compared with an increase in pre-cycle monocyte count from cycle 1 to cycle 3 had a mean ± SD change in PLD clearance of −11.5 ± −3.5 mL/h and −5.3 ± −3.0 mL/h, respectively ($P = 0.09$) (Fig. 3). Patients <60 years old and ≥60 years old had a mean ± SD change in PLD clearance from cycles 1–3 of −5.2 ± −5.4 mL/h and −8.7 ± −4.3 mL/h, respectively ($P = 0.16$).

Discussion

Doxorubicin has been studied and used in cancer patients extensively since its discovery in the 1960s, and its clinical pharmacology is well established [19]. Factors that affect doxorubicin pharmacokinetics and pharmacodynamics include preexisting or co-morbid physiological conditions such as hepatic impairment, patient age, prior chemotherapy or radiation treatment, and polymorphisms in genes such as the efflux transporter ABCB1 and drug metabolizing enzymes such as carbonyl reductase 1 [20]. However, encapsulation of doxorubicin into pegylated liposomes, such as PLD, significantly alters its pharmacokinetics and pharmacodynamics. In addition, the clearance of doxorubicin is via cytochrome P450 3A (CYP3A) isoenzymes, whereas the clearance of liposomal agents is via the RES. Thus, the factors affecting the pharmacokinetic and pharmacodynamic variability of PLD should be different than for non-liposomal doxorubicin. This is the first study evaluating the effects of age, gender, body composition, and monocyte counts on the pharmacokinetics of PLD. There was significant inter-patient variability in PLD clearance. These results suggest that the use of BSA-based dosing for PLD does not sufficiently reduce the large inter-patient variability in drug exposure. In addition, this study suggests that alternate dosing strategies should be evaluated for PLD.

Our study findings suggest that female patients have lower PLD clearance than male patients ($P < 0.0001$). The basis for a difference in clearance associated with gender is unclear, however, may be due to different effects of sex hormones such as testosterone and estrogen on immune cell function [21, 22]. While there is evidence of different effects of sex steroids on the immune system, there are not any published findings that would explain the differences in clearance observed in our study. The effect of gender on

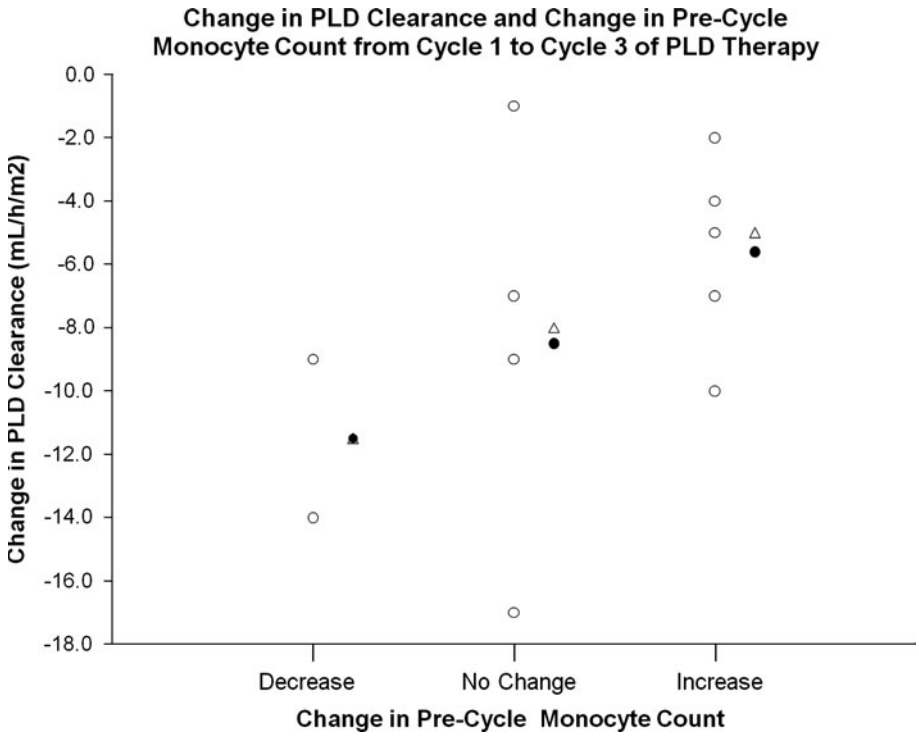

Fig. 3 The relationship between changes in pre-cycle monocyte count and changes in PLD clearance from cycle 1 to cycle 3 of therapy. *Open circles* represent individual patient data, *closed circles* represent the mean, and *triangles* represent the median. Patients with a decrease in monocyte count had a larger, although non-significant, decrease in PLD clearance as compared with patients who had no change or an increase in monocyte count ($P = 0.09$). One patient was excluded due to incomplete monocyte data

PLD clearance is clearly a significant effect, which warrants further investigation.

In addition to the effect of gender on PLD clearance, our study suggests that patients ≥60 years old have a lower PLD clearance compared with patients <60 years old ($P < 0.0001$). However, these results may be confounded by the larger number of Kaposi's sarcoma patients in the group <60 years old. We previously reported that low doses of PLD (approximately 20 mg/m^2), such as that used in the Kaposi's sarcoma population, are cleared much faster than standard doses of 40–60 mg/m^2, which is used in the solid tumor population [23]. Exclusion of the Kaposi's sarcoma patients showed a trend toward higher clearance in the patients <60 years old; however, this was not statistically significant due to the small number of patients remaining in that age group. The effect of age on PLD pharmacokinetics is consistent with our previous findings with another nanoparticle anticancer agent, S-CKD602 [24]. S-CKD602 is a pegylated liposomal formulation of CKD-602, a camptothecin analog. Patients ≥60 years old and <60 years old had mean ± SD S-CKD602 clearance of 0.81 ± 1.25 and 1.3 ± 1.4 L/h/m^2, respectively, with a corresponding 2.7-fold higher exposure of S-CKD602 in patients ≥60 years old as compared with patients <60 years of age ($P = 0.02$). The difference in PLD and S-CKD602 clearance between older and younger patients may be due to age-related changes in the immune system affecting RES cells such as monocytes, macrophages, and dendritic cells [5, 14, 25]. Potential alterations in RES function associated with age are consistent with age-related decreases in renal clearance, immune function, and hormone levels [14, 25].

We also reported that patients with a lean body composition (ABW/IBW < 1.35) have a higher plasma exposure of S-CKD602 ($P = 0.02$) as compared with patients with ABW/IBW ≥ 1.35, possibly due to a smaller volume of distribution. Unlike the S-CDK602 study, here, there was no relationship between body composition and PLD clearance; however, this could be due to a lower number of patients with very high ABW/IBW ratios in the PLD studies. The mean ± SD ABW/IBW ratios for PLD and S-CKD602 patients were 1.11 ± 0.26 and 1.27 ± 0.28, respectively. More data are required to define accurately the relationship between body mass and clearance of PLD.

As previously reported, PLD clearance decreased significantly from cycle 1 to cycle 3 ($P < 0.0001$) [11]. We found that a decrease in pre-cycle monocyte count was associated with a larger decrease in PLD clearance compared with increased or no change in pre-cycle monocyte count ($P = 0.09$). In this particular study, patients ≥60 years old had a larger, although not significant, decrease in clearance compared with patients <60 years old ($P = 0.16$). This study was originally powered to detect cycle and dose-dependent effects on PLD clearance and was not adequately powered to detect monocyte and age effects on PLD clearance. However, these results suggest that monocytes are involved in the clearance of PLD and that older patients may have lower RES function and/or reserve and thus may be more likely to have a larger decrease in PLD clearance

with subsequent treatment cycles. The effect of monocyte count on PLD clearance should be confirmed in further studies. In addition, the effect of RES function on PLD clearance needs to be elucidated.

A decrease in clearance of PLD has clinical significance since a longer PLD half-life has been found to be associated with a greater risk of skin toxicity [12], and drugs such as taxanes that retard the clearance of PLD increase the incidence and severity of skin toxicity [13]. In addition, increased clearance of PLD may result in lower systemic exposure to the drug that could theoretically affect clinical efficacy. Moreover, monocyte count could be a potential marker of RES activity, which may be predictive of PLD clearance.

In this initial study, we have identified associations between changes in PLD clearance, clinical response and toxicity, and patient age, gender, and monocyte count, which may be a promising approach for prospective dose optimization of PLD thereby enabling personalization of therapy. However, further clinical studies are needed to support our initial findings and to develop a clinical algorithm for individualizing PLD therapy. Since PLD has been extensively studied in clinical trials, the possibility of conducting a meta-analysis across the different trials to evaluate the effects of age, gender, and monocyte count on PLD pharmacokinetics, toxicity, and response should be considered. One challenge of such a study would be variable documentation of PLD toxicity and response due to heterogeneity in classification criteria and study protocol. In addition, other limitations of such a study are the lack of PLD pharmacokinetic analysis in many of the trials, the fact that monocyte counts may not be available in all patients as it may not be part of their routine laboratory work up, and the dominant presence of women in most of the studies because of the focus of PLD on ovarian and breast cancer indications. As a result, prospective studies as part of current and future clinical trials will most likely be required. Moreover, the development of phenotypic probes of RES activity and function may be used to explain the high inter- and intra-patient variability and to individualize therapy with PLD and other pegylated liposomal agents.

These prospective studies are especially important in light of the efforts to develop biosimilar formulations of PLD since the factors that we have identified may affect the criteria for establishing biosilimarity. Biosimilar or bioequivalent formulations of PLD would have to demonstrate at the least no clinically meaningful differences in the physico-chemical characterization and in the pharmacokinetics of the product when compared with the reference Doxil® product [26]. Our data suggest that PLD may have pharmacokinetic and pharmacodynamic interactions with components of the RES, such as monocytes. Thus, additional pharmacodynamic and phenotypic studies may need to be conducted as part of the evaluation of new PLD formulations. In addition, the evaluation of novel formulations of PLD for biosimilarity in clinical trials should include double cross-over PK studies with test and reference product and evaluations of RES function since inter-patient variability (age, sex, prior treatments, monocyte counts), and small variations in particle size, pegylation, and uniformity may significantly alter interactions with the RES, thus potentially altering toxicity and antitumor efficacy.

It has been demonstrated that minor changes in liposome characteristics can result in substantial alterations of pharmacokinetics and pharmacodynamics of PLD. For example, two formulations of PLD with identical lipid composition and lipid/drug ratio, but different sizes (75 and 100 nm) and internal ammonium sulfate concentrations (ammonium sulfate 300 and 250 mM, respectively) appeared to have similar in vivo plasma pharmacokinetics but significantly different biodistribution, acute toxicities, and antitumor effects [27]. In another study, six different formulations of PLD, having minor changes in composition and size, were compared with Doxil® in murine and nonhuman primate models [28]. Again, despite similar pharmacokinetics, the authors reported significant differences in toxicity and antitumor efficacy. In humans, the PK of the prototype formulation of PLD, which had an internal ammonium sulfate concentration of 155 mM, showed a shorter median half-life (45 h) and faster clearance (80–90 mL/h) than what was observed later with the final, approved, PLD formulation concentration (half-life, 70–80 h; clearance, 30–40 mL/h), which has an internal ammonium sulfate concentration of 250 mM (reviewed in 23). Thus, generating a generic formulation of PLD with identical formulation characteristics appears to be critical in achieving bioequivalence.

Conclusions

There is significant inter-patient variability in the pharmacokinetics of PLD, which may affect clinical response and toxicity. We have identified age, gender, and pre-cycle monocyte count as factors, which may be associated with pharmacokinetic differences in certain patients. However, the impact of these factors on clinical response and toxicity with PLD therapy remains unclear. These patient factors and the development of phenotypic probes of RES function warrant further investigation as potential methods to individualize and optimize PLD therapy. The effect of age, gender, and monocyte count on PLD and S-CKD602 pharmacokinetics may be a class-wide effect for other pegylated liposomes. In addition, the effect of these patient factors on the pharmacokinetics and pharmacodynamics of non-pegylated

liposomes and other nanoparticle agents is unclear and should be elucidated.

Conflicts of interest William C. Zamboni received minor compensation (<$10,000) as a consultant for Johnson & Johnson. All other authors declare that they have no conflicts of interest.

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