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Meta-analysis of inter-patient pharmacokinetic variability of liposomal and non-liposomal anticancer agents

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Abstract

Purpose—A meta-analysis was conducted to evaluate the inter-patient pharmacokinetic (PK) variability of liposomal and small molecule (SM) anticancer agents.

Methods—Inter-patient PK variability of 9 liposomal and SM formulations of the same drug were evaluated. PK variability was measured as coefficient of variance (CV%) of area under the plasma concentration versus time curve (AUC) and the fold-difference between AUC_{max} and AUC_{min} (AUC range).

Results—CV% of AUC and AUC ranges were 2.7-fold ($P<0.001$) and 16.7-fold ($P=0.13$) greater, respectively, for liposomal compared with SM drugs. There was an inverse linear relationship between the clearance (CL) of liposomal agents and PK variability with a lower CL associated with greater PK variability ($R^2 = 0.39$). PK variability of liposomal agents was greater when evaluated from 0–336 h compared with 0–24 h.

Conclusion—PK variability of liposomes is significantly greater than SM. The factors associated with the PK variability of liposomal agents needs to be evaluated.

Keywords

CKD-602; S-CKD602; pharmacokinetic; variability; sampling schema; liposomes

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Introduction

Most anticancer agents have high inter-patient variability in pharmacokinetic (PK) disposition, with systemic exposure following standard doses varying as much as 10-fold between patients [1–3]. This contributes in part to variability in a drug's pharmacodynamic (PD) effects, making it difficult to predict how a particular patient will respond in terms of efficacy and/or toxicity [4]. The same dose of drug may result in a sub-therapeutic response in one patient and unacceptable toxicity in another [5]. This problem is highlighted in cytotoxic agents that often display a narrower therapeutic index compared with other drug classes, such as statins and most antibiotics, where a wide range of doses may elicit the desired response with few adverse effects. Thus, anticancer agents have a small range of doses and exposures in which a drug is efficacious but not overly toxic [1]. Many factors such as patient demographics (age, gender, and body surface area), genetics, and the environment are known to alter the PK of a drug. Hence, these factors serve as potential causes of the inter-patient PK and PD variability associated with anticancer agents [1, 6, 7].

Various strategies have been proposed to increase the therapeutic index of anticancer drugs while minimizing side effects. One such approach is altering conventional drug delivery systems through use of carrier vehicles to deliver active agents to the site of action [9]. Liposomes represent a promising carrier vehicle with the potential for targeting specific organs or tissues [8]. Furthermore, delivering agents via liposomes has demonstrated advantages over conventional chemotherapeutics including increased solubility of hydrophobic agents, greater stability of large compounds, prolonged systemic drug exposure, and potential for improved efficacy and reduced toxicity [9].

A liposome is a type of nanoparticle carrier, usually 50 to 200 nm in diameter, consisting of an aqueous core surrounded by one or more phospholipid layers [10, 11]. Active drugs are encapsulated in the liposome, with hydrophilic and lipophilic compounds entrapped in the aqueous core and phospholipid bilayer, respectively [12]. While a drug is encapsulated in a liposome, its PK disposition depends on the physiochemical properties of the carrier. An encapsulated agent remains an inactive prodrug and therefore must be released from the liposome to elicit its effects [13]. Once released, the PK disposition of the drug resembles that of the active drug administered in the absence of a carrier [14, 15]. Thus, the PK of liposomal encapsulated drug and released drug is very different. In addition, the PK disposition of liposomal agents is significantly different than conventional anticancer agents. Moreover, the PK variability of liposomal formulations appears to be much greater than small molecule drugs. Inter-patient variability in drug exposure, represented by area under the concentration-time curve (AUC), of encapsulated drug can be 20- to 100-fold [28]. However, some liposomal agents report relatively low PK variability [41].

The factors with the potential to affect liposomal PK include liposomal-associated formulation characteristics (particle size, surface charge, lipid composition, ligand conjugation) [8, 16–20] and host-associated characteristics (age, gender, body composition, prior treatment) [21–24]. Additionally, dose schedule and drug-drug interactions may alter drug response between patients. Perhaps the greatest influence on the PK variability of liposomes; however, is the mononuclear phagocytic system (MPS) and its role in driving the clearance of liposomes [45, 46]. The MPS is a family of cells comprised of bone marrow precursors, blood monocytes, and tissue macrophages [25]. The MPS clears liposomes by its capacity to engulf liposomes via their phagocytic function, which removes them from circulation [26, 27].

While inter-patient variability in the PK disposition of a liposome is often higher than that of a conventional formulation of the same drug, comprehensive differences in PK variability

between liposomal agents compared with non-liposomal agents has not been systematically evaluated. Therefore, we conducted a systematic review and meta-analysis investigating AUC variability differences between liposomal and non-liposomal formulations of 9 anticancer agents.

Considering the large inter-patient PK variability and the inconsistent reports of PK variability of some liposomal agents, we sought to determine how study design and sampling schema might affect the documentation of PK variability. Due to prolonged systemic exposure of encapsulated drug, PK studies of liposomes must extend sample collection to include later time points (e.g. day 7 to 14) than those required with conventional formulations with shorter half-lives in order to accurately calculate PK parameters and fully characterize PK variability in patients. Thus, we hypothesized that studies utilizing limited sampling schemas (e.g. 0 to 24 h) underestimate inter-patient PK variability in drug exposure of liposomal agents. To test our hypothesis, we evaluated the estimated PK variability of PEGylated liposomal CKD-602 (S-CKD602) and non-liposomal CKD-602 (NL-CKD602) using data obtained from two separate phase I studies of patients with advanced solid tumors. NL-CKD602 is currently approved in Korea under the trade name Belotecan® for the treatment of newly diagnosed small-cell lung cancer and relapsed ovarian cancer [21]. NL-CKD602 is administered at a dosage of 0.5 mg/m^2/day IV for 5 consecutive days repeated every 21 days. S-CKD602 is a PEGylated liposomal formulation of CKD-602 that has completed phase I studies. We compared differences in estimated inter-patient PK variability when using a short (0–24 h) versus a long (0–336 h) sampling schema for S-CKD602 and NL-CKD602.

Patients and Methods

Systematic Review and Meta-analysis

To directly compare interpatient PK variability of multiple liposomal and non-liposomal anticancer agents, a systematic review and meta-analysis was conducted utilizing PubMed (1966–2011) and manual searches of reference sections of key articles. Phase I and II studies that included PK studies were included in our analysis. The systematic review yielded 9 liposomal and non-liposomal formulations of the same anticancer agents. A complete list of evaluated agents with a brief description of each is listed in Table 1. The mean ± SD AUC were collected for liposomal and non-liposomal formulations of each agent at similar doses. Inter-patient variability in drug exposure was quantified using the coefficient of variation (CV%). The ratio of CV% of AUC of the liposomal formulation to the non-liposomal formulation of the same drug at similar doses was calculated using the following equation:

$$\text{Ratio of CV\% of AUC} = \frac{\text{Liposomal CV\% of AUC}}{\text{Non-Liposomal CV\% of AUC}} \quad \text{(Eq 1)}$$

The maximum AUC (AUC_{max}) and minimum AUC (AUC_{min}) reported for each formulation at similar doses were also collected. The ratio of AUC_{max} to AUC_{min} of the liposomal formulation to the non-liposomal formulation of the same drug was also calculated using the following equation:

$$\text{Ratio of AUC}_{max}\text{ to AUC}_{min} = \frac{\text{Liposomal AUC}_{max}/\text{AUC}_{min}}{\text{Non-liposomal AUC}_{max}/\text{AUC}_{min}} \quad \text{(Eq 2)}$$

Influence of Drug Clearance on Interpatient PK Variability

To evaluate how a drug's clearance rate may impact observed interpatient PK variability, we calculated average total body clearance of each agent evaluated in the meta-analysis and plotted these values against CV% of AUC values. This analysis was performed for both the liposomal and non-liposomal formulations of each agent. Doses evaluated for each liposomal formulation represent the MTD determined from published PK studies. The closest corresponding non-liposomal doses available in the literature were used in the non-liposomal analysis.

Impact of Sampling Schema on Reported Interpatient PK Variability

To investigate differences in the reported interpatient PK variability of a liposomal agent when using a long versus short sampling schema, PK parameters for patients who were given S-CKD602 as part of a phase I study in patients with refractory solid tumors were calculated using a non-compartmental analysis in WinNonlin 5.2 software (Pharsight, Mountain View, California). Written informed consent, approved by the Institutional Review board of the University of Pittsburgh Medical Center, was obtained from all patients prior to entry into the original phase I study. Based on published PK study designs used in liposomal and non-liposomal studies in patients and logistical issues with performing PK studies after 24 h, we defined the short and long PK sampling schemas as 0 to 24 h and 0 to 336 h, respectively. The mean ± SD, and CV% of AUC was calculated for encapsulated CKD-602 from 0 h to 24 h ($AUC_{0–24}$) and from 0 h to 336 h ($AUC_{0–336}$) at each dose level in the S-CKD602 study. CV% of $AUC_{0–24}$ and CV% of $AUC_{0–336}$ were calculated for each dose level. Furthermore, the ratio of CV% of $AUC_{0–336}$ to CV% of $AUC_{0–24}$ was calculated for each dose level to assess the fold-difference in interpatient PK variability between a long and short sampling schema using the following equation:

$$\text{Ratio of CV\% of AUC}_{0-336}\text{ to AUC}_{0-24}=\frac{\text{S}-\text{CKD602 CV\% of AUC}_{0-336\text{h}}}{\text{S}-\text{CKD602 CV\% of AUC}_{0-24\text{h}}} \quad \text{(Eq 3)}$$

As another means of quantifying variability in S-CKD602 exposure, the maximum AUC (AUC_{max}) and minimum AUC (AUC_{min}) were determined for each dose level. The ratio of AUC_{max} to AUC_{min} of the long sampling schema to the short sampling schema was then calculated for each dose level using the following equation:

$$\text{Ratio of AUC}_{\max}\text{ to AUC}_{\min}=\frac{\text{S}-\text{CKD602 AUC}_{\max:0-336\text{h}}/\text{AUC}_{\min:0-336\text{h}}}{\text{S}-\text{CKD602 AUC}_{\max:0-24\text{h}}/\text{AUC}_{\min:0-24\text{h}}} \quad \text{(Eq 4)}$$

Statistical Analysis

In the meta-analysis comparing PK variability between liposomal and non-liposomal formulations of the same anticancer agent, paired t-tests were used to compare the ratios of both CV% of AUC and AUC_{max} to AUC_{min} of the liposomal formulation to the non-liposomal formulation of the same drug. A paired t-test was also used in the S-CKD602 PK analysis to evaluate differences between estimated AUC values calculated using a short and long sampling schema.

Results

Meta-analysis of PK Variability

We compared inter-patient PK variability differences of corresponding liposomal and non-liposomal anticancer agents at similar doses. Figure 1 represents the plasma concentration

versus time profiles of liposomal and non-liposomal CKD-602, one of the 9 agents evaluated in the meta-analysis. Here, each agent was administered to 6 patients at the respective MTD (S-CKD602 at 2.10 mg/m^2 and NL-CKD602 at 0.5 mg/m^2). Visual inspection reveals a tighter grouping of profiles between patients administered NL-CKD602 compared to those receiving S-CKD602, demonstrating a reduction in PK variability observed in a non-liposomal agent compared with that of a liposomal agent.

To further evaluate the degree of PK variability of liposomal and non-liposomal agents, a meta-analysis was performed comparing the PK variability of liposomal and conventional small molecule formulations of the same drug. CV% of AUC values for both liposomal (n = 9) and conventional (n = 9) formulations of each evaluated agent are depicted in Figure 2A. Mean CV% of AUC values and mean ratio of AUC_{max} to AUC_{min} values are depicted in Figure 2B. The PK variability of every liposomal agent was greater than the corresponding non-liposomal agent (Figure 2A). The mean CV% and range of PK variability for liposomal and non-liposomal agents were approximately 2.1-fold and 8.7-fold higher, respectively, for liposomal compared with non-liposomal agents.

CV% of AUC, ratio of AUC_{max} to AUC_{min} values (mean ± SD), and corresponding ratios of liposomal to non-liposomal agents are reported in Table 2. For liposomal agents, the mean ± SD of CV% of AUC was 65.6 ± 18.6%. For non-liposomal agents, the mean ± SD of CV% of AUC was 30.7 ± 16.0%. The ratio of liposomal to non-liposomal CV% of AUC for each pair was 2.7 ($P<0.001$) (Eq 1). The mean ± SD ratio of AUC_{max} to AUC_{min} was 34.1 ± 41.9 for liposomes and 3.6 ± 1.8 for non-liposomal drugs. The ratio of liposomal to non-liposomal ratio of AUC_{max} to AUC_{min} for each pair was 16.7 ($P=0.13$) (Eq 2).

Influence of Drug Clearance on Interpatient PK Variability

Given the high interpatient variability in the pharmacokinetic disposition and the slower clearance rates often observed with liposomal anticancer agents, we evaluated the relationship between total body clearance and CV% of AUC for liposomal and non-liposomal formulations of the same anticancer agents. Graphical representations of the relationship between clearance (CL) and PK variability for liposomal and non-liposomal formulations are depicted in Figure 3A and Figure 3B, respectively. There was an inverse relationship between the CL and PK variability of liposomal agents where liposomal agents with a lower CL have a greater degree of PK variability (Figure 3A). For small molecule agents, there was no relationship between CL and PK variability (Figure 3B).

Impact of Sampling Schema on Reported Interpatient PK Variability

To investigate how study design and sampling schema affects the estimated PK variability, CV% of AUC and ratio of AUC_{max} to AUC_{min} were estimated using short (0–24 h) and long (0–336 h) sampling model for patients at each dose level of S-CKD602 and NL-CKD602. A complete list of reported CV% of AUC values and ratio of AUC_{max} to AUC_{min} for 0 to 24 h and 0 to 336 h sampling, along with corresponding ratios are listed in Table 3 and Table 4, respectively. Matching values for NL-CKD602, obtained in the meta-analysis section, are also listed here. A corresponding graphical representation is depicted in Figure 4A and Figure 4B. The estimated PK variability of S-CKD602 using concentration versus time data from 0 to 366 h was greater at all doses compared with data from 0 to 24 h. At the maximum tolerated dose of 2.1 mg/m^2, there was a significant difference between $AUC_{0–24}$ (19,121 ± 9,498 ng/mL·h) and $AUC_{0–336}$ (52,390 ± 38,007 ng/mL·h) ($P=0.037$). Also at 2.1 mg/m^2, the CV% of $AUC_{0–24}$ and the CV% of $AUC_{0–336}$ were 63.6 and 86.1, respectively. The ratio of CV% of $AUC_{0–336}$ to CV% of $AUC_{0–24}$ was 1.4 (Eq 3). At this same dose, the ratio of AUC_{max} to AUC_{min} was 4.9 when sampled from 0 h to 24 h and 12.1 when sampled

from 0 h to 336 h. The ratio ofAUC_{max} to AUC_{min} of long schema to short schema was 2.5 (Eq 4).

Discussion

High inter-patient PK variability observed with many anticancer agents makes it difficult to predict a patient's response to a particular drug. Moreover, liposomes often report higher PK variability compared with small molecules and non-liposomal agents, further clouding predictions of outcomes associated with these carrier agents. We comprehensively evaluated these differences in a meta-analysis of 9 liposomal and non-liposomal anticancer agents. This is the first meta-analysis evaluating the PK variability of liposomal versus non-liposomal agents. The results of our study show that there is significantly higher interpatient PK variability of liposomal agents compared with non-liposomal agents. We also report that liposomal agents with lower CL have a higher degree of PK variability. In addition, we evaluated the impact a study's design and sampling schema may have on reported inter-patient PK variability in liposomes. There was higher reported AUC variability when samples were obtained up to 14 days compared with 24 h. Thus, limiting sample collection to 24 h after administration of a liposomal agent underestimates inter-patient PK variability.

Compared to non-liposomal anticancer agents, overall PK variability was demonstrated to be greater for liposomes. First, variability in S-CKD602 was 9.8-fold higher than that of NL-SCK602 when measured by the ratio of AUC ranges. Moreover, the meta-analysis provided a broad assessment of PK variability differences between liposomal versus non-liposomal forms of the same drug. Using a comprehensive list of liposomal anticancer agents that were FDA approved or in clinical development, the PK variability of all liposomal agents were significantly greater than non-liposomal small molecules ($P<0.001$). When measured by CV %, the inter-patient PK variability associated with liposomal agents is 2.7-fold higher than that of conventional formulations.

While the PK variability of liposomal agents was shown to be 17.3-fold higher when measured by AUC range, this result was non-significant ($P = 0.13$). This can be attributed to the small amount of reported AUC range data that was available, which lower our statistical power. However, when evaluating the mean +/− SD CV% of AUC the PK variability between liposomal and SM is statistically significant ($P < 0.001$). This issue high lights the need for additional analyses and need for complete PK data (mean +/− SD, range) to be published in all PK studies of liposomal and SM agents in order to provide an accurate representation of the complete PK variability.

In addition to increased overall PK variability in S-CKD602 compared to NL-CKD602, we also observed dose-dependent changes in PK variability with the liposomal formulation. The trend of high PK variability at lower doses compared with higher doses of a liposomal agent suggests the factors affecting the PK variability become more uniform at higher doses. One potential mechanism for the reduced PK variability at higher doses is a saturation of liposomal CL mediated by the MPS. This is further supported through analysis of AUC variability of NL-CKD602, which was much more constant at low and high doses. Saturation of NL-CKD602 clearance would not be expected to occur through the same mechanism as liposomal agents as non-liposomal drugs are not thought to be cleared via the MPS.

Our results showing an inverse relationship between the CL of liposomal agents and the degree of interpatient PK variability has interesting ramifications for the design and development of liposomal and nanoparticle agents. Liposomal agents with a lower CL have a greater degree of PK variability (Figure 3A). This data suggests that liposomal agents with

a lower CL is due to a slower and more variable recognition and uptake of the liposomal agent by the MPS which leads to the higher PK variability. Consistent with this theory is that for small molecule agents, there was no relationship between CL and PK variability as these agents are not cleared by the MPS (Figure 3B). Thus, while engineering liposomal, nanoparticle, and conjugated agents to achieve a slower CL and prolonged circulation time in plasma to achieve higher exposures of drug delivered to target tissues (e.g. tumor), this may introduce more PK and PD (toxicity and response) variability.

While liposomal anticancer agents often have high inter-patient variability in PK parameters, levels of reported PK variability can also vary greatly between independent studies of the same or similar liposomal technology. Reasons for this are multifactorial, with plausible explanations being attributed to different patient demographics and disease states represented in each study. However, differences in experimental design and sampling schema between studies may also play a role by altering documentation of PK variability. In a PK study of liposomal cisplatin (SPI-077) by Terwogt and colleagues, the calculated AUC from 0 to 7 days following a dose of SPI-77 at 200 mg/m^2 IV x 1was 71.1 ± 2.5 h·mM (CV % = 3.5; n=3) [29]. In a different study performed by White et al., the reported SPI-077 AUC at this same dose determined from samples collected out to 22 days after administration was 101.6 ± 31.7 h·mM (CV% = 31.2; n=12) [30]. Inspection of AUC CV% values reveals that variability in SPI-077 exposure was reported to be 8.9-fold higher with the extended sampling schema compared to a shorter collection model. These findings are consistent with our analysis of S-CKD602, which showed that collecting PK samples out to 14 days resulted in as high as 2.5-fold higher reported PK variability than would be documented if a shorter sampling model (0 to 24 h) were used in the same patients. Thus, when plasma drug levels beyond 24 h were not included in AUC calculations, variability in patient PK parameters was significantly underestimated. While this is not a concern for conventional anticancer drugs, many of which are mostly cleared from the body after 24 h, liposomal agents, such as S-CKD602 and PEGylated liposomal doxorubicin (Doxil), are retained in circulation for much longer time periods (e.g. 7 to 28 days). Consequently, sample collection must be extended to later time points when studying liposomes to ensure accurate characterization of PK parameters of these agents.

It is important to note; however, that reported liposomal PK variability is not always larger when an extended sampling model is utilized. In an example of two independent studies of Doxil, PK variability following a dose of 40 mg/m^2 IV x 1 was reported to be 1.5 fold higher when sampled from baseline to 4 days (CV% 35.4; n=3) [31] than when sampled from baseline to 7 days (CV% 23.1; n=4) [32]. While this data does not directly follow our hypothesis, it is significant by revealing differences in variability that may be incorrectly documented with an inadequate study designs. These findings further support the necessity of employing a study design that allows adequate sample collection to ensure accurate characterization of a liposomal agent's PK disposition. This necessity also holds true for any other nanoparticle, monoclonal antibody, or antibody-drug conjugate with a long half-life.

There are a multitude of properties that make carrier-mediated and liposomal agents unique from the active small molecule drug that is contained within the nano-carrier. These differences lead to significant variability in the pharmacokinetics and pharmacodynamics of the carrier mediated drugs. It has been shown that physical properties of the carrier, the MPS, presence of tumors in the liver, enhanced permeability and retention effect, drug-drug interactions, age, and gender all contribute in varying degrees to the pharmacokinetic disposition and pharmacodynamic endpoints of carrier mediated agents in patients [45,46. Due to the unique and highly variable clearance mechanisms of liposomes, it is important to continue to extensively evaluate them during all phases of preclinical and clinical development. Areas of research that can aid in our understanding of how these agents are

handled and how we may predict their actions in patients, include: pharmacogenomics, cellular function (probing the MPS), more sensitive and accurate analytical PK methods, and identification of the optimal preclinical (animal and in vitro) models [48–50].

In conclusion, this is the first study that systematically reporting greater inter-patient PK variability of liposomal agents compared with non-liposomal agents and the impact that a study's sampling schema has on reported PK variability. Our results also have interesting ramifications for the design and development of liposomal and nanoparticle agents. Development of a standardized sampling strategy that may be applied to all liposomal agents and potentially all nanoparticle and conjugated agents is warranted as a means of reducing inaccurate documentation of PK variability that arises from suboptimal study designs. Future studies must also further evaluate the sources of PK variability and develop additional tools to accurately measure and predict PK and PD variability in patients administered liposomal, nanoparticle and conjugated agents.

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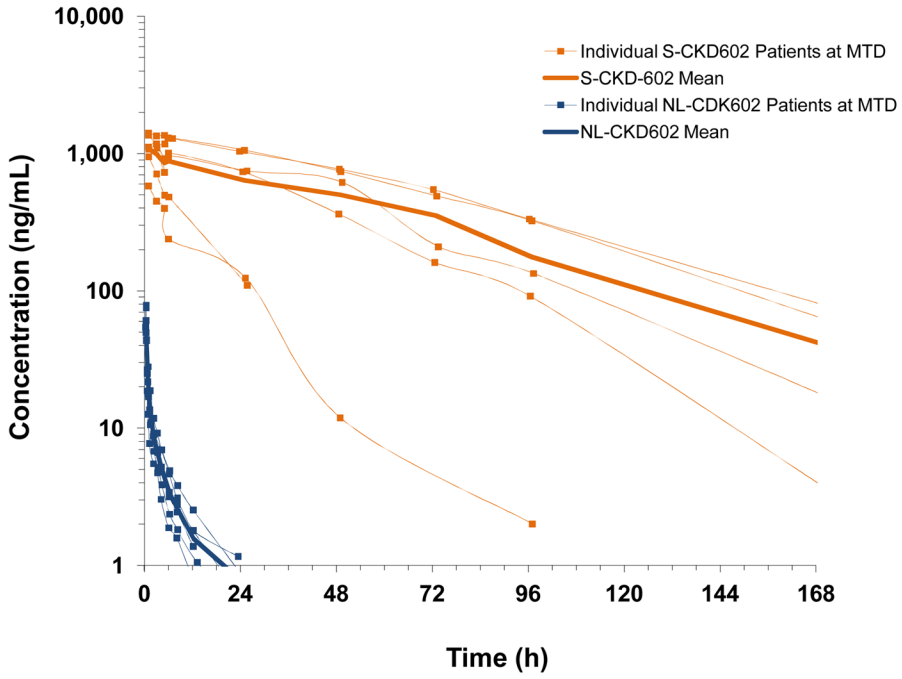

Figure 1.

Representative plasma concentration-vs.-time profiles of encapsulated S-CDK602 at 2.1 mg/m^2 IV x 1 and NL-CKD602 at 0.5 mg/m^2 IV x 1. Doses represent the MTD of each respective agent.

Figure 2A.

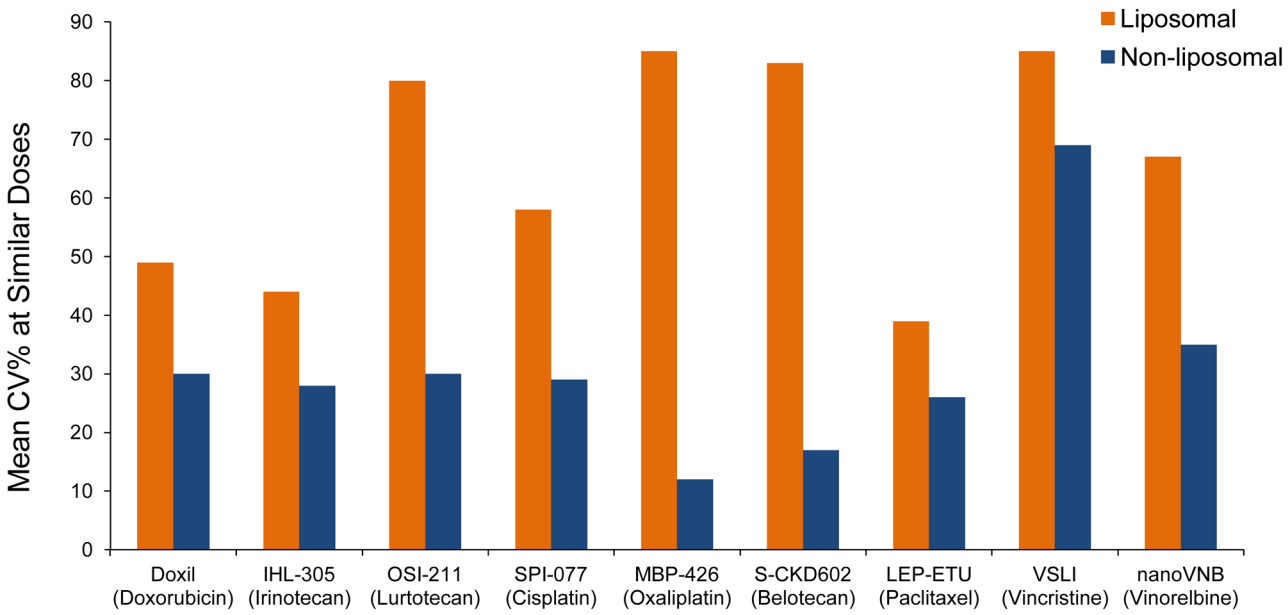

Figure 2B.

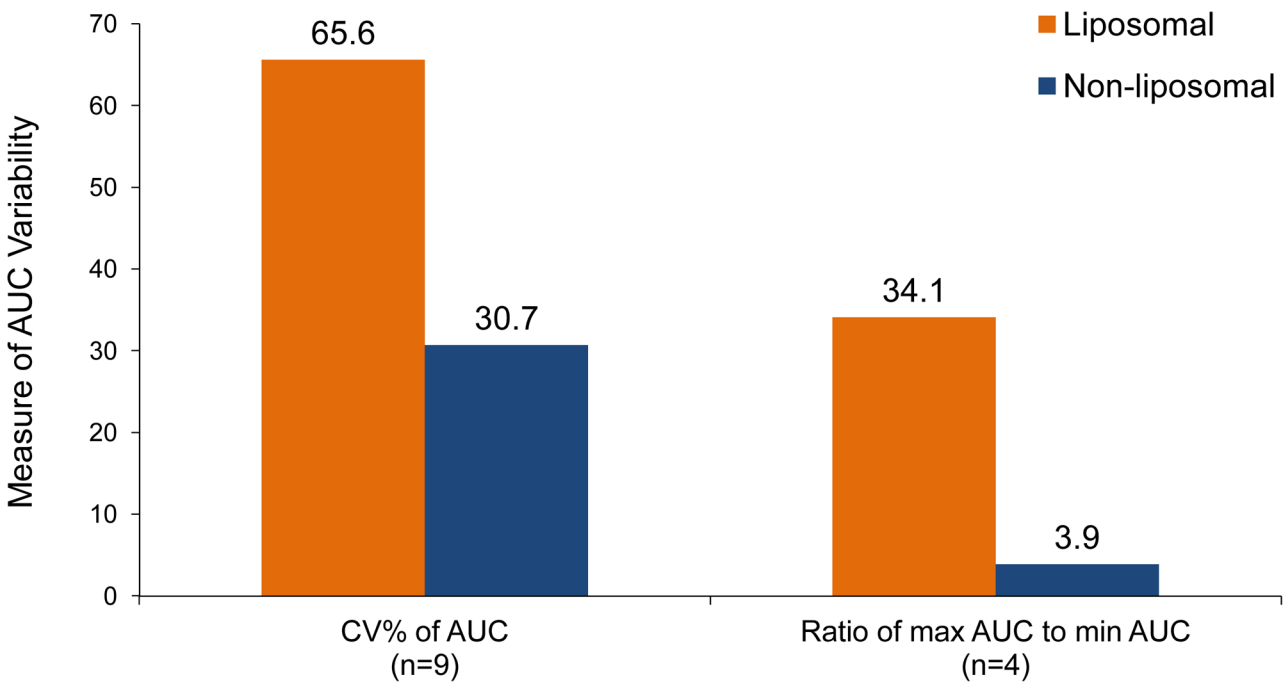

Figure 2.

Figure 2A. Reported inter-individual PK variability for 9 anticancer agents as measured by CV% of AUC. Black bars represent liposomal formulations of each agent. Dotted gray bars represent corresponding non-liposomal formulations at similar doses.

Figure 2B. Comprehensive inter-individual PK variability for liposomal and non-liposomal anticancer agents. Black bars represent liposomal formulations of each agent. Dotted gray bars represent corresponding non-liposomal formulations at similar doses.

Figure 3A.

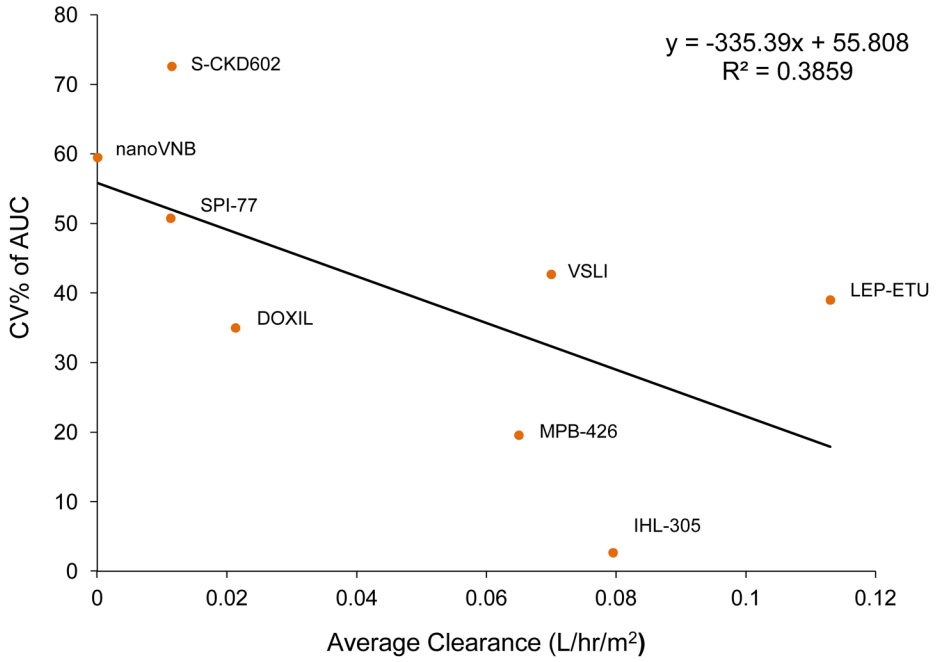

Figure 3B.

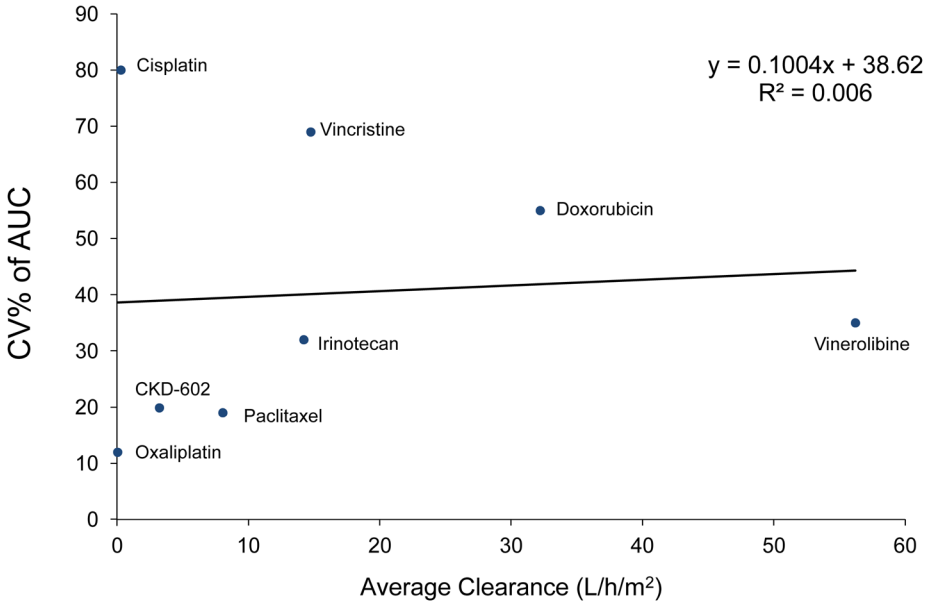

Figure 3.

Figure 3A. The relationship between total body clearance and PK variability of each liposomal agent evaluated in the meta-analysis. Each agent is evaluated at its respective MTD determined in published PK studies

Figure 3B. The relationship between total body clearance and PK variability of each non-liposomal agent evaluated in the meta-analysis. Each agent is evaluated at available doses that corresponded most closely to the liposomal MTD determined in published PK studies

Figure 4A.

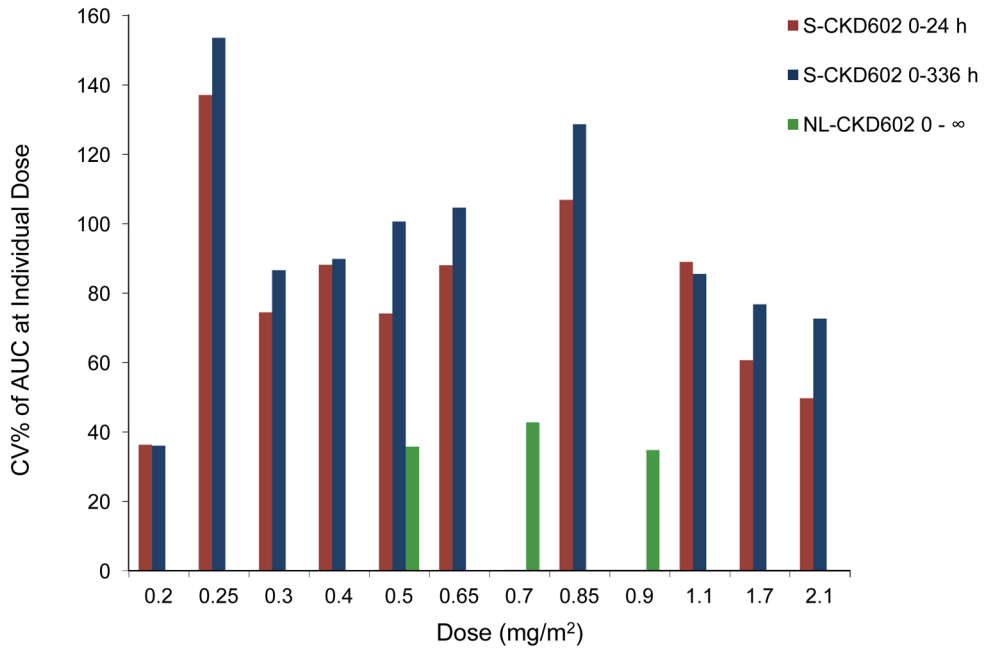

Figure 4B.

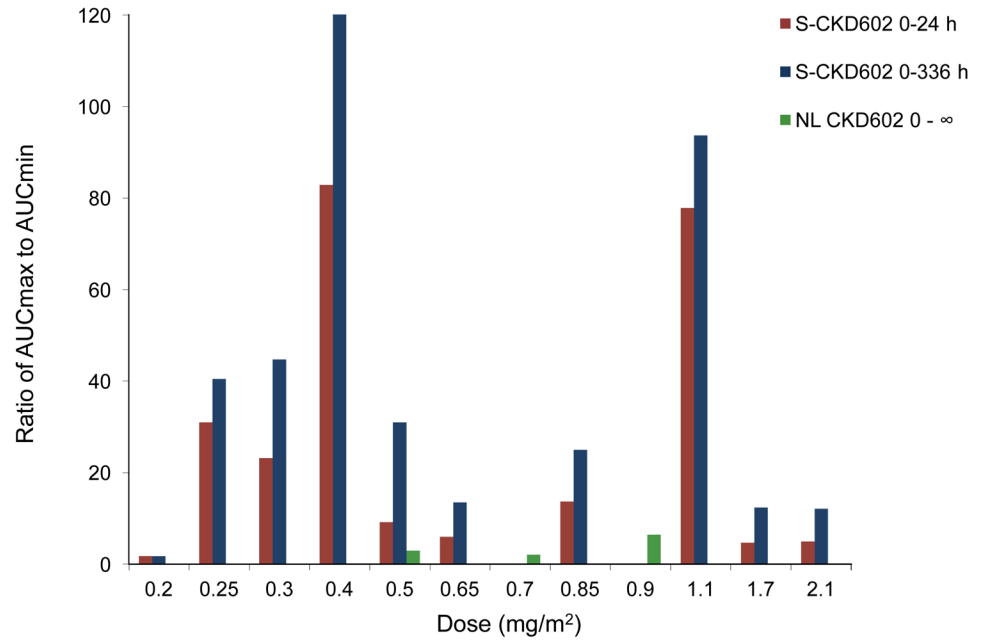

Figure 4.

Figure 4A. Reported variability of S-CKD602 AUC measured for 0–336h and 0–24h, as well as NL-CKD602 at 0 - ∞. PK variability is depicted as comparisons of CV% of AUC values at each dose.

Figure 4B. Reported variability of S-CKD602 AUC measured from 0–336h and 0–24h, as well as NL-CKD602 at 0 - ∞. PK variability is depicted as comparisons of ratio of AUC_{max} to AUC_{min} values at each dose.

Table 1

Summary of Liposomal Agents Evaluated in the Meta-Analysis

Liposomal agents evaluated in meta-analysis. HSPC = hydrogenated soy phosphatidylcholine. MPEG-DSPE = N-(carbonylmethoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt. NGPE = N-glutaryl phosphatidylethanolamine. DOPC = dioleolyl phosphatidyl choline. α-TAS = α-tocopheryl acid succinate

Active Drug	Product Name	Components of Liposome	Developmental Status	PK Study Dose – mg/m^2 Liposomal (Non-liposomal)	PK Sampling Schema	Ref.
Doxorubicin	Doxil®/Caelyx®	Cholesterol, HSPC, MPEG- DSPE	Approved	20 (39)	0 to 504 h 0 to 168 h 0 to 504 h	[33–36]
Irinotecan	IHL-305	Cholesterol, HSPC, PEG5000-DSPE, ammonium sulfate, sucrose, L-histidine, dilute HCL	Phase I	160 (350)	Not reported	[37]
Lurtotecan	OSI-211/NX-211	Cholesterol, HSPC, sucrose, citric acid, ammonium chloride	Phase II	2.4 (1.5)	0 to 24 h	[38]
Cisplatin	SPI-77	Cholesterol, HSPC, MPEG-DSPE, sucrose, sodium chloride, histidine	Phase II	120 (75)	0 to 168 h 0 to 504 h	[29, 39]
Oxaliplatin	MBP-426	Transferrin (Tf), NGPE	Phase I	226 (130)	0 to 72 h	[40]
Belotecan (CKD-602)	S-CKD602	MPEG-DSPE, 1,2- distearoyl-*sn*-glycero- phosphocholine	Phase I	1.1 (0.5)	0 to 336 h	[28]
Paclitaxel	LEP-ETU	DOPC, cardiolipin, cholesterol, α-TAS	Phase I	175 (230)	Not reported	[41, 47]
Vincristine	VSLI/Marqibo®	Sphingomyelin, cholesterol, mannitol, sodium citrate, citric acid, sodium phosphate, sodium chloride	Approved	2 (2)	0 to 72 h 0 to 97 h	[42, 43]
Vinorelbine	nanoVNB®	Cholesterol, MPEG-DSPE, distearoyl phosphatidylcholine, histidine, sucrose	Phase I	23 (35)	0 to 144 h	[44]

Table 2

Summary of PK Variability of Liposomal and Non-Liposomal Anticancer Agents

CV% of AUC (n=9) and ratio of AUC_{max} to AUC_{min} (n=4) for liposomal and non-liposomal anticancer agents in patients. Mean CV% of AUC and ratio of AUC_{max} to AUC_{min} (AUC Range) values for liposomal and non-liposomal formulations are listed, as well as ratios of liposomal to non-liposomal agents. The PK variability of liposomal agents was significantly greater than non-liposomal agents as measured by CV% of AUC ratio ($P < 0.001$). NF = not found.

Liposomal (Non-liposomal)	CV%		CV% Ratio	Ratio of AUC_{max} to AUC_{min} (AUC Range)		Ratio of Liposomal AUC Range to Non-liposomal AUC Range
	Liposomal	Non- Liposomal	Liposomal CV%/Non-Liposomal CV%	Liposomal	Non- Liposomal	
Doxil (Doxorubicin)	49	30	1.6	40.1	3.03	13.2
IHL-305 (Irinotecan)	44	28	1.6	2.7	3.8	0.71
OSI-211 (Lurtotecan)	80	30	2.7	113.5	2.1	53.5
SPI-077 (Cisplatin)	58	29	2.0	3.1	NF	NF
MBP-426 (Oxaliplatin)	85	12	7.1	NF	NF	NF
S-CKD602 (Belotecan)	83	17	4.9	32.6	NF	NF
LEP-ETU (Paclitaxel)	39	26	1.5	NF	NF	NF
VSLI (Vincristine)	85	69	1.2	12.3	6.7	1.87
nanoVNB (Vinorelbine)	67	35	1.9	NF	NF	NF
Mean	65.6	30.7	2.7	34.1	3.9	17.3
SD	18.6	16.0	2.0	41.9	1.9	24.8
Min	39	12	1	3	2	1
Max	85	69	7	114	7	54

Table 3

PK Variability as Measured by CV% of S-CKD602 and NL-CKD602 using PK Samples from 0–24 h and 0–336h

Inter-patient PK variability in S-CKD602 and NL-CKD602 measured by CV% of AUC. Estimated CV% of AUC values for S-CKD602 when sampled from 0 h to 336 h (long schema) and 0 h to 24 h (short schema) are listed for each dose. CV% of AUC values for and NL-CKD602 when sampled from 0 h to 24 h (AUC of NL-CKD602 calculated from 0 h to ∞) are listed for each dose of non-liposomal drug administered. CV% of AUC ratios for long schema to short schema and S-CKD602 (0 h to 336 h) to NL-CKD602 (0 h to ∞) are listed. Patient CV% values for 2.50 mg/m^2 are not listed, as PK studies stopped at 48 h, 96 h, and 96 h in the three patients due to toxicity.

Dose Level (mg/m^2)	CV% of S-CKD602 AUC at Each Dose		CV% of NL-CKD602 AUC at Each Dose	Ratio CV% of AUC at Each Dose	
	Estimated from 0–24 h	Estimated from 0–336 h	Estimated from 0-∞	S-CKD602 0–336h to 0–24h	S-CKD602 to NL-CKD602
0.2	36.2	36.0	--	1.0	--
0.25	136.9	153.4	--	1.1	--
0.3	74.3	86.5	--	1.2	--
0.4	88.1	89.7	--	1.0	--
0.5	74.0	100.6	35.7	1.4	2.8
0.65	87.9	104.5	42.7	1.2	2.5
0.85	106.8	128.6	34.7	1.2	3.7
1.1	88.9	85.5	--	1.0	--
1.7	60.6	76.7	--	1.3	--
2.1	49.7	72.6	--	1.5	--
Mean ± SD	78.0 ± 20.8	94.7 ± 20.9	37.7 ± 4.3	1.2 ± 0.2	3.0 ± 0.6

Table 4

PK Variability as Measured by AUC Range of S-CKD602 and NL-CKD602 using PK Samples from 0–24 h and 0–336h

Inter-patient PK variability in S-CKD602 and NL-CKD602 measured by ratio of AUC_{max} to AUC_{min} (AUC Range). Estimated AUC Range values for S-CKD602 when sampled from 0 h to 336 h (long schema) and 0 h to 24 h (short schema) are listed for each dose. AUC Range values for and NL-CKD602 when sampled from 0 h to 24 h (AUC of NL-CKD602 calculated from 0 h to ∞) are listed for each dose of non-liposomal drug administered. AUC Range ratios for long schema to short schema and S-CKD602 (0 h to 336 h) to NL-CKD602 (0 h to ∞) are listed. Patient AUC Range values for 2.50 mg/m^2 are not listed, as PK studies stopped at 48 h, 96 h, and 96 h in the three patients due to toxicity.

Dose Level (mg/m^2)	Ratio of AUC_{max} to AUC_{min} (AUC Range) at Each Dose: S-CKD602		Ratio of AUC_{max} to AUC_{min} (AUC Range) at Each Dose: NL-CKD602	Ratio of AUC Ranges at Each Dose	
	Estimated from 0–24 h	Estimated from 0–336 h	Estimated from 0-∞	S-CKD602 0–336h to 0–24h	S-CKD602 to CKD-602
0.2	1.7	1.7	--	1.0	--
0.25	31.0	40.4	--	1.3	--
0.3	23.1	44.7	--	1.9	--
0.4	82.8	349.2	--	4.2	--
0.5	9.2	31.1	3.2	3.4	9.8
0.65	5.9	13.5	2.9	2.3	4.6
0.85	13.7	25.0	2.1	1.8	11.7
1.1	77.8	93.6	--	1.2	--
1.7	4.7	12.4	--	2.7	--
2.1	4.9	12.1	--	2.5	--
Mean ± SD	19.4 ± 28.8	31.2 ± 31.5	2.7 ± 0.5	2.3 ± 0.7	8.7 ± 3.7