Review Article

A comparison between liposomal and nonliposomal formulations of doxorubicin in the treatment of cancer: An updated review

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ABSTRACT

Cancer remains a major cause of hospitalization and death every year. From time to time, new formulations of anticancer drugs are available in the market and draw the concern of healthcare professionals in terms of the superiority, toxicology, and cost-effectiveness of the new formulations in comparison to the conventional formulation of the same drugs. Doxorubicin, which is a highly potent chemotherapeutic agent, comes with three formulations (pegylated liposomal, nonpegylated liposomal and nonliposomal conventional formulations). English-language literature in relation to the three formulations has been reviewed to inform the healthcare professionals regarding the differences between these formulations. In terms of efficacy, there is only one study supporting the superiority of liposomal doxorubicin, but there are more data which supports the non-inferiority of liposomal doxorubicin in comparison to conventional non-liposomal doxorubicin. It is emphasized that liposomal doxorubicin promotes better toxicology profile than nonliposomal conventional doxorubicin with an increased cost. The cost-effectiveness of liposomal doxorubicin is not well defined as there are very limited studies in this area. Apart from that, this review highlights the interpatient variability in regards to the clearance and volume of distribution following the administration of liposomal doxorubicin. In conclusion, further studies will be required to better define the superiority of liposomal formulation of doxorubicin regarding the efficacy and dose standardization of liposomal doxorubicin should be sought in the near future.

Key words: Cancer, doxorubicin, liposome

INTRODUCTION

Cancer, which is associated with the rapid and uncontrolled proliferation of cells, is a leading cause of death worldwide. In 2015, it is estimated that there will be 1,658,370 new cases of cancer and account for 589,430 death around the world.[1] There are three distinct approaches to the treatment of cancer, which includes surgical excision, irradiation, and drug therapy.[1,2] In terms of drug therapy, side effects are almost inevitable and are a common cause of therapeutic limitation.[2]

Doxorubicin is a very potent cytotoxic anticancer that directly inhibits topoisomerase II and nucleic acid synthesis.[3] As a result, the proliferation of cancer cells will be terminated. However, anticancer treatment of doxorubicin is always limited by its severe side effects such as cardiotoxicity like as dysrhythmia and heart failure.[3] Fortunately, this

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limitation could be resolved through the clinical application of liposomes.[2-4]

Liposomes are bilayered phospholipid vesicles with an aqueous core that can encapsulate both hydrophilic and hydrophobic drugs.[2] In fact, liposomes can retain the drugs until being disrupted, indicating that they can promote sustained release formulation of drugs.[1-4] Besides, they are also concentrated in malignant tumors, so that enhance the selectivity of the anticancer drugs with reduced toxicity.[2-4]

There are several liposomal formulations of anticancer drugs authorized by United State Food and Drug Administration including doxorubicin.[2] A long-acting form of doxorubicin encapsulated in liposomes has been marketed since the mid-1990s for the treatment of various malignancies.[2-4] It is also known as Doxil in the USA or Caelyx in Europe.[2] This liposomal formulation contains polyethylene glycol (PEG) coated-liposomal doxorubicin, which is capable of targeting doxorubicin to tumor sites. In the present, liposomal doxorubicin is a therapeutic option in the treatment of AIDS-related Kaposi's sarcoma, metastatic breast cancer, advanced ovarian cancer, and relapsed/refractory multiple myelomas.[5]

To investigate the differences among the formulations of doxorubicin *in vivo*, a literature search is conducted. It is hypothesized that liposomal doxorubicin encompasses increased efficacy and better toxicology profile compared to nonliposomal conventional doxorubicin.

PHARMACOLOGICAL ACTION OF DOXORUBICIN

Although the exact mode of action remains unknown, the potency of doxorubicin is believed to be associated with topoisomerase II, which is a DNA gyrase and is responsible for the relaxation of supercoiled structure of DNA during transcription.[2,3] Specifically, doxorubicin intercalates in the DNA and stabilizes the DNA–topoisomerase II complex during the transcription process thus prevents the relaxation of the DNA double helix and promotes termination of the process.

Nevertheless, therapeutic limitations of doxorubicin involve severe adverse effects such as dysrhythmia, heart failure, leukocytopenia, moderate to severe nausea, and vomiting and hemorrhage.[2-4] Its cardiotoxicity such as dysrhythmia and heart failure arises from the formation of cytotoxic free radicals in the heart tissue.[2-4] Therefore, this problem can be resolved by increasing the specificity of doxorubicin through the utilization of liposomes.[2-4]

CLINICAL APPLICATION OF LIPOSOMES IN CHEMOTHERAPY OF CANCER

Liposomes feature an aqueous core, one or more phospholipid membranes with/without coating groups on the surfaces of the membranes.[2,3] These amphiphilic characteristics allow liposomes to carry both hydrophobic and hydrophilic drugs within the lipophilic bilayer or aqueous compartment.[2] For instance, hydrophilic drugs dissolve in the aqueous core or adsorb on the hydrophilic head of the phospholipid bilayer whereas lipophilic drugs are filled with the hydrophobic tails of the bilayer.[2-6]

There are numerous liposome-based anticancer agents being marketed as a liposomal preparation, which are commonly known as Caelyx/Doxil, Myocet, DOX-SL, Lipo-Dox, and DaunoXome. Myocet, Caelyx/Doxil, Liposomal Doxorubicin SUN, and Lipo-Dox are liposomal formulations of doxorubicin whereas DaunoXome is the liposomal formulation of Daunorubicin.[2,3,6]

LIPOSOMAL FORMULATION OF DOXORUBICIN

Specifically, the liposome formulated in Caelyx/Doxil is a type of small unilamellar vesicles (SUV), which is a type of liposomes with a single bilayer and is 30–100 nm in size.[2,3,6] Apart from that, the liposome in the formulation is coated with a hydrophilic polymer, PEG, indicating that it is able to escape from mononuclear phagocytic system uptake and to target the tumor cells through the enhanced permeability and retention effect.[2,6] Doxorubicin in the formulation is manifested in a form of doxorubicin sulfate complex and is covered in the aqueous core of liposome.[2,3]

The main difference between Lipo-Dox and Caelyx/Doxil is the type of liposome being used. The lipid membrane of Caelyx/Doxil is made of hydrogenated soybean phosphatidylcholine and coated with PEG-distearoylphosphatidylethanolamine (HSPC/PEG-DPSE) whereas the membrane of Lipo-Dox is made of distearoylphosphatidylcholine (DSPC) coated with the same coating material PEG-DSPE.[6] Since DSPC has a higher transition temperature than HSPC,

Lipo-Dox offers higher stability and longer half-life compared to Caelyx/Doxil.[6]

Liposomal Doxorubicin SUN contains a liposome coated with sodium methoxy PEG-40-carbonyl-DPSE.[4] Although its coating material is different to Caelyx/Doxil, it is proven to be therapeutically equivalent to Caelyx/Doxil.[5]

Myocet is a type of non-pegylated liposomal doxorubicin (non-PLD) composed of SUV. Similar to Caelyx/Doxil, doxorubicin is located within the aqueous core of the liposome but is manifested in a form of doxorubicin citrate complex.[2,5]

LITERATURE REVIEW

Data sources and selection

In respect of research strategies, a search of PubMed, Cochrane Library, and EMBASE using the MeSH search terms doxorubicin, liposome, and cancer was performed. Additional search terms are the brand name of doxorubicin which includes DOX-SL, Lipo-Dox, Doxil, Caelyx, Lipo-Dox, and DaunoXome. All articles being reviewed were primary sources and published within the last 5 years (2010–September 2015) except one primary source, which is thought to be vitally important for the quality of life analysis. Apart from that, secondary sources such as textbook, systematic reviews, and meta-analysis were used as a background reference to support the analysis of the primary sources [Table 1].

PHARMACOKINETIC

Large area under the curve (AUC), slow clearance rate (CL), small distribution volume (VD), and long elimination half-time (t½) characterize the pharmacokinetics (PK) of pegylated liposomal doxorubicin (PLD).[8,9,22] The VD of PLD is close to the blood volume so that the PK of PLD undergoes single compartment model.[8,9] The pegylated lipids in the liposomes result in a long circulation half-time, typically 3–4 days.[8,9]

Nonliposomal conventional doxorubicin has a large VD indicating that a significant amount of the drug is taken up in normal tissues.[8,22] Apart from that, the AUC for conventional nonliposomal doxorubicin is about three orders of magnitude smaller than PLD resulting in a CL rate about three orders of magnitude larger. The t½ for conventional doxorubicin is about 20–25 h.[8,9]

Non-PLD has a shorter t½ than PLD but a longer t½ than conventional nonliposomal doxorubicin.[7] It is due to the absence of PEG coating in the formulation, which indicates that it can be easily taken up by the reticuloendothelial system (RES) and undergo metabolism.[5]

Despite the fact that there are imperative benefits associated with PLD and non-PLD than nonliposomal conventional doxorubicin, its interpatient variability in terms of PKs are more clinically significant in comparison to conventional nonliposomal doxorubicin.[8,9]

Regarding the nonliposomal conventional doxorubicin, factors contributing to interpatient variability are hepatic impairment, patient age and polymorphism in efflux transporter and metabolizing enzymes.[27] Doxorubicin is hepatically cleared by carbonyl reductases (CBR) and cytochrome P-450 enzymes, especially CBR1, CBR3, CYP3A4, CYP2C9, and CYP2D6, which implies that genetic polymorphism of CBR affects the CL of doxorubicin.[27] In relation to that, patients with hepatic impairment as well as elderly population are less capable to metabolize doxorubicin due to their insufficient metabolizing enzymes of doxorubicin.[27] Apart from that, a various subfamily of ATP-binding cassette (ABC) is responsible for pumping out doxorubicin, including ABCB1, ABCB5, ABCB8, ABCC5, and ABCG2. Provided that, polymorphism of the efflux transporter ABC can positively or negatively affect the plasma concentration of doxorubicin.[27]

In comparison to conventional nonliposomal doxorubicin, PLD and non-PLD undertake a more complicated metabolizing pathway.[9] Theoretically, the CL of liposomes depends upon the RES, involving monocytes, macrophages, and dendritic cells. Hence, besides the metabolism of doxorubicin in the aqueous core, the CL of both PLD and non-PLD bears upon the immune system as well as the RES function of different individuals.[8,9,22] Deterioration of immunity is common in the aging population, which is scientifically known as immunosenescence.[28] Hence, the CL of doxorubicin in an elderly patient is further reduced which is possible to prolong t½ and AUC of doxorubicin. In spite of the unclear reason, gender is discovered to be an important contributing factor for the CL of liposomal doxorubicin. Clinical significantly, female patients have a lower CL of liposomal doxorubicin than male patient.[8] Although the exact reason for this phenomenon remains unknown, it is

Table 1: Synopsis of original articles related to liposomal formulation of doxorubicin present in the market

Study	Setting	Participants and follow-up	Study design	Intervention evaluated	Main outcomes	Findings	Limitations
Berger *et al*.[6]	Magee-Women Hospital, University of Pittsburgh Medical Center. 2012	18 patients treated with liposomal doxorubicin	Retrospective study	Liposomal doxorubicin	RRs and toxicity associated with lipodox	No patients had a complete or partial response to lipodox. Disease control rate of 11%	Underpowered sample size and no statistical data provided, indicating the lack of statistical significance. High contamination due to pretreatment prior to liposomal doxorubicin
Wasle *et al*.[7]	11 Austrian and 1 Italian cancer center. March 2008-December 2013	326 patients with lymphoproliferative disease received, at least, one dose of Myocet, which is a nonpegylated form of liposomal doxorubicin	Observational study	Myocet	Evaluation of toxicity graded according to NCI CTCAE, version 4.0	The most common grade 3/4 toxicities were hematologic toxicity, including leukopenia, neutropenia, thrombocytopenia and febrile neutropenia	Contaminations during the study period were not taken into account as some patients received not only Myocet but also other cytotoxic drugs such as cyclophosphamide, vincristine, prednisone, and rituximab. Additionally, baseline characteristic of the patients such as organ function had not been taken into consideration of the study
La-Beck *et al*.[8]	Unknown settings	70 patients >18 years of age with histologically or cytologically confirmed solid tumors or Kaposi's sarcoma and adequate organ function without prior cumulative treatment of doxorubicin	There are 3 studies being conducted. study 1 and 2 are observational studies whereas study 3 is a randomized controlled trial	PLD	The relationship between age as well as gender and the CL of PLD	The factors affecting the CL of PLD are different in comparison to nonliposomal doxorubicin. Female patient has lower CL of PLD than male (P<0.0001). Apart from that, patients <60 years old have higher CL than patients >60 years old (P<0.0001)	The detailed co-intervention had not been reported. Unknown settings limit the clinical applicability of the results
Boers-Sonderen *et al*.[9]	Single center in Finland. Unknown timeline	20 patients with histological proven advanced breast, endometrial or ovarian cancers, who are more than 18 years old and have life expectancy of more than 12 weeks	Phase Ib clinical trial	Caelyx in combination with temsirolimus	To assess the factors affecting the PK/PD of Caelyx	The caelyx exposure (log AUC) was higher in patients who experienced rash (P=0.002) and mucositis (P=0.001) compared to patients who did not experience these adverse events. Additionally, there is no relationship between Caelyx exposure and the occurrence of common side effects of Caelyx such as leukocytopenia, stomatitis, and hand-foot syndrome	Underpowered sample size indicates the questionable significance in clinical settings

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Study	Setting	Participants and follow-up	Study design	Intervention evaluated	Main outcomes	Findings	Limitations
Hunault-Berger *et al*.[10]	26 centers in Finland. March 2002-October 2006. Outcome data was updated on 1 April 2009	60 untreated patients aged 55 years or more with nonBurkitt's, Philadelphia chromosome-negative or BCR-ABL negative acute lymphoblastic leukemia without severe arrhythmia, coronary artery disease, acute heart failure, left ventricular ejection fraction <50%, renal or liver dysfunction, positivity for human immunodeficiency virus, or psychiatric disease	RCT	Continuous-infusion doxorubicin in combination with vincristine on one arm or PLD (Caelyx) and standard vincristine on the other arm	Primary Outcome: composite efficacy and toxicity consisting of continuous complete remission rate, hematologic and extra-hematologic toxicity. Secondary Outcome: complete remission rate, safety, cumulative incidence of relapse and failure, cumulative incidence of death in first complete remission and treatment-related death, event-free survival and OS	Despite the fact that more patients in conventional doxorubicin arm dead, conventional doxorubicin (90%) gave rise to higher complete remission rate after two induction cycles in comparison to PLD (72%). Apart from that, pegylated liposomal doxorubicin decreased the toxicity of doxorubicin in terms of myelosuppression (P=0.005-0.9), infections (P=0.04-0.12) and cardiotoxicity (P=0.12). Despite the reduced toxicity, pegylated doxorubicin does not promote better survival rate	Some results interpreted by the article can be due to chance (P>0.05)
Fiegl *et al*.[11]	Australia. 2003-2009	129 consecutive patients with advanced breast cancer, who received PLD as monotherapy within licensed approval	Observational phase IV study	PLD	Response to PLD which includes toxicity and efficacy associated with PLD	There were encouraging results with PLD as a mono-therapeutic agent I the treatment of metastasized breast cancer. The most common side effect observed was dose-dependent PPE	The article is deemed to be a cross-sectional study, indicating that large performance bias is almost inevitable
Wong *et al*.[12]	A single institution in Singapore. Unknown timeline	84 Asians who are newly diagnosed with locally advanced or metastatic breast cancer	Clinical trial	Nonliposomal doxorubicin	PK and hematologic toxicities of doxorubicin	Increased body fat composition, especially intra-abdominal fat content, is associated with increased doxorubicin exposure and rate of grade 4 leukopenia (P<0.0001). Therefore, individuals with excessive body fat in relative to LBM will have a high risk of doxorubicin-associated toxicity, in regardless of BMI. Furthermore, body surface area does not determine the PK and toxicity of doxorubicin	Baseline characteristics such as patient age are not taken into consideration

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Study	Setting	Participants and follow-up	Study design	Intervention evaluated	Main outcomes	Findings	Limitations
Jurczak *et al*.[13]	Data collected in Polish Lymphoma Research Group. Timeline unknown	610 newly diagnosed NHL Caucasians	Retrospective analysis	Nonliposomal doxorubicin, non-PLD and PLD	Response to treatment according to Cheson criteria, cardiotoxicity, and OS	Response to treatment according to Cheson criteria in patients treated with liposomal doxorubicin is noninferior compared to nonliposomal doxorubicin. Moreover, the OS of patients with high risk of fatal cardiac events is comparable to those patients with low risk of cardiac fatal event, indicating that liposomal doxorubicin increases the OS in patients with high-risk fatal cardiac events	In relation to OS, the observed noninferiority of liposomal doxorubicin in comparison to nonliposomal doxorubicin can due to chance (P=0.9)
Lotrionte *et al*.[14]	Unknown settings	52 patients with nonmetastatic cancer	RCT	Non-PLD-based regimen and EPI-based treatment	TDI examined systolic function	Lower cardiotoxicity is observed in the arm with nonpegylated liposomal doxorubicin-based regimen (P=0.006)	Unknown settings limit the clinical applicability of the data
Chastagner *et al*.[15]	Unknown location. October 2010-January 2013	13 children aged 6-17 years old with histologically documented malignant glioma	Phase I clinical study	Myocet	Maximum RD and PK	Despite the acceptable safety promoted by Myocet, PK differences between the adult and the pediatric population remain unclear. Large interpatient variability in terms of PK was highlighted in this study	Underpowered sample size indicates the questionable significance in clinical settings
Xu *et al*.[16]	China. 2006	22 Chinese patients with histologically or cytologically confirmed breast cancer	Cross-over RCT with 4-week wash-out time	2 PLD product	Das software calculated PK profile	The PK demonstrated by the 2 products was similar. In comparison to European study regarding the PK profile, The CL and VD of the Chinese patients are higher than European patients. Therapeutic efficacy was not observed in this study	Underpowered sample size indicates the questionable significance in clinical settings. The name of the PLD product had not been mentioned. Unknown randomization procedure indicates the possibility of selection bias. Unknown blinding indicates the possibility of performance bias
Turini *et al*.[17]	Italian, German, and French. 2013-2014	Oncologists and oncology nurses	Cross-sectional study (an online survey)	Chemotherapy	To assess the chemotherapy-induced nausea and vomiting direct cost	It highlighted the significant cost of chemotherapy-induced nausea and vomiting on the NHS in European Countries	It is questionable that the finding may not be applicable to Asian countries
Monk *et al*.[18]	124 centers in 21 countries. April 2005-May 2007	672 patients with histologically confirmed pithelial ovarian, fallopian tube, or primary peritoneal carcinoma	Phase III RCT	Trabectedin plus PLD and PLD	To assess the safety and efficacy of the two intervention	It confirmed the superiority of the combination treatment compared to single treatment. (P<0.05)	No blinding indicates the risk of performance bias

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Study	Setting	Participants and follow-up	Study design	Intervention evaluated	Main outcomes	Findings	Limitations
Crivellari *et al*.[19]	Multinational. Recruitment from November 2005 and December 2007. Follow-up 42 months	77 multinational elderly (>66 years old) patients with endocrine nonresponsive (ER <10%; and PgR <10%) breast cancer	Phase III RCT	PLD regimen and metronomic cyclophosphamide plus methotrexate	The primary endpoint is BCFI. Secondary outcomes included tolerability, adverse events, and quality of life	The occurrence of BCFI was similar in two arms. No cardiac toxicity had been observed. Patients on PLD reported worse QL scores than those on non-PLD for all measures except for nausea and vomiting. The measures consist of physical well-being, functional performance, overall disease/ treatment burden, mucosa inflammation of the mouth	No allocation concealment indicates the risk of selection bias. No blinding indicates the risk of performance bias
Lee *et al*.[20]	South Korea. 2013	A Markov model with a 10-year time horizon	Cost-utility analysis	PLD/carboplatin versus paclitaxel/ carboplatin	QALY	PLD/carboplatin combination is more effective and costly than paclitaxel/carboplatin combination, with an additional USD 21,658 QALY	There is a variation in PLD cost and PLD administration cost. Additionally, patients are assumed to accept six doses of chemotherapy on average from the diagnosis of ovarian cancer until death
Staropoli *et al*.[21]	Clinical Data of Italy. 2001-2011	108 patients with histologically confirmed ovarian cancer	Retrospective cohort study	On the exposure arm, the patients are treated with PLD. On the control arm, the patients are treated with other drugs such as topotecan, gemcitabine, etoposide. Patients underwent PLD had high platinum-sensitivity	Primary outcome: OS. Secondary outcome: PFS, RR, and toxicity	OS and PFS of the control arm are higher than exposure arm (P<0.08). Common PLD-associated toxicity observed are neutropenia (14%), thrombocytopenia (7%), anemia (1%), hand-foot syndrome (5%), mucositis	The patient had been treated by drugs other than doxorubicin. Hence, it is important to underline that co-intervention might interfere the results. Other limitations mentioned in the article include small sample size, long enrollment time and selection bias
Anders *et al*.[22]	Unknown settings	46 tumor-bearing mice following inoculated intracerebrally with MDA-MB-231-BR-luciferase-expressing cells	Laboratory study	PLD versus nonliposomal doxorubicin	PK and efficacy	In comparison to nonliposomal doxorubicin, PLD promotes better efficacy and PK profile in terms of OS and AUC in the treatment of intracranial breast cancer	Further examination is required in human setting

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Study	Setting	Participants and follow-up	Study design	Intervention evaluated	Main outcomes	Findings	Limitations
Bosetti *et al*.[23]	European countries	153 patients with recurrent or progressive ovarian cancer	Cost-effectiveness analysis based on the data of an RCT	PLD versus gemcitabine	Costs and QALWs	PLD has a higher drug cost than gemcitabine. (€2814.13 vs. €1528.85; *P*<0.0005). The hospitalization cost of gemcitabine is higher than PLD. (€4008.80 vs. €1394.38; *P*<0.0005). The OS is comparable for both groups (56 weeks for PLD vs. 51 weeks for gemcitabine; *P*=0.048). The cost-effectiveness of PLD was €170 and €318 per QALW while the cost-effectiveness of gemcitabine was between €317 and €589 per quality-adjusted life week	It is uncertain that the same cost will apply to other countries
Vici *et al*.[24]	4 oncologic centers of the Gruppo Oncologico Italia Meridionale. March 2003-November 2005	104 patients with histologically confirmed advanced breast cancer who are not previously treated with adjuvant anthracyclines	RCT	EPI/V and PLD/V	Efficacy according to RECIST criteria and toxicity according to National Cancer Institute Common Toxicity Criteria (version 3.0)	3 complete response (5.6%) and 20 partial responses (37%), for an overall RR of 42.6% (95% CI, 29.3-55.9) in EPI/V and 8 complete responses (16%) and 18 partial responses (36%), for an overall RR of 52% (95% CI, 38.2-65.8) in PLD/V. In terms of toxicology, both arms showed a tolerable adverse effect	No allocation concealment indicates the risk of selection bias. No blinding indicates the risk of performance bias
Osoba *et al*.[25]	25 centers in Canada. 2001	258 male patients with biopsy-proven AIDS-related Kaposi's sarcoma	RCT	PLD or doxorubicin plus bleomycin plus Plus vincristine	Change in HRQL from baseline to end of treatment related to general health, pain, social functioning, mental health, cognitive functioning, energy/fatigue, health distress, health transition, and overall QL	The patients treated with PLD had high statistically significant improvement on 4 of the 9 domains (*P*<0.01), which includes pain, cognitive functioning, social functioning and health distress. The patients treated with doxorubicin plus bleomycin plus vincristine had deteriorated energy and experienced fatigue	No allocation concealment indicates the risk of selection bias. No blinding indicates the risk of performance bias. Additionally, he study was conducted on 2001, which may not represent the latest actuality

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Study	Setting	Participants and follow-up	Study design	Intervention evaluated	Main outcomes	Findings	Limitations
Kushnir *et al.*[26]	Johns Hopkins Hospital and Duke University Medical Center. 2002-2014	184 patients with gynecologic malignancy	Retrospective chart review	PLD	Cost savings following selective cardiac surveillance	There were no significant difference in relation to cardiotoxicity between the selective cardiac surveillance and routine cardiac surveillance. More than 182,000 USD in 184 patients will be saved for not performing cardiac imaging prior to PLD treatment	The investigators did not consider that the cost of PLD is more than 100 times higher than nonliposomal conventional doxorubicin[27]. Hence, the opportunity of saving more than 4,400,000 USD will be missed if not performing routine cardiac surveillance

€=Euro, RCT=Randomized controlled trial, PLD=Pegylated liposomal doxorubicin, CL=Clearance, VD=Volume of distribution, NHS=National Health Service, BCFI=Breast cancer-free interval, BMI=Body mass index, LBM=Lean body mass, HRQL=Health Related Quality of Life, QALWs=Quality-adjusted life weeks, RR=Response rate, PPE=Palmar-plantar erythrodysesthesia, TDI=Tissue Dropper Imaging, RD=Recommended dose, PK=Pharmacokinetics, NHL=NonHodgkin lymphoma, QALY=Quality adjusted life year, OS=Overall survival, CTCAE=Common Terminology Criteria for adverse events, PFS=Progression-free survival, EPI/V=Epirubicin/vinorelbine, PLD/V=Pegylated liposomal doxorubicin/vinorelbine, AUC=Area under the curve, RECIST=Response evaluation criteria in solid tumors

thought to be closely associated with the hormone. As hormone plays a key role in the immunosuppressive and immunostimulatory activity, the reason behind this observation can be rationalized.[28] There are many factors contributing to the immune status of individuals, indicating the dramatic interpatient variability of liposomal doxorubicin.

Other factors contributing to interpatient variability of PLD are body fat composition and genetic viability.[12] The phenomenon of significantly increased AUC of PLD as a result of high intraabdominal fat content had been observed. In terms of genetic viability, higher VD and CL rate had been detected in Asian in comparison to European.[16]

EFFICACY

The efficacy of the different formulations which involve doxorubicin was evaluated based on response rate, including complete response, partial response, and overall response. The survival rate, which includes overall survival and progression-free survival, is also deemed to be an indicator of efficacy.[6,7,10,13,22,24]

The efficacy of PLD as a single agent in the treatment of metastatic breast cancer has been confirmed. However, there is a lack of scientific consensus that the liposomal formulations of doxorubicin increase the survival rate of the treatment, in comparison to nonliposomal conventional doxorubicin.[6,7,10,13,22,24] Nevertheless, it is clinically significant that PLD decreases the risk of fatal cardiac events such as acute myocardial infarction and congestive heart failure.[6,7,18] As a result, the utilization of PLD increases the survival rate of patients with high cardiac risks compared to nonliposomal conventional doxorubicin.[13,14]

Despite the efficacy of doxorubicin in the treatment of glioma *in vitro*, its utilization is limited by the efflux effect of the blood-brain barrier (BBB).[15,22] Fortunately, the development of liposomal doxorubicin allows penetration of doxorubicin into the malignant glioma cells in the brain.[15] In spite of the fact that PLD shows high potency in the treatment of glioma, its dosing regimen in children remains unclear. Hence, further studies are necessary to balance the toxicology profile and efficacy of PLD in the treatment of glioma.

Moreover, there are some discrepancies regarding the potency between two formulations (Lipo-Dox and Doxil) of PLD.[6] An observational study indicates that Lipo-Dox is inferior to Doxil in terms of potency.[6] However, this observation might not be clinically

significant as a larger sample size is needed to confirm the finding.

In addition, laboratory data have showed the efficacy of PLD in the treatment of intracranial model of breast cancer in mice.[22] In this model of breast cancer, PLD promotes higher survival rate and efficacy with reduced toxicity than nonliposomal doxorubicin in mice.[22] Clinical data regarding the utilization of PLD in this model of metastasis breast cancer is eagerly awaiting.

TOXICOLOGY

In comparison to nonliposomal conventional doxorubicin, it is certain that the liposomal formulations of doxorubicin promote better cardiac safety.[7,9-14,19,21] The reduced cardiac toxicity had also been observed in comparison to other anthracycline-based chemotherapy.[14] Therefore, it is recommended that the liposomal formulations of doxorubicin should be used in the patients with high risk of cardiac events such as arrhythmia, congestive heart failure, and myocardial infarction.[13,21]

Furthermore, the reduced toxicity has also been observed in terms of myelosuppression and infection in comparison to nonliposomal conventional doxorubicin.[10] However, the myelotoxicity of liposomal doxorubicin is not uncommon.[7,12] The myelotoxic effects in association with liposomal doxorubicin include leukopenia, neutropenia, thrombocytopenia, and febrile neutropenia.[7,9-14,19]

In terms of extra-myelotoxicity other than cardiotoxicity, the occurrence of Palmar-Plantar Erythrodysesthesia (commonly known as a hand-foot syndrome) is similar in both liposomal and nonliposomal formulations of doxorubicin.[9,11,21] Nausea and vomiting are moderate to severe in patients treated with nonliposomal doxorubicin but are usually mild in patients treated with liposomal doxorubicin.[3,19]

As the liposomal formulations of doxorubicin undergo viability in relation to PKs, dose-dependent myelotoxicity cannot be effectively predicted.[7,9-14] Factors affecting the PKs of liposomal doxorubicin are likely to affect the toxicology profile of such formulations. In general, higher risk of toxicity is expected to be seen in elderly patient, immunosuppressive" and female individuals.[8] Patients with high body fat composition, particularly intraabdominal fat, are also more susceptible to experience doxorubicin-associated myelotoxicity if they are treated with liposomal doxorubicin.[12]

Under the extremely rare scenario, acute peculiar mucous reaction following administration of PLD had been reported.[29] No study had been conducted in this area as the occurrence of this reaction had not been observed prior to the case report. Hence, further study has to be carried out in this area.

QUALITY OF LIFE AND COST-EFFECTIVENESS ANALYSIS

Although the improved survival rate with the use of liposomal doxorubicin has not been proven, it is observed that the patients receiving liposomal doxorubicin have a higher quality of life than the patients treated with nonliposomal doxorubicin in terms of pain, cognitive functioning, social functioning, and health distress.[21,25] The improved quality of life is believed to be associated with the decreased adverse drug effects and the elevated selectivity promoted by the liposome in the liposomal formulation of doxorubicin.

However, the improved quality of life other than nausea and vomiting related to liposomal doxorubicin has not been detected in elderly patients with metastatic breast cancer.[19] This phenomenon can be explained by the deteriorated immune system of the elderly patients, resulting in a significant decrease in the CL of liposomal doxorubicin.[28] Consequently, a significant increase in AUC accounts for the dose-dependent toxicity following the administration of liposomal doxorubicin.[11]

Since the utilization of liposomal doxorubicin reduces the severity of chemotherapy-induced nausea and vomiting (CINV) in conjunction with the treatment of nonliposomal conventional doxorubicin, it is deemed to reduce the direct cost related to the CINV. As the CINV had been highlighted to be a significant cost to the National Health Service in European countries, the possibility of cost reduction is clinically significant.[17] Nonetheless, further investigation is needed to confirm the actuality of this extrapolation.

Regarding the routine cardiac surveillance prior to PLD treatment, it is believed to be unnecessary as selective cardiac surveillance will save more than 180,000 USD in 184 patients received PLD.[26] However, as PLD is 100-times more costly than conventional

nonliposomal doxorubicin, it is debatable that an opportunity of saving more than 4,400,000 USD will be ignored if practicing selective cardiac surveillance.[30]

As there is a lack of updated primary sources comparing the cost-effectiveness of liposomal doxorubicin and nonliposomal conventional doxorubicin, the cost-effectiveness studies comparing liposomal doxorubicin with other nonliposomal anticancer drugs have been included. The assumption being made is that similar result will be expected in nonliposomal conventional doxorubicin in comparison to other nonliposomal anticancer drugs as they belong to the class of chemotherapy whereas liposomal doxorubicin belongs to the class of nanotherapy.

In comparison to anticancer drugs other than doxorubicin, PLD has a higher efficacy and cost than gemcitabine, the incremental cost-effectiveness ratio (ICER) observed for PLD was between €170 and €318 per QALW, which is between €8864 and €16581 per quality-adjusted life year (QALY) gained.[23] In terms of paclitaxel, PLD possesses higher efficacy and cost, with an ICER of 21,658 USD per QALY gained.[20] Overall, PLD is deemed to be cost-effective in some most countries, referring to the willingness-to-pay (WTP) threshold recommended by World Health Organization (WHO).[31] However, based on the gross domestic product stated by WHO, PLD may not be cost-effectiveness in some developing countries.[31]

DISCUSSION AND CLINICAL IMPLICATION

This review highlights the clinical significance of the interpatient variability associated with the use of liposomal doxorubicin. It is impacted by age, gender, race, immune status, and body fat composition of an individual treated with liposomal doxorubicin.[8,9,12] An important clinical concern is that most cancer patients are middle-aged or elderly, indicating a need for dose adjustment in the treatment of liposomal doxorubicin. Otherwise, the dose-dependent toxicity associated with liposomal doxorubicin cannot be extrapolated and managed. However, the effective way of individualizing the dose of liposomal doxorubicin has not been identified.

In the near future, the liposomal doxorubicin will be prescribed in more conditions such as pediatric glioma and intracranial model of breast cancer as the utilization of the liposome brings about the penetration across BBB.[15,22] As the PK model of the liposomal doxorubicin in children remains unclear, more comprehensive precautions will be required to prevent or manage the adverse drug reaction of the liposomal doxorubicin in this population. Concerning the intracranial model of breast cancer, further studies are needed to investigate how the liposomal doxorubicin behaves in human settings.[22]

In terms of efficacy, there is limited evidence base to support the superiority of the liposomal doxorubicin compared to the nonliposomal conventional doxorubicin.[6,7,10,13,22,24] Nevertheless, stringent precautions are recommended before choosing a formulation of doxorubicin for high-risk patients to protect against fatal cardiac events, as the reduced cardiotoxicity promoted by the liposomal doxorubicin has been confirmed. Subsequently, the clinical concern aroused is the cost-effectiveness of the routine cardiac surveillance prior to the introduction of liposomal doxorubicin. Overall, there remains a considerable controversy over the relative importance of routine cardiac surveillance in the patients accepting doxorubicin-based therapy.

Although the updated cost-effectiveness of the liposomal doxorubicin compared to nonliposomal doxorubicin remains unclear, the cost-effectiveness of liposomal doxorubicin in comparison to other chemotherapy is within the Willingness to Pay (WTP) threshold in most developed countries, so that the use of liposomal doxorubicin is deemed to be cost-effective only in this particular countries.[20,23,31] In healthcare settings, liposomal doxorubicin is considered to be more tolerable than nonliposomal conventional doxorubicin as regards of cardiotoxicity, myelotoxicity, nausea and vomiting with an estimation of 100 times the additional cost. Therefore, further pharmacoeconomic studies comparing liposomal and nonliposomal formulations of doxorubicin will be required to confirm the cost-effectiveness of liposomal doxorubicin.

In addition, this review reveals some limitations and weaknesses in relation to the updated evidence. The lack of blinding and allocation concealment in the randomized control trials could probably lead to a bias toward the superiority of liposomal formulation of doxorubicin compared to nonliposomal conventional doxorubicin. Another common weakness in most of the literature is the underpowered sample size. Therefore, it is identified that the sample present in the studies may not represent the whole population. Hence, larger studies are required to confirm the actuality

of the results. Notwithstanding, the contamination, and co-intervention in most of the studies are well controlled, indicating that the results could be statistically and clinically significant. Further, our review did not compare the efficacy and toxicology of liposomal doxorubicin with other marketed chemotherapy, which is thought to be closely related to the current healthcare settings.

CONCLUSION

In summary, there remains a substantial gap in the scientific literature on the superiority of liposomal doxorubicin in relation to efficacy. While there is some experimental evidence that liposomal doxorubicin is able to increase survival rate in mice having an intracranial model of breast cancer, there is less evidence on its efficacy in healthcare settings. Current research has several limitations including the possibility of selection bias and performance bias as well as underpowered samples. However, it is confirmed that PLD and non-PLD encompass better safety profile compared to nonliposomal conventional doxorubicin in terms of cardiotoxicity and myelosuppression. However, larger interpatient variability in terms of PK is common in liposomal doxorubicin resulting in the difficulty in dose standardization. Moreover, the utilization of liposomal doxorubicin in the treatment of brain tumor will be developed in the near future. Large intervention studies in this area are likely to provide the best evidence of the efficacy of liposomal doxorubicin in increasing the survival rate in comparison to nonliposomal conventional doxorubicin. Finally, dose standardization is an urgent priority to manage the doxorubicin-induced toxicity following the administration of liposomal doxorubicin.

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Conflicts of interest
There are no conflicts of interest.

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