Review article

Liposomal Drug Products Used in Hematology

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LEARNING OBJECTIVES

- Define Liposomes; review their discovery and their clinical applications.
- Describe Liposomal Drug Delivery System and its use in various drug products in Clinical Use.
- Describe in details indications, efficacy and safety of old and current liposomal drug products used in benign and malignant hematology.
- Describe clinically relevant pharmacokinetic and efficacy differences between conventional drugs and liposomal drugs used in hematology.

INTRODUCTION TO LIPOSOMES AND THE LIPOSOMAL DRUG DELIVERY SYSTEM

DEFINITION

Liposomes derived by the combination of two Greek words, "lipos" meaning fat and "soma" meaning body. They are synthetic spherical molecules 20nm-20 µm in diameter formed from self-assembly of lipids. [1] They are composed of self-assembled spherical vesicles consisting of one or multiple lipid bilayers surrounding an internal aqueous core. [2]

Since their discovery, liposomes have become one of the most highly investigated nanostructures used in nanomedicine and Bionanotechnology. [2]

HISTORICAL PERSPECTIVES

In their 1965 citation classic, the late Alec Bangham and colleagues published the first description of swollen phospholipid systems that established the basis for model membrane systems. [3] Within a few years, a variety of enclosed phospholipid bilayer structures

consisting of single bilayers, initially termed 'bangosomes' and then 'liposomes' , were described, and the early pioneers such as Gregory Gregoriadis, established the concept that liposomes could entrap drugs and be used as drug delivery systems.[4]

STRUCTURE OF LIPOSOMES

Figure 1 showed the structure of the liposomes. As seen in **Figure 1A**, liposomes are composed of self-assembled spherical vesicles consisting of one or multiple lipid bilayers surrounding an internal aqueous core. Bilayer thickness is 5 nm thick composed of hydrophobic acyl lipid tail region and a hydrophilic headgroup region. **Figure 1 B**- Electron Microscopy photo of the liposome structure. [2]

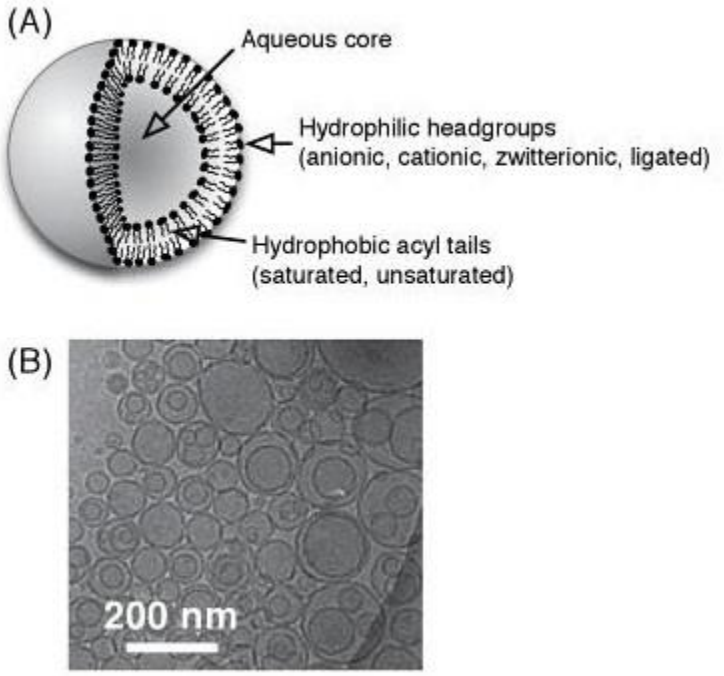
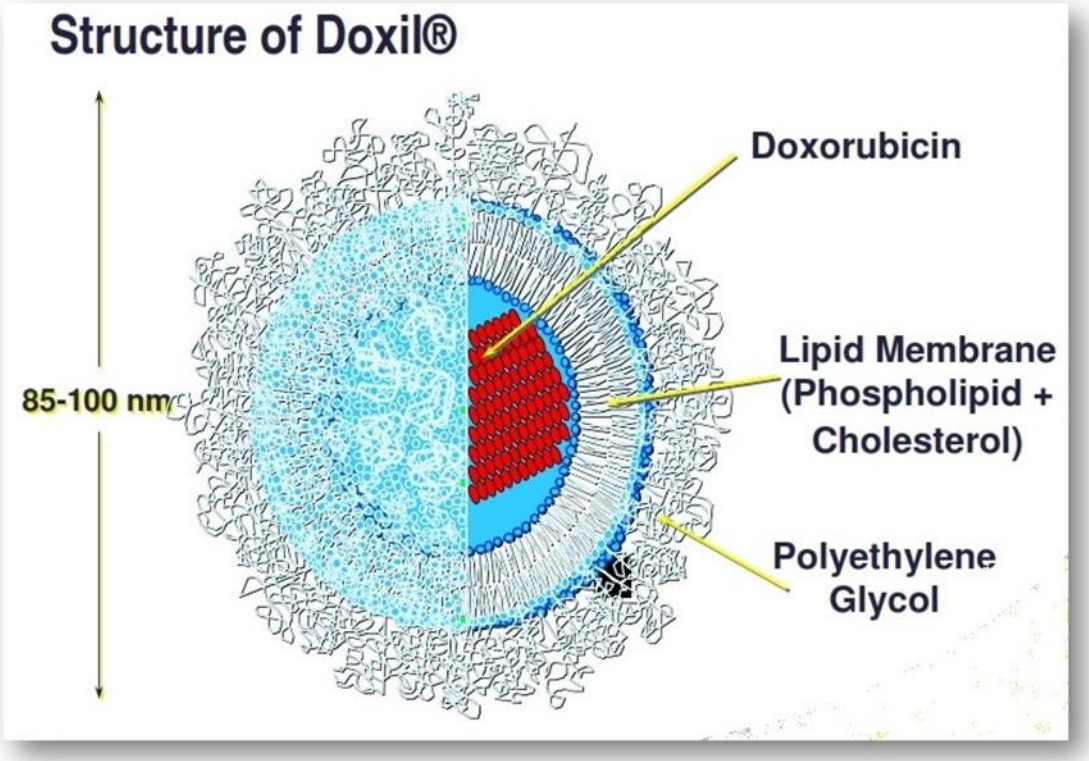


Figure 2: structure of Doxil



Adapted from: Barenholz Y. Doxil® — the first FDA-approved Nano-drug: Lessons learned. Journal of Controlled Release 2012; 16:117–134.

CLASSIFICATION OF LIPOSOMES

According to the number and size of lipid bilayers, liposomes can be classified according to their diameter , small (<100nm) , large (100-1000nm) or giant (>1000 nm) , and number of bilayer , single (unilamellar) or multiple (multilamellar) as seen in **Table 1** . [1]

Table 1- Classification of Liposomes according to Size and Lamellarity

Suffix	Name	Size (Nanometer)
SUV	Small Unilamellar	<40
LUV	Large Unilamellar	100-1000
MLV	Multilamellar	>1000

Adapted from: Çağdaş M, Sezer AD, Bucak S. Liposomes as Potential Drug Carrier Systems for Drug Delivery. In: Sezer AD, Application of Nanotechnology in Drug Delivery. InTech 2014; p: 1-50

LIPOSOMES AS A DRUG CARRIER (THE LIPOSOMAL DRUG DELIVERY SYSTEM):

Liposomes are well-established vehicles for the administration of therapeutic and diagnostic agents. [3,4] . Constituted by an aqueous core surrounded by one or several phospholipid bilayers, liposomes are biocompatible and biodegradable entities able to entrap hydrophilic drugs into their cavity, while allowing water insoluble drugs to be inserted into the lipid bilayers.[5]

Liposomes are reliable drug delivery systems because they are non-toxic, biocompatible, and capable of prolonging bioavailability of the encapsulated agent by reducing or preventing drug degradation and enhancing solubility and stability. Liposomes also open the therapeutic window, reducing adverse effects by altering the pharmacokinetic and pharmacodynamics characteristics of the encapsulated agent. [6]

FDA-APPROVED LIPOSOMAL AND LIPID-BASED PRODUCTS USED IN HAEMATOLOGY

Table 2 – FDA-Approved liposomal and lipid-based products used in Hematology

Drug Product	Generic Name	Indication	Year of Approval
Doxil®/Caelyx®	Doxorubicin	Multiple Myeloma	1995
DaunoXome®	Daunorubicin	Acute Myeloid Leukemia	1996
AmBisome®	Amphotericin	Invasive aspergillosis	1997
Abelcet®	Amphotericin	Invasive aspergillosis	1995
Amphotec®	Amphotericin	Invasive aspergillosis	1996
DepoCyt®	Cytosine Arabinoside	Lymphomatous and Neopalstic Meningitis	1999
Marqibo®	Vincristine	Acute lymphoblastic leukemia	2012

Adapted from: Theresa TM. Allen, Cullis PR. Liposomal drug delivery systems: From concept to clinical applications. Advanced Drug Delivery Reviews 2013; 65: 36–48

ANTIFUNGAL DRUGS

FDA-approved liposomal Amphotericin B formulations include Ambisome® , Abelcet® and Amphotec®. [2]

Lipid formulations of amphotericin (Abelcet ® , Amphotec and AmBisome ®) are polyene antifungals used for the treatment of aspergillosis and yeasts and are significantly less toxic and are recommended when the

conventional formulation of amphotericin is contra-indicated because of toxicity, especially nephrotoxicity or when response to conventional amphotericin is inadequate; and are more expensive. [7]

Liposomal amphotericin B is as effective as conventional amphotericin B for empirical antifungal therapy in patients with fever and neutropenia, and it is associated with fewer breakthrough fungal infections, less infusion-related toxicity, and less nephrotoxicity. [8]

ANTICANCER DRUGS

Nanomedicine is an attractive option to palliate the shortcomings of chemotherapy, including severe adverse side effects and multidrug resistance. [5]

Most of the therapeutic agents encapsulated in liposomes are anti-cancer drugs. [9, 10] Nevertheless, albeit the increasing number of liposomal formulations of anticancer agents entered into clinical trials, few of them have been granted approval for cancer treatment. [11]

Liposomes have been by far the most used nanovectors for drug delivery, with liposomal doxorubicin receiving US FDA approval as early as 1995. [5]

Liposomal Doxorubicin (Doxil® /Caelyx®)

Doxorubicin is an anthracycline widely used to treat solid and hematological tumors, but its major drawback is its related cardiotoxicity. In cardiotoxicity, positively charged doxorubicin's affinity for negatively charged cardiolipin, a lipid abundant in heart tissue, is thought to be involved in drug localization in the heart tissue. [5] Polyethylene glycol (PEG)-Liposomal doxorubicin (PLD) (**Figure 2**) is a formulation of the anthracycline doxorubicin in which the drug is encapsulated in PEG-coated liposomes. [12] This alters the pharmacokinetic properties of doxorubicin, prolong circulation time and enhancing localization to the tumor and avoiding opsonization and destruction by reticuloendothelial system (RES) agents (hepatocytes and Kupffer cells) [5] . It is associated with significantly reduced cardiotoxicity. [13]

Doxil is the first FDA-approved nano-drug and has the most extensive clinical

use in the treatment of solid and Haematological Malignancies and AIDS-Related Kaposi's Sarcoma. [14]

Table 3 showed the toxicity differences between PLD and conventional doxorubicin. [15]

Side Effect	Doxorubicin	Caelyx/Doxil
Vesicant effect	+++	+/-
Infusion reaction	-	+*
Nausea/Vomiting	++	+/-
Myelo-suppression	+++	+ (no gr. 4)
Stomatitis/Mucositis	++	+++
Hand-Foot (HPS)	-	+++
Cardiotoxicity	+++	+
Alopecia	+++	+
Max. Tolerated Dose	60 mg/m^2	50 mg/m^2
Dose Intensity	20 mg/m^2 /wk	12.5 mg/m^2 /wk.
Max. Cum. Dose	450 mg/m^2	>1000 mg/m^2

Adapted from: Alberts DS1, Muggia FM, Carmichael J, et al. Efficacy and safety of liposomal anthracyclines in phase I/II clinical trials. Semin Oncol 2004; 31(6 Suppl 13):53-90.

Palmo-Plantar Erythrodysaesthesia (PPE), also known as hand-foot syndrome is a unique adverse effect of liposomal doxorubicin. It is a cutaneous reaction to the liposomal formulation of doxorubicin due to leakage of small amounts of Caelyx into the capillaries in the palms of hands and soles of feet. It may results in redness, tenderness, and peeling skin that generally seen after 2–3 treatment cycles and can be managed with pyridoxine and corticosteroids and may requires an altered dosing pattern for Caelyx administration. [5, 16]

Indications of Doxil/Caelyx in Hematology: PLD is FDA-approved for the treatment of multiple myeloma in 2007 in combination with bortezomib in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant... The dose is 30 mg/m^2 on day 4 of the bortezomib 3-week regimen as a 1-h infusion given immediately after the bortezomib infusion .The bortezomib regimen consists of 1.3mg/m^2 on days 1, 4, 8, and 11 every 3 weeks. Caelyx dosing should be repeated as long as patients respond satisfactorily and tolerate treatment. [16]

Non-FDA Approved off-label indications of Doxil/Caelyx include:

1. Aggressive Non-Hodgkin's lymphoma such as diffuse large B-cell lymphoma where it replaced the doxorubicin in R-CHOP (DRCOP regimen). The dose of PLD is 40 mg/m^2 (maximum 90 mg) IV infusions over 1 hour. [17]

2. Cutaneous T-cell Lymphoma: PLD dose is 20 mg/m^2 days 1 and 15 every 4 weeks for 6 cycles. [18]

3. Relapsed /refractory Hodgkin's lymphoma: PLD was incorporates in the salvage GVD regimen. The dose is 10 mg/m^2 (post-transplant patients) or 15 mg/m^2 (transplant-naïve patients) days 1 and 8 every 3 weeks (in combination with gemcitabine and vinorelbine) for 2-6 cycles.

Liposomal Daunorubicin (DaunoXome)®

DaunoXome® is a commercial liposomal formulation of daunorubicin

in which the drug is entrapped into small unilamellar vesicles. It is FDA approved in the treatment of AIDS –related Kaposi's sarcoma and does not yet gain FDA approval for hematological malignancies. [20]

DaunoXome® has been tested as a single agent or in combination with arabinosyl cytosine in the treatment of patients with acute myeloid leukemia (AML) in relapse or in patients with newly diagnosed AML or with disease failing initial remission-induction therapy. The results have indicated that DaunoXome® can be used at high doses, up to 150 mg/m^2 for 3 days, safely with acceptable toxicity. The anti-leukemia activity has been reported to be at least equal or superior to that of free daunorubicin. Mucositis appeared more frequently than cardiotoxicity and high complete remission rates have been reported in patients with AML in first relapse. [21]

Latagliata et al. explored the efficacy of liposomal daunorubicin versus daunorubicin in acute myeloid leukemia patients aged older than sixty years. Liposomal Daunorubicin seemed to improve overall survival and disease-free survival in the long-term follow-up, because of a reduction on late relapses. [22]

Liposomal Cytarabine (Depocyt)®

DepoCyt (e)® (cytarabine liposome injection) is a sustained-release liposomal formulation of the chemotherapeutic agent cytarabine. DepoCyt(e) is indicated for the intrathecal treatment of lymphomatous meningitis. and is the only liposomal drug administered for intrathecal administration . The drug was granted accelerated approval by the FDA in 1999 and full approval in 2007. [23]

As opposed to conventional cytarabine, which is administered in the hospital twice weekly by spinal injection, DepoCyt(e) ® extends the duration of cytarabine efficacy to allow for injection once every two weeks in an outpatient setting. [23]

A randomized Phase III study has shown that liposomal cytarabine injected once every two weeks produced a high response rate (71% versus 15%, P = 0.006) and a better quality of life as measured by Karnofsky score (P = 0.041) relative to that upon treatment

with free cytarabine injected twice a week. [24]

In a phase II European trial of DepoCyt(e)® in central nervous system relapse of acute lymphoblastic leukemia or Burkitt's lymphoma/leukemia , the use of Liposomal cytarabine (50 mg) given intrathecally together with systemic or intrathecal dexamethasone once every 2 weeks, liposomal cytarabine showed excellent antileukemic activity. [25]

Liposomal Vincristine (Morqibo)®

Morqibo® is a liposome-encapsulated form of vincristine sulfate, FDA-approved in 2012 and is indicated for the treatment of adult patients with Philadelphia negative acute lymphoblastic leukemia in second or greater relapse or whose disease has progressed following two or more anti-leukemic therapies. The recommended dose is 2.25 mg/m^2 weekly over 1 hour. [26],Compared to vincristine sulfate injection, the risk of teratogenicity in pregnancy, death after intrathecal administration and neuropathy seems comparable to vincristine sulfate while the risk of myelosuppression including grade 3-4 cytopenia and tumor lysis syndrome occur with increasing frequency with Morqibo®. Liposomal vincristine may also not be immediately bioavailable compared to vincristine sulfate injection but can be used in relapsed patients as monotherapy resulting in a meaningful clinical outcome such as the ability to bridge to transplantation. [26 , 27]

Marqibo® [Package insert] .San Francisco , CA .Talon therapeutics , Inc. October 2012 .

LIPOSOMAL PRODUCTS USED IN HAEMATOLOGY IN CLINICAL TRIALS

Table 4 showed liposomal drugs used in malignant hematology that are non-FDA approved and still in clinical trials.

Drug Product	Generic Name	Indication	Trial Phase
Atragen®	Tretinoin	Acute promyelocytic leukemia	Phase II
L-Annamycin®	Doxorubicin	Pediatric and Adult Relapsed ALL and AML Adult Relapsed ALL Doxorubicin-resistant blood cancer	Phase I /II
CPX-351®	Cytarabine: daunorubicin	Acute myeloid leukemia	Phase II
LEM-ETU	Mitoxantrone	Acute Leukemia	Phase I
Sideral® Forte	Ferric diphosphate	Iron deficiency anemia , anemia of chronic Kidney disease	Phase II/III

Adapted from : Theresa TM. Allen , Cullis PR . Liposomal drug delivery systems: From concept to clinical applications . Advanced Drug Delivery Reviews 2013 ; 65: 36–48

Liposomal Iron (Sideral Forte)®

For the treatment of all anemia's responsive to oral iron therapy, such as hypochromic anemia associated with pregnancy, chronic or acute blood loss, dietary restriction, metabolic disease and post-surgical convalescence. Useful in treating iron deficiency anemia or increased requirements of Iron and Vitamin C. The iron

Included in SIDERAL FORTE®, is uniquely coated with liposomal technology that allows the molecule to pass through the stomach, avoiding any gastrointestinal irritation, to be directly through the lining of the gastrointestinal tract. Oral Liposomal iron allows protecting gastrointestinal mucosal tissue from pro-oxidant effect of iron and guarantees the absolute absence of any side effects, such as gastralgia , nausea , constipation and stain of faeces . [28]

Clinical studies performed confirm the better tolerability of liposomal iron .

Indications of Sideral Forte ® in Hematology :

1.Iron deficiency anemia [28]

2.Chemotherapy –related anemia [28]

3.Refractory anemia treated with Epo alpha [28,29]

4.Inflammatory bowel disease [28]

5.Coeliac disease- liposomal iron is glutean-free and is useful in the treatment of coeliac disease patients with iron deficiency anemia [28]

6.Dialysed and Pre-dialysed patients with chronic kidney disease CKD .

In a recent study , 99 patients with chronic kidney disease CKD (stage 3–5, not on dialysis) and iron deficiency anemia [hemoglobin (Hb) ≤12 g/dL, ferritin ≤100 ng/mL, transferrin saturation ≤25%] were assigned (2:1) to receive oral liposomal iron (30 mg/day or a total dose of 1000 mg of IV iron gluconate for 3 months . Oral liposomal iron is a safe and efficacious alternative to IV iron gluconate to correct anemia in ND-CKD patients, although its effects on repletion of iron stores and on stability of Hb after drug discontinuation are lower. [30]

Liposomal All-Trans Retinoic Acid (Lipo-ATRA) (Atragan) ®

Liposomal ATRA (Atragan) ® is an intravenous liposomal formulation of ATRA used in the treatment of acute promyelocytic leukemia . It can cure acute promyelocytic leukemia when used as monotherapy and is of value in patients who cannot swallow or absorb capsules, patients with a nasogastric tube, or small children and in unconscious and intubated patients but does not gained approval from the FDA . [31]

In a study aimed to investigate single-agent liposomal all-trans retinoic acid (Lipo-ATRA) in untreated acute promyelocytic leukemia (APL) , Induction therapy consisted of Lipo-ATRA 90 mg/m^2 i.v. every other day. Patients in complete remission (CR) continued to receive Lipo-ATRA 90 mg/m^2 i.v. three times a week for 9 months. The results were compared with those of a historical control group treated with oral ATRA and idarubicin. Lipo-ATRA induced CR in 79% of patients; CR rates were 92% and 38% in patients with white blood cell (WBC) counts <10 × 10^9/L and >10 × 10^9/L, respectively. [32]

Liposomal Annamycin

Annamycin is a highly lipophilic form of the anthracycline doxorubicin with the ability to bypass multidrug resistance mechanisms of cellular drug resistance. Clinical trials on this drug include its use in pediatric and Adult relapsed ALL and AML .

In a phase I/II multicenter, open-label, study to determine the maximally tolerated dose (MTD) of nanomolecular liposomal annamycin in adult patients with refractory ALL , Single-agent nanomolecular liposomal annamycin appears to be well tolerated, and shows evidence of clinical activity as a single agent in refractory adult ALL.

Liposomal Cytarabine Daunorubicin (CPX-351)®

(CPX-351)® is a liposomal cytotoxic combination of Cytarabine : Daunorubicin in a fixed 5:1 molar ratio for the treatment of relapsed and refractory acute myeloid leukemia. In the first Phase II study conducted in man, CPX-351 induction was administered on days 1, 3, and 5 by 90-minute infusion to 48 relapsed or

refractory patients with acute myeloid leukemia (AML) or high-risk myelodysplasia. CPX-351 appears to be well-tolerated and capable of inducing CRs in patients with relapsed or refractory AML. The recommended dose and schedule for phase II study (MTD) is 101 units/m^2 administered on days 1, 3, and 5 of each induction course. [34]

CONCLUSION

Liposomal drugs are effective and relatively safe drugs and showed promise in the treatment of difficult –to-treat blood diseases , both benign and malignant . Although the cost and remote toxicity concerns are an issue , extensive preclinical knowledge and clinical expertise is being accumulated and it is quite likely that liposomes will replace many drugs used in the hematology in the future .

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