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Review

Recent Clinical Successes in Liposomal Nanomedicines

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Abstract: The intrinsic limitations of cancer therapies promoted the development of safer liposomal nanocarriers capable of better distributing the payload away from normal tissues. Since then, liposomal nanocarriers have been considered the primary drug delivery system for many active pharmaceutical ingredients. These systems are now frequently investigated for the treatment of many infectious diseases. Along with the tremendous progress in the anticancer and antifungal liposomal nanomedicines, we have also gradually realised the difficulties associated with the existing liposomal nanocarrier designs. A better understanding of the nanocarrier-bio interactions may provide a new paradigm in liposomal nanocarrier design and better clinical endpoint efficacy. This short review focuses on the progress and benefits of two market-approved liposomal nanomedicines for cancer and fungal treatments.

Keywords: liposome, nanomedicine, cancer, antifungal, nanocarriers, therapeutic index, safety, efficacy.

1. Introduction

Nanomedicine is a rapidly expanding medical field centred around developing nanoparticles (NPs) for diagnostic and therapeutic purposes [1]. Many NP-based therapeutics are clinically approved, including lipids, polymers, nanocrystals, inorganic materials, and proteins [2]. Among them, lipid nanoparticle (LNP)-based drug delivery systems, especially liposomes, account for approximately 60% of marketed and on-trial nanomedicines [3]. Liposome was first described as swollen phospholipid bodies by Bangham et al. in 1965, consisting of at least one lipid bilayer [4]. Active pharmaceutical ingredients (APIs) can be incorporated into these liposomal vesicles' lipid bilayer or hydrophilic core. Liposomes have several advantages over other nanocarriers, such as high loading efficiency, biocompatibility, and stability in biological environments [5-8]. Liposomes can also encapsulate hydrophilic and hydrophobic APIs in the same nanoparticles for possible combinational therapies [9,10]. As a result, liposome nanocarrier is considered one of the most successful nanoparticle drug delivery systems for detecting and treating various diseases. Furthermore, responsive liposomal nanocarriers can also be developed with novel lipids. For example, the successful clinical use of ionisable lipids has enabled the approval of Onpattro®. Onpattro is the first FDA-approved siRNA liposomal nanomedicine for the treatment of nerve damage caused by hereditary transthyretin (hATTR) amyloidosis [11–13]. The use of ionizable cationic lipids display positively charged at acidic pH values, but nearly neutral at physiological pH, resulting a reduction of immunological toxicity and cytotoxicity comparing to a permanent positive-charged lipids [13]. In addition, polyethylene glycol (PEG)-lipids with relatively short acyl chains can form an unshielded particle at 100 nm or less, facilitating the cell uptake at the target [13].

Currently, 16 liposomal nanomedicines have been approved by the FDA for clinical uses in cancer therapy, fungal infection, pulmonary infection, nucleic acid therapy, pain management, viral vaccines, and photodynamic therapy (Table 1) [14,15]. Numerous liposomal nanomedicines, such as T4N5 liposomal lotion and Liprostin™ are also in clinical trial phase III [5,16]. Except for Arikayce® (inhalation administration), all of these approved nanomedicines require intravenous/spinal administration. Perhaps other routes of

administration can be explored for liposomal nanomedicines, such as oral, subcutaneous, and sublingual routes [17, 18]. However, the lack of an alternative route of administration for liposomal nanomedicines may be impeded by the physiologic conditions of these routes, difficulties in crossing biomembranes, and stability of the liposomes [19, 20]. Furthermore, the production of liposomal nanomedicines at commercially viable scales for these routes of administration is also a significant challenge. Therefore, liposomal nanomedicine will remain an enabling formulation strategy for the parenteral route of administration.

This short review focuses on the small molecule drugs that are difficult to deliver due to low water solubility and high toxicity, with particular attention to doxorubicin and amphotericin B [20, 21]. The clinical

Table 1. Examples of FDA-approved liposomal products.

Name	Route	Drug	Liposome composition (molar ratio)	Size (nm)	Year of approval
Cancer					
Doxil®	i.v.	Doxorubicin	HSPC, cholesterol, PEG 2000-DSPE (56:39:5)	100	1995
DaunoXome®	i.v.	Daunorubicin	DSPC, cholesterol, daunorubicin (10:5:1)	45-80	1996
DepoCyt®	Spinal	Cytarabine	Cholesterol, triolein, DOPC, DPPG (11:1:7:1)	20	1999
Marqibo®	i.v.	Vincristine	Sphingomyelin, Cholesterol (60:40)	100	2012
Onyvide™ MM-398	i.v.	Irinotecan	DSPC, PEG 2000-DSPE (3:2)	80-140	2015
VYXEOS® CPX-351	i.v.	Cytarabine + daunorubicin	DSPC, DSPG, cholesterol (7:2:1); Cytarabine, daunorubicin (5:1)	100	2017
Fungal					
AmBisome®	i.v.	Amphotericin B	HSPC, DSPG, cholesterol, amphotericin B (2:0.8:1:0.4)	45-85	1997
Pain management					
DepoDur®	Epidural	Morphine	DOPC, DPPG, cholesterol and triolein	17000-23000	2004
Exparel®	i.v.	Bupivacaine	DEPC, DPPG, cholesterol, tricaprylin	31200	2011
Photodynamic therapy Ocular histoplasmosis, macular degeneration, pathologic myopia					
Visudyne®	i.v.	verteporfin	Verteporfin, EPG, DMPC (1:3:5)	150-300	2000
Inhalation therapy Mycobacterium avium complex (MAC) lung disease					
Arikayce®	Inhalation	Amikacin	DPPC, cholesterol	300	2018
Nucleic acid therapy Transthyretin (TTR)-mediated amyloidosis					
ONPATTRO®	i.v.	siRNA for disease-causing TTR protein	DLin-MC3-DMAlipid, Cholesterol, DSPC, PEG_{2000} -C-DM	<100	2018

Listed FDA-approved liposomal products all require intravenous/spinal administration, except for Arikayce® (inhalation administration). i. v. (intravenous); HSPC (hydrogenated soy phosphatidylcholine); PEG2000-DSPE (poly(ethylene glycol) - distearoylphosphatidylethanolamine); DMPC (dimyristoylPEGphosphatidylcholine); DMPG (dimyristoylphosphatidylglycerol); DSPC (distearoylphosphatidylcholine); DSPG (distearoylphosphatidylglycerol); egg phosphatidylglycerol (EPG); EPC (egg phosphatidylcholine); DOPC (dioleoylphosphatidylcholine); DPPG (dipalmitoylphosphatidylglycerol); DSPC (distearoylphosphatidylcholine); DLin-MC3-DMA (4-(dimethylamino)-butanoic acid, (10Z, 13Z)-1-(9Z, 12Z)-9, 12-octadecadien-1-yl-10,13-nonadecadien-1-yl); PEG2000-C-DMG ([3-[3-(2-methoxyethoxy)propylcarbamoyloxy]-2-tetradecanoyloxypropyl] tetradecanoate); dierucoylphosphatidylcholine (DEPC).

constraints of the drugs, their conventional formulations, and the clinical benefits of the marketed liposomal nanoformulations are summarised.

2. Doxorubicin

Cancer is one of the most devastating infectious diseases, contributing to approximately 10 million fatalities yearly [22]. The FDA has approved 132 anticancer drugs, with anthracycline as the main class [23]. Since its first discovery in the 1960s, doxorubicin remains the most widely used chemotherapy drug, demonstrating broad-spectrum anticancer activity against hematologic and solid tumours [24]. Unfortunately, despite its wide applications, the long-term clinical use of doxorubicin has been restricted due to its toxic side effects. Cardiotoxicity is the primary dose-limiting effect of doxorubicin as the preferred interaction with the anionic di-phosphatidylglycerol in the cardiac muscle [25, 26]. Clinical data showed that up to 26% of patients receiving conventional doxorubicin developed arrhythmias, atrial and ventricular, which may progress to congestive heart failure (CHF) [27–30]. A cumulative dose of doxorubicin from 550 to 700 mg/m^2 can increase the CHF rate from 5% to 48% [24–26]. Other common doxorubicin-induced toxicity effects are acute nausea and vomiting, stomatitis, and myelosuppression [24,31,32]. Given the severe side effects, efforts have been made to improve the therapeutic index of conventional doxorubicin, including low-dose infusion regimens, new drug discovery, and drug nanocarriers [33–35]. Several nanocarriers have been explored for the delivery of doxorubicin; only liposomes have been extensively researched and ultimately approved for clinical use. As of today, there are four FDA-approved liposomal doxorubicin formulations: Doxil®, LipoDox®, Myocet®, and ThermoDox®[36]. Liposomal doxorubicin has been broadly shown to improve the safety, pharmacokinetics, and biodistribution, as yet no marketed liposomal nanotherapeutics have exhibited overall survival benefit comparing with the conventional doxorubicin [37].

Doxil was the first liposomal doxorubicin approved by the FDA for treating AIDS-related Kaposi's sarcoma and later for ovarian cancer and multiple myeloma [38,39]. Doxil contains doxorubicin encapsulated in PEGylated unilamellar liposomes less than 100 nm in diameter [40]. Therefore, following the intravenous administration, the liposomal doxorubicin nanoparticles can decrease uptake by the mononuclear phagocyte system (MPS) and thus enter the bloodstream for an extended period. After capillary extravasation, the PEGylated layer and relatively small particle size aid in accumulating these nanoparticles in tumour tissue much more than in normal tissues via the enhanced permeability retention (EPR) effect [41]. Meanwhile, the encapsulated doxorubicin molecules are transferred away from sites of potential toxicity, significantly reducing cardiac and gastrointestinal toxicity [42–44].

Clinically, all liposomal doxorubicin formulations have been reported to reduce the incidence rate of CHF even at higher cumulative doses (>500 mg/m^2) [45, 46]. For example, in one AIDS-related Kaposi sarcoma study, only one adverse event was recorded for 82 patients treated with a high doxorubicin dose (>500 mg/m^2). This critical data has ultimately led to the FDA's approval of Doxil for treating AIDS-related Kaposi's sarcoma patients [32]. In another meta-analysis of over seven million patients, significantly fewer adverse events were observed in patients receiving liposomal formulations (Doxil, LipoDox, and non-PEGylated Myocet) in comparison to conventional doxorubicin [47]. Doxil also showed increased response rates (45.9% of patients for Doxil versus 24.8% for vincristine) compared to other anticancer therapies [48,49].

However, following the intravenous administration, Doxil has a preferential concentration in the skin due to the PEGylated coating [35]. A small amount of doxorubicin may leak out of capillaries on the palms of the hands and soles of the feet. The result of this leakage is tenderness, redness, and peeling of the skin. This side effect of Doxil is known as palmar-planar erythrodysesthesia (PPE) or hand-foot syndrome (HFS), which is dose-limiting. Thus, Rafiyath et al. have highlighted that PEGylated liposomal doxorubicin formulations (such as Doxil) must be used carefully for patients suffering from PPE [41]. Myocet is a liposomal doxorubicin formulation without a PEG coating; hence, its concentration in the skin is non-preferential, which does not result in the similar prevalence of PPE [35]. Furthermore, Myocet is directed away from the heart, resulting in decreased cardiotoxicity associated with the release of doxorubicin [50]. Currently, Myocet has been approved by the European Medicines Agency (EMEA) for treating metastatic breast cancer in combination with cyclophosphamide [41]. The FDA has also granted Fast Track status for HER2-positive metastatic breast

cancer (Myocet, produced by Sopherion Therapeutics) [14, 51]. Moreover, other novel formulations of doxorubicin have been studied, including antibody-coated, temperature-sensitive, sulfatide-mediated liposomes, polymer-based nanoparticles, hydroxyapatite implants, thermosensitive poly(organo)phosphazenes hydrogels and even biological particles like modified erythrocytes and bacterial [52-60].

3. Amphotericin B

In contrast to the rapid advancements of liposomal anticancer nanomedicine, the applications in other indications are falling behind. One significant clinical application has been encapsulating and delivering the amphotericin B (AmB) antifungal drug. The Global Action Fund for Fungal Infections (GAFFI) estimates that over 300 million people suffer from severe fungal infections, and over 1.5 million deaths occur yearly [61]. Invasive Fungal Diseases (IFDs) are now emerging as part of the Neglected Tropical Diseases worldwide, where chronic conditions can have long-term consequences for patients [62]. Furthermore, the COVID-19 outbreak has accelerated the burden of IFDs and global shortages of antifungal medicines [63,64].

Since the 1950s, AmB has been the medicine of choice for IFDs and is listed on the WHO Essential Medicine List [65]. AmB was isolated as a by-product of the fermentation process of the soil actinomycete *Streptomyces nodosus* and the first report of antifungal activity in 1956 [66]. Due to its low water solubility, the first approved formulation Fungizone® was developed using deoxycholate-AmB micellar formulation. However, Fungizone must be used with care in patients, and frequent monitoring of renal function in the hospital setting is required [67]. AmB remains the main treatment of priority fungal infections despite its dose-depended toxicity and efficacy issues. Infusion-related toxicities induce acute reactions of high fever, hypotension, nephrotoxicity, and chills after infusion [68]. Nephrotoxicity from AmB is common and severe [69]. The proposed mechanism of nephrotoxicity is due to the direct cytotoxicity of AmB to renal tubular cells, resulting in acute tubular necrosis of the kidney [68]. In particular, serum creatinine doubled in 53% of patients, and 29% had serum creatinine levels of 250 mmol/L, indicating a 70% decline in renal function. In addition, 15% of the trial participants needed dialysis. Heinemann also listed several factors which limit the clinical use of AmB: (1) at standard doses of conventional AmB (Fungizone, 1 mg/kg), the drug plasma concentration is low for aspergillus species that are more resistant to AmB; (2) the bioavailability of AmB in organs tissue is negligible due to unspecific binding of AmB with cholesterol-containing cell membranes; (3) dose-liming toxicities of AmB (<1.5 mg/kg daily dose) significantly limit the tolerability [70]; and (4) current conventional treatment with deoxycholate-AmB is associated with significant long hospitalisation time [71].

Several FDA-approved LNPs or liposomes have been successfully employed to deliver AmB with improved safety and efficacy, namely AmBisome® (liposomal amphotericin B, LAmB), Abelcet® (amphotericin B lipid complex, ABLC), and Amphotec® (amphotericin B colloidal dispersion, ABCD). AmBisome/LAmB is regarded as the gold standard among these lipid-based formulations, offering the optimum safety and efficacy for treating presumptive fungal infections, systemic fungal infections and HIV-associated fungal infections. Like the Doxil formulation, the small particle size (<100 nm) of the LAmB allows for longer plasma circulation time and enhanced secondary tissue distribution of the AmB [72]. Based on the structural feature, LAmB is optimised to intact ergosterol-rich fungal cell walls, facilitating the intracellular delivery of AmB. The key lipid compositions of LAmB have been proposed to achieve the balance between safety and efficacy: (1) a combination of hydrogenated soy phosphatidylcholine (HSPC) and di-stearoyl phosphatidylglycerol (DSPG) offers better rigidity and stability, (2) formation of the ionic complex between DSPG and AmB limits drug release, and (3) aggregation of AmB molecules within the lipid bilayers improves the safety [65].

Clinically, all lipid-based formulations, such as LAmB, ABLC, and ABCD, can achieve 15 to 75 times higher drug concentrations (C_{max}) and total systemic exposure (AUC) than with conventional AmB (5 mg/kg) [73]. Adverse events of these lipid-based formulations have also been evaluated in many clinical studies. For example, in a randomised, double-blind trial, over 250 patients were subjected to empirical treatments using LAmB and ABLC [74]. ABLC was administered at 5 mg/kg/day, while LAmB was administered at 3 and 5 mg/kg/day. The incidence rate of nephrotoxicity was 40% for the ABLC and only 15% for the LAmB groups. Other

adverse events, such as fever (4% vs 13%), elevated creatinine (2% vs 17%), and hypokalemia (4% vs 33%), were all significantly lower for patients treated with LAmB [73]. In another randomised, double-blind comparative trial, the safety of LAmB and ABLC was also evaluated [74]. During the trial, 244 patients were randomised to treatments of LAmB 3 mg/kg, LAmB 5 mg/kg, and ABLC 5 mg/kg. LAmB groups (3 mg/kg/day and 5 mg/kg/day) have resulted in lower rates of fever, chills, nephrotoxicity, and toxicity-related discontinuations of therapy. However, there was no significant difference in endpoint efficacy [74].

LAmB has been proven for its superior safety in delivering higher doses of AmB in multiple disease-bearing animal models, such as at 10 to 20 mg/kg/day in mice and rabbit models for treating cryptococcal meningoencephalitis [75]. These findings led to later clinical trials in IFD patients using high-dose LAmB. Thomas et al. conducted a Phase I-II study evaluating the safety, tolerance, and pharmacokinetics of LAmB to determine its maximally tolerated dosage (MTD) in patients infected with *Aspergillus spp.* and other filamentous fungi [64]. They reported that a 15 mg/kg/day dose was well tolerated and can effectively treat aspergillosis and other filamentous fungal infections [76]. Lorna et al. also concluded that a high dose of LAmB (10 mg/kg/day) is efficacious and well tolerated in treating IFD in haematology patients [77]. These significant clinical findings have led to the largest AMBITION-cm global trial for HIV-associated cryptococcal meningitis patients in low-resource countries. A single, high-dose injection of LAmB in combination with oral flucytosine and fluconazole is the preferred regimen due to significantly fewer adverse events [71]. Although it was found to be non-inferior to the conventional deoxycholate-AmB regimen, the new high-dose LAmB regimen was well tolerated and associated with less hospitalisation time. Widespread implementation would reduce the clinical workload of healthcare workers caring for patients with HIV-associated cryptococcal meningitis. Subsequently, the LAmB regimen was adopted by WHO as the preferred treatment for cryptococcal meningitis patients [78]. Such high-dose single injection of LAmB will likely be trialled for other IFDs in immunocompromised patients, such as disseminated histoplasmosis and chronic pulmonary aspergillosis [68, 79]. It is also the reference treatment for visceral leishmaniasis, deep and systemic refractory fungal infections and presumptive fungal infections [80]. However, it should also be noted that, even with pouring evidence of the clinical benefits of LAmB, access to this old essential nanomedicine is still considered very limited. Over 2.8 billion population is currently unable to access LAmB at an affordable price [81].

4. Conclusions

Liposomal nanocarriers have been the main category of nanoparticle drug delivery systems in marketed nanomedicines. Within these approved nanomedicines, liposomal anticancer and antifungal nanotherapeutics are the two most researched fields. The liposomal nanocarriers enable the delivery of drugs at significantly higher doses, such as doxorubicin and amphotericin B, that otherwise cannot be delivered. Although no marketed liposomal nanotherapeutics have exhibited overall endpoint efficacy benefits compared to conventional formulations, significant safety and economic benefits have been realised. Better liposomal nanocarriers may be achieved through an improved understanding of the biophysical microenvironment, nano-bio interaction, rational design, and scalable production technologies.

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References

1. Ventola C. L. The nanomedicine revolution: part 2: current and future clinical applications. *P&T*, **2012**, *37*(10): 582-591.
2. Ventola C.L. Progress in nanomedicine: approved and investigational nanodrugs. *P&T*, **2017**, *42*(12): 742-755.
3. Wang Y. W.; Grainger D. W. Regulatory considerations specific to liposome drug development as complex drug products. *Front. Drug. Deliv.*, **2022**, *2*: 901281.
4. Bangham A. D.; Standish M. M.; Watkins J. C. Diffusion of univalent ions across the lamellae of swollen

phospholipids. *J. Mol. Biol.*, **1965**, *13*(1): 238-252.
5. Bulbake U.; Doppalapudi S.; Kommineni N.; et al. Liposomal formulations in clinical use: an updated review. *Pharmaceutics*, **2017**, *9*(2): 12.
6. Asadi K.; Gholami A. Virosome-based nanovaccines; a promising bioinspiration and biomimetic approach for preventing viral diseases: a review. *Int. J. Biol. Macromol.*, **2021**, *182*: 648-658.
7. Gulati M.; Bajad S.; Singh S.; et al. Development of liposomal amphotericin B formulation. *J. Microencapsulation*, **1998**, *15*(2): 137-151.
8. Liu P.; Chen G.L.; Zhang J.C. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. *Molecules*, **2022**, *27*(4): 1372.
9. Bozzuto G.; Molinari A. Liposomes as nanomedical devices. *Int. J. Nanomed.*, **2015**, *10*: 975-999.
10. Beltrán-Gracia E.; López-Camacho A.; Higuera-Ciapara I.; et al. Nanomedicine review: clinical developments in liposomal applications. *Cancer Nanotechnol.*, **2019**, *10*(1): 11.
11. Hou X.C.; Zaks T.; Langer R.; et al. Lipid nanoparticles for mRNA delivery. *Nat. Rev. Mater.*, **2021**, *6*(12): 1078-1094.
12. Kisby T.; Yilmazer A.; Kostarelos K. Reasons for success and lessons learnt from nanoscale vaccines against COVID-19. *Nat. Nanotechnol.*, **2021**, *16*(8): 843-850.
13. Akinc A.; Maier M. A.; Manoharan M.; et al. The Onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. *Nat. Nanotechnol*, **2019**, *14*(12): 1084-1087.
14. He H., Yuan D. F.; Wu Y.; et al. Pharmacokinetics and Pharmacodynamics modeling and simulation systems to support the development and regulation of liposomal drugs. *Pharmaceutics*, **2019**, *11*(3): 110.
15. Boafo G. F.; Thapa K. T.; Ekpo M. D.; et al. The role of cryoprotective agents in liposome stabilization and preservation. *Int. J. Mol. Sci.*, **2022**, *23*(20): 12487.
16. Li Z.L.; Zhang Y.L.; Wurtz W.; et al. Characterization of nebulized liposomal amikacin (Arikace) as a function of droplet size. *J. Aerosol Med. Pulm. Drug Delivery*, **2008**, *21*(3): 245-254.
17. LLS Health Technical Team. Excipients for solubility enhancement: enabling oral and injectable formulations. (accessed on 18 January 2023). https://www.lubrizol.com/Health/Blog/2022/03/Excipients-for-Solubility-Enhancement---Enabling-Oral-and-Injectable-Formulations.
18. Savjani K. T.; Gajjar A. K.; Savjani J. K. Drug solubility: importance and enhancement techniques. *ISRN Pharm*., **2012**, *2012*: 195727.
19. He H.S.; Lu Y.; Qi J.P.; et al. Adapting liposomes for oral drug delivery. *Acta Pharm. Sin. B*, **2019**, *9*(1): 36-48.
20. Giardiello M.; Liptrott N. J.; McDonald T. O.; et al. Accelerated oral nanomedicine discovery from miniaturized screening to clinical production exemplified by paediatric HIV nanotherapies. *Nat. Commun.*, **2016**, *7*: 13184.
21. Bakshi R. P.; Tatham L. M.; Savage A. C.; et al. Long-acting injectable atovaquone nanomedicines for malaria prophylaxis. *Nat. Commun.*, **2018**, *9*(1): 315.
22. World Health Organization. Cancer. (accessed on 2 December 2022). https://www.who.int/health-topics/cancer#tab=tab_3.
23. Carvalho C.; Santos R.X.; Cardoso S.; et al. Doxorubicin: the good, the bad and the ugly effect. *Curr. Med. Chem.*, **2009**, *16*(25): 3267-3285.
24. Brown J.R.; Imam S.H. 5 recent studies on doxorubicin and its analogues. *Prog. Med. Chem.*, **1985**, *21*: 169-236.
25. Yingchoncharoen P.; Kalinowski D.S.; Richardson D.R. Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come. *Pharmacol. Rev.*, **2016**, *68*(3): 701-787.
26. Chang H.I.; Yeh M.K. Clinical development of liposome-based drugs: formulation, characterization, and therapeutic efficacy. *Int. J. Nanomed*., **2012**, *7*: 49-60.
27. O'Bryan R.M.; Luce J.K.; Talley R.W.; et al. Phase II evaluation of adriamycin in human neoplasia. *Cancer*, **1973**, *32* (1): 1-8.
28. Lefrak E.A.; Piťha J.; Rosenheim S.; et al. A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer*, **1973**, *32*(2): 302-314.
29. Chlebowski R.T. Adriamycin (doxorubicin) cardiotoxicity: a review. *West. J. Med*., **1979**, *131*(5): 364-368.
30. Cancer Chemotherapy Reports. U.S. department of health, education, and welfare, public health service, national institutes of health; 1975.
31. Park K. The beginning of the end of the nanomedicine hype. *J. Controlled Release*, **2019**, *305*: 221-222.
32. Hortobágyi G.N. Anthracyclines in the treatment of cancer. An overview. *Drugs*, **1997**, *54*(4): 1-7.
33. Waterhouse D.N.; Tardi P.G.; Mayer L.D.; et al. A comparison of liposomal formulations of doxorubicin with drug administered in free form: changing toxicity profiles. *Drug Saf.*, **2001**, *24*(12): 903-920.
34. Birtle A.J. Anthracyclines and cardiotoxicity. *Clin. Oncol.*, **2000**, *12*(3): 146-152.
35. Rivankar S. An overview of doxorubicin formulations in cancer therapy. *J. Cancer Res. Ther.*, **2014**, *10*(4): 853-858.
36. Anon. Celsion Announces Enrollment Completion Pivotal Phase III OPTIMA Study of ThermoDox® in Primary Liver Cancer–Duke OTC. (accessed on 12 December 2022). https://otc.duke.edu/news/celsion-announces-enrollment-completion-pivotal-phase-iii-optima-study-of-thermodox-in-primary-liver-cancer/.
37. Petersen G. H.; Alzghari S. K.; Chee W.; et al. Meta-analysis of clinical and preclinical studies comparing the anticancer efficacy of liposomal versus conventional non-liposomal doxorubicin. *J. Controlled Release*, **2016**, *232*: 255-264.
38. Morigi V.; Tocchio A.; Bellavite C.B.; et al. Nanotechnology in medicine: from inception to market domination. *J. Drug Delivery*, **2012**, *2012*: 389485.

39. Bharali D. J.; Mousa S. A. Emerging nanomedicines for early cancer detection and improved treatment: current perspective and future promise. *Pharmacol. Ther.*, **2010**, *128*(2): 324-335.
40. Seigneuric R.; Markey L.; Nuyten D. *S.* A.; et al. From nanotechnology to nanomedicine: applications to cancer research. *Curr. Mol. Med*., **2010**, *10*(7): 640-652.
41. Rafiyath S.M.; Rasul M.; Lee B.; et al. Comparison of safety and toxicity of liposomal doxorubicin vs. conventional anthracyclines: a meta-analysis. *Exp. Hematol. Oncol*., **2012**, *1*(1): 10.
42. Safra T. Cardiac safety of liposomal anthracyclines. *The Oncologist*, **2003**, *8*(S2): 17-24.
43. Šimůnek T.; Štěrba M.; Popelová O.; et al. Anthracycline-induced cardiotoxicity: overview of studies examining the roles of oxidative stress and free cellular iron. *Pharmacol. Rep.*, **2009**, *61*(1): 154-171.
44. Allen T. M.; Mumbengegwi D. R.; Charrois G. J. R. Anti-CD19-targeted liposomal doxorubicin improves the therapeutic efficacy in murine B-cell lymphoma and ameliorates the toxicity of liposomes with varying drug release rates. *Clin. Cancer Res.*, **2005**, *11*(9): 3567-3573.
45. Safra T.; Muggia F.; Jeffers S.; et al. Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m^2. *Ann. Oncol.*, **2000**, *11*(8): 1029-1033.
46. Kesterson J.P.; Odunsi K.; Lele S. High cumulative doses of pegylated liposomal doxorubicin are not associated with cardiac toxicity in patients with gynecologic malignancies. *Chemotherapy*, **2010**, *56*(2): 108-111.
47. Fukuda A.; Tahara K.; Hane Y.; et al. Comparison of the adverse event profiles of conventional and liposomal formulations of doxorubicin using the FDA adverse event reporting system. *PLoS One*, **2017**, *12*(9): e0185654.
48. Northfelt D.W.; Dezube B.J.; Thommes J.A.; et al. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. *J. Clin. Oncol.*, **1998**, *16*(7): 2445-2451.
49. O'Brien M.E.R.; Wigler N.; Inbar M.; et al. Reduced cardiotoxicity and comparable efficacy in a phase IIItrial of pegylated liposomal doxorubicin HCl(CAELYX™/Doxil®) versus conventional doxorubicin forfirst-line treatment of metastatic breast cancer. *Ann. Oncol*., **2004**, *15*(3): 440-449.
50. Swenson C.E.; Perkins W.R.; Roberts P.; et al. Liposome technology and the development of Myocet™ (liposomal doxorubicin citrate). *The Breast*, **2001**, *10*, *Supplement 2*: 1-7.
51. Anon. FDA fast track designation for myocet for metastatic breast cancer. *Oncology Times*, **2010**, *32*(3): 24.
52. Immordino M. L.; Dosio F.; Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. *Int. J. Nanomed.*, **2006**, *1*(3): 297-315.
53. Schnyder A.; Huwyler J. Drug transport to brain with targeted liposomes. *NeuroRX*, **2005**, *2*(1): 99-107.
54. Shao K.; Hou Q. S.; Duan W.; et al. Intracellular drug delivery by sulfatide-mediated liposomes to gliomas. *J. Controlled Release*, **2006**, *115*(2): 150-157.
55. Saul J. M.; Annapragada A.; Natarajan J. V.; et al. Controlled targeting of liposomal doxorubicin via the folate receptor *in vitro*. *J. Controlled Release*, **2003**, *92*(1/2): 49-67.
56. Itokazu M.; Kumazawa S.; Wada E.; et al. Sustained release of adriamycin from implanted hydroxyapatite blocks for the treatment of experimental osteogenic sarcoma in mice. *Cancer Lett.*, **1996**, *107*(1): 11-18.
57. Bromberg L.; Alakhov V. Effects of polyether-modified poly(acrylic acid) microgels on doxorubicin transport in human intestinal epithelial Caco-2 cell layers. *J. Controlled Release*, **2003**, *88*(1): 11-22.
58. Zocchi E.; Tonetti M.; Polvani C.; et al. Encapsulation of doxorubicin in liver-targeted erythrocytes increases the therapeutic index of the drug in a murine metastatic model. *Proc. Natl. Acad. Sci. U. S. A.*, **1989**, *86*(6): 2040-2044.
59. Olivier J.C. Drug transport to brain with targeted nanoparticles. *NeuroRX*, **2005**, *2*(1): 108-119.
60. Petri B.; Bootz A.; Khalansky A.; et al. Chemotherapy of brain tumour using doxorubicin bound to surfactant-coated poly (butyl cyanoacrylate) nanoparticles: revisiting the role of surfactants. *J. Controlled Release*, **2007**, *117*(1): 51-58.
61. Gaffi. Improving outcomes for patients with fungal infections across the world a road map for the next decade. (accessed on 15 December 2022). https://gaffi.org/wp-content/uploads/GAFFI_Road_Map_interactive-final0415.pdf.
62. Rodrigues M.L.; Nosanchuk J.D. Fungal diseases as neglected pathogens: a wake-up call to public health officials. *PLoS Neglected Trop. Dis*., **2020**, *14*(2): e0007964.
63. Raut A.; Huy N.T. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? *Lancet Respir. Med*., **2021**, *9*(8): e77.
64. Hoenigl M. Invasive fungal disease complicating coronavirus disease 2019: when it rains, it spores. *Clin. Infect. Dis.*, **2021**, *73*(7): e1645-e1648.
65. Rivnay B.; Wakim J.; Avery K.; et al. Critical process parameters in manufacturing of liposomal formulations of amphotericin B. *Int. J. Pharm.*, **2019**, *565*: 447-457.
66. Gallis H.A.; Drew R.H.; Pickard W.W. Amphotericin B: 30 years of clinical experience. *Rev. Infect. Dis*., **1990**, *12* (2): 308-329.
67. Drugs. com. Fungizone prescribing information. (accessed on 12 December 2022). https://www. drugs. com/pro/ fungizone.html.
68. Min Y.Z.; Caster J.M.; Eblan M.J.; et al. Clinical translation of nanomedicine. *Chem. Rev.*, **2015**, *115*(19): 11147-11190.
69. Wingard J.R.; Kubilis P.; Lee L.; et al. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin. Infect. Dis.*, **1999**, *29*(6): 1402-1407.
70. Heinemann V.; Bosse D.; Jehn U.; et al. Pharmacokinetics of liposomal amphotericin B (Ambisome) in critically ill patients. *Antimicrob. Agents Chemother.*, **1997**, *41*(6): 1275-1280.
71. Jarvis J.N.; Lawrence D.S.; Meya D.B.; et al. Single-dose liposomal amphotericin B treatment for cryptococcal

meningitis. *N. Engl. J. Med.*, **2022**, *386*(12): 1109-1120.
72. Rodrigues A.V.; Valério-Bolas A.; Alexandre-Pires G.; et al. Zoonotic visceral leishmaniasis: new insights on innate immune response by blood macrophages and liver Kupffer cells to *Leishmania infantum* parasites. *Biology*, **2022**, *11* (1): 100.
73. Boswell G. W.; Buell D.; Bekersky I. AmBisome (liposomal amphotericin B): a comparative review. *J. Clin. Pharmacol.*, **1998**, *38*(7): 583-592.
74. Wingard J.R.; White M.H.; Anaissie E.; et al. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. *Clin. Infect. Dis.*, **2000**, *31*(5): 1155-1163.
75. Lestner J.; McEntee L.; Johnson A.; et al. Experimental models of short courses of liposomal amphotericin B for induction therapy for cryptococcal meningitis. *Antimicrob. Agents Chemother.*, **2017**, *61*(6): e00090-17.
76. Walsh T.J.; Yeldandi V.; McEvoy M.; et al. Safety, tolerance, and pharmacokinetics of a small unilamellar liposomal formulation of amphotericin B (AmBisome) in neutropenic patients. *Antimicrob. Agents Chemother.*, **1998**, *42*(9): 2391-2398.
77. McLintock L.A.; Cook G.; Holyoake T.L.; et al. High loading dose AmBisome is efficacious and well tolerated in the management of invasive fungal infection in hematology patients. *Haematologica*, **2007**, *92*(4): 572-573.
78. World Health Organization. New guidelines from WHO recommend a simpler, safer treatment for cryptococcal disease in people living with HIV. (accessed on 14 December 2022). https://www. who. int/news/item/20-04-2022-rapid-advice-new-guidelines-for-simpler-safer-treatment-for-cryptococcal-disease-in-plhiv.
79. Meyerhoff A. U.S. food and drug administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. *Clin. Infect. Dis.*, **1999**, *28*(1): 42-48.
80. Sundar S.; Chakravarty J. Liposomal amphotericin B and leishmaniasis: dose and response. *J. Global Infect. Dis.*, **2010**, *2*(2): 159-166.
81. MSF Access Campaign. Open letter to Gilead and Viatris: we need affordable treatments for the rise of serious invasive fungal diseases. (accessed on 25 January 2023). https://msfaccess.org/open-letter-ambisome-Gilead.

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