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Potential of Nanovesicles in the Treatment of Myeloid Leukemia

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ABSTRACT

Chronic Myeloid leukemia also known as chronic myelogenous leukemia, is a cancer of white blood cells. Chronic Myeloid leukemia counts 15% of all leukemia, the incidence of Chronic Myeloid leukemia is similar in all the countries worldwide, per year 1.6 to 2.0 cases per 100,000 persons are recognized. The median age range is 30-60 yrs. and Chronic Myeloid leukemia is rare in children Although he traditional Chronic myeloid leukemia therapies are effective, they have numerous shortcomings including low bioavailability and side effects. The emerging novel drug delivery systems may result in a promising approach for its early identification and efficient treatment. Currently, cancer research focuses on improving Chronic Myeloid leukemia treatment using various novel drug delivery systems of chemotherapeutic agents such as nanoformulations, liposomes, exosomes, microspheres, nanoparticles, phytosomes, micelles, etc. The delivery of Tyrosine Kinase inhibitor drugs via novel drug delivery systems has become a research hotspot in recent years. In this review we include the existing novel concepts for the design of novel drug delivery for Tyrosine Kinase inhibitor drugs and we have analyzed the latest research in the field of nanotechnology as a potential step for the Chronic Myeloid leukemia treatment We also provide a summary of the research that has been done as well as some novel development in formulations.

INTRODUCTION

Leukemia is a cancer of blood or bone marrow and is characterized by an abnormal proliferation of blood cells, usually white blood cells (leukocytes).[1] This excessive production of blood cells can lead to overcrowding of the bone marrow, and spreading into the peripheral blood and to other organs. The lack of functional blood cells can lead to symptoms like anemia, infections, and bleeding. If left untreated, leukemia is fatal, often due to complications resulting from the leukemic infiltration of the bone marrow and replacement of normal hematopoietic precursor cells. Traditionally, leukemia was classified as chronic or acute by how fast the disease progressed to a fatal clinical outcome[2]. This was found to correlate well with the degree of maturation of the predominant malignant cell. The disease is further classified into lymphoid or Myeloid leukemia according to the predominant cell type involved [3].

Table 1: Classification of leukemia.

Cell type	**Acute**	**Chronic**
Lymphocytic leukemia (or "lymphoblastic")	Acute lymphocytic leukemia (ALL)	Chronic lymphocytic leukemia (CLL)
Myelogenous leukemia (also "myeloid" or "nonlymphocytic")	Acute myelogenous leukemia (AML	Chronic myelogenous leukemia (CML)

Acute myeloid leukemia is also known as acute myelogenous leukemia it starts in the bone marrow of the soft inner part of certain bones, where new blood cells are made. But most often it quickly moves into the blood as well. It can sometimes spread to other parts of the body including the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testicles. Most often Acute myeloid leukemia, develops from cells that would turn into white blood cells (other than lymphocytes), but sometimes develops in other types of blood-forming cells.[4]

Chronic Myeloid Leukemia is a chronic myeloproliferative disorder That predominately affects the granulocytic cell line and there is often an increased proliferation of granulocytes, but their differentiation is relatively normal. Chronic Myeloid Leukemia primarily affects

adults between 25-60 years of age and accounts for 15-20% of all leukemia [5]. It represents the most common type of adult leukemia in India [6]. In 2020, it is estimated about 8,450 new Chronic Myeloid Leukemia will be diagnosed in the United States, and about 1,080 patients will die of Chronic Myeloid Leukemia Since the introduction of imatinib in 2000, the annual mortality in Chronic Myeloid Leukemia as decreased from 10-20% to 1- 2%.1 Consequently, the prevalence of CML the United States estimated at 30,000in 2000, has increased by approximately 7,000-8,800/year to an estimated 150-180,000 in 2020 based on an incidence of 5,000 cases/year in 2020[6].

Chronic myelogenous leukemia has 3 phases.

I. Chronic phase: In chronic phase CML, fewer than 10% of the cells in the blood and bone marrow are blast cells.

II. Accelerated phase: In accelerated phase CML, 10% to 19% of the cells in the blood and bone marrow are blast cells.

III. Blast Crisis/ Blastic phase: In blastic phase CML, 20% or more of the cells in the blood or bone marrow are blast cells. When tiredness, fever, and an enlarged spleen occur during the blastic phase, it is called a blast crisis. Fig. 1 depicts the various phases of CML.

As the amount of blast cells increases in the blood and bone marrow, there is less room for healthy white blood cells, red blood cells, and platelets. This may result in infections, anemia, and easy bleeding, as well as bone pain and pain or a feeling of fullness below the ribs on the left side. The number of blast cells in the blood and bone marrow and the severity of symptoms determine the phase of the disease [8].

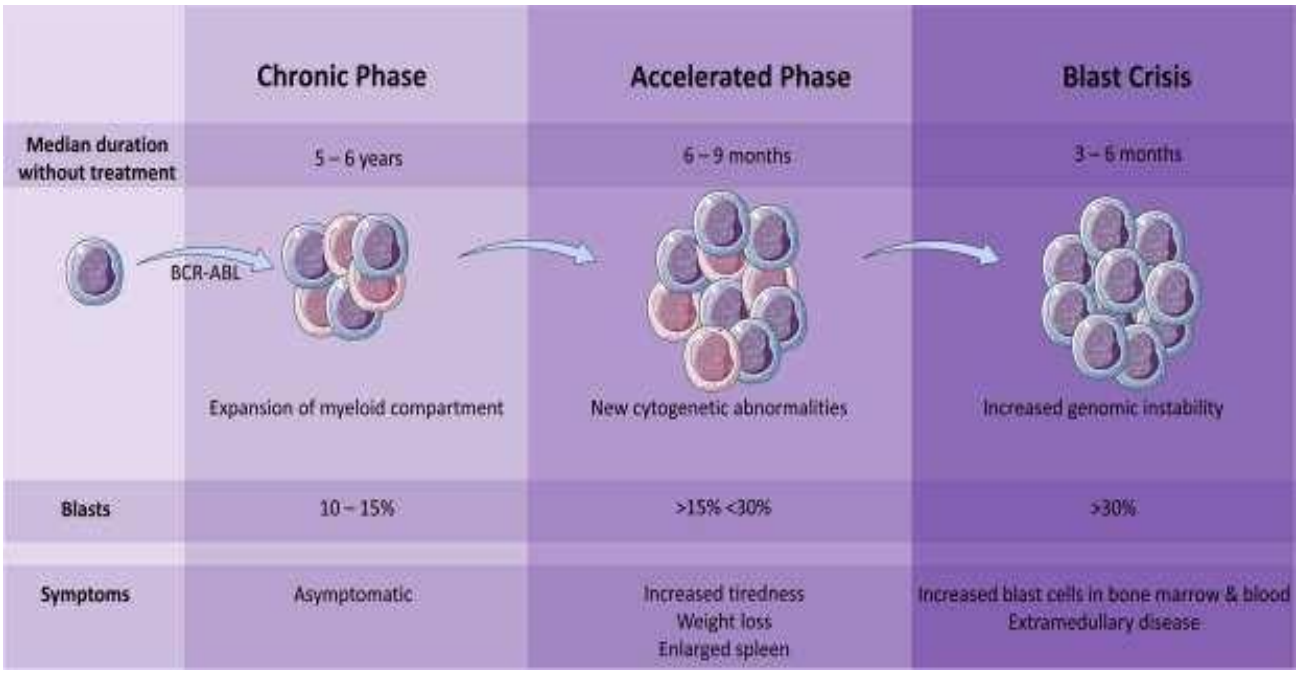

Figure 1: Phases of Chronic Myelogenous Leukemia.

Presently fewer curative options are available for such patients suffering from CML. Emerging novel delivery systems may result in a promising approach for early recognition and its treatment. Currently, cancer research focuses on improving CML treatment using various novel delivery systems of chemotherapeutic agents. These novel drug delivery systems include Nano formulations, liposomes, hydrogels, exosomes, dendrimers, microspheres, phytosomes, micelles, etc. Hence, most up-to-date conclusions and any crucial findings of CML treatment are required to be broadly spread to scientific, medical, and research societies.

Epidemiology:

The incidence of chronic myeloid leukemia (CML) ranges between10- 15 cases /year without any major geographic or ethnic differences [9]. The median age at diagnosis ranges between60 65 years in Europe but is considerably lower in countries with a younger population. The prevalence of CML is steadily rising due to the substantial prolongation of survival that has been achieved with targeted therapy[10]. CML in children is rare; biology and treatment strategies in pediatric patients reveal specific aspects [11].

Therefore, these recommendations are:

- According to the American Cancer Society's estimates for chronic myeloid leukemia (CML) in the United States for 2022 are[12]:

- Nearly 8,860 new cases will be diagnosed with CML (5,120 in men and 3,740 in women).

- Approximately 1,220 people will die of CML (670 men and 550 women).

About 15% of all new cases of leukemia are chronic myeloid leukemia. About 1 person in 526 will get CML in their lifetime in the United States.

The average age at diagnosis of CML is around 64 years. Almost half of cases are diagnosed in people 65 and older. This type of leukemia mainly affects adults and is rarely seen in children, primarily intended for use in adult patients. CML has an incidence of one to two cases per 1,00,000 people per year10[13].

Pathophysiology Of Chronic Myeloid Leukemia:

It is a clonal bone marrow stem cell disorder and the first malignancy to be linked to a clear genetic abnormality, chromosomal translocation called the Philadelphia chromosome[14]. In this translocation, parts of two chromosomes (the 9th and 22nd by conventional karyotypic numbering) switch places. As a result, part of the BCR gene from chromosome 22 is fused with the ABL gene on chromosome 9[15]. This abnormal "fusion" gene generates a protein of p210 or sometimes p185 weight. Because ABL carries a domain that can add phosphate groups to tyrosine residues (a tyrosine Kinase), the BCR-ABL fusion gene product is also a tyrosine Kinase[16]. The fused BCR-ABL protein interacts with the interleukin 3beta(c) receptor subunit. The BCR-ABL transcript is continuously active and does not require activation by other cellular messaging proteins[17]. In turn, BCR-ABL activates a cascade of proteins that control the cell cycle, speeding up cell division. Moreover, the BCR-ABL protein inhibits DNA repair, causing genomic instability and making the cell more susceptible to developing further genetic abnormalities[18]. The action of the BCR ABL protein is the pathophysiologic cause of chronic myelogenous leukemia. (Fig 2)

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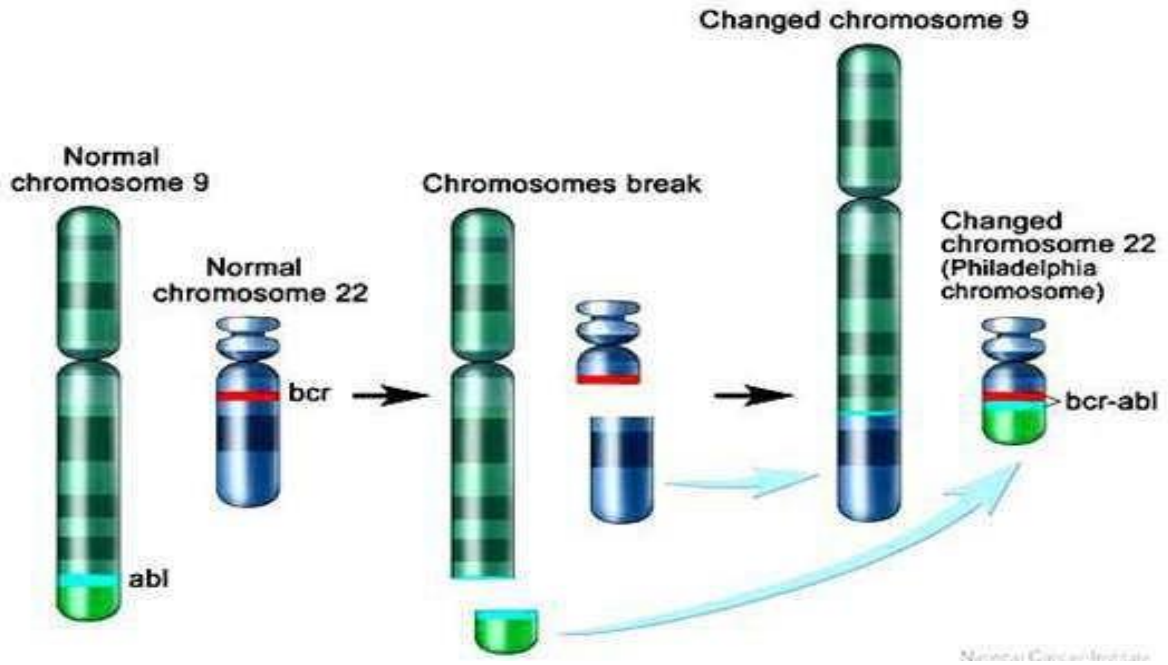


Figure 2: Molecular mechanism of pathogenesis of CML

Nanotechnology-Based Novel Drug Delivery System:

Nanotechnology-based therapeutics are highly used in cancer therapy for enhancing drug solubility, and stability, decreasing multidrug resistance as well as enhancing the safety and efficacy of cancer treatment. The drug is dissolved, entrapped, encapsulated, or attached to a nanoparticle's matrix [19]. Nanoparticulate systems are being commenced to provide an adequate delivery for drug and tissue-specific targeting [20]. Engineered Colloidal drug carriers such as liposomes and other nanoparticles have been largely exploited for targeted drug delivery [21] Nanoparticles, dendrimers, polymeric micelles, liposomes, and exosomes are some of the efficient carriers in nanotechnology-based drug delivery systems; which are presently investigated extensively for augmented cancer therapy.[22]

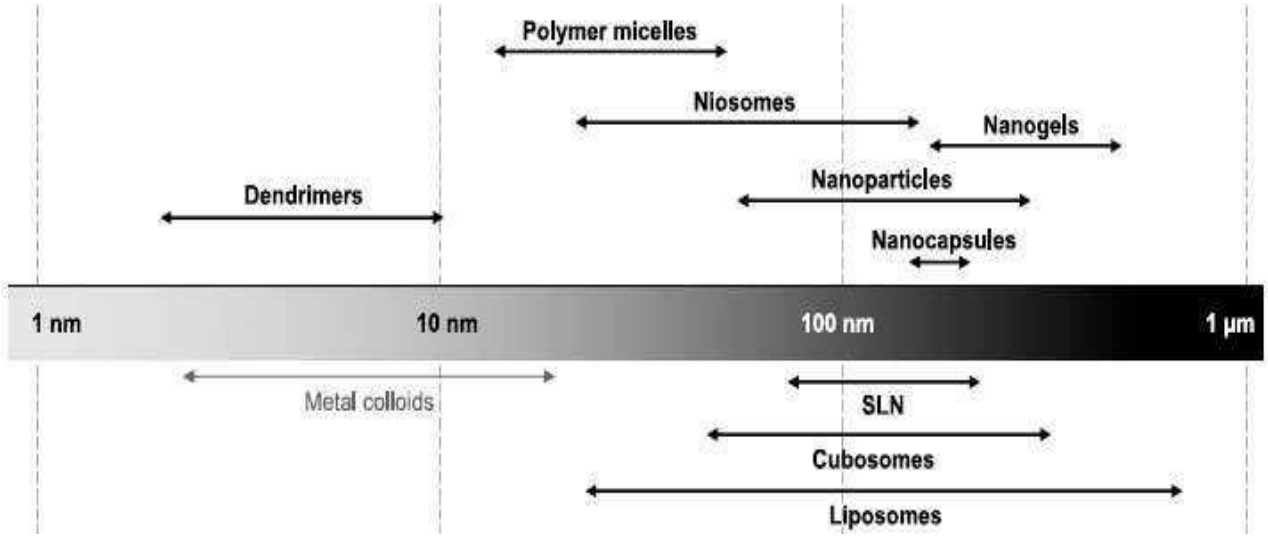


Figure 3: Size comparison of different types of Nano Materials.

Liposome:

Liposomes are self-assembling colloidal Nano-sized structures consisting of lipid bilayers surrounding an aqueous compartment and have the unique ability to encapsulate a wide variety of drugs both in an aqueous and a lipid phase making them attractive for hydrophilic and hydrophobic drugs. Such encapsulation reduces drug toxicity while retaining or improving the therapeutic efficacy [23]. Liposomes are used effectively in diverse fields like biology, biochemistry, and medicine since their invention [24]. Liposomes are one of the promising classes of nanomedicines with the ability to exert site-specific chemotherapy, hence convalescing the excellence of care for cancer patients. [25]

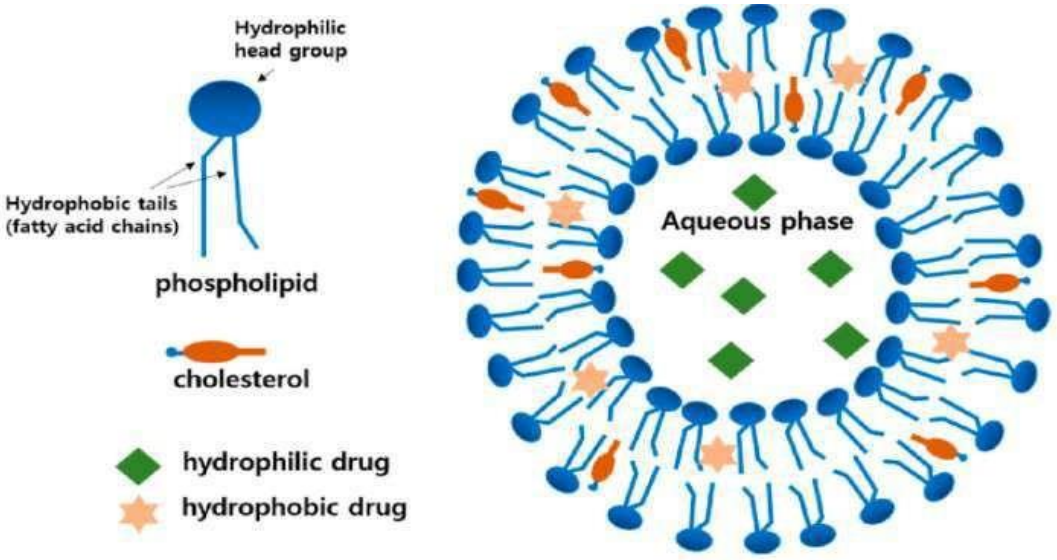
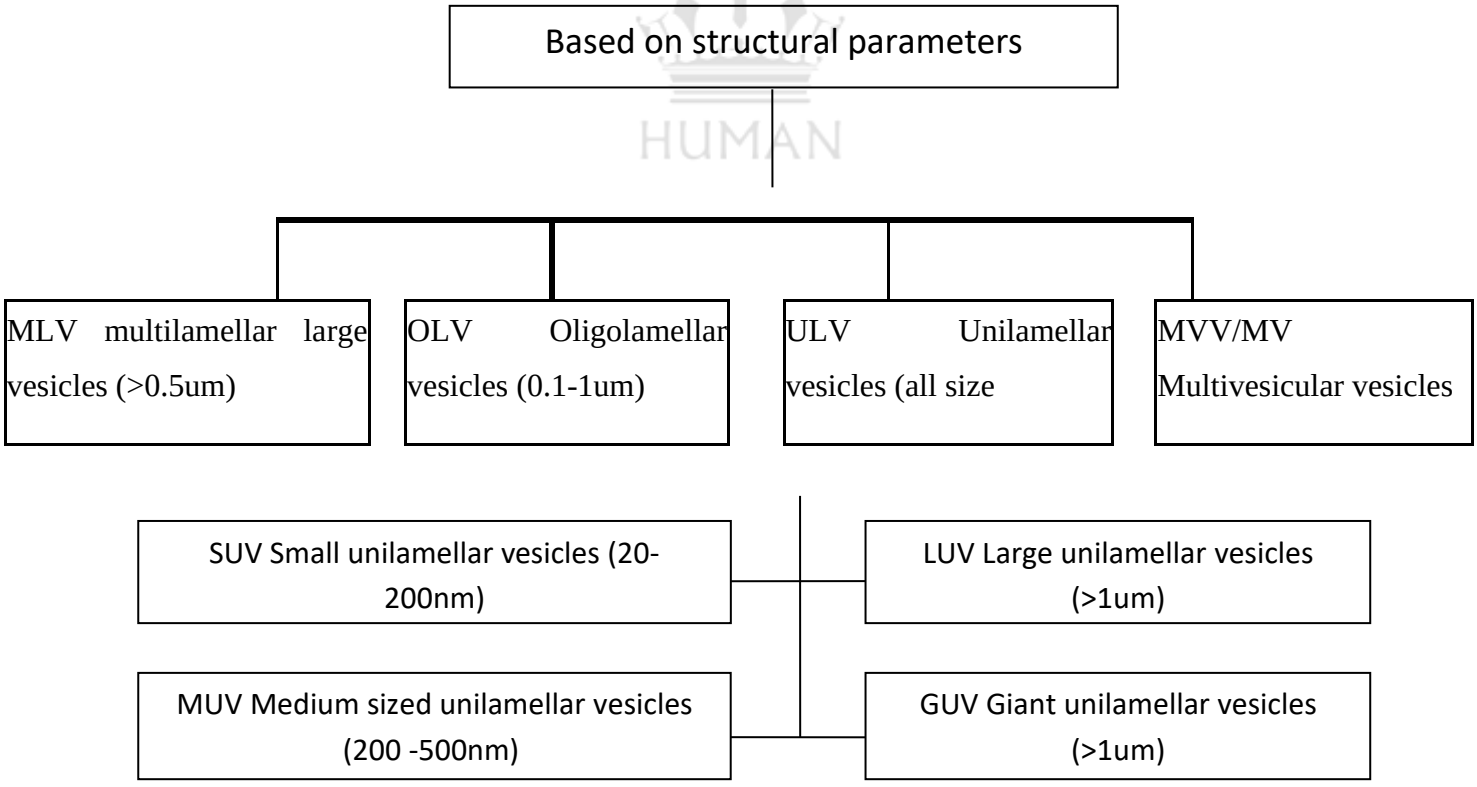


Figure 4: Structure of liposome.

Types of Liposomes[26]:



Advantages of liposome drug delivery [27][28]

It reveals several advantages resembling amphiphilic character, biocompatibility, and ease of surface modification rendering it an appropriate candidate delivery system for a diversity of molecules.

Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parental administration.

They control and sustain the release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug to achieve an increase in drug therapeutic efficacy and reduction in side effects.

Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.

Site-specific targeting can be achieved by attaching targeting ligands to the surface of particles or use of magnetic guidance.

The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular, etc.

Other advances like Increase drug solubilization, Protecting the drug from degradation, Improving the bioavailability of the drug, and Modifying the pharmacokinetics and tissue distribution of the drug can assure a high degree of affectivity.

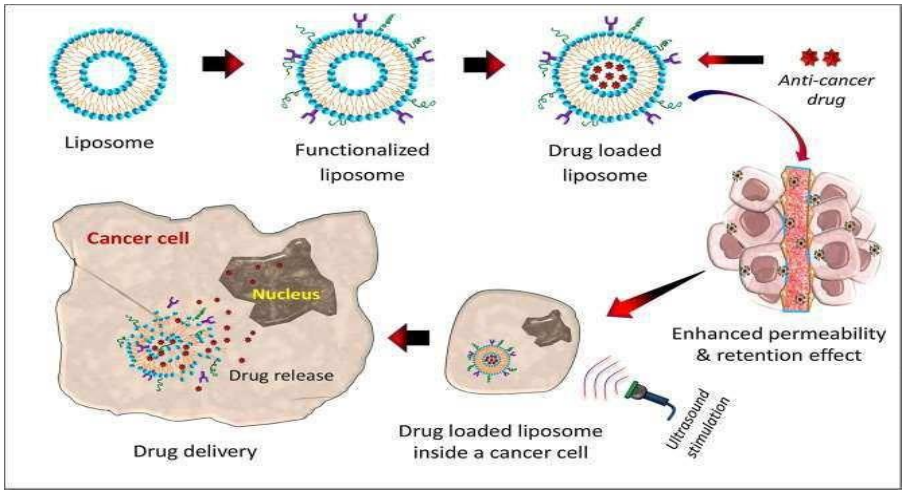


Figure 5: Liposome targeting cancer cells [29].

Table 2: Clinically used Liposome-based products [30].

Sl no	Clinical products	Administration	Active ingredient	Indication	Company
1	Doxil®	I.V	Doxorubicin	Ovarian, breast cancer, leukemia	Sequus Pharmaceuticals
2	DaunoXome®	i.v.	Daunorubicin n	Neoplastic meningitis	Sky Pharma Inc.
3	Depocyt®	Spinal	Cytarabine	Neoplastic meningitis/CML	Sky Pharma Inc
4	Myocet®	i.v.	Doxorubicin	Combination therapy with cyclophosphamide in metastatic breast cancer	Elan Pharmaceutical
5	Mepact®	i.v.	Mifamurtide	High-grade, resectable, non-metastatic osteosarcoma	Takeda Pharmaceutical Limited
6	Marqibo®	i.v.	Vincristine	Acute lymphoblastic leukemia	Talon Therapeutics
7	Visudyne®	i.v.	Verteporphin n	Choroidal neovascularisation	Novartis
8	Abelcet®	i.v.	Amphotericin n B	Invasive severe fungal infections	Sigma-Tau Pharmaceutical
9	Ambisome®	i.v.	Amphotericin n B	Presumed fungal infections	Astellas Pharma
10	Velcade	i.v.	Bortezomib	Multiple myeloma	Takeda Oncology

Recent Summary Of The Main Research On Myeloid Leukemia Using Liposomes As Nano-Drug Delivery System:

Liposome-based drug delivery systems have made a remarkable difference in the site-specific release of drugs especially Chemotherapeutic agents, owing to their physical and chemical characteristics and biological attributes. Table 2 summarizes the recent applications of liposome-based drug delivery for Myeloid leukemia.

Table 3: Recent Summary Of The Main Research On Myeloid Leukemia Using Liposomes As Nano-Drug Delivery System*:*

Title of the article	Author	Year	Results	Inference	Ref.
Liposomal Cytarabine for treatment of myeloid central nervous system relapse in chronic myeloid leukemia occurring during imatinib therapy	K.J. Aichberger et al.	2007	Here we describe two patients with CML in whom a pure myeloid CNS relapse occurred after four years of therapy with imatinib. In both cases, liposomal cytarabine was applied intrathecally in one case additional radiation of the CNS was performed, whereas the other patient received dasatinib because of systemic relapse. In response to therapy, clinical symptoms were resolved and leukemic cells in the CSF disappeared.	In this study the researchers found that Anatomic resistance against imatinib in the CNS which can lead to a myeloid CNS relapse. The Liposomal Cytarabine with or without radiation is effective as local therapy in these patients and for the systemic treatment and prophylaxis, BCR/ABL kinase inhibitors crossing the blood-brain barrier such as dasatinib should be considered in Patients with CNS relapse.	[31]
Liposomal bortezomib is active against chronic myeloid leukemia by disrupting the Sp1-BCR/ABL axis	Xiaojuan yang et al	2016	To enhance BORT efficiency scientists designed L-BORT and TfR- targeted L- BORT (Tf- L- BORT). A remote-loading method was used to load BORT into liposomes. Drug entrapment efficiency is higher than 1 5 %. By comparing various methods, it was found that remote loading method had the highest drug entrapment (97.3%) and appropriate particle size (~100 nm) for enhanced permeability and retention (EPR) effect.	Authors demonstrated that the Inactivation of Sp1 by genetic and pharmacological approaches for BCR/ABL expression, leading to suppression of BCR/ ABL Kinase signaling and CML cell proliferation. Because of potential adverse side effects of bortezomib (BORT) in imatinib- refractory CML patients, researches designed transferrin (Tf)-targeted liposomal formulation (Tf-L-BORT) for BORT delivery. Cellular uptake assay s showed that BORT was efficiently delivered into K562 cells, with the highest	[32]

				efficacy obtained in Tf-targetedgroup. After administered into mice, L-BORT exhibited s lower clearance with less toxicity compared to free BORT. L-BORT had less toxicity than Free BORT with approximately 20-time and 10-time increases of IC_{50} from 39 nM to 814 nM and 305 nM, respectively, for L-BORT and Tf-L BORT, which could probably be explained by the hypothesis of slow release of L-BORT following the cellular uptake via endocytosis. These results identified the advantage of liposome, especially Tf-liposome, as drug delivery systems to efficiently and specifically, deliver BORT to targets and it could be helpful to decrease the side effects of treating leukemia patints.	
Co-encapsulation Of anti-BCR-ABL si RNA and Imatinib Mesylate in Transferrin Receptor-	Liliana S. Mendonc¸a et al	2010	In this work, Trf-coupled Sterically stabilized liposomes co encapsulating imatinib and anti-BCR-ABL siRNA in different molar ratios (1:3; 1:8; 1:16; 1:32; 1:42), were designed by	The scientist stated that the present work aimed at the development and application of transferrin receptor (TrfR) targeted liposomes co - Encapsulating anti-BCR-ABL i RNA and imatinib at different molar ratios.	[33]

Targeted Sterically Stabilized liposomes for Chronic myeloid Leukemia Treatment			modification of the liposome preparation Technique was developed. The encapsulation yields of imatinib increased with decreasing of imatinib/total lipid ratios, being 11.88 2.09% for the 1:3 ratio and of 19.8 2.32% for the 1:8 ratio. For ratios above 1:16, the encapsulation yields were very similar, being around 25%. For ratios exhibiting the same yield, the higher loading of imatinib was obtained with increasing imatinib/ lipid ratios (i.e., 1:16 > 1:32 > 1:42) Thus, the formulations prepared with higher amounts of imatinib (higher imatinib/total lipid ratios, e.g., 1:3) resulted in lower siRNA encapsulation formulations prepared with lower amounts of imatinib indicates that when siRNA is encapsulated alone, under the same conditions as those in this co-encapsulating process, the encapsulation yield is 92.17 1 . 39 %. Overall, these results demonstrate that when imatinib is co-encapsulated with siRNA, the siRNA encapsulation yield decreases in a manner dependent on the imatinib/total lipid ratio pre-incubated with the liposomes.	The encapsulation yields and drug loading of each molecule was evaluated. Anti-leukemia activity of the developed formulations co-encapsulating siRNA and imatinib and of the combination of Trf-liposomes carrying siRNA and free imatinib under two different treatment schedules of pre-Sensitization was assessed. Theresults obtained demonstratethat the presence of imatinib significantly decreases the encapsulation yields of siRNA, whereas imatinib encapsulation yields are increased by the presence of siRNA.	

CD123/CD33 dual-antibody modified liposomes effectively target acute myeloid leukemia cells and reduce antigen-negative escape	Shili sun	2019	The total protein amount on CD123/CD33-LP-DNR is equal to CD123-LP-DNR. BCA kit assay shows the coupling efficiency was 52.25 ± 7.8%, and 50.75 ± 6.4% respectively, and Size distribution, zeta potential, and morphology was observed by TEM According to the DLS measurement , The average particle sizes of CD123-LP-DNR and CD123/CD33-LP-DNR obtained were 110.2 ± 2.4 nm, 116.8 ± 3.7 nm, and 115.5 ± 3.1 nm respectively, The PDI values range from 0.15 to 0.25, which shows a narrow distribution, and the zeta potential of different formulations were approximately −26 mV . indicating that the se particles could remain stable for in vitro storage due to electrostatic repulsion. The TEM results shows the diameters are between (90 and 130 nm)which is similar to the results of DSL, and there is no obvious difference	In this study, antibody mixture of CD123 and CD33 (1 : 1 , molar ratio) were thiolated and coupled to Mal-PEG2000-DSPE, then the antibody-Mal-PEG2000-DSPE conjugations were inserted on the DNR-loaded PEGylated liposomes (PEG- LP-DNR) via a post-insertion method to prepare CD123/CD33-LP-DNR (Antibody/S100PC, molar ratio, 0.06%). Compared to the unmodified liposome, CD123/CD33-LP-DNR showed higher cellular uptake which was 1.8-times and 1.6-times in both THP-1 and HL-60 cells, respectively, while the cellular uptake increased to 1.5-times only in the CD123bright cells for the single-antibody modified liposome, CD123-LP-DNR. MTT assay indicated stronger cytotoxicity of CD123/CD33-LP-DNR than CD123-LP-DNR on AML cells. The results indicated that CD123/CD33- LP-DNR might present an effective delivery strategy to enhance the targeting ability against AML cells and potentially reduce the antigen-negative escape.	[34]
In vivo efficacy of a novel liposomal formulation of safingol in the treatment of acute myeloid leukemia	Panel KuanBooneTanaLeong	2012	The liposomal formulation of safingol was prepared by lipid film formation. By this method, safingol will be entrapped in the lipid bilayer of liposomes formed. The encapsulation efficiency of safingol into the DPSC/Chol liposomes at 7.5 mol% in the presence of pH gradient was 98.6± 7.0%. The cytotoxicity of liposomal safingol was investigated in NB4 and U937 cells. the cytotoxicity of liposomal safingol was completely abolished when it was encapsulated in the liposomes prepared with pH gradient The zeta potential of non drug loaded DSPC/Chol liposomes in the absence and presence of pH gradient was −0.63± 0.40 mV and −7.64± 0.45 mV, respectively. The zeta potential of liposomal safingol in the absence and presence of pH gradient was +39.6±2.2 mV and −6.87 ± 0.96 mV, respectively. The obtained results are supportive of the motion that the anti- leukemic activity.	They stated that the present study showed to describe a rationally designed liposome formulation of safingol and demonstrate the anti-leukemic potential using a panel of human AML cell lines and patient samples as well as a human xenograft model in SCID mice. Encapsulation efficiency of safingol into liposomes was 100% and the release of drug followed by square-root-of- time-release model. Liposomal safingol was effective against a wide range of AML subtypes with minimal hemolytic toxicity and was able to extend the median survival time of the U937-inoculated mice to 31 days as compared to 23 days by free drug. The increase in therapeutic efficacy is related to the increase in systemic drug exposure as a result of liposome encapsulation.	[35]

Novel Curcumin Liposome Modified with Hyaluronan Targeting CD44 Plays an Anti-Leukemic Role in Acute Myeloid Leukemia in Vitro and in Vivo	Dan Sun	2017	The mean diameter, zeta potential, EE, and DL of both HA-Cur-LPs and HA- LPs formulation were negatively charged and retained low PDIs(<0.24) The mean diameter of HA- Cur-LPs is about 230nm or less, while HA-LPs had smaller particles size (101 nm).HA-LPs PDI was found to be 0.124 , zeta potential −24.7 ± 0.24 and HA-Cur-LPs PDI was found to be0.232 , zeta potential was f−36.8 ± 1.9 and EE 65.8 ±3.3 , DL is 13.2 ± 0.7.	In this present work scientist as formulated a novel curcumin liposome modified with hyaluronan (HA-Cur-LPs) was developed for AML therapy. It exhibited small particle size (236 nm) with approximately 66% EE of curcumin and excellent stability over storage, and high affinity to CD44-Fc. It also showed favorable biocompatibility and pharmacokinetic performance of increased drug exposure. The development and assessment of the HA-CurLPs provides another potential choice for AML therapy, using HA-Cur- LPs as either a single treatment agent or incombination with other treatments.	[36]
Efficacy of multi- functionalliposomes containing daunorubicin and emetine fortreatmento f acute myeloid leukaemia	Lene Myhr en	2014	The liposomeswere prepared by post-loading acid precipitation technique is well established for anthracyclines. To know whether this was feasible for the protein synthesis inhibitor emetine, scientist performed an in silico prediction of its net charges as a function of pH . Both Eme and DNR had close to zero net charge at pH above 8, and were protonated at pH below 6. The EE was about 55% loading of Eme, and more than 90% drug loading efficacy for DNR. zeta potential of liposomes was measured by dynamic light scattering. Z-ave for Unloaded was 122 and PDI 0.04 , Loaded (DNR + Eme)1 Z-ave is 121 and PDI is 0.03 . with FA Loaded1 Z-ave 125 , PDI is 0.04 of (DNR + Eme). .	In this present study, authors have formulated a multi-functional liposomal for anti-leukemic drug, to overcome some of the problems in chemotherapy including drug resistance. By adding Eme to aid cell death induction in p53-deficient cells. Adverse side-effects can be reduced by loading the drugs into ‘‘stealth’’ carriers’ surface-modified to target surface proteins on cancer cells. Drug delivery into the cancer cells can be enhanced by priming the leukaemia cells with MTX prior to administration of the drug formulation. By the use of labelled liposomes, it will be possible to follow the fate of the drug carriers, and find whether they are home to AML- infiltrated tissues. This can be done by dual label in vivo imaging, using different fluorescent probes for cells and liposomes. However, based on the presented data, a therapeutic regime consisting of priming of the leukaemia cells with antifolate therapy such as MTX, followed by intravenous injection of the liposomal formulation could be used to improve anti-AML therapy.	[37]

Development of a novel cationic liposome: Evaluation of liposome mediated transfection and anti-proliferative effects of miR-101 in acute myeloid leukemia.	Narges Nikoonahad Lotfabadi	2018	The liposomes were prepared by thin film hydration method. The Diameter (nm) of CL 84.5±1.3 , zeta potential (mv) was 20.11±2.06 and PDI is 0.15. CL/ miR- diameter (nm) 126.6±2.7 Zeta potential 4.31±0.00 and PDI was found to be 0.258 . These results show that the size of CLs increased after entrapment of miR-101 into them and the zeta potential of CLs decreased because of the negative charge of miR-101. Positively charged nano vesicles were obtained by	In this study authors had formulated a miRNA-loaded cationic liposomes (CLs) was prepared for bone 34 marrow cells. CLs and miRNA-load ed cationic liposomes (CL/miR-101) were prepared and their 35 characteristics were assessed using Dynamic light scattering (DLS) technique. MTT assay was used 36 for bone marrow cell lines (KG-1 and HBMF-SPH cell lines) to evaluate the cytotoxicity of CLs and 37 CL/miR-101. The results have shown that the size and charge of the prepared CLs with new 38	[38]
			using DOTAP, which partially neutralized 228 the negatively charged nucleic acid. .	formulation was 84.5 nm and 20.1 mV and for CL/miR- 101 were 126.6 nm and 4.31 mV. MTT 39 assay results have demonstrated different concentrations of CLs had no obvious cytotoxicity in 40 both KG-1 and HBMF-SPH cells. A new formulation of cation ic liposome was successfully designed to deliver miRNA into bone marrow cells effectively. The suitable size and charge of CLs made them capable to form an efficient CL/miR-1 complex, which was stable and penetrated significantly into the cells. CL/miR-101 complex proved to be cytotoxic for cancer cells and hence it can be considered as a novel gene therapy system.	
Pegylated liposomal doxorubicin for myeloid neoplasms	Zhang C	2019	The results showed that the Peg-Dox and Peg-Dox- based protocols had a similar killing ability in myeloid cell lines and in primary myeloid leukemia cells compared to that of conventional doxorubicin. The complete remission rate was 87.5% and 100% for patients with refractory/relapsed acute myeloid leukemia and myelodysplastic syndrome with excess blasts, respectively, after treatment with Peg-Dox. All patients developed grade 3 or 4 hematological toxicity and recovered	In this study Scientist as formulated Pegylated liposomal doxorubicin (Peg- Dox) and Peg-Dox based protocols for treatment of myeloid neoplasm. The result showed that Peg-Dox is a good outcome for the patients with lymphoma and multiple myeloma, which reduced the cardiotoxicity in patients and improved pharmacokinetic profile when compared to those of conventional doxorubicin.	[39]

			approximately 2 weeks after completing chemotherapy. No deaths or other severe complications were reported. .		
Targeting Chronic Myeloid Leukemia Stem/Progenitor Cells Using Venetoclax - Loaded Immunoliposome	Mohammad Houshmand	2021	The average diameter of immunoliposome was measured by DLS and corresponded to 145 ± 20 nm with a PDI of 0.15 ± 0.06. Antibody was conjugated on the lipo- some surface through an amide linkage occurring between the NHS group of PEGS (DSPE-PEG2000-NHS) and the ε-amine of lysine residues of antibodies. The results indicated a concentration of antibody of 1 mg/mL in the liposome suspension corresponding to 16.6 ± 0.2 % of conjugation efficiency. .	Researches designed a Venetoclax - loaded immunoliposome (IL-VX)for treatment of CML . Results showedthatby using Venetoclax - loaded immunoliposome system will selectively target CD26+ cells and sparing CD26− cells. The efficiency of Venetoclax in targeting CML LSCs has showed a higher potency in cell death induction in comparisontofree Venetoclax. Meanwhile, treatment of patient samples with IL- VX significantly reduced CD26+ cells in both stem cells and progenitor cellspopulation. This approa ch showed that selective elimination of CD26+ CML LSCs/progenitor cells can be obtained in vitro, which might allow in vivo reduction of side effects and attainment of treatment-free, long-lasting remission in CML patients.	[40]
Preparation and *in vivo* safety evaluations of antileukemic homoharringtonine-loaded PEGylatedliposomes	Dong Liu	2020	The mean diameter of the prepared LCLipo-HHT is 75.6 ± 3.2 nm and the zeta potential is −16.9 ± 2.5 mV. The entrapment efficiency of HHT in the liposomes is 69.5 ± 1.7%. Inpharmacokinetic experiments the result shows increased plasma concentration as well as blood circulation time was obtained .when distearoyl phosphoethanolamine-PEG 2000 lipid was added to the formulation, which results in enhancing drug delivery efficiency.	Author developed PEGylated liposomes to encapsulate homoharring tonine-a potent antileukemic drug. The PEGylated liposomes showed high EEs and LC, with size around 70 nm and PDI below 0.25, which are favorable for pharmaceutical applications of nanomedicines. However, incorporationof PEG-derivatives into HHTPEGylatedliposomes decreased uptake efficiency by RES resulting in a prolonged circulation time and enhanced safety in vivo. The prepared LCLipo-HHT can be used as a promising anticancer formulation for antileukemic therapy in the future.	[41]

Dan Sun et al[42] had developed a novel curcumin liposome modified with hyaluronan (HA-Cur- LPs) to specifically deliver curcumin to AML by targeting CD44 on AML cell surface. When compared with free curcumin and nontargeted liposome (Cur-LPs), the HA-Cur-LPs exhibited good stability, high affinity to CD44, increased cellular uptake, and more potent activity on inhibiting AML cell proliferation.

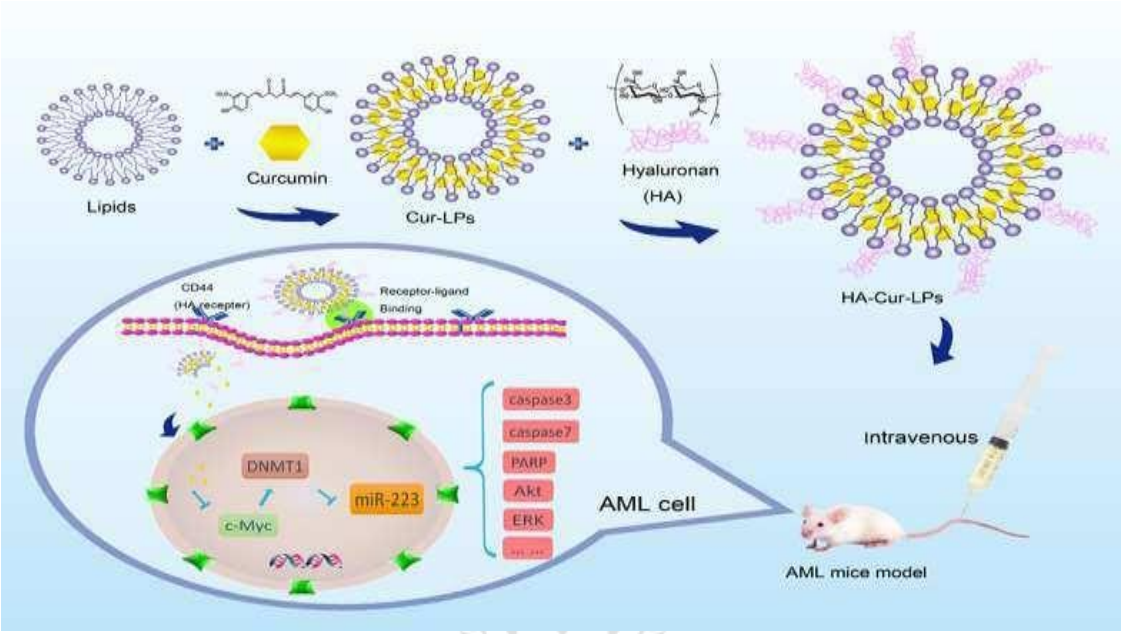


Figure 6: Schematic representation of the preparation of novel curcumin liposome modified with hyaluronan (HA-Cur- LPs) to specifically deliver curcumin to AML by targeting CD44 on AML cell surface.

Conventional curcumin liposomes (Cur-LPs) were prepared by thin-film evaporation.[43][44] The prepared (cur –LPs) were characterized for particle size, polydispersity index (PDI), zeta- potential and entrapment efficiency of liposome using a dynamic light scattering (DLS) method. In vivo imaging of HA-DiD-LPs in mice and Physicochemical characteristics of different HA-DiD-LPs. And the results are reported as below mentioned.

Table 4: characteristics of conventional liposomes (Cur-LPs).

Characteristic	HA-LPs	HA-Cur-LPs
Curcumin/lipids (w/w)	**0%**	**20%**
Mean diameter (nm)	101.3 ± 1.5	236.4 ± 5.2
Polydispersity (PDI)	0.124	0.232
Zeta potential (mV)	−24.7 ± 0.24	−36.8 ± 1.9
EE (%)		65.8 ± 3.3
DL (%)		13.2 ± 0.7

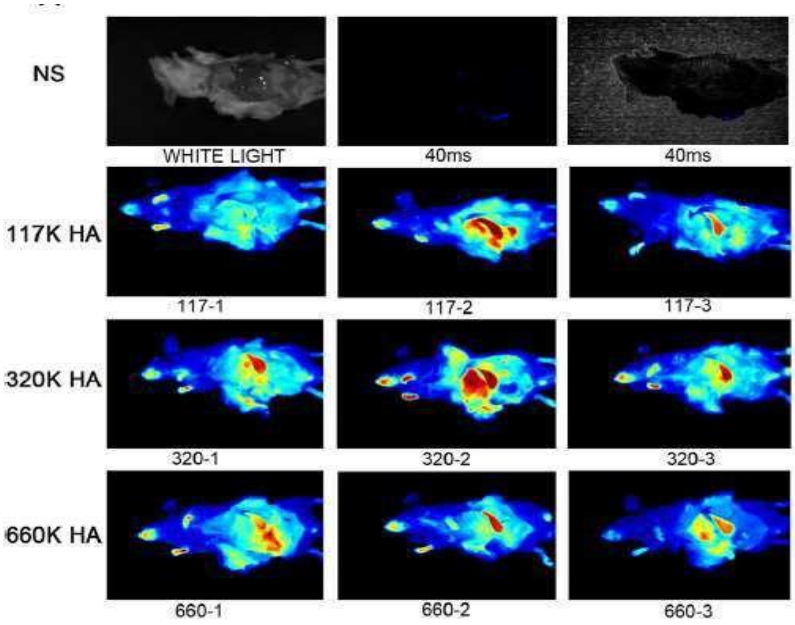


Figure 7: Representative in vivo fluorescent images of mice 12 h post-injection of normal saline (NS).

NO.	HA (MW)	HA:lipid (ug/umol)	Mean diameter (nm)	Polydispersity (PDI)	Zeta potential (mV)
117k-1	117,000	24.8	105.3	0.265	-29.9
117k-2	117,000	41.6	174.5	0.286	-30.7
117k-3	117,000	99.8	176.2	0.309	-29.6
320k-1	320,000	30.4	146.1	0.331	-29.6
320k-2	320,000	55.3	102.4	0.230	-31.9
320k-3	320,000	105.7	110.5	0.275	-31.3
660k-1	660,000	33.3	173.3	0.366	-30.9
660k-2	660,000	57.8	117.3	0.331	-32.4
660k-3	660,000	101.2	118.1	0.265	-31.3

Figure 8: Physicochemical characteristics of different HA-DiD-LPs.

Safety study of liposomes in vivo was evaluated by hematoxylin and eosin (H&E) staining of major issues. After the sacrifice of the BALB/c mice was treated by i.v. administration of curcumin formulation and slides were stained with hematoxylin and eosin (H&E). The histopathological alterations were observed and imaged with a light microscope (OlympusBX43).

The pharmacokinetic study was assessed in BALB/c mice. Following overnight fasting, nine mice were randomized into three groups and received i.v. injection of free curcumin in

DMSO, Cur- LPs, or HA-Cur-LPs in normal saline solution. at 10 mg/kg curcumin dose. the preset sampling time points, 20 μL blood samples were collected through caudal vein bleeding into a heparinized centrifuge tube, followed by the centrifugation to obtain plasma, which was then stored at −80 °C until a determination of the drug concentration. For curcumin quantitation, plasma samples were thawed to room temperature, and curcumin was extracted using acetonitrile and quantified by HPLC with the tandem mass spectrometry (LC/MS/MS) method.[45]

In Vitro Cytotoxicity and Pharmacology Assessments of Curcumin Liposomes was evaluated to investigate whether HACur-LPs and Cur-LPs are effective in inhibiting for AML cell growth, KG-1 cells were exposed to a series of concentrations of free curcumin, , Cur-LPs and HA-Cur-LPs. It was observed that LPs and HA-LPs had no cytotoxicity to KG-1 cells (data not shown), so LPs and HA-LPs were used as a negative control to determine the cytotoxicity of Cur-LPs and HA-Cur-LPs, respectively. It clearly shows that HA-Cur-LPs, Cur-LPs, and free curcumin inhibited KG-1 cell proliferation in a dose-dependent manner (Figure 8). The IC50 for 96 h incubation with free curcumin in KG-1 cells was 23.88 μM, which was 2.2-and 1.6-fold higher than that of HA-Cur-LPs (10.90 μM) and Cur-LPs (14.86 μM), respectively, indicating that HA-Cur-LPs enhanced antitumor potency of curcumin via liposome formulation and the HA modification.

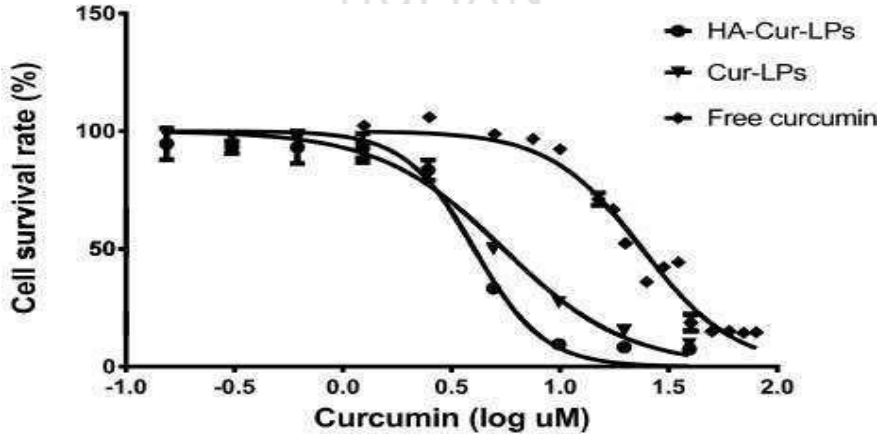


Figure 9: Cytotoxicity of free curcumin, Cur-LPs, and HA-Cur-LPs. KG-1 cells were treated with different concentrations of free curcumin, Cur-LPs, and HA-Cur-LPs for 96 h, and cell survival was measured by MTT assay. Data are presented as mean ± SD,n= 3.

Pharmacokinetics and safety of HA-Cur-LPs in mice were performed the pharmacokinetic study was observed in mice after i.v. administration of free curcumin, Cur-LPs, and HA-Cur-

LPs, respectively, at a curcumin dose of 10 mg/kg. The concentration−time profiles of curcumin are shown in (Figure 9) Pharmacokinetic parameters, such as the area under the plasma concentration−time curve (AUC) and clearance (CL), were presented in Table 2. These results suggested that Cur-LPs and HA-Cur-LPs had overcome free curcumin's shortcomings of low.

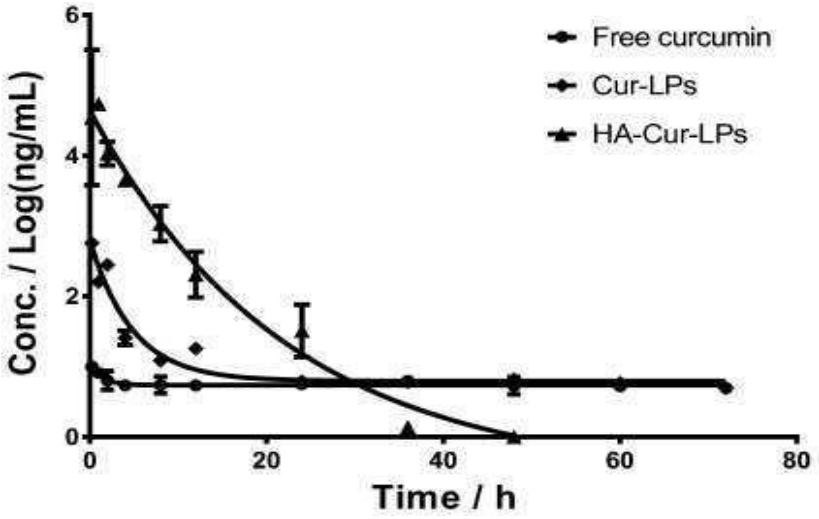


Figure 10: Pharmacokinetic curves of free curcumin, Cur-LPs, and HACur- LPs in mice. Data were presented as mean ± SD, n = 3.

Table 5: Pharmacokinetic Parameters.

Pharmacokinetic Parameters	free curcumin	Cur-LPs	HA-Cur-LPs
AUC0−24h (ng/mL × h)	139	1157	128761
AUC0−48h (ng/mL × h)	281	1307	128997
AUC0−72h (ng/mL × h)	407	1447	128998
CL (mL × h/kg)	5824	5393	78

Here, bioavailability and poor pharmacokinetics, whereas HACur- LPs presented slower clearance and higher drug exposure than free curcumin and nontargeted liposomes. In addition, there were no adverse effects such as vomiting, diarrhea, and significant difference in body weight, indicating that HA-Cur-LPs at 10 mg/kg dose level are safe to mice and can be used for subsequent treatment in AML mice model.

From all the above-mentioned results it was concluded that the novel curcumin liposome modified with hyaluronan (HA-Cur-LPs) was developed for AML therapy. It exhibited small particle size (236 nm) with approximately 66% EE of curcumin, excellent stability over storage, and high affinity to CD44-Fc. It also showed favorable biocompatibility and pharmacokinetic performance of increased drug exposure, implying the few safety concerns compared to free drug and high therapeutic potential. HA-Cur-LPs exhibited high potential in inhibiting AML cell growth in vitro (IC50 = 10.9μM) Akt/ERK pathways and activating caspase-dependent apoptosis. Moreover, HA-Cur-LPs played a critical role in the downregulation of DNMT1 expression in myeloid leukemia (ML) 12 and decreasing the expression of c-Myc in Hodgkins Lymphoma (HL)37 and leading to DNA hypomethylation and reactivation of tumor suppressor genes such as miR-223. The developed HA-Cur- was effective in treating with AML therapy and using HA-Cur-LPs as either a single treatment agent or in combination with other treatments.

CONCLUSION:

Following numerous years of study, researchers have applied nano-drug delivery systems for delivering tyrosine kinase cancer drugs, and the use of these systems enhances targeted drug delivery, increase efficacy, reduces side effects, ensure a slow and controlled drug release, and reverse the multidrug resistance of tumors, among others. The emerging novel delivery system may result in promising approach for the early recognition and its treatment. Recently liposomal-loaded anticancer drugs provide improved pharmacokinetics and reduced toxicities to several organ sites and provide potentially increased tumor uptake. This novel drug delivery system can efficiently suppress the cancer cell's growth and significantly induced apoptosis and thus could lead to a new path for eradication of CML. Further studies on nano-drug delivery systems and designing a simple and effective drug delivery system for clinical application are necessary at present. Toxicology research and clinical trials on nano-drug delivery systems are essential for obtaining a clear understanding of their toxicity profiles and *in vivo* behavior.

REFERENCES

1. Raymond W. R., Cancer Biology, Fourth Edition, Oxford University Press, 2007
2. Center for Disease Control and Prevention.Archived (PDF) from the original on 30 July2021. Retrieved 8 August 2021.
3. *"Leukemia - Symptoms and causes". Mayo Clinic. Retrieved 8 August 2021.*
4. https://www.cancer.org/cancer/acute-myeloid-leukemia/about/what-is-aml.html

5. Kantarjian HM, Talpaz M, O'Brien S, Giles F, Garcia-Manero G, Faderl S, Thomas D, Shan J, Rios MB, Cortes J. Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. Blood, The Journal of the American Society of Hematology. 2003 Jan 15;101(2):473-5.
6. Alikian M, Gerrard G, Subramanian PG, Mudge K, Foskett P, Khorashad JS, Lim AC, Marin D, Milojkovic D, Reid A, Rezvani K. BCR-ABL1 kinase domain mutations: methodology and clinical evaluation. American journal of hematology. 2012 Mar;87(3):298-304.
7. https://cancerstatisticscenter.cancer.org/?_ga=2.209219538.1329106158.1646620510-813548224.1639383099
8. https://www.cancer.net/about-us/cancernet-editorial-board
9. Hehlmann R, Berger U, Pfirrmann M, Heimpel H, Hochhaus A, Hasford J, Kolb HJ, Lahaye T, Maywald O, Reiter A, Hossfeld DK. Drug treatment is superior to allografting as first- line therapy in chronic myeloid leukemia. Blood, The Journal of the American Society of Hematology. 2007 Jun 1;109(11):4686-92.
10. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population.
11. Hijiya N, Schultz KR, Metzler M, Millot F, Suttorp M. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood, The Journal of the American Society of Hematology. 2016 Jan 28;127(4):392-9
12. American Cancer Society. *Cancer Facts & Figures 2022*. Atlanta, GA: American Cancer Society; 2022
13. Kantarjian H, Cortes J. Chronic myeloid leukemia. In: Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE, Kastan MB, McKenna WG. *Clinical Oncology*. 4th ed. Philadelphia, Pa. Elsevier: 2008: 2279-2289.
14. Nowell P. C., Hungerford D. A., A minute chromosome in human chronic granulocytic leukemia, Science, 1960, 132, 1497.
15. Rowley J. D., A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature, 1973,243, 290–293.
16. Kurzrock R., Gutterman J. U., Talpaz M. The molecular genetics of Philadelphia chromosome-positive leukemias. N Engl J Med, 1988, 319, 990–998.
17. Deininger M. W., Goldman J. M., Melo J. V., The molecular biology of chronic myeloid leukemia, Blood, 2000, 96, 3343–3356.
18. Lugo T. G., Pendergast A. M., Muller A. J., Witte O. N., Tyrosine kinase activity and transformation potency of bcr–abl oncogene products, Science, 1990, 247, 1079–1082.
19. Mohanraj V. J., Chen Y., "Nanoparticles – A Review", Tropical Journal of Pharmaceutical Research, 2006, 5 (1), 561-573
20. Kawashima Y., Nanoparticulate systems for improved drug delivery, Advanced Drug Delivery Reviews, 2001, 47, 1–2
21. Frank A., Eric M. P., Robert L., and Omid C. F., Nanoparticle Technologies for Cancer Therapy,M.Schafer-Korting (ed.), Drug Delivery, Handbook of Experimental Pharmacology, 197, Springer-Verlag Berlin Heidelberg, 2010, 55-86.
22. Yang Z, Yu B, Zhu J, Huang X, Xie J, Xu S, Yang X, Wang X, Yung BC, Lee LJ, Lee RJ. A microfluidic method to synthesize transferrin-lipid nanoparticles loaded with siRNA LOR- 1284 for therapy of acute myeloid leukemia. Nanoscale. 2014;6(16):9742-51.
23. Schettini D. A., Ribeiro R., Demicheli C., Improved targeting of antimony to the bone marrow of dogs using liposomes of reduced size, Int J Pharm, 2006, 315, 140–147.
24. Lisa B. P., James O. B., Nanoparticle and targeted systems for cancer therapy,Advanced Drug Delivery Reviews, 2004, 56, 1649– 1659
25. Sun D, Zhou JK, Zhao L, Zheng ZY, Li J, Pu W, Liu S, Liu XS, Liu SJ, Zheng Y, Zhao Y. Novel curcumin liposome modified with hyaluronan targeting CD44 plays an anti-leukemic role in acute myeloid leukemia in vitro and in vivo. ACS Applied Materials & Interfaces. 2017 May 24;9(20):16857-68.
26. Khan YY, Suvarna VA. Liposomes containing phytochemicals for cancer treatment-an update. Int J Curr Pharm Res. 2017;9(1):20-4.
27. Fielding F. M., Liposomal drug delivery. Clin. Pharmacokinet. 1991, 21, 155-164
28. Lasic D. D., Papahadjopoulos D. Liposomes revisited. Science 1995, 267, 1275- 1276

29. Hossen S, Hossain MK, Basher MK, Mia MN, Rahman MT, Uddin MJ. Smart nanocarrier- based drug delivery systems for cancer therapy and toxicity studies: A review. Journal of advanced research.
30. Sharma A, Sharma US. Liposomes in drug delivery: progress and limitations. International journal of pharmaceutics. 1997 Aug 26;154(2):123-40.
31. Aichberger KJ, Herndlhofer S, Agis H, Sperr WR, Esterbauer H, Rabitsch W, Knöbl P, Haas OA, Thalhammer R, Schwarzinger I, Sillaber C. Liposomal cytarabine for treatment of myeloid central nervous system relapse in chronic myeloid leukaemia occurring during imatinib therapy. European journal of clinical investigation. 2007 Oct;37(10):808-13.
32. Yang X, Pang J, Shen N, Yan F, Wu LC, Al-Kali A, Litzow MR, Peng Y, Lee RJ, Liu S. Liposomal bortezomib is active against chronic myeloid leukemia by disrupting the Sp1- BCR/ABL axis. Oncotarget. 2016 Jun 14;7(24):36382.
33. Mendonça LS, Moreira JN, de Lima MC, Simoes S. Co-encapsulation of anti-BCR-ABL siRNA and imatinib mesylate in transferrin receptor-targeted sterically stabilized liposomes for chronic myeloid leukemia treatment. Biotechnology and bioengineering. 2010 Dec 1;107(5):884-93.
34. Sun S, Zou H, Li L, Liu Q, Ding N, Zeng L, Li H, Mao S. CD123/CD33 dual-antibody modified liposomes effectively target acute myeloid leukemia cells and reduce antigen- negative escape. International journal of pharmaceutics. 2019 Sep 10;568:118518.
35. Tan KB, Ling LU, Bunte RM, Chng WJ, Chiu GN. In vivo efficacy of a novel liposomal formulation of safingol in the treatment of acute myeloid leukemia. Journal of controlled release. 2012 Jun 10;160(2):290-8.
36. Sun D, Zhou JK, Zhao L, Zheng ZY, Li J, Pu W, Liu S, Liu XS, Liu SJ, Zheng Y, Zhao Y. Novel curcumin liposome modified with hyaluronan targeting CD44 plays an anti-leukemic role in acute myeloid leukemia in vitro and in vivo. ACS Applied Materials & Interfaces. 2017 May 24;9(20):16857-68.
37. Myhren L, Nilssen IM, Nicolas V, Døskeland SO, Barratt G, Herfindal L. Efficacy of multi- functional liposomes containing daunorubicin and emetine for treatment of acute myeloid leukaemia. European Journal of Pharmaceutics and Biopharmaceutics. 2014 Sep 1;88(1):186-93.
38. Lotfabadi NN, Kouchesfehani HM, Sheikhha MH, Kalantar SM. Development of a novel cationic liposome: Evaluation of liposome mediated transfection and anti-proliferative effects of miR-101 in acute myeloid leukemia. Journal of Drug Delivery Science and Technology. 2018 Jun 1;45:196-202.
39. Zhang C, Yao H, Kong PY, Liu Y, Gao L, Gao L, Ma YY, Liu J, Tan X, Zhang X. Pegylated liposomal doxorubicin for myeloid neoplasms. Anti-cancer drugs. 2019 Oct;30(9):948.
40. Houshmand M, Garello F, Stefania R, Gaidano V, Cignetti A, Spinelli M, Fava C, Nikougoftar Zarif M, Galimberti S, Pungolino E, Annunziata M. Targeting chronic myeloid leukemia stem/progenitor cells using venetoclax-loaded immunoliposome. Cancers. 2021 Jan;13(6):1311.
41. Liu D, Xing J, Xiong F, Yang F, Gu N. Preparation and in vivo safety evaluations of antileukemic homoharringtonine-loaded PEGylated liposomes. Drug development and industrial pharmacy. 2017 Apr 3;43(4):652-60.
42. Sun D, Zhou JK, Zhao L, Zheng ZY, Li J, Pu W, Liu S, Liu XS, Liu SJ, Zheng Y, Zhao Y. Novel curcumin liposome modified with hyaluronan targeting CD44 plays an anti-leukemic role in acute myeloid leukemia in vitro and in vivo. ACS Applied Materials & Interfaces. 2017 May 24;9(20):16857-68.
43. Wang D, Veena MS, Stevenson K, Tang C, Ho B, Suh JD, Duarte VM, Faull KF, Mehta K, Srivatsan ES, Wang MB. Liposome-encapsulated curcumin suppresses growth of head and neck squamous cell carcinoma in vitro and in xenografts through the inhibition of nuclear factor κB by an AKT-independent pathway. Clinical Cancer Research. 2008 Oct 1;14(19):6228-36
44. Thangapazham, R. L.; Puri, A.; Tele, S.; Blumenthal, R.; Maheshwari, R. K. Evaluation of a Nanotechnology-Based Carrier for Delivery of Curcumin in Prostate Cancer Cells. Int. J. Oncol. 2008, 32 (5), 1119−1123.
45. Li K, Wang S. Preparation, Pharmacokinetic Profile, and Tissue Distribution Studies of a Liposome-Based Formulation of SN-38 Using an UPLC–MS/MS Method. Aaps Pharmscitech. 2016 Dec;17(6):1450-6.
46. Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen JJ, Hjorth-Hansen H, Richter J, Buske C. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2017 Jul 1;28:iv41-51.9(Reference article)

47. Bhutani N. Chronic myeloid leukemia in India: a review. Int J Sci Health Care Res. 2020;5:6-11. (Reference article)
48. Haznedaroğlu İC, Kuzu I, İlhan O. WHO 2016 definition of chronic myeloid leukemia and tyrosine kinase inhibitors. Turkish Journal of Hematology. 2020 Mar;37(1):42.

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