REVIEW ARTICLE

Targeted-based Nanocarriers for Control of Non-Hodgkin Lymphoma: Current Aspects and Future Perspectives

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Abstract

Oncology faces many challenges with non-Hodgkin lymphoma (NHL) a varied group of lymphatic system tumors. Immunotherapeutic methods have supplemented or replaced chemotherapy for NHL treatment. Immune checkpoint inhibitors improve NHL patient outcomes and quality of life. CAR-T cell treatments also enhance patient prospects. Monoclonal antibody therapy is advancement. Several treatments are still used. Radiation therapy is a part of this. Multimodal therapy approaches also include stem cell transplantation. The study also examines treatment resistance and long-term side effects. Nano medicine uses nanomaterial's to treat cancer. Oncology entered a new age. This study gives hope for nanomaterial-based NHL treatment. A treatment more successful, focused and humane.

Key words: Heterogeneity, nanomedicine, non-Hodgkin lymphoma, oncology, pathophysiology

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a broad category of hematological malignancies. These develop from lymphocytes which are crucial immune system components. Contrary to Hodgkin lymphoma, NHL is a broad term. It refers to various subtypes [Figure 1].

Each has unique medical morphological and genetic characteristics. Knowing, identifying, and dealing with this complicated disease are made more difficult. They are also made more advantageous by their heterogeneity.[1] The immunological system is in charge. It preserves fluid balance. It also generates immunity cells.[2]

With different cell types, NHL represents a wide range of disorders, clinical symptoms genetic alterations, and treatment outcomes. Nanoparticles have various benefits over conventional chemotherapeutic drugs. They can be readily modified to increase their selectivity and efficiency toward tumor cells. Even though lymphoma-like illnesses were initially documented in the 19th century. The development of distinct classifications did not start until the mid-1900s. The latter half of the 20th century witnessed the emergence of sophisticated methods, such as histopathology and molecular genetics. These advancements revolutionized our knowledge of NHL subtypes. They opened the door to targeted treatments and customized medicine.[3,4]

NHL and cancer research in historical context and evolution

Recent advances in NHL research have highlighted tumor heterogeneity and the function of the tumor microenvironment (TME) by identifying certain genetic aberrations and immunological markers.[5] The TME's non-malignant cells promote the growth of cancer cells and their resistance to therapy, which increases patient recurrence and reduces the efficacy of many treatments.[6]

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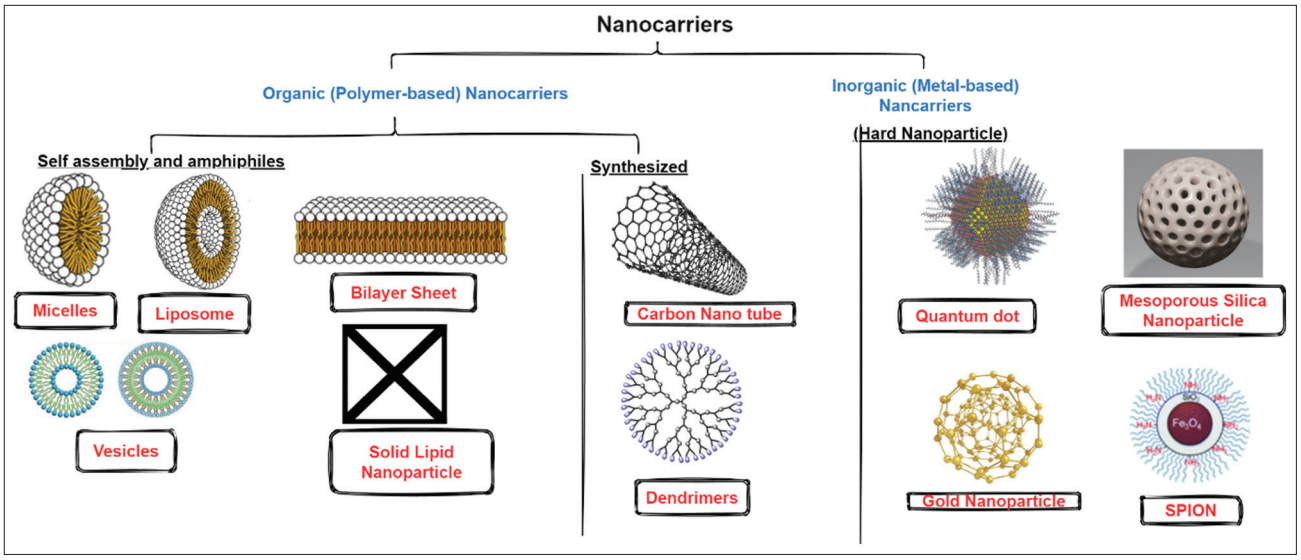

Figure 1: The most employed organic and inorganic nanocarriers

Importance of NHL study

In addition, NHL research sheds light on fundamental ideas in oncology. This includes genetics and immunology.[7,8] It provides an understanding of the broader context of cancer biology. Furthermore, improvements in the investigation and medical management of other types of hematological malignancies and solid tumors are also influenced by developments in NHL research.[9,10]

THE CATEGORIZATION OF NHL

Subtypes of lymphoma present with distinct biological characteristics and therapeutic outcomes. The development of gene profiling has made tailored therapy possible for diseases like diffuse large B-cell lymphoma (DLBCL). While mantle cell lymphoma presents treatment hurdles, follicular lymphoma advances slowly. Therapy results are influenced by variations in ALK positivity among ALCL and PTCL subtypes. Treatment for cutaneous T-cell lymphoma is based on the presence of skin lesions.[11]

PATHOLOGY OF NON-HODGKIN'S LYMPHOMA

The immune system interacts with itself in a complicated way during the development of NHL. Molecular and genetic components are also present to disperse a prevalent subtype of B-cell NHL is large B-cell lymphoma. Common subtypes include mantle cell lymphoma and follicular lymphoma. T cells are involved in the NHL subtype known as anaplastic large cell lymphoma. Peripheral T-cell lymphoma is another kind of lymphoma. Each has distinct clinical and pathological characteristics.[12]

CLINICAL PRESENTATION

A diverse range of cancers originating from lymphoid tissues is referred to as NHL. Early identification of NHL can be difficult because of its variable clinical presentation, which frequently resembles benign illnesses. Accurate and fast diagnosis depends on knowing the subtleties of its clinical presentations and using a variety of diagnostic techniques.[13]

NHL signs and symptoms

MYC and BCL2 translocations are the primary cause of aggressive "double-hit" NHL lymphomas. Immune evasion is made possible by dysregulated checkpoints (PD-1/PD-L1, CTLA-4) and persistent inflammation. Potential therapeutic targets and genetic aberrations are revealed by high-throughput sequencing.

EPIDEMIOLOGY AND NHL RISK FACTORS

A subtype of white blood cells called lymphocytes is the initial stage of NHL, a kind of blood cancer. Developing preventive, early diagnosis, and treatment solutions requires a thorough understanding of the disease's epidemiology and risk factors.[14]

1. Global prevalence and incidence rates

   Because of aging populations, better diagnosis techniques, genetic predispositions, and environmental exposures, NHL is increasingly prevalent in wealthy nations.

2. Trends associated with age, gender, and ethnicity

   Age and gender variations in NHL subtypes are caused by a combination of genetic and environmental variables that change depending on the ethnic group.

3. Genetic and environmental risk factors
   UV light, chemicals, viruses (hepatitis C virus, human immunodeficiency virus [HIV], Epstein-Barr virus [EBV]), family history, and genetic predispositions impacting apoptosis and cell control all have an impact on NHL risk.

4. Connection with immunodeficiency diseases
   NHL is more prevalent in immunocompromised people (HIV/acquired immunodeficiency syndrome, post-transplant), as a compromised immune system encourages the growth of lymphomas.

CHALLENGES IN EARLY DIAGNOSIS AND POTENTIAL SOLUTIONS

- Challenges

1. NHL's vague symptoms can resemble those of common conditions, which can delay diagnosis.
2. Targeted studies are necessary for accurate identification of extranodal presentations.
3. Timely referrals are hampered by patients' and healthcare providers' lack of awareness.[15]

- Potential Solutions

1. Improve medical education to enable prompt diagnosis and testing.
2. Start public awareness efforts about the symptoms of NHL.
3. Invest in cutting-edge imaging methods to enhance diagnosis.[15]

DIAGNOSTIC METHODS

NHL is confirmed by immunohistochemistry and molecular testing, and the disease's spread is evaluated by imaging methods such as positron emission tomography and computed tomography scans.[16,17] Targeted nanoparticles can improve cancer diagnosis and personalized treatment by monitoring tumor genetic profiles noninvasively, thanks to recent advancements in nanotechnology.[18]

APPROVED NANOPHARMACEUTICALS BASED ON LIPIDS

Liposomes have been widely used for drug administration since 1975; nevertheless, organ build-up and restricted circulation led to the creation of lipid-based nanodrugs which are listed in Table 1.[19,20] Treating NHL (NHLCL), especially DLBCL, requires a multimodal strategy, with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) being the recommended treatment for patients of all ages.[21-23]

TREATMENT MODALITIES

One type of lymphoid malignancy that requires a multimodal strategy of therapy is NHL. 40% of newly diagnosed cases are of the most frequent form, DLBCL. Given that more than half of DLBCL patients are older than 60, treatment can be challenging.[24]

Regardless of age, patients receive the standard treatment, CHOP. Elderly patient management is challenging since about 40–50% of older patients fully react to treatment; the 3-year overall survival rate is approximately 40%, and the event-free survival rate is approximately 30%.[25]

- Chemotherapy protocols and their performance
  Significant success has been demonstrated in inducing remission in non-Hodgkin's lymphoma (NHL) with the R-CHOP and CHOP regimens, particularly in B-cell lymphomas, which account for 85% of NHL patients. For DLBCL, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) are the mainstay of treatment. The anti-CD20 monoclonal antibody rituximab is added to chemotherapy to improve its therapeutic benefits.[26] Since almost all B-cell lymphomas express CD20, rituximab is an essential treatment. More than 90% of patients respond to R-CHOP, which has a better safety profile and higher response rates than CHOP alone, according to studies like those conducted by the Groupe d'Etude des Lymphomes de l'Adulte.[25,27-30]

Treatment for relapsed or refractory B-cell NHL is still difficult, and striking a balance between toxicity and efficacy is crucial. Although only 30% of older people attain a three-year event-free survival, the total survival rate for these patients is between 35% and 40%. For indolent and aggressive lymphoma patients who have relapsed or become resistant, rituximab presents hope.[31-34]

- Immunotherapy: CAR-T cell treatment with monoclonal antibodies

Immunotherapy boosts the body's defenses against cancer by utilizing CAR-T cell therapy and monoclonal antibodies like rituximab. In addition, Dendrimers function as adjuvants, enhancing the efficacy of treatment and tackling difficulties in the treatment of cancer [Figure 2].[28]

Nanotechnology based carrier platforms

NHL may be treated with nanotechnology-based carriers such liposomes, polymeric nanoparticles, Dendrimers, and gold nanoparticles [Figure 3]. These platforms lessen side

Table 1: Lipid-based nanodrugs

Product	Drug	Mechanism of action-effect
Doxil and Caelyx	Doxorubicin	Cytotoxicity activity • Intercalation into tRNA and DNA duplex • Topoisomerase II activity inhibition • Replication arrest and double-strand breakage in DNA
Daunoxome	Daunorubicin	
Myocet	Doxorubicin	
Mepact	Mifamurtide	Innate immunity activation • Ligand for NOD2 and TRL4 in macrophages and monocytes • An immunostimulatory response
Ameluz	5-aminolevulinic acid	Cytotoxic activity • Production of oxygen-free radicals
Marqibo	Vincristine	Cytotoxicity activity • Ties itself to tubulin • Interfere with the metabolism of glutathione, AMPc, and CMCa+2 transport ATPase function. • Stem cell respiration • The production of lipids and nucleic acids and antimitotic action
Onivyde	Irinotecan	Cytotoxic activity • Apoptotic death inductor • Intercalation into DNA duplex • Topoisomerase I activity inhibition • Replication arrest and DNA double-strand breakage
Vyxeos	Daunorubicin, cytarabine	Cytotoxin activity • Cytarabine 1. Antimetabolite 2. DNA synthesis inhibition 3. Inducer of apoptotic death • Daunorubicin 1. Intercalation into tRNA and DNA duplex 2. Reduction of activity of topoisomerase II 3. Double strand breaks in DNA and replication arrest

effects while improving medicine delivery, targeting, and efficacy. By specifically targeting CD20 on NHL B-cells, functionalizing nanoparticles with ligands such as rituximab enhances selectivity.

Prognosis and survival rates

A multitude of intricately intertwined elements. These include the disease's features the patient's general health and the efficacy of the prescribed treatment plan.[28] They impact the prognosis and survival rates of NHL. Comprehending these variables is of utmost importance for healthcare practitioners and patients alike. It facilitates informed decision-making and fosters reasonable anticipations of results.[35,36]

FACTORS AFFECTING THE PROGNOSIS

- NFL subclasses
- Stage at diagnosis
- Histological grade
- B-cell versus T-cell lymphomas
- Bulky disease
- Performance status.[37]

SURVIVAL RATES BASED ON NHL SUBTYPES AND STAGES

- Follicular lymphoma: For localized instances, the 5-year survival rate is approximately 90%. Early identification is often associated with a favorable prognosis.
- DLBCL: With targeted therapy, this aggressive subtype can achieve a 60–70% 5-year survival rate. It is important to treat DLBCL promptly.
- Mantle cell lymphoma: Although the prognosis was once poor, it is now improving thanks to advances in targeted therapies.
- T-cell lymphoma: The prognosis differs greatly depending on the subtype; peripheral T-cell lymphomas typically have a worse prognosis than other subtypes.[38]

THE POSSIBLE EFFECTS OF PERSONALIZED MEDICINE ON NHL TREATMENT

Liquid biopsies

Liquid biopsies analyze circulating tumor DNA and proteins for disease tracking, while machine learning

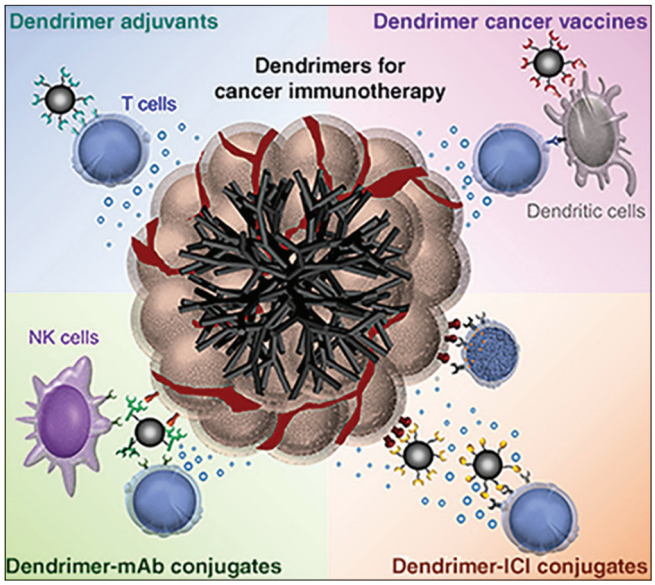

Figure 2: Dendrimers for cancer immunotherapy

predicts treatment responses, enabling oncologists to tailor personalized treatment plans based on genetic and clinical data.[39]

A THOROUGH ANALYSIS OF NHL STAGING AND PROGNOSIS

Assessing patient performance with instruments such as the Eastern Cooperative Oncology Group scale provides information about patient resilience to therapy and overall health. Tailored treatment regimens are made possible by improved NHL staging and prognosis due to advanced imaging, immunohistochemistry, and genetic investigations. Beyond the conventional Ann Arbor classification, ongoing research and interdisciplinary collaboration improve patient outcomes and survival estimates [Table 2].[40]

Five pre-treatment markers (age, stage [III or IV], number of additional nodal locations of illness, performance status, and blood lactate dehydrogenase level) were found to be independently relevant in a study of 12 variables later examined by the International NHL Prognostic Factors Project. It was demonstrated that the Ann Arbour staging system's capacity to forecast results varied.

PROGNOSTIC FACTORS AFFECTING OUTCOME

1. Age and performance status
2. Tumor burden and bulk
3. Histological subtype and molecular features
4. Reaction to first therapy
5. Tumor and immune microenvironments

The staging and prognosis of NHL have been revolutionized by the integration of modern imaging and molecular insights, resulting in more individualized treatments and better outcomes. This highlights the significance of interdisciplinary collaboration and continuous research in cancer.[41]

TARGETED THERAPIES: ACCURATE METHODS FOR TREATING NHL

Clonal B or T cell proliferation is the source of NHL, which is often treated with radiation and chemotherapy, both of which have serious side effects and are not very selective. More precise choices are provided by targeted medicines, such as kinase and proteasome inhibitors, which target specific pathways within cancer cells. By using next-generation sequencing to precision medicine, treatment efficacy can be maximized while side effects are reduced, potentially leading to better outcomes and a higher standard of living for patients with NHL [Figure 4].[42]

TRIGGRED RELEASE, TARGETING, AND FUNCTIONALIZATION OF NANOPARTICLES

In Nanomedicine, the production of specific nanoparticles for targeted therapy is still difficulty.[43]

Nanoparticles can concentrate in tumors due to the EPR effect; nevertheless, passive targeting has disadvantages such as poor diffusion and possible multi-drug resistance.[44,45]

Active targeting and triggered release are two methods of targeted medication delivery that increase treatment efficacy while reducing harm to healthy tissues.[46,47]

PROSPECTIVE ROUTES AND ONCOMING TREATMENTS

NHL research is progressing through the use of targeted medicines that take advantage of genetic flaws in cancer cells through genomic analysis.[48] By changing gene expression, epigenetic modulation seeks to change the behavior of cancer cells. Combination medicines and a greater comprehension of TMEs are driving advancements in immunotherapy, increasing treatment efficacy and encouraging individualized strategies to enhance patient outcomes.[38]

- Difficulties in clinical nanopharmaceutical translation
  Although there is great promise for using nanotechnology in the development of cancer medicines, there are a few challenges that must be resolved before it can be used clinically.

- Limitations in toxicology, production, and costs
  A significant obstacle is an expensive expense of developing nanopharmaceuticals, such as Doxil and

Table 2: Ann Arbor staging system

Stage	Defining status
Phase I	Restricted to a single lymph node region (I) or a single extranodal site (I–E)
Phase II	Two or more nodal involvement locations on the same side of the diaphragm (II) or one or more lymph node regions with an extranodal site (II-E)
Phase III	Both sides of the diaphragm (III) are involved in lymphatic flow, which can also occasionally involve the spleen* (III-S), another nodal region (III-E), or both (III-SE)
Phase IV	Illnesses affecting the marrow, liver, or other sizable extra nodal organs
Substage	
Sub phase E	Extranodal illness that is localized
Sub phase A	Lack of systemic indicators
Sub phase B	10% of the body weight lost in 6 months without a known cause, along with an inexplicable fever and/or night sweats

*The spleen is thought to be nodal.

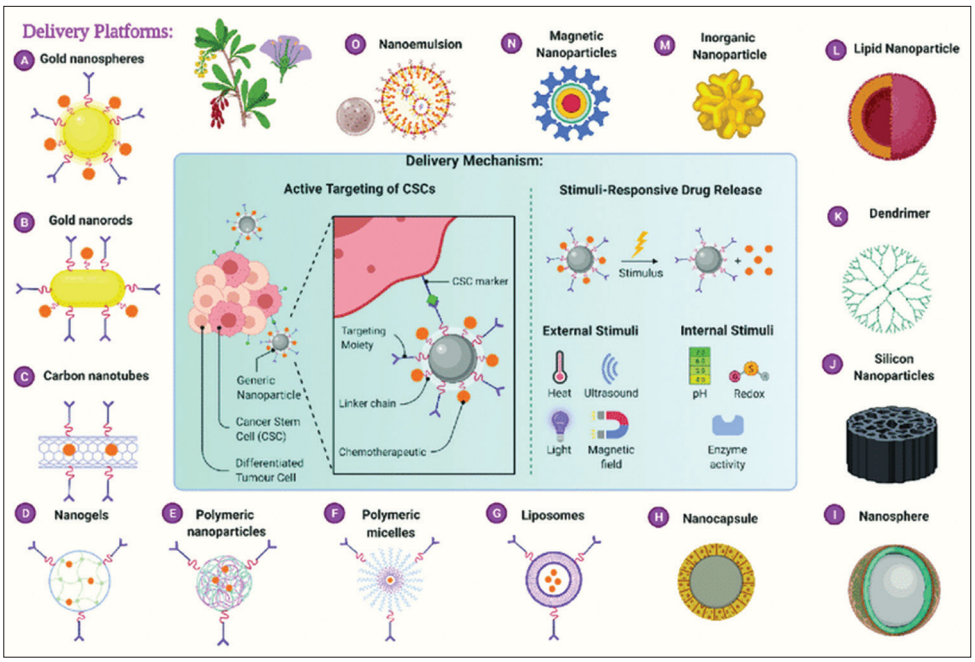

Figure 3: Nanotechnology based carrier platforms

Abraxane, which can cost up to $1 billion and take 10–15 years to commercialize.[49] Their increased cost relative to generic medications must be supported by demonstrable clinical advantages. Furthermore, consistent characterization of nanomedicine products is complicated by controlled manufacture under GMP settings.[50,51]

- Clinical application of nanoparticle drugs

Current research on Nano formulations—which include both organic and inorganic nanoparticles—highlights their versatility in terms of size, shape, and functionality for targeted therapeutics, especially those aimed at curing cancer [Figure 5]. Clinical translation is still minimal despite encouraging preclinical outcomes. Nevertheless, better approaches should increase Nano medicine's usefulness and efficacy.[52]

TREATMENT VOLUME FUNDAMENTALS

1. Radiation therapy is the main course of care
   - Treatment for indolent localized lymphoma.
   - Effective for people who cannot tolerate chemotherapy for locally advanced nodal NHL.
   - Ideal in situations that are localized and do not respond to chemotherapy.

2. RT in the Context of a Multimodal Approach
   - Used as consolidation treatment for localized aggressive lymphomas following systemic chemotherapy.
   - Significant in that it permits shorter treatment regimens for elderly individuals with low tolerance to chemotherapy.[53]

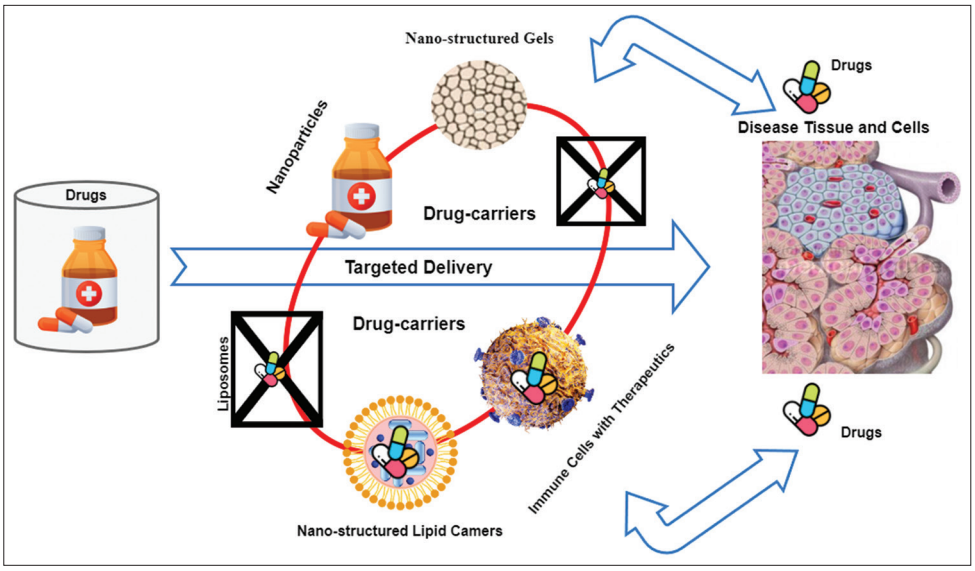

Figure 4: Carrier based systems for targeted and site specific therapeutic delivery

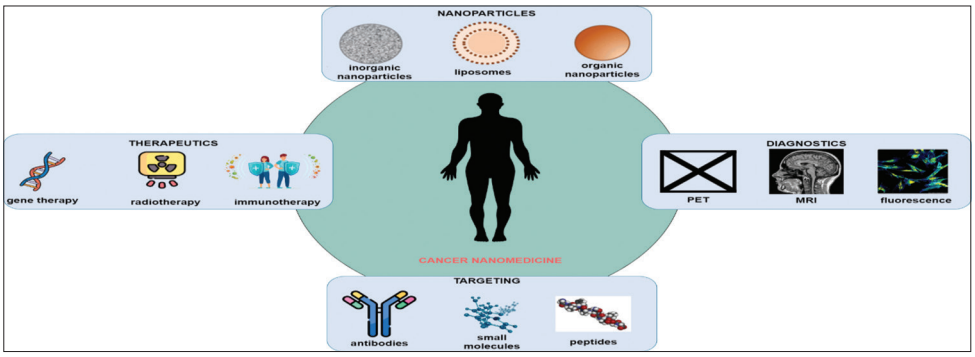

Figure 5: Nanocarriers as a delivery platform for anticancer treatment

PREVENTION AND FUTURE PERSPECTIVES

Understanding and treatment of NHL have improved thanks to research, with a focus on precision medicine and preventative measures. In Nano medicine, active targeting improves selectivity for cancer cells. The goal of emerging technology is to locate and eradicate cancer stem cells (CSCs). Tailored medicines are made possible by thorough genomic profiling, but there are still financial and logistical obstacles to overcome. Subsequent research on NHL will prioritize cooperation between researchers, clinicians, and pharmaceutical corporations with the goal of lowering incidence and improving outcomes using creative, multimodal approaches.[54,55]

FURTHER GENETIC VARIABLES

There may be a genetic component to the increased risk of lymphoma in siblings of individuals with the disease. While research on individual genes has revealed widespread genetic variations, strong susceptibility sites are yet unknown.[56]

Infectious substances

Malignant lymphomas have been associated with HTLV-1, EBV, and HHV-8 herpes viruses. With the availability of adaptable nanoparticles for focused therapy, nanomaterials have improved cancer detection and therapy. However, further research is needed to address issues with immunogenicity and cytotoxicity, particularly in inorganic systems.[57,58]

Immunotherapy resistance is associated with signaling pathways associated with CSCs. SEER Stat software from the National Cancer Institute's Close Modal Surveillance Research Program Version 5.2.2.[59,60]

CONCLUSION

The treatment of NHL may benefit from the use of targeted nanocarriers. Nanotechnology breakthroughs have completely changed the treatment of cancer by enabling targeted medicine delivery to tumor cells with the least amount of negative effects on healthy organs. The selectivity and effectiveness of cancer treatments are improved by

the use of nanocarriers, such as liposomes and polymeric nanoparticle therapy. Three main research topics are targeted treatments, immunomodulation, and genomic profiling, which are important for developing precise and customized therapy choices for NHL. For nano medicines to be widely used, issues with toxicological, manufacturing costs, and clinical translation must be resolved. Future improvements in outcomes and quality of life for NHL patients will be made possible by cooperative efforts and continuing clinical trials.

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