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Tanvi Gandhi, B.Pharm
Butler University

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Nanomedicine for the Treatment of Non-Hodgkin Lymphoma

Tanvi Gandhi, B.Pharm

Abstract: Non-Hodgkin lymphoma, or NHL, is the predominant category of lymphoma. NHL is a type of lymphoid hematopoietic malignancy which approximately 70,000 Americans are diagnosed with annually, with the number of diagnoses growing annually. For decades, chemotherapy was the standard treatment of care, but since the discovery in 1997, monoclonal antibodies are increasingly used as an alternate form of therapy. Nonetheless, almost 20,000 Americans succumb to NHL annually, which highlights the translational gap between preclinical research and the market. Although a lot of progress has been made in therapy options by immunotherapy and combination chemotherapy, the ingenuity of nanomedicine may bridge the translational difficulties while serving as a novel form of therapy capable of eradicating solid tumors. The versatility of nanoparticles allows for personalized approach to NHL, as opposed to generalized medicine, since the subtypes of lymphoma are pathologically very different from one another.

EMERGENCE OF NANOMEDICINE

Non-Hodgkin lymphoma (NHL) affects many Americans annually, with a growth of over 5,000 diagnoses in the U.S. annually, totaling approximately 75,000 diagnoses in 2018.^{1,2} Commonly used treatment options for oncological diseases comprise of chemotherapy, radiation, and stem cell transplants.^{2,3} The most common off-target complication for all these current therapy alternatives is the death of non-cancerous cells due to non-specificity of the treatment used. The translational laboratory-to-market pathway is facing a major road block due to this adverse effect which in turn undermines the efficacy of the original treatment.³ This provides opportunity for better suited carriers or a formulation system which will show higher efficacy than nonspecific binding of cells.⁴ In this regard, since the discovery in the 1980s, nanoparticles have been rapidly conquering the translational medicine sector. There is a growing interest in nanomedicine, which is the application of nanoparticles for therapeutic purposes.⁴ Nanoparticles are not only making it possible to use newly discovered molecular entities in a more suitable formulation but are also bridging the time gap between laboratory discovery and patient use.

Since its introduction in 1974, nanotechnology has rapidly been researched, allowing its movement into clinical trials.³ Ever since the first FDA approval for Doxil®, an increasing number of phase II and phase III clinical trials are now focusing on nanomedicine.⁴ The major advantage of using nanoparticles is the versatility in size, solubility, and drug loading.⁵ Based on the desired targeting and candidate drug properties, an ideal system can be selected as a carrier. Sizes for nanoparticles range from 50 nanometers to 200 nanometers, where the smaller size helps to improve the pharmacokinetic profile of the drug by ensuring it stays in the system longer. Drug loading can be improved based on hydrophilicity of the drug. More hydrophobic drugs should be loaded into nanoemulsions or liposomes while hydrophilic drugs are better suited with micelles.⁵

Where most formulations struggle with delivery of the drug within the cancer cells due to the barrier of penetrating the cell membranes, nanoparticles use the process of endocytosis or cell

membrane fusion for cell internalization.^{6,7} Although endocytosis is the more prevalent of the two methods, there are still issues with insufficient drug release due to endosomal escape or degradation by lysosomes.⁸ Cell membrane fusion is a mechanism proposed to be used particularly by liposomes, wherein the similarity in phospholipid composition of cell membrane and liposomal membrane causes the membranes to fuse.⁸ Newer targeting mechanisms involve the use of stimuli-response release, which may be based on temperature, pH, light, or enzymes.^{6,7}

Due to the advancement and increasing success of nanomedicine in cancer, scientists are applying the same principles of nanoparticles to the research in the fields of other chronic illnesses like diabetes and cardiovascular disease.⁹ Engineered nanoparticles have unlocked new avenues by not only providing sophisticated treatment options but also giving us access to early diagnosis of various cancers. The diagnostic capabilities combined with the therapeutic power has enabled nanoparticles to be designed with target specificity, thereby reducing the off-target adverse effects.⁹ Table 1 highlights the nanoparticulate formulations currently approved by the FDA on the market.

CHALLENGES IN CLINICAL TRANSITION

Clinical translation of nanomedicine is not only expensive but also a very time-intensive process. From a formulation aspect, it is harder to manufacture nanoparticles with the same reproducibility and quality as the traditional forms of medicine, such as tablets, injectables, and suspensions.^{9,10} There are several factors, including cancer pathophysiology, manufacturing scale-up, toxicology profile, and biocompatibility, which pose as market barriers, irrespective of the increasing number of pre-clinical research articles being published.^{11,12}

Drug	Formulation	Indication(s)	Manufacturer	FDA approval date
Oncaspar	PEG-asparaginase	ALL	Sigma-Tau Pharmaceuticals	1994
Doxil/Caelyx	Pegylated liposomal doxorubicin	Ovarian cancer, multiple myeloma and AIDS-related Kaposi's sarcoma	Janssen-Cilag International	1995
DuanoXome	Liposomal daunorubicin	Advanced HIV-related Kaposi's sarcoma	Galen US	1996
DepoCyt	Liposomal cytarabine	Lymphomatous meningitis	Pacira Pharmaceuticals	1999
Myocet	Liposomal doxorubicin	Metastatic breast cancer	Teva Pharmaceuticals	2000
Abraxane	Albumin-bound paclitaxel nanospheres	Metastatic pancreatic cancer and other related cancers	Celgene	2005
Genexol-PM	Paclitaxel loaded polymeric micelle	Metastatic breast cancer and NSCLC	Samyang	2007 (in Korea)
Marqibo	Liposomal vincristine sulphate	Philadelphia chromosome-negative lymphoblastic leukemia	Talon therapeutics	2012

TABLE 1: FDA approved nanoparticle formulations for cancer (NSCLC: Non-small cell lung cancer; ALL: Acute lymphoblastic leukemia)⁸

TYPES OF NANOCARRIERS

Although most of the nanoparticle products on the market comprise of liposomes as the nanocarrier, polymers and some metals are now being used in the formulation as well.^{13,14} The choice of the carrier is crucial to efficacy of the formulation and depends largely on the therapeutic material to be encapsulated. For instance, delivery of siRNA demands high endosomal escape, hence a carrier with that ability must be designed.¹³ Choice of vehicle has an impact on the ADME profile of the final product and each carrier has its own merits and pitfalls. Nanoparticles may be broadly classified as rigid, such as polymeric and inorganic nanoparticles, or non-rigid, such as liposome, micelle and solid lipid nanoparticle. Another form of classification divides them into organic nanoparticles, including micelle, liposome, nanogel and dendrimer, and inorganic nanoparticles, including SPIONs, gold nanoparticles, quantum dot nanoparticles and paramagnetic lanthanide ions.¹³

CONCLUSION AND FUTURE SCOPE

Although over 5% of newly diagnosed cancers are categorized as NHL, not many chemotherapeutic regimens are approved by the FDA to improve the patient survival and quality of life.¹³ Immunotherapy has greatly improved the NHL outcomes, but the prognosis of NHL remains poor as compared to other cancers.¹⁵ The introduction of nanotherapeutics might revolutionize the NHL market by providing better tolerance for the current drugs while obtaining the desired cytotoxicity for cancer cells. Currently, five different types of nanoparticles are being investigated in clinical trials.¹⁵

Moving forward, identifying and overcoming the crucial challenges will help NHL-directed nanomedicine to evolve and reach the market. Some of these challenges include targeting and selectivity, making it able to move beyond the EPR (enhanced permeability and retention) effect.¹⁶ Nanoparticles can be engineered to target a ligand as well as encapsulate molecular targeting agents. In addition to delivering encapsulated drugs, nanoparticles can be used to effectively deliver nucleic acids, antibodies and other genetic materials.¹⁶

Another challenge in developing anti-lymphoma nanotherapeutics is the translation from lab to market. Very few of the formulations which work in vivo translate those results in humans since the physiologies of the two species are different.¹⁶ For clinical trials, the enrolment is a lengthy process and most of the subjects are patients who have failed to respond to the standard of care treatments. Taking into consideration the outcome of this disease in the absence of medicine, blinding of clinical trials would be unethical and could lead to a further reduction in the trial participation. More recently, canine clinical trials are being conducted with dogs which naturally contracted NHL.¹⁶ Since disease progression is faster in dogs, the time for clinical trials is also relatively reduced.¹⁵

In the future, nanomedicine synthesized using lipids, polymers and chemotherapeutic drugs will play an important role in the treatment regimen for NHL. Coupling the recent and exciting discovery of CRISPR-Cas9 with nanoparticles would serve as a powerful permanent genetic manipulation tool allowing mutations and correction of translocations.^{16,17} Since the vast majority of NHL arises due to genetic aberrations, such as mantle cell lymphoma, the disease could be a perfect target for this new technology.¹⁷ This system could also have advantages over some

of the other commonly used nucleic acids, including siRNA and DNA.¹⁷

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