ABSTRACT

Generally, it is said that the lymph node plays very important role in the cancer immunotherapy. So, delivering immunomodulating compounds to lymph node can be useful strategy for cancer immunotherapy. In case of this lymph node drug delivery system, lipid nanoparticles are widely used. High amount of drugs, nucleic acids and various other compounds can easily load in lipid nanoparticle, and they are easy to be manufacture on industrial scale also. In this review, we have focused on the potential of lipid nanoparticle technology to aim lymph nodes. However, there are many factors that control the delivery of drugs to lymphatics. Before the lymphatic detection, lipid nanoformulations are necessary to go through interstitial hindrance which alters delivery of them. So, the distribution and detection of lipid nanoformulations by means of lymphatic system depend on charge present on nanoparticles, hydrophobicity, particle size and molecular weight, form & type of lipid and emulsifier concentrations are as well significant factors disturbing the delivery of drugs in the lymphatic system.
Keywords: Cancer immunotherapy; lipid nanoparticle; Lymph node; Lymphatic system; Nanocarriers.

1. INTRODUCTION

Recently immunotherapy has become an important therapy of treating few types of cancer. The immunotherapy is tested and approved, and various other methods of improving the immune system are discovering at a faster rate. Immunotherapy works better for few types of cancers only. While immunotherapy is the only treatment for some of the cancers, but for others it effectively work when used with other types of cancer treatment like chemotherapy. Lymph nodes are most common site for metastatic niches and lympho-proliferation also most of cancer their metastases occur via blood or lymphatic system. One of the best methods for delivering immune functional compounds to lymph nodes is the use of nanocarrier systems. The lymph node access requires a specific sizes and surface properties. In this article, we will discuss the potential of lipid-based nanocarriers via lymphatic system to lymph nodes in the view of the cancer immunotherapy. For the past 25 years, vascular research has focused more on blood biology than on lymph biology due to the complexity involved in observing the lymphatic system and the lack of awareness of its unique function. Presently, the lymphatic system is gaining more significance and achieving more recognition and its correlation with cancer biology.

2. IMMUNOTHERAPY IN CANCER

When we talk about the cancer treatment there are mostly used therapies called surgery chemotherapy and radiation therapy but there is recently developed therapy called immunotherapy. Immuno-oncology is another name for cancer immunotherapy. Its a cancer treatment that relies on the bodys own immune system to prevent, monitor, and remove cancerous cells. Immunotherapy aids the immune system in identifying and attacking specific cancer cells, as well as increasing the development of immune cells to combat cancer [1]. Despite the fact that the immune system can stop or delay cancer development, cancer cells have many ways to avoid being destroyed by immune cells. For example cancer cells (as shown in Fig.1), may:

1. Undergo genetic changes that render them immune system-invisible.

II. Switching off the T-cells by producing proteins or a false receptor on their surface.

Alter the normal cells in the vicinity of the tumors so that they obstruct the immune systems response to the cancer.

2.1 Non-specific Immune Stimulation

It is the type of cancer immunotherapy which uses drug substances to modulate the immune system that help the body to fight against cancer. Immune-modulating agents include; Cytokines-these are proteins made by the WBCs which include Interferons and Interleukins [2]. Interferon especially INFα slows down the growth of cancer cells. There are so many types of interleukins available there but especially IL2 (Interleukin 2) also called as T-cell growth factor which boosts the number of Natural killer cells and Killer T-cells and also helps the β-cells to produce substance that target cancer cells [3]. Erythropoietin boosts the production of RBCs, Granulocyte macrophage colony stimulating factor and Granulocyte colony stimulating factor both increases the quantity of WBCs and improve the immune system to fight cancer by rising number T-cells, Immunomodulatory drugs like- Thalidomide, Pomalidomide & Lenalidomide (as shown in Fig. 2) causes the cells to release IL-2 and stops tumor forming new blood vessels so they are also called as angiogenesis inhibitor. Imiquimod is available in the form of creams to rub on skin which then releases the cytokines at site of application [4].

2.2 T-cell Transfer Therapy

T-cells are dominant weapons of the bodys cancer-fighting system. T-cell transfer treatment is a form of immunotherapy that prepares your immune cells to fight cancer [5]. There are two main types of T-cell transfer treatment: CAR T-cell therapy and tumor-infiltrating lymphocytes (or TIL) therapy. Both these therapy involve collecting your immune cells, producing large numbers of these cells in laboratory, and then returning the cells to patient in vein through a needle [6]. This therapy is also known as adoptive cell therapy, T-cell therapy and adoptive immunotherapy. The method of growing T-cells in lab can take two to eight weeks. Throughout this period, patient may receive chemotherapy and, perhaps, radiation therapy to eliminate other
cells from body [7]. Reducing other immune cells helps the transferred T-cells to function appropriately. After this treatment, T-cells grown in the laboratory and will be returned with a needle in vein (as shown in Fig. 3).

2.2.1 TIL-therapy

It uses the T-cells, specifically Tumor Infiltrating Lymphocyte which is seen in tumors. The best lymphocytes are then identified by the doctors in the lab [8]. Then these desired lymphocytes are treated with certain substance which grow them and make numerous copies of them. The concept behind this approach is the lymphocyte which present near the tumors have ability to recognize them quickly [9]. But the fact is that there are no specific numbers of these cells to kill tumor or decreasing the signals which are generated by tumors to suppress the immune system. Hence to overcome this problem large numbers of lymphocytes which are capable of fighting tumor are given [10].

2.2.2 CAR T-cell therapy

It is same as that of TIL therapy, only the difference is that the T-cells are modified genetically in lab [11]. The modification done is that the genes which are responsible for producing the protein called CAR is added which stands for Chimeric Antigen Receptor [12]. This specialized T-cells containing CAR protein are better to bind with proteins preset on cancerous cell, which helps the T-cell to kill tumor efficiently.

2.3 Immune Checkpoints Inhibitor

The immune system is located on the surface of the cells and is an important part of the immune system [13]. Their main purpose is to suppress the body's response, which is highly powerful to it kills healthy normal cells of the body. As proteins present on the surface of immune cells are known as T-cells identify and attach proteins to further cells, for example cancer cells, the immune system is active [14]. Immune test proteins are the name of these proteins. As the test site and the associated proteins come together, T cells receive an inactive signal. This will prevent cancer from being destroyed by the immune system. Immunotherapeutic drugs known as immune checkpoint inhibitors work by inhibiting the binding of experimental proteins to other proteins [15]. As a result, a closed signal is not sent, allowing T cells to invade cancer cells (as shown in Fig. 4). CLTA-4 and PD-1 are two types of experimental proteins found in the body. Some immune checkpoint inhibitors target the CLTA-4 signaling protein, while others target the PD-1 testing protein or PD-L1 affiliate protein [16]. One tumor suppresses T cell responses by releasing large amounts of PD-L1.
3. APPROACHES FOR TARGETING LYMPH NODE WITH NANOPARTICLES

The lymphatic system plays a major function in metastasis cancer. If we look at metastasis cancer, the condition of the lymphatic node is the most important factor for a diagnosis of patient [17]. Although surgery is one of the important treatment modalities of cancer, minor infections can persist and lead to local recurrence. The standard drug delivery system of chemotherapeutic agents does not work to deliver drugs to the lymph node without dose limiting toxins. The lymphatic system works in the drainage of waste material from the interstitium [18]. Molecule formation is important in determining its lymphatic acquisition and retention inside lymph node. Colloidal synthetic materials such as polymeric particles, activated carbon particles, liposomes, lipids, emulsions, and, are highly absorbed by lymphatics, so these days these substances rise as possible carriers in the lymphatic direction [19].

Most drugs that follow the oral route enter directly into the circulatory system, but most lipophilic molecules can enter the circulatory system in a lymphatic way. Identifying drugs in the lymphatic system is a difficult and difficult task, which depends entirely on complex functioning of lymphatic system [20]. The regulation helps to make direct contact with the drug in one area, reducing the dose of the drug elsewhere and minimizing the side effects shown by them. Presently, nanocarriers rely on lymphatic guidance, but there is still the challenge of identifying drugs and the use of a specific area, to maintain a popular action by overcoming all physical barriers [21]. These challenges are capable of overcome by the use of synthetic nano-systems that are achievable through many landscape modifications. The spread of lymph nodes is a major reason of the spread of solid cancers. The most important factor determining proper patient care is the proper stage of the lymph node [22]. However patient survival has been revealed to improve with therapeutic interventions which treat metastatic cancer in lymph nodes with radiation therapy or by surgery limits [23].

3.1 Passive Targeting

Passive targeting involves the transport or distribution of inactive carriers and cells across the tumor vasculature that can be found in the tumor interstitium. The improved effect of replenishment and retention (EPR) causes nanocarriers and drugs to accumulate in the target area [24]. By identifying cancer, the effect of EPR is well known (as shown in Fig.5). In addition, the effect of EPR applies to almost any solid plant that grows rapidly [25]. If nanocarriers can avoid physical exposure and fly for a long time...
time, the EPR effect will be positive. Within 1 to 2 days, the highest local concentration of drug-laden nanocarriers can be reached at the target location, for example, approximately 10 to 50 times more than normal tissue [26]. However, there are some restrictions on the direct targeting of cancer cells. The first is the measure of tumor vascularization and angiogenesis, which is required for the administration of an inactive nanocarrier. Second, as the tissues have a smaller lymphatic duct, the internal pressure of the fluid increases, leading to a combination of nanocarrier size and EPR effect: larger and longer-circulating nanocarriers (100 nm) are stored inside the tissue, while smaller molecules disperse with the systemic release of blood [27].

3.2 Active Targeting
Attachment of ligands to the surface of the nanocarrier to obtain appropriate receptor binding in the target area is required for active direction. The ligand binds primarily to the overprotected receptor in diseased cells and tumor vasculature [28], but not to normal cells. Targeted receptors should also be present in any targeted cell in the same way (as shown in Fig. 5). Monoclonal antibodies (mAbs), antibody fragments, and non-antibody ligands are examples of ligand direction. This is also known as ligand-targeted therapeutics [29].

4. METHODS OF PREPARATION OF LIPID NANOPARTICLE
Several interesting chemical methods have been developed for the preparation of nanoparticles. Some common body systems that have a logical mode in their pathways have been well developed in the controlled production of nanoparticles [30].

5. FACTORS AFFECTING PREPARATION OF LIPID NANOPARTICLE FOR LYMPHATIC TARGETING
The suitable absorption of the lymphatic system by colloid is altered by physicochemical properties. These factors contribute to the biodistribution particles in vivo, especially in the protection of the reticulo-endothelial system (RES) by intravenous administration [31]. Numerous studies have shown that the absorption of the lymphatic system of lipid nanoparticles and their distribution in lymphatic circulation is linked to a management pathway [32]. Other factors affecting the absorption and distribution of lipid based nanoparticles in the lymphatic system include molecular weight, lipid type, net charge, hydrophobicity, scale, and filtration of the emulsifier used.

Fig. 3. Active and passive targeting approaches
5.1 Particle Size

Size can play a role in determining how particles behave after treatment. Minute particles with a diameter of small nanometers are converted to capillaries, while bigger particles with diameter of a few tens of nanometers are absorbed in the lymphatic capillaries [33]. Particles larger than a few hundred nanometers, on the other hand, remain stuck in space for a long time. A particle size of 10 to 100 nm is ideal for absorption in lymph when applied under the skin. Particles less than 10 nm are absorbed by the circulatory system, and those above 100 nm are absorbed through the lymphatic system, albeit at a slower pace. Injection of particles bigger than 100 nm in the buttocks space was not recommended, and particles adhered to the site of injection for a long period [34].

5.2 Surface Charge

In lymphatic absorption, net charges for drug or drug carriers are significant. Many poorly charged carriers, such as proteins, dendrimers, and lipid-based nanoparticles (e.g., liposomes), and polylactic-co-glycolic acid nanospheres, have been shown to have higher lymphatic absorption than well-charged or neutral areas. This may be due to improper matrix charging of the matrix [35]. By lymphatic absorption, the lipid nanoparticle in the lymph nodes follows a certain order: Negative > Good > Neutrality.

5.3 Effect of PEGylation

Covering the carrier with a highly concentrated and hydrophilic PEG layer can increase lymphatic absorption by reducing the clear contact of particles with the internal environment and preventing the formation of very large particles [36]. The use of PEG to alter the location of liposomes has no significant effect on lymph node retrieval. PEG-coated liposomes have very good clearance through the subcutaneous injection site with 86-nm small PEG-infused liposomes remain at the injection site 40% of the time after 24 hours [37]. At the first injection site, large, neutral, and poorly charged liposomes have a clearance of >60%. However, increased retention of large liposomes in the lymph node compensates for the low number of large liposomes removed from the site of injection.

5.4 Effect of Ligand Modification

Carriers bound by immunosuppressive antibodies such as ligands show better lymphatic detection and retention. Liposomes bound with
5.7 Partition Coefficient

Lipid deficiency and coefficient of differentiation are important components of drug therapy and play a major role in the transport of lymphatic drugs [43]. It has been shown that drug-induced lipid melting is an important means of lymphatic transport and is possible with proper consideration of lipid melting and the degree and magnitude of chylomicron formation to measure the potential for lymphatic transport of lipophilic drugs [44]. High lipid melting and the coefficient of computer separation, while necessary for significant intestinal transport in the intestine, are not the only requirements to ensure intestinal transport. Generally, the dividing coefficient should be between 5 and 6 [45].

5.8 Type of Lipid Used

Lipid nanoparticles are mainly consisting of triglycerides which are arranging them in specific way that the polar head is exposed to outer aqueous phase [46]. This special arrangement mimics the arrangement of chylomicrons. The type of lipid used in lipid nanoparticles influences their absorption via transcellular route through intestinal epithelial cells which are polar in nature [47]. There are various types of lipid present like stearic acid, captopril 888 ATO, tristerim, monosterin and all these show different effect in and lymphatic uptake [48].

5.9 Concentration of Emulsifier

The concentration of emulsifier show affect on the separation of the drug in lipid based formulations [49]. Therefore, it may affect indirectly the delivery of the drug to lipid based formulations at the targeted site. The high concentration of the emulsifier reduces the hydrophobicity of the lipid nanoparticle and reduces the lymphatic absorption of the drug leading to lower oral drug availability [50].

5.10 Clinical Assays in Cancer Immunotherapy

Various researchers have extensively explored different combinations of NPs with immunotherapeutic agents in several clinical studies. Nano-immunotherapy has achieved marked results, some of the nano-immunotherapeutic agents have been approved by the FDA. Atezolizumab (Tecentriq®) was the first nano-immunotherapy approved for management of advanced triple-negative breast cancer (TNBC) [51,52]. Hensify®/NBTXR3, 50 nm crystalline hafnium oxide (HfO2) NP designed by Nanobiotix, received European market approval (CE Mark) in April 2019 for the management of advanced soft tissue sarcoma in combined with radiation therapy [53]. It was designed by for physically destroying the tumors and locally stimulating the immune system locally [54]. Nanobiotix has been conducting various clinical trials and has obtained US FDA approval for combination trial with NBTXR3 and PD-1 antibodies for treatment of lung cancer. Atezolizumab combined with nab-paclitaxel and carboplatin chemotherapy exhibited significant improvements in overall survival rate in a multicentric, randomized, open-label, phase 3 trial study for the treatment of metastatic non-squamous non-small-cell lung cancer [55].

an antibody i.e. IgG, have been revealed to increase the localization of lymph node liposomes to 4.5% of injected dose in 1 hour, but this level dropped to 3% in 24 h. In the study, liposomes having well-charged lipids were nearly 2-3 times lymph node localization than liposomes having neutral or weakly charged lipids [38]. Mannose attachment to the surface of the liposome has triple lymph node detection compared to control liposomes.

5.5 Molecular Weight of Drug

Macromolecule with a large molecular weight has reduced ability to replace across lymphatic arteries and blood capillaries becoming a drag from the site of injection showing a balanced relationship among the weight of the macromolecule cells and the amount of fingerprint by lymphatics [39], Dalton less than 1000 easily absorbs capillaries prior to implant in the lymphatic circulation. On the contrary, molecules weighing more than 16000 Dalton are usually absorbed through the lymphatic system and not the capillaries. Therefore combined to absorb lymphatic system, the molecular weight must be in the range of 1000 and 16000 Daltons [40].

5.6 Hydrophobicity

The most important determinant of lymphatic uptake is hydrophobicity [41]. The hydrophobicity of particles is associated with the surface properties and is mostly responsible for lymphatic uptake and phagocytosis. So as the hydrophobicity increase there is an increase in lymphatic uptake [42].
Table 1. Some patents related to nanoparticles in immunotherapy

| Sr. No. | Title of patent | Patent No. | Application date | Publication date | Assignee |
|---------|-----------------|------------|------------------|------------------|----------|
| 1       | Targeting of antigen presenting cells with immunonanotherapeutic s | KR101732744B1 | 2009-10-09 | 2017-05-04 | President and Fellows of Harvard College, The Brigham and Womens Hospital, Inc. |
| 2       | Methods and compositions for localized nanoparticle delivery to a tumor | EP2398466B1 | 2009-11-24 | 2021-02-17 | Massachusett s Institute of Technology |
| 3       | Nanoparticles for immunotherapy | EP2341897B1 | 2009-08-28 | 2021-02-17 | Ecole Polytechnique Federale de Lausanne EPFL |
| 4       | Targeted liposomes encapsulating iron complexes and their uses | WO2016027264A1 | 2015-06-18 | 2016-02-25 | Tel Hashomer Medical Research Infrastructure And Services Ltd. |

6. CONCLUSION

The lymphatic system plays a major role in treatment of cancer, as the lymphatic spread is recognized to have more than the hematological spread in most of the cancers like melanoma, breast cancer, colon cancer, lung and prostate cancers. So, the focus should be on the development of novel drug delivery that targets the lymphatic system, thereby improving the treatment of localized disease while minimizing the exposure of other body tissue and organs to cytotoxic drugs. The lipid nanotechnology has high potential in the targeted delivery of the drug, especially the lymph node targeting drug delivery. One of the best approaches was the lymph node targeting of drug lipid nanoparticles made with micro-fluid technology. Lipid nanoparticle-mediated immunoregulation has also a wide scope because most of the immune cells are present in the lymphatic system. So lipid nanoparticle technology cannot be the alternative therapy but can be the supportive therapy to chemotherapy.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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