Nanoparticles in Cancers Immunotherapy

Subjects: Materials Science, Biomaterials
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Cancer immunotherapy becomes an important tactic for cancer treatment. Immunotherapy of cancer must activate the host's anti-tumor response by enhancing the innate immune system and the effector cell number, while, minimizing the host's suppressor mechanisms. However, many immunotherapies are still limited by poor therapeutic targeting and unwanted side effects. Hence, a deeper understanding of tumor immunology and antitumor immune responses is essential for further improvement of cancer immunotherapy.

Keywords: cancer immunotherapy ; nanoparticles

1. Introduction

Cancer becomes one of a killer disease and its burden is anticipated to increase worldwide due to population growth, and lifestyles changes (such as smoking, poor diet, physical inactivity) [1][2]. According to global cancer observatory data (GLOBOCAN), 9.6 million deaths from cancer were estimated in 2018 [3]. The widely known conventional treatment methods for cancer include surgery, chemotherapy, and radiotherapy [4]. Due to the increasing knowledge of molecular and cancer biology, a notable change was observed in cancer treatment for the last few decades. However, conventional cancer treatment has certain limitations, which urges further research investigation. Recently, different research has been underway to improve the survival rate of cancer patients which includes immunotherapy, stem cell transplantation, and targeted cancer therapies [5][6][7][8][9][10].

2. Nanoparticles and Nanoparticles-Based Drug Delivery Systems

The majority of drugs delivered through a different route of injection, encounter the physiological, biochemical, and chemical barriers [11]. Hence, it is important to know the physicochemical and biochemical nature of the pharmaceutical agents such as solubility, permeability, and metabolic stability which are crucial factors in the design of NPs for drug delivery systems [12]. In comparison to conventional drug formulation, NPs-based drug delivery systems are under extensive development for several applications including cancer treatment due to their unique physical, chemical, and structural properties. In the last few decades, the term nanomedicine is popularized to describe the application of nanotechnology, by exploiting the unique properties of nano-scale materials, in medicine for the diagnosis and treatment of disease.

Tumor blood vessels possess special characteristics in comparison to the normal blood vessels such as uncontrolled angiogenesis, aberrant vascular architecture, hypervascular permeability, and impaired lymphatic clearance from the interstitial space of tumor tissues (i.e., enhanced permeability and retention (EPR) effect) [13][14]. EPR effect is a crucial point in the drug delivery systems [15][16]. Several kinds of the literature showed that NPs with the diameter 10–100 nm in the bloodstream are too large to escape the vasculature and enter normal tissues or to be cleared by the kidneys, while NPs can easily escape and accumulate in the tumor tissues due to dysfunctional vasculature and defective lymphatics clearance [17].

The efficacy of nanoformulated pharmaceutical agents also determined based on NPs characteristics such as sizes, shapes, and surface charge [18][19]. As mentioned above, NPs with a diameter range of 10 to 100 nm are the best candidates for cancer therapy, as they can effectively deliver their cargo and achieve EPR effect, while NPs with smaller (<10 nm) and larger particle size (>200 nm) can be easily filtered by kidneys and phagocytosed by reticuloendothelial systems, respectively [20]. However, failures of NPs-based chemotherapy in clinical trials have raised some questions about the clinical relevance of the EPR effect and much more research investigation is required to understand the tumor microenvironment (TME). In addition, ligand-modified NPs are widely explored for the active tumor targeting that can enhance bioavailability and selective tumor accumulation which in turn enhance the therapeutic efficacy while reducing normal cytotoxicity.

Moreover, shape and surface charge are crucial in cellular uptake and bio-distribution of NPs. For example, unlike spherical NPs which vulnerable to protein adsorption, non-spherical NPs show less protein adsorption and prevent non-specific cellular phagocytosis which extends their stability and half-life in circulation [21]. Another important parameter is the surface charge of NPs which has a great effect on cellular uptake and in the induction of immune response. For example, cationic NPs show good transfection effects, and have a lysosomal escape tendency which helps to release cargo in the cytoplasm or other subcellular organelles [22]. However, due to their cationic nature, they adsorb more negatively charged serum proteins which hinders their bioavailability [23][24]. As the result, NPs are coated with hydrophilic materials such as polyethylene glycol (PEG), or polysaccharides such as dextran to minimize protein corona, which in turn enhance circulation half-life and its bioavailability [25][26][27].

NPs-based drug delivery shows a promising result in preclinical and clinical studies. Currently, approximately 50 nanopharmaceuticals agents are approved for cancer and other disease treatments by US FDA [28][29][30]. However, some nanomedicine products that have undergone extensive clinical trials were later withdrawn due to efficacy or safety concerns e.g., superparamagnetic iron oxide formulations Resovist and SINEREM [31][32].

3. Clinical Translation of Nano-Immunotherapy

In the last few decades, several researchers have deeply explored a regulatory mechanism of antitumor immunity, particularly the immune checkpoint pathways, which lays a basic foundation for the invention of ICIs, that have revolutionized cancer treatment [33][34]. However, different literature showed that the activity of ICIs as monotherapy is not satisfactory for all cancer patients [35]. To address this clinical challenge, the different researchers tried to combine NPs with immunotherapeutic agents or conventional cancer treatment with ICIs [36][37]. Several kind of the literature showed that, conventional cancer treatments such as chemotherapy, photodynamic therapy, and radiotherapy can initiate the immune system to elicit a specific antitumor immunity, due to its ability to induce immunogenic cell death, in addition, to directly killing cancer cells, which can induce a release of certain damage-associated molecular patterns (DAMPs) that can activate APCs [38]. Activated APCs in turn phagocytose dying tumor cells and present tumor antigens to initiate T cell responses [39]. By taking this into consideration, NPs-based chemotherapeutic agents or photosensitizer delivery can be used to exploit the ICD inducing properties to achieve potent antitumor efficacy in combination with immunotherapeutic agents such as ICIs [40]. Most importantly, NPs based drug delivery can enhance selective target delivery and reduce off-target cytotoxicity of chemotherapeutic or immunotherapeutic agents which in turn extends the therapeutic index, especially for combination therapy.

As briefly discussed above, targeting APCs, cancer cells or TME clearly indicates that NPs significantly improved the therapeutic efficacy of immunotherapeutic agents. Based on the progress made so far, nano-immunotherapy has been achieving remarkable results, some of them were approved by the FDA, and the majority of them are in the preclinical stage, for the treatment of cancer. The first nano-immunotherapy approved for the treatment of advanced triple-negative breast cancer (TNBC) was Atezolizumab (Tecentriq®), an ICI against PD-L1, in combination with albumin-bound paclitaxel NP (nab-paclitaxel) [41][42]. The result showed that atezolizumab plus nab-paclitaxel significantly prolonged progression-free survival (PFS) compared to nab-paclitaxel in the intent-to-treat population and the PD-L1 positive subgroup.

Furthermore, Hensify®/NBTXR3, 50 nm crystalline hafnium oxide (HfO_2) NP, received European market approval (CE Mark) in April 2019 for the treatment of locally advanced soft tissue sarcoma in combination with radiation therapy [43]. Hensify® is designed by Nanobiotix to physically destroy tumors and stimulate the immune system locally [44]. Nanobiotix is also running several clinical trials and has received US FDA approval to launch a combination trial with NBTXR3 and PD-1 antibodies to treat lung cancer (NCT03589339).

Similarly, the multicentre, randomized, open-label, phase 3 trial study was conducted as a first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130, NCT02367781) using Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone [45]. The result revealed that there were significant improvements in median overall survival (OS), 18.6 months in the atezolizumab plus chemotherapy group, 13.9 months in the chemotherapy group, median PFS 7.0 months in the atezolizumab plus chemotherapy group, and 5.5 months in the chemotherapy group.

Furthermore, there is the first randomized phase 3 JAVELIN Ovarian 200 trial (NCT02580058) study which is designed to demonstrate that Avelumab (human immunoglobulin G1 anti-PD-L1 monoclonal antibody) alone or in combination with Pegylated liposomal doxorubicin (PLD) is superior to PLD alone in prolonging OS in patients with platinum-resistant/platinum refractory ovarian cancer [46]. The results revealed that PLD combined with avelumab slightly improved OS (15.7), PFS (3.7), and objective response rate (ORR) (13.3) compared to either PLD (13.1, 3.5, and 4.2 for OS, PFS, and ORR, respectively) or avelumab (11.8, 1.9, and 3.7 for OS, PFS, and ORR, respectively) alone (Reference:

ClinicalTrials.gov; NCT0258005). In addition, RNA formulated NPs alone or in combination with immunotherapeutic agents, such as ICIs, were also explored and the majority of them are under clinical trials as listed in Table 1. Moreover, in his recent review, Yang Shi was briefly reviewed several studies that are FDA approved or under clinical trials using nano-immunotherapy, such as NPs albumin-bound paclitaxel, Pegylated liposomal doxorubicin, mRNA nanovaccines, and WDVAX [47].

Table 1. FDA approved nano-Immunotherapy and studies under clinical trials to treat cancer [48][49][50].

Compound Name	Formulation Description	Mechanism of Action	Clinical Trials	Approved by the FDA	Ref
RNA-LPX (Lipoplex®)	RNA-lipoplexes	DC maturation, T cell response	Phase I (2016)		[51]
MRX34	miRNA-34a-loaded liposome	Downregulation of immune evasion tumor genes	Phase I (2016)		[52]
mRNA-4157	mRNA-4157 encapsulated in Lipids	induce neoantigen specific T cells and associated anti-tumor responses.	Phase I (2019)		[53]
Ferumoxytol (Ferahem®)	Iron oxide nanoparticles (IONP)	M2 Macrophage polarization to M1-like		Yes, for anemia and kidney diseases	[54]
PTX-LDE	Paclitaxel-loaded lipid core NPs	DC maturation	Phase II (2017)		[55][56]
Anti-EGFR-IL-dox	Doxorubicin-loaded anti-EGFR immunoliposomes	Block EGFR-mediated growth signaling and induce immunogenic cell death	Phase II (2016)		NCT02833766
JVRS-100	Cationic liposome incorporating plasmid DNA complex	Immune system stimulation	Phase I (2016)		NCT00860522
NBTXR3	Hafnium oxide nanoparticles in combination with anti-PD1	Enhance tumor cell death via electron production, induce immunogenic cell death leading to activation of the immune system	Phase I (2019)		[57], NCT03589339

In summary, several clinical and preclinical study results demonstrate that NPs are highly important in immunotherapy as the delivery of immunotherapeutic agents or as the direct immunomodulators. However, due to the multifactorial nature of cancer-immune interactions, identifying unique biomarkers are crucial to designing multifunctional NPs (i.e., which have a diagnostic and theranostic application). Hence, in order to design a novel biomarker-guided multifunctional and biocompatible NPs to enhance the efficacy and to promote clinical translation of nano-immunotherapy, a unique biomarker must be identified to distinguish which immune-activating or immunosuppressive cells or pathways are targeted.

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