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Applications of Liposomal Arsenic Trioxide (ATO) on Cancer Treatment

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Abstract. Arsenic trioxide (ATO) is a therapeutic agent that is recognized for its antitumor efficacy and has been widely used in the treatment of acute promyelocytic leukemia. The agent is widely used with tretinoin to treat relapsed patients by damaging a fusion protein. However, specific limitations of the agent, such as its dose-limiting toxicity and rapid renal clearance, have hindered its clinical applications. As the nanomedicine field has continued to grow, researchers have had an interest in studying the effect of the encapsulation of drugs by nanoscale drug delivery systems, liposomal nanoparticle-based delivery systems are currently the majority of approved DDS, which minimizes side effects by enabling site-specific delivery, improving drug stability, and prolonging circulation period. Previous research on the liposomal encapsulation of ATO suggested that the encapsulation might beneficially affect tissue distribution. However, the ATO liposomes were also unstable during the experiment due to the rapid diffusion of the agent. Globally, Scientists have made progress in studying the application of liposomal ATO in different cancers, including multiple myeloma, acute promyelocytic leukemia, HPV-positive cervical cancer, prostate cancer, and breast cancer. Future research on liposomal ATO may focus on a more thorough understanding and analysis of its safety data by conducting more clinical trials and developing a better understanding of its biological activity and toxicity levels, etc., aiming to develop more control of the nanomedicine system and decrease production costs to maximize the demonstration of the potential role of Liposomal ATO.

Keywords: Arsenic trioxide, cancer, liposome.

1. Introduction

As one of the leading causes of death worldwide, accounting for nearly one in six deaths, Cancer is one of the most universal diseases prompting lethal effects. Cancer led to the death of 10 million people in 2020. In short, Cancer arises from the abnormal growth of tumor cells, which were transformed from normal cells. Cancer can be caused by the effect of external factors or mutants on a person's genetic material. Carcinogens are a popular cancer-causing agent, common examples include ultraviolet radiation, tobacco smoke, alcohol, infections from viruses, etc. Contemporarily, cancer treatment includes surgery, radiotherapy, systemic therapy, targeted therapy, etc. [1]. However, despite the advances and innovations made in existing treatment strategies, cancer therapies are still far from being at their maximum due to the non-specific biodistribution of current therapeutic agents.

Current therapeutic strategies are mainly constructed and implemented based on systemically administered non-selective chemotherapeutics of small molecular size. Due to their small molecular

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sizes, small molecular drugs can experience filtration at a faster rate, resulting in short circulation time and lack of specificity of discrimination. The lack of specificity directly results in non-specific drug distribution, which harms healthy cells and other undesirable side effects. These harmful limitations of conventional therapy strategies have triggered the development of nanomedicine. The usage and development of drug delivery system (DDS) can be traced back to the 1950s. These delivery systems offer targeted versions of therapeutic drugs or elements and enhance antitumor efficacy. Targeted Drug Delivery systems (TDDS) can overcome common limitations such as low specificity, large volume of distribution, etc, by drugs of low-molecular-weight and untargeted nanopharmaceuticals through two different functional targeting strategies: active targeting, stimuli stimuli-responsive targeting. Among DDS, lipid-based pharmaceuticals are the most developed and utilized. Currently, many approved nanopharmaceuticals have already been developed with lipid-based nanotechnology platforms. Nanomedicine may continue to expand, with over 30,000 articles published subjected to nanomedicine after 2000 [2]. The specific nanoparticle that is analyzed in this paper is liposomal arsenic trioxide (ATO). ATO has long been used for the treatment of multiple diseases, including malaria, psoriasis, syphilis, etc. Moreover, the therapeutic potentials of ATO have also been recognized through scientific research, suggesting the drug's potential in the management of solid tumors and cell lines. Most importantly, ATO is crucial in the treatment of APL by inducing differentiation and promoting apoptosis [3].

This review summarizes the applications of Liposomal ATO on cancer, specifically, Leukemia, HPV-positive cervical cancer, and others such as Prostate and Breast cancer.

2. Nanoparticle technology

2.1. Nanomedicine and liposome technology

Nanomedicine offers a selection of bio-friendly DDS that are capable of delivering conventional therapeutic drugs with selection and specificity around tumor tissues, resulting in minimized side effects in comparison to conventional therapy strategies. The majority of approved DDS, by the FDA (U.S. Food and Drug Administration) and the EMA (European Medicines Agency) are lipid or protein based. Breakthroughs in liposome technology have enabled the development of a new generation of pharmaceuticals competent for clinical evaluation. Existing therapeutic approaches or agents are constructed upon systemically administered non-selective chemotherapeutics that are of small molecular size, resulting in short circulation time and fast distribution speed through the body without specific distinction between tumor and normal cells. This is converted to many undesirable side effects on patients due to the lack of specificity, causing damage to both healthy and cancerous, specifically to tissues with high replication rates, such as intestinal lining and immune cells. Side effects include bleeding, anemia, diarrhea, fatigue, etc. Therefore, the development of nanomedicine has been promoted by the limitations of conventional treatments [2].

Nanoparticle-based drug delivery systems have been utilized and promoted to their maximum through the delivery of complex molecules to specific sites or tissues and gene therapy. Nanoparticle-based delivery benefits multiple areas of disease, including cancer, diabetes, infectious diseases, etc. Specifically, in cancer, nanoparticles aid and benefit patients by their functional ability to deliver drugs to specific affected areas, minimal side effects, and efficiency against drug-resistance of cancerous cells. Nanoparticles enable the encapsulation of drugs with low solubility and biocompatibility and deliver drugs to specific sites through the bloodstream. Currently, the most challenging aspect of the study and usage of nanomedicine relates to analysis of safety data from clinical trials, given evidence of the variation of their biological activity and toxicity levels. Other challenges faced include low control of the system, low production rate, high costs for production, etc. [4].

2.2. ATO

To deeply understand Liposomal Arsenic trioxide, ATO is a therapeutic agent that has been widely used in the treatment of acute promyelocytic leukemia. Unfortunately, the agent's antitumor efficacy in

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treating solid tumors has only been assessed and proved through preclinical studies and has not been shown in clinical trials. Limitations in the application of the agent (ATO) in clinical trials include dose-limiting toxicity and rapid renal clearance. Liposomal carriers have been widely discussed and investigated in terms of developing their ability to encapsulate and deliver drugs to specific sites, improving drug stability, and prolonging the blood circulation period. Hence, it increases antitumor efficacy and reduces undesirable side effects. Previous efforts to encapsulate ATO to liposomes show that the encapsulation might beneficially affect tissue distribution, however, evidence also suggests that ATO liposomes were unstable due to the rapid diffusion of ATO through the liposomal bilayer [5,6].

3. Liposomal ATO treatment on caners

Liposomal ATO has been approved a higher efficacy and anti-cancer effect compared to free ATO in multiple cancer models (Table 1).

3.1. Leukemia

Multiple myeloma is a malignancy that arises in plasma cells, a type of white blood cell found in the bone marrow that is a part of the immune system, and responsible for fighting off infections, Multiple myeloma is currently the second most frequent hematologic malignancy in adults, and standard treatment strategies such as chemotherapy are palliative. Therefore, the interest of combining agents with vincristine, doxorubicin, and dexamethasone (DVd) has sparked. There is preclinical evidence indicating and proving the utility and efficacy of ATO combined with DVd agents, with its abilities of overcoming steroid resistance in myeloma cell lines and potentially overcoming resistance to vinca alkaloids. Therefore, research was conducted on the foundation of access to preclinical evidence that ATO could enhance the activity of DVDs. The research investigated the combination of ATO agents and DVd's in MM patients as part of a prospective phase II clinical trial. However, the researchers observed that the addition of ATO did not improve the response rate of MM to DVd [7].

Acute Promyelocytic Leukemia, one of the most fatal diseases in the past, has been converted to one of the most curable blood cancers by the innovation of ATRA, all-transretinoic acid. Recently, oncologists and scientists have drawn their attention to ATO, shown to be an effective therapeutic agent. Moreover, relapsed patients in the United States and Europe have been approved to be treated with ATO. The field is currently assessing the usage of the agent in aiding conventional treatments along with recognizing its potential role [8].

3.2. HPV-positive cervical cancer

Cervical cancer is the second most common cancer for women worldwide, responsible for 14% of all female gynecological cancers, and has triggered efforts in the development of anticancer innovations. HPV infections have been recognized as the casual agent of cervical cancer, therefore targeting HPV infection has been prominent in managing HPV positive cervical cancer [9,10]. Since ATO has been successfully used to treat acute promyelocytic leukemia, it has also been investigated as a possible treatment for other types of cancer. Research indicates that ATO can be used for the specific targeting of HPV-infected cervical cancer cells. However, wider usage of the agent has been limited by its toxicity characteristic at higher concentrations and poor pharmacokinetics. The drug can only be stably used in doses under 2uM. Therefore, the selection of an effective drug-delivery system is necessary and crucial for the expansion of the drug's clinical utility or therapeutic index [11]. If the drug carrier could deliver the agent to specific cancer cells and release the medication slowly, a constant flow of medication could be maintained, enhancing its therapeutic effects. Under the current nanotechnology field, liposomal drug delivery systems have the ability to guide targeting ligands to specific sites [9]. To research and investigate the effectiveness of liposomal ATO on HPV-related cancers, an in vitro experiment was conducted to compare the anticancer efficacy of liposomal-encapsulated ATO and free-form ATO by observing protein expression levels of the HPV-E6 oncogene and caspase-3. The results of the experiment indicated that liposomal delivery systems enhance the effectiveness of drug delivery. Specifically, cell lines were double immunostained for the oncogene and caspase-3 after an exposure to

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5uM liposomal ATO or free-form ATO, under confocal microscope examination, cells treated with free ATO experienced a decrease in HPV-E6 expression level and increased in caspase-3 protein expression. Furthermore, cells treated with liposomal ATO further enhanced this effect by eliminating E6 expression and experiencing an elevation in caspase-3 levels. This confirmed that liposomal encapsulation reduces cell membrane permeability and allows ATO build-up which reduces HPV oncogene E6 expression levels and reduces cellular toxicity. As research shows promising results and strategies in targeting HPV-infected cells using liposomal Arsenic Trioxide, the delivery system could potentially provide a therapeutic approach to reverting cancerous cells to healthy cells [11].

3.3. Others

Developments in the Nanotechnology field has prompted novel efforts in the research of targeted drug delivery systems to delivery anti-cancer therapeutic agents targeting the apoptosis pathway. Therefore, an experiment was conducted to assess the efficacy of liposomal based co-delivery systems, modified with RGD peptide, in Prostate cancer treatment. The complex (liposomal co-loaded curcumin and ATO modified by RDG) was evaluated through DLS analysis and TEM. The co-delivery system was then assessed of its cytotoxicity and apoptotic effect through MTT assay, etc. The results showed that liposomal co-loaded curcumin and ATO modified by RDG displayed a significant reduction in EGFR gene expression level and increased the number of apoptotic cells, indicating the propitiousness of the NLPs-RDG-Cur-ATO co-delivery system in prostate cancer treatment [12].

ATO has reached success in treating hematologic malignancies. However, due to limitations in poor pharmacokinetics and its dose-limiting toxicity, ATO has not yet reached success in clinical trials of solid tumors, such as triple-negative breast carcinomas. Therefore, researchers investigated a new nanoparticulate formation, encapsulating the agent, to test if the encapsulation would affect the agent's therapeutic index. The results of the experiment showed that the nanoparticulated agent had a significantly lower toxicity and higher antitumor efficacy compared with the free agent, indicating the therapeutic potential of the nanoscale agent [13].

Table 1. Applications of liposomal Arsenic Trioxide (ATO) on cancers.

Cancer	Model/trial	Treatments	Results	Ref (s)
Leukemia	Multiple myeloma (MM) patients	ATO combined with DVd (Doxiltrade mark, vincristine, and dexamethasone)	Addition of ATO did not improve the response rate of MM to DVd	[7]
Cervical cancer	HeLa, C33a, human keratinocytes	Free or liposomal formal ATO for 48 h of treatment	Liposomal-delivered ATO showed higher efficiency and lower toxicity compared to free ATO	[11]
Prostate cancer	PC3 cells	Liposomal co-loaded curcumin and ATO modified by RDG peptide, NLPs-RDG-Cur-ATO co-delivery system	A high encapsulation efficiency for ATO; significant anti-proliferation effect; decrease of EGFR gene expression	[12]
Triple-negative breast carcinomas	Human breast cancer cell lines; murine orthotopic breast cancer model	Liposomal ATO	Improved pharmacokinetics and anti-cancer efficacy	[13]

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4. Conclusion

As the field of nanomedicine consistently expands innovatively, the study of liposomal encapsulations of medical agents has sparked curiosity. Liposomal ATO has been studied through preclinical trials to test and analyze how the liposomal encapsulation enhances the antitumor efficacy of ATO. Furthermore, researchers have conducted experiments on cancer cell lines to study the application of liposomal ATO on cancers including Multiple myeloma, APL, HPV-positive cervical cancer, Prostate cancer, and triple-negative breast carcinomas. Experimental results indicated that the liposomal encapsulation version of the ATO agent has enhanced the antitumor efficacy of ATO. Specifically, the combination of the drug-delivery system and ATO agents did not enhance the response rates of Multiple Myeloma cells to delivery systems. On the other hand, ATO has been utilized with ATRA to treat APL-relapsed patients, and liposomal encapsulated ATO has demonstrated anticancer efficacy in targeting HPV-infected cells and reducing EGFR gene expression in Prostate cancer, along with increasing the therapeutic index of ATO in breast cancer. Future studies are required to further understand the mechanisms of ATO function. Clinical trials are required for future clinical applications of liposomal ATO on cancers.

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