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Review Article

Pharmacological Advancements in Anticancer Drugs:- An Updated Review

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ABSTRACT

The cancer is one of the prominent causes of death worldwide. As the life expectancy increases, the number of cancer cases has reached unprecedented levels. Despite the use of conventional therapy such as the use of chemotherapy, radiation therapy or both and other conventional anticancer therapy, there has been an increase in the incidence of cancer patients. Despite these efforts, cancer drug research remains a remarkably challenging field, and therapeutic innovations have not yet achieved expected clinical results. Multiple noteworthy advancements among which the development of targeted therapies is the most significant have been made. The use of monoclonal antibodies and antibody small molecule conjugates as anticancer innovative treatment modalities have emerged as a worthwhile approach to improve drug selectivity and reduce adverse effects. This constant development of novel antineoplastic agents continues to be a foremost patient car need, despite the current availability of many anticancer drugs in the market. The current panorama of drug research and development with emphasis on some of the major advances brought to clinical trials and to the market in the past few years. Various breakthrough discoveries are highlighted along with the medicinal chemistry strategies used throughout the discovery process. In addition, the review provides perspectives and updates on the discovery of novel molecular targets as well as drugs with innovative mechanisms of action.

Key words: anticancer, drug targets, prodrug, nanoparticles, cancer therapy.

Running Title: Advancements in Anticancer drugs.

INTRODUCTION

The development and progression of different types of cancer are increasingly prevalent worldwide especially in India population with an estimate of 14,61,427 number of new cases of cancer in India per year. It has been estimated that one in nine people worldwide develop cancer in their lifetime, while one in eight men and one in eleven women die from the disease. The aging population growth, as well as socio-economic risk factors, could contribute to the increase in these estimated numbers [1].

Cancer treatment options include surgery, radiation and chemotherapy, or a combination of them. The primary treatment options include the conventional radiotherapy and chemotherapy which are plagued by significant toxicity and resistance issues, resulting in incomplete tumor eradication [2]. Chemotherapy is a systemic approach and consists of administering one or more chemicals that can damage fast-growing cells, such as cancerous ones. However, these agents, being non-selective, usually damage healthy cells and tissues with rapid turnover, causing severe toxic effects. The rapid emergence of drug resistance, the instability of the molecules and the poor solubility in water, which makes them unable to permeate through cell membranes, represent further drawbacks of chemotherapy. This presents a distinct challenge for researchers and clinicians engaged in treatment of cancer patients. Therefore, there is an urgent need for new anticancer drugs and innovative drug delivery strategies to address these shortcomings and potentially offer more effective and safer therapeutic alternatives. The author focuses on pioneering research into the development

and validation of novel anticancer approaches that could have a significant clinical impact in the near future. Understanding the underlying mechanisms of cancer cell biology is essential for the development of new therapeutic strategies [3]. This insight is crucial for developing therapies that address the complexity of cancer cell biology.

The disadvantages of conventional anticancer drugs are the reason why the development of alternative treatments with reduced adverse side effects and improved therapeutic efficacy is still demanding. An effective strategy to increase the selectivity of chemotherapeutics involves the use of prodrugs. The latter are inactive compounds that are chemically or enzymatically metabolized in the active drug, reducing the systemic toxicity of conventional therapies [4].

The incorporation of anticancer drugs into drug delivery systems (DDS) represents another approach to successfully address pharmacological and pharmacokinetic limitations and to directly carry drugs to the therapeutic site of action while reducing adverse side effects. Accordingly, innovative nanotechnologies had a profound impact on clinical therapeutics, including anticancer drugs [5,6]. Among the most studied incorporation systems, vesicular matrices, such as niosomes, cubosomes or polymeric systems, have shown the best results [7,8,9]. Innovative targeting approaches can also be represented by nanocarriers containing chemotherapeutics conjugated to molecules able to bind to overexpressed antigens (monoclonal antibodies, mAb) [10,11,12].

Antibody drug conjugates (ADCs) represent a transformative approach in cancer therapy, utilizing antibodies to deliver cytotoxic drugs directly to cancer cells [13]. The field of targeted therapies continues to advance with the development of kinase inhibitors for cancer bioimaging and therapy, as well as strategies targeting EGFR and glucose metabolism [14]. Genetic and epigenetic research is uncovering biomarkers that could significantly impact cancer treatment [15]. Cancer immunotherapy is increasingly focusing on the development of bispecific antibodies, immune cell engagers, chimeric antigen receptor (CAR)-modified T and NK cells (CAR-T and CAR-NK), overcoming resistance mechanisms and harnessing the immune system's full potential [16,17]. Innovations in pharmacology and drug delivery are crucial for improving cancer treatment outcomes. The research highlights the potential of gold nanoparticles for targeted pancreatic cancer therapy, as well as the benefits of laparoscopic versus robotic assisted surgery for colon cancer. New formulations for LED-based photo-chemotherapy are also showing promise, providing more effective drug delivery and treatment options for skin cancer [18].

Optimizing treatment outcomes through clinical trials and novel therapies remains a priority The research includes the validation of predictive biomarkers used in cancer clinical trials, the management of neuroendocrine neoplasms of unknown primary origin, and the use of combination therapies involving local ablative techniques with radiotherapy. These studies aim to refine therapeutic strategies, enhance efficacy, and improve patient quality of life. Some of the potential newer technological advancements in the cancer treatment therapies were enumerated.

Anticancer Monoclonal Antibody

Recently a significant breakthrough has been achieved in cancer therapy by applying mAb-based immunotherapy as the antibodies are able to directly target cancerous cells while simultaneously promoting the induction of long-lasting immune responses against cancer cells. this approach having proven to be very effective for the treatment of different forms of cancer. Unfortunately, the drug resistance and poor stability due to the glycoprotein nature of mAb continue to be the major hurdles. Variations in temperature or pH can induce the unfolding of proteins, leading to a direct loss of mAb functions and favoring their aggregation, which represents the main cause of physical instability. The presence of several aromatic amino acid residues in the primary structure of mAb makes them particularly sensitive to light, thereby inducing photodegradation with the formation of oxygenated radicals but also fragmentation and cross-linking. The authors concluded that mAbs are currently one of the most important classes of biotechnological drugs for the treatment of diseases with increasing incidence in the population, such as cancer, autoimmune, inflammatory, infectious and degenerative diseases, and, since the beginning of the COVID-19 pandemic, they have been explored as potential therapeutic tools. Therefore, stability studies are crucial during the development of therapeutic proteins to ensure the quality and safety of the final medicine. Deeper knowledge of the mechanisms involved in a protein can help to avoid the onset of conformational and colloidal changes that reduce its therapeutic efficacy [19,20,21].

Anticancer Drugs in Nanoparticle Systems

The development and application of vesicular systems capable of ensuring controlled delivery of anticancer drugs to the desired site of therapeutic action in adequate quantities to exert their actions are increasing. These systems improve therapeutic efficacy while reducing negative side effects, providing many advantages, including improved pharmacodynamic and pharmacokinetic profiles, which result in a prolonged half-life and enhanced drug stability, ensuring protection from chemical or physical degradation. The currently available nanocarriers for anticancer drugs vary in structures, sizes and physicochemical properties. These systems can be of natural origin, and, therefore, made up of simple structures derived from phospholipids, such as lecithin, and of synthetic nature and thus characterized by more complex structures consisting of polymers sometimes complexed with metals. Niosomes (non-ionic surfactant vesicles) are one of the most commonly applied carriers for anticancer drugs. Over the last few decades, the use of nanoparticle (NP)-based DDS has shown numerous advantages in cancer treatment, including the ability to overcome

drug resistance caused by overexpression of drug efflux transporters, defective apoptotic pathways and a hypoxic environment [22,23].

Anticancer Prodrugs in Nanoparticles Systems

Despite the promising anticancer potential of many anticancer prodrugs, their clinical use is limited due to sensitivity to acid and enzymatic hydrolysis. To overcome these limitations, prodrugs have also been incorporated into different controlled delivery systems. As an example, capecitabine has been formulated in co-polymeric hydrogel as a smart pH-responsive network to facilitate its oral administration, reducing its sensitivity to gastric pH [24].

Combination Therapy in Nanoparticles Systems

Nowadays, combination therapy is a widely adopted strategy for cancer treatment since acting simultaneously on multiple targets allows the reduction in the dose for each single drug and slows down the onset of drug resistance. Recently, vesicular systems for encapsulating combination drugs have been designed to further improve efficacy. Fludarabine/mitoxantrone combination therapy has been successfully adopted for the treatment of different types of lymphoma and chronic leukemia. The efficacy of this combined therapy has been further enhanced by co-incapsulating both compounds in liposomes: fludarabine has been passively encapsulated during liposome formation, while the loading of mitoxantrone has been driven by a transmembrane pH gradient. This formulation would not only represent a promising and efficient therapeutic strategy but could also improve the long-term stability of both drugs, as evidenced by a recent study after a three-month monitoring period [25].

Monoclonal Antibody in Nanoparticles Systems

Despite their proven efficacy as anticancer drugs, the clinical use of mAbs is severely limited by their poor chemical and enzymatic stability and consequent aggregate formation. A valid strategy to overcome these hurdles and achieve an adequate intracellular release of non-aggregated antibodies in the desired site of action consists of the encapsulation of the mAb into polymeric or lipid NPs. Because these systems are resistant to several chemical and physical factors, including body temperature, they can protect the antibody during the drug's persistence in the bloodstream. Bevacizumab lipid NPs have been developed as an innovative delivery system for intravitreal injection capable of ensuring high drug stability. Furthermore, such a formulation improved the drug intraocular bioavailability and patient compliance by avoiding repeated intravitreal injections. The association of docetaxel with trastuzumab is a therapeutic regimen successfully used to treat breast cancer [26].

Recent Advances in Anticancer Drug Targets and Biomarkers

The targeted therapy holds the key to raising overall survival rates along with lowering the side effects of cancer treatment. Compared to patients who did not receive matched targeted therapies, patients who did both overall survival and progression free survival significantly improved [27].

Kinases as targets

A group of anticancer medications known as kinase inhibitors directly interact with the active site of the target enzyme to prevent kinase activity. Despite having the same mode of action competitive ATP inhibition at catalytic binding site they are distinct from one another in terms of the range of targeted kinases, their pharmacokinetics, and the negative effects that are substance-specific [28].

Tubulin/ microtubule as target

The development of microtubule-targeting agents for the treatment of cancer is being investigated because they are essential for cell division and growth. As a result, the development of anticancer medications now includes tubulin as one of their key targets. A number of tubulin-targeting agents have been synthesized, and structure-activity relationship studies have been carried out [29].

Vascular targeting agents

Vascular targeting agents are primarily cancer therapies that are created specifically to target the tumor's vasculature and, as a result, prevent the growth and development of tumors. A steady flow of oxygen and nutrients is necessary because tumor cells divide rapidly. Therefore, the growth of blood vessel networks is necessary for the development, progression, and metastasis of tumors and vascular disrupting agents (VDAs) can stop blood flow to tumors [30].

Angiogenesis inhibitors

A new class of medicines called angiogenesis inhibitors is intended to prevent tumor vascularization. Non small cell lung cancer (NSCLC) is treated with angiogenesis inhibitors, such as bevacizumab and ramucirumab. These medicines aim to block VEGFs [31].

Recent advances in drug repurposing as new anticancer drugs

Drug repositioning, another name for drug repurposing, is a tactic that looks at additional diseases besides the one for which a drug has already received approval [32].

Antiplatelet Agents
Although aspirin's clinical use as an anticancer medication has been expanded and regular use of the medication is associated with a lower risk of breast cancer, aspirin is primarily used as an antiplatelet medication for cardiovascular diseases.

Anti-inflammatory drugs
Diclofenac successfully slows the growth of pancreatic tumors in animal studies. Diclofenac therapy resulted in a rise in apoptosis and a fall in angiogenesis, according to analysis of the tumor tissue removed during surgery. Moreover, selective COX-2 inhibitor celecoxib inhibited the growth of breast cancer cells and decreased tumor development in animal model.

Antidiabetic agents
The first line of treatment for type 2 diabetes mellitus is metformin, an oral medication. Numerous cancer types, including pancreatic, endometrial, breast, lung, and prostrate, have shown it to have anti-neoplastic activity. Through numerous preclinical and clinical studies, thiazolidinediones (TZDs) have been identified as a potent lead in the treatment of breast and prostate cancer [33].

Antiviral drugs
Zidovudine, a reverse transcriptase inhibitor, was the first drug approved to treat HIV infection. It also exhibits anti-cancer properties against a number of cancer types, including pancreatic, leukemia, and Kaposi sarcoma. Brivudine, a medication used to treat herpes simplex virus, demonstrated anti-cancer properties by reducing chemoresistance.

Antibacterial agents
Doxorubicin has been found to be effective in treating breast cancer. By intercalating breaks into the DNA, it prevented DNA replication. When combined with a COX-2 inhibitor, doxycycline prevents the growth of colon cancer cells by causing G0/G1 arrest and blocking matrix metalloproteinase. Doxycycline inhibits both the mitochondrial biogenesis process and the stem cell phenotype of cancer cells in the context of breast cancer [34].

Heterometallic compounds
Heterometallic materials have a promising future for efficacy above those based on platinum, in addition to their minimum toxicity. Platinum, gold, and titanium are more prevalent among the many heterometallic based promising compounds for cancer treatment. Thiadiazoles and thiazoles bearing thymol under mild conditions, exhibit significant anticancer activity [35].

CONCLUSIONS

Inspite of their significant contributions an anti-cancer treatment, all conventional chemotherapy drugs suffer from several drawbacks, including rapid elimination, poor bioavailability, low intratumoral release, non specific cytotoxicity and consequent systemic side effects, followed by drug resistance in most of the cases. To overcome these limitations, a innovative pharmacological approaches have been developed, resulting in a significant improvement in the pharmacodynamic and pharmacokinetic profiles of the drugs, as well as in their physicochemical stability. The therapeutic efficacy of anticancer agents has now been widely established since they ensure a controlled release of an adequate amount of the drug at the desired site of action and reduce the drug sensitivity to physicochemical factors during the preparation, managing and storage phases. Authors still focused on several studies on the development of innovative formulations which are still ongoing. Many newer formulations have already been approved, and others that are in clinical or preclinical development stages. These developments offer great hope for safer and more efficient options to be adopted in the near future for cancer treatment.

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