Anti Cancer-Drugs: Current Challenges and Future Direction

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***Abstract*—Cancer is a complex disease that has evolved in understanding from early surgical and radiation approaches to today's molecular classification and precision therapies. Current treatments including targeted drugs, immunotherapy, nanomedicine, and emerging stem cell based strategies have significantly improved the results but still have serious obstacles in clinical translation, such as biological barriers, toxicity and safety issues, and regulatory difficulties. The use of drugs such as doxorubicin not only improves the efficacy but also drawbacks of traditional chemotherapy because of such side effects as cardiotoxicity. Recent progress of targeted delivery and immunotherapy have great benefits of specificity and less side effects. The future direction are on next generation therapeutics, such as genome-directed therapeutic approach, novel nanocarrier and sustainable development of drugs to realize safer, more effective and accessible to global cancer care.**

***Index Terms*—Cancer, Nanomedicine , Immunotherapy, Stem cell therapy, Doxorubicin, Immunotherapy, Targeted Therapy, cardiotoxicity, Nanocarrier.**

I. INTRODUCTION

Cancer is a term, which is used to describe a number of diseases that are characterized by abnormal and uncontrolled proliferation of cell growth in the body. Over 100 varieties of cancers are classified under this category and they are all related in that they are characterized by the unnecessary division of cells and the capacity of the cancer cells to spread into nearby tissues and organs.[1] The existing conventional methods of treating cancer normally entail precise disease staging that is followed by surgery, chemotherapy and/or radiotherapy. Nonetheless, chemotherapy and radiotherapy are both linked with serious side effects, and both, as they are aimed at the rapid dividing cells, be they malignant or healthy. Moreover, most anticancer drugs also have an unfavorable pharmacokinetic profile with a low level of solubility, instability, and rates of metabolism leads to toxicity, limited activity, and insufficient body distribution.[2] Nanomedicines have been studied to deliver drugs to their specific targets in many diseases, but most of the research has focused on oncology-related applications almost two-thirds. In cancer treatment, nanomedicine has been the main focus of improving the therapeutic index of anticancer agents through changes in pharmacokinetics and tissue distribution to maximize delivery at the tumor site. the first application of which was liposomal doxorubicin (Doxil 1995:Caelyx 2000), the first FDA-approved anticancer nanomedicine.[3] Approximately 18.1 million new cancer cases have been reported in 2020 (excluding non-melanoma skin cancers) out of which 8.8 million (48 percent) were in women and 9.3 million (52 percent) in men, or 10 males per 9.5 females as a ratio. The global, age standardized incidence was estimated to be 178.1 per 100,000 in females, and 206.9 per 100,000 in males. The four most common cancers breast, lung, colorectal (including anal) and prostate cancers each contributed 43% of the new cases. On its own, 1,958,310 new diagnoses and 609,820 cancer-related deaths are anticipated in 2023 in the United States alone. It is important to note that the incidence of prostate cancer increased by 3 percent per year in 2014-2019 and led to about 99,000 more cases.[4]

II. HISTORICAL PERSPECTIVE

The history of Oncological chemotherapy dates back to the 19th century. In 1861, Robert Bentley documented the local anticancer effects of an extract from the roots of Podophyllum peltatum. The active

ingredient, podophyllotoxin, isolated 20 years later, was shown to inhibit the formation of the mitotic spindle, thus keeping cancer cells in metaphase. This discovery inspired the design and chemical synthesis of two structural analogs of Podophyllotoxin, Etoposide and Teniposide.[5]

some comprehensive of different pharmaceutical chemotherapeutic drugs that have been served in different cancer sorts in last decades:

1. Alkylation Chemotherapy
2. Anti metabolite Chemotherapy
3. Vinca Alkaloid
4. Daunorubicin

III. CURRENT AND EMERGING CANCER THERAPY

A general overview of the most advanced and novel cancer therapy was provided. In addition, also new strategies currently under investigation at the research stage that should overwhelm the drawbacks of standard therapies; different strategies to cancer diagnosis and therapy; and their current status in the clinical context, underlining their impact as innovative anti-cancer approaches.[6]

1. ADVANCED AND INNOVATIVE CANCER THERAPIES:

Drug resistance in cancer treatment and restriction in the drug delivery systems are also one of the most significant problems of cancer treatment as they protect effective cure and symptom regulation. Though various treatment methods and medicines have been accepted, the performance of the traditional therapies is usually impaired by the tumor pathology and unnatural structure of the tumor angiogenesis. The next section presents methods of cancer treatment that are highly innovative and advanced, pointing out their benefits and the problems that they introduce.[6]

2. STEM CELL THERAPIES:

The undifferentiated cells located in the bone marrow (BM) can develop into different types of cells in the body and are referred to as stem cells. Stem cell therapy is also a new promising and comparatively safe method of treatment of cancer. Today, they are at the experimental phase of clinical trials and researches on their use to repair damaged body organs are also undertaken. One of the most widespread trials under investigation is connected to mesenchymal stem cells (MSCs) obtained on the basis of BM, adipose tissue, and connective tissue.[6]

- Pluri potent stem cells
- Adult stem cells
- Cancer stem cells

IV. CURRENT CHALLENGES

Genotype-driven precision oncology has its basis on the principle that tumor-specific molecular alterations can be focused on and treated with effective, precise, and lower-toxicity therapy. The developments of high-throughput technologies, with international efforts like the International Cancer Genome Consortium have now made possible more comprehensive molecular characterization of the tumors, as well as the identification of genes and biomarkers that can be used in treatment. To be clinically useful, a biomarker must satisfy three key criteria, namely: biological plausibility (the genetic change should be associated with cancer progression), analytical validity (it should be reliably measurable using clinically practicable tests), and clinical validity (must be prognostic or predictive in clinical studies).[7]

Predictive genomic changes, in their turn, are not very common, are quite variable, and happen in various types of tumors. This complexity, and the increasing number of mutations found in each type of cancer, render comprehensive and sensitive sequencing methods to be of relevance to clinical practice. However, there are certain mutations that are difficult to assess their clinical significance due to their low frequency and widespread distribution. In order to overcome this, genotype-enriched clinical trials are used that can either be histology-based or histology-independent. One of them, the basket trial, it is the treatment of patients with a wide range of tumors, but a common genetic alteration, using the identical targeted therapy, which is often conducted in Phase I or II.[7]

1. Biological barriers:

Modern targeted therapies against solid tumors have not proven to be very effective enough to portray results that are not yet of expected standards of efficacy and safety. Contemporary therapeutics are designed to recognize and selectively bind a particular

molecular target with low specificity. However, when administered in an intravenous form, they tend to be insufficient in reaching solid tumors, which reduces their pharmacological activity. In contrast to the situation in the liquid tumors, the delivery of the drug to the malignant cells in a solid tumor is hindered by a well-developed vascular barrier.[8] At present, systemic anti-cancer molecular therapies are being utilized with an anti-cancer agent, where it is delivered passively through the trans vascular system to primary and secondary tumors. Nevertheless, it is typically a slow and inefficient passive trans endothelial process and tumor endothelial barrier to drugs needs to have a steep concentration gradient on each side of the tumor to allow drug penetration into solid tumors.[8] Even highly engineered antibody based therapies created to specifically target and destroy cancerous cells cannot be effectively used through passive trans vascular delivery without entering into their full therapeutic potential. Such investigations have found that a large number of intravenously injected radiolabeled antibodies penetrate and concentrate in tumors slowly, and also have a slow excretion into the blood.[8] Because poor drug delivery can seriously limit - or even eliminate - the treatment efficacy of treatments of solid tumors, there is an immediate need to develop new methods that will not only extend our knowledge of these biological impediments but will also offer solutions to address them.[8]

2. Safety And Toxicity Issues:

Drug safety is an important challenge in the process of developing and approving new medicines. Sudden toxicity is a significant cause of failure in clinical trials and safety problems in the post-marketing can lead to preventable morbidity and mortality. Adverse events (AEs) when confirmed to have a direct relationship with the drug or adverse drug reactions (ADRs) when the connection is confirmed are harmful effects that are experienced despite the appropriate dosage. The use of artificial intelligence (AI) in pre-market drug safety has become useful, especially in toxicity evaluation. Quantitative Structure Activity Relationship (QSAR) is a method that relates chemical or structural properties of compounds and their pharmacological activity. Various drug safety parameters, which include median lethal dose (LD50), skin and eye irritation, and toxicity in individual organs or tissues have been predicted using QSAR techniques. A QSAR model is practically a model that assesses the relationship between many predictors (e.g., molecular characteristics) and a biological response (e.g., activity such as binding affinity). Good QSAR models will be those that are well predictive and relatively easy to understand.[9]

3. Regulatory And Clinical Trial Challenges:

The field of clinical research is regulated by a set of laws, regulations, and controlling organizations that are aimed at preventing the harm, exploitation, and privacy violation of patients as well as at preventing the abuse of the common resources. These regulations have become more elaborate, stringent and costly over the years. They embody various purposes, but often, they are justified by patient safety. To determine the impact of a stricter regulation on patient safety, we compared toxic death rates in phase I cancer trials at the NCI. Among 460 studies on 11935 patients 1991-2002, 58 treatment-related deaths were found, which corresponded to 0.5 percent of the participants. The indirect effect of these regulatory requirements is a decrease in the number of patients and physicians who wished to get involved in clinical research or had the capacity to do so. Only less than 5 percent of adult cancer patients are entering into clinical trials today, and probably the regulatory burdens are adding significantly to low cancer patient participation. In many cases, an initially positive response to treatment later changes, resulting in cancer relapse and recurrence. This acquired resistance to therapy remains a major obstacle to fully effective anticancer treatment.[10]

V. DOXORUBICINE

Currently widely uses of Doxorubicin is known to be an excellent and FDA-approved chemotherapeutic, which is commonly used due to its capacity to target fast dividing cells and retard cancer development but is restricted by its toxicity to normal cells. It is a nonselective class I anthracycline, which is comprised of tetracyclic aglycone attached to sugar moieties with structural characteristics being quinone-hydroquinone groups, a methoxy group, and a short carbonyl-forming side chain.[11] Dox remains a highly efficacious first line anti-cancer drug used in the treatment of various cancers. Despite years of use and the amount of scientific investigation, the chemotherapeutic efficacy of Dox remains hindered by its cardiotoxic

side effect. This review elaborated on the mechanisms associated with Dox-induced cardiotoxicity, as understanding of this mechanistic process might lead to the development of new or novel drug targets that can prevent or lessen the Dox insult on cardiac cells. Various studies suggested that oxidative stress, lipid peroxidation, and DNA damage are the major mechanisms associated with Dox-induced cardiotoxicity.[12]

- Major Challenges of Doxorubicine:

In the development of Doxorubicin some Challenges in Formulation, Characterization and Manufacturing is faces like;

- ✓ Biological barrier to drug delivery
- ✓ Delivery of hydrophobic drug
- ✓ Desire For Targeting
- ✓ Nanoparticle components and characteristics
- ✓ Scale-up and Manufacturing
- ✓ Safety in nanomedicine development.[13]

VI. CURRENT ADVANTAGES IN DRUG DELIVERY

Immunotherapy Innovation:

The effect of chemotherapy is both cytotoxic and cytostatic, which kills cells of the cancer that have a rapid division but damages normal swifter growing cells. Through this, chemotherapy and radiotherapy have many side effects, and the chances of recurrence are high because of the remaining or metastatic cancer cells. Immunotherapy, on the other hand uses the immune system of the body to specifically identify and destroy cancer cells. It has become a promising form of treatment and provides a new line of thought, as it causes the immune response to occur against the tumor and involves the natural defenses of the patient in the anti-cancer battle. Cancer immunotherapies operate through boosting the immune system in the host to destroy cancerous cells, mainly by the production of a stable population of highly active tumor specific T-cells.[14] Bladder cancer was the first indication for which an immunotherapy was used in 1970. Currently, there are a number of additional immune-based bladder cancer treatments under development.[15]

Advanced Targeted Drug Delivery And Nanotechnology:

Controlled drug delivery increases bioavailability since drugs are not exposed to early degradation and this increases absorption. It is also able to maintain therapeutic levels by controlled release and reduce side effects by supplying drugs to target disease sites and target cells.

Advances in material design for drug delivery include:

- ✓ Development of biodegradable drug carriers to ensure safe elimination after therapy.
- ✓ Use of block copolymers for controlled and sustained release.
- ✓ Polymer–drug conjugates that improve solubility and therapeutic efficiency.
- ✓ Exploration Creation of recombinant protein–based drug carriers for precision delivery.
- ✓ Creation of recombinant protein–based drug carriers for precision delivery.
- ✓ Design of smart drug delivery systems that respond to specific stimuli such as pH, temperature, or enzymes.[16]

The first nanomedicine approved by FDA in 1995 in the case of Kaposi sarcoma and subsequently in Europe in 1997 as Caelyx under the brand name, was developed by entrapping doxorubicin in liposomes. Although liposome based nanocarriers have demonstrated excellent clinical advancement, they are not without challenges in their further application as a first line drug delivery system. They are problems with controlling the drug release in vivo, limited drug-loading capacity, the oxidation of liposomal phospholipids, and the problems with long-term shelf stability. More specifically, nanoparticles design has been widely used with engineered monoclonal antibodies that possess the capacity to avoid immune detection. Continued developments have yielded chimeric and humanized types of antibodies, which assist in decreasing immunogenicity and increasing therapeutic activity.[17]

VII. FUTURE DIRECTION

Next Generation Therapeutics:

As nanobodies are not naturally produced in humans, their therapeutic implementation brings into question their overall safety. As evidenced by existing preclinical studies, the targeting of critical intracellular tumor antigens may be the next pivotal step to revolutionizing a new wave of cancer therapeutics.[18]

Tumor heterogeneity: another obstacle for anticancer treatment:

The observation of interconversion between CSCs and their offspring suggests the necessity to evolve current anticancer strategies to target both types of cancer cells with self-renewal potential and the bulk differentiated bulk cancer cells.[19] Development of peptide-based nano drugs have presented promising advances in cancer therapy but their successful clinical development is a major challenge. The drug molecules, peptide constituents, and their pharmacokinetic behavior in vivo must be given due consideration in order to be clinical-applied. As an example, enhancing the binding of peptides and therapeutic agents can be used to reduce drug leakage and the problems of multidrug resistance.[20]

Towards sustainable And Accessible Cancer Care:

The pandemic highlighted the need to maintain cancer care to prevent the occurrence of a parallel health crisis because disruptions and restricted access to treatment were a significant problem.[21] In this the treatment procedures have been constantly growing over time, probably due to a combination of various factors like population development, aging, SUS-accredited hospital expansion, enhanced diagnostic ability, better medical service accessibility, and better reference center management.[22] Significant and synergistic interventions have the potential to bring about long-term improvements to the management of patients with life-limiting conditions.[23]

VIII. CONCLUSION

To conclude, the process of cancer treatment is a very complicated and dynamic sphere that requires new studies and innovations. Although drug resistance, toxicity, and biological barriers remain a problem, nanomedicine, stem cell therapy, immunotherapy, and targeted therapy show potential promises. . Development of new technologies and strategies will also be a major factor in improving patient care. The extensive knowledge about the disease and its pathophysiology is a key to a complex treatment plan. Through this collaboration, researchers and clinicians can develop superior therapeutic options and enhance the quality of life of the cancer patients. As the world advances faster and new findings appear on a regular base, the future of cancer treatment is bright, and further innovation is likely to present even more effective means of its treatment.

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