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MiniReview

Innovative Translation Strategies in the Emergence of Next-Generation Drugs in Precision Cancer Medicine

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Abstract

There has been a conscientious momentum to evolve more efficacious and potent chemotherapeutics that could cure advanced cancers. Although, the conventional cancer therapeutics can cause dramatic tumor regressions in some patients, many patients inexplicably reveal no benefit. This is a unique characteristic of tumor recurrence in human cancers, linked with several resistance mechanisms. Recent past years witnessed enormous ground-breaking advancements in genomic medicine symbolizing a culmination of patients' genomic, proteomic, metabolomic, including cellular profiles which have significantly transformed understanding and therapeutic options for cancer management. Furthermore, the ability of combination chemotherapy to cure advanced cancers, immensely facilitated the prospects of adjuvant chemotherapy. Many global pharmaceuticals have accelerated translational research strategies on proteomics and genomic technologies paving the way to emerge next-generation drugs to strengthen personalized cancer medicine. Numerous forthcoming cancer therapies are at most vital phase in their innovation and development for the unfulfilled clinical need to turn into futuristic cancer treatment strategies. There is a growing optimism about the innovative strategies on emergence of the new generation of immunotherapy, targeted therapies, and Oligonucleotide therapy to improve patient outcomes, and to make real dream of accomplishing personalized cancer therapy.

Keywords: innovative translation strategies, emergence of next-generation therapies, future treatment strategies, precision cancer medicine

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1 INTRODUCTION

Cancer is one of the leading causes of death worldwide. American Cancer Society lately reported that over 1.9 million new cancer cases are expected to be diagnosed in the US during the year 2022[1], recent past years witnessed enormous ground-breaking advancements in genomic medicine symbolizing a culmination of patients' genomic, proteomic, metabolomic, including cellular profiles which have significantly transformed understanding and therapeutic options for cancer management.

Precision cancer medicine (PCM) is a rapidly growing health care theme that is focused on more-efficient prevention and treatment options encompassing predictive, preventive,

personalized, and healthcare service delivery models. Personalized combinational therapies through new techniques will be the next promising strategies for future cancer treatment options[2]. The recent innovative technological advancements immensely revolutionized the initiatives of risk assessment and therapeutic strategies of PCM.

A growing number of evidence have clearly defined that cancer is a disordered event of genetic rearrangements, mutations, deletions, and amplifications. In addition, epigenetics affects gene expression and evolution under therapeutic magnitude and the formulation of inventing effective. At present, there is no straightforward path to cure advanced stages of cancer.

Chemotherapeutic refractoriness in several human cancers is reflective of several resistance mechanisms resulting from the tumor heterogeneity, and outgrowth of resistant clones, thus facilitating tumor recurrence and metastasis. Despite a long history of successfully discovered drugs for cancer treatment, their treatment benefit is only among in a fraction of patients and all too often for a limited time. Therefore, the formulation of inventing effective treatments becomes more intricate.

2 CANCER IMMUNOTHERAPY

Cancer immunotherapy has now decisively established itself as a novel pillar of cancer management option, from the metastatic stage to the adjuvant and neo-adjuvant settings in several human cancer types[3]. Indeed, there is great optimism about a new era for cancer immunotherapy based on emerging immune-active drugs as well as the unexpected finding of positive interaction between immunotherapy and chemotherapy[4]. A unique subset of hyperactive immune regulatory cells can accomplish diverse roles in orchestrating the immune response. These cells can coordinate defenses against a variety of diseases, or equally, promotes inflammation, toxicity, and disease progression. Emerging cancer immunotherapies offer improved efficacy, greater safety, and higher patient adherence with possibilities of fewer side effects and improved patient lives, immunotherapies vary in their approach from life-changing to lifesaving. The United States Food and Drug Administration has now diligently approved immunotherapy as a first line of effective treatment for several human cancers, which are resistant to prior treatment. Immunotherapy may be given alone or in combination with other cancer treatments, including tyrosinase-kinase inhibitors, chimeric antigenic receptor (CAR) T-cell (CAR-T), and radioligand therapies for patients with cancer. Despite increasing popularity and transformative trends in an effective immunotherapeutic option, treatment benefit is fewer patients with advanced stages of cancer.

2.1 Immune Checkpoint Inhibitors in Cancer Management

Recent ground-breaking pre-clinical and clinical trials have ignited interest in learning more about immunomodulatory pathways, and their impact on the development of new treatments for cancer patients.

Immune checkpoint blockade is proved to be more efficacious strategy in the activation of antitumor immunity, in a variety of human cancers. It is now clear that a combination of therapeutic strategies, simultaneous immune activation, and targeting a tumor may be achieved. However, this approach enables a more durable response or prolong immunity response. In addition, multiple biomarkers need to be simultaneously analyzed to monitor the combinational treatment response. It is now clearly understood that the biomarkers are implored to stratify patients and demarcate target engagement in clinical trials and decision-making steps.

In-depth research into immune checkpoints and intrinsic mechanisms of cancer growth immensely enhanced the development of targeted therapies including small molecule inhibitors, monoclonal antibodies as well as CAR-T therapy[5]. Checkpoint inhibitors such as programmed death protein 1 (PD-1) and programmed death-ligand 1 revealed substantial advancement in the clinical applications in some types of cancer. However, their treatment benefits are partial by a rapid post-therapy resistance and inherent lacking tumor neo-antigens to empower blockade, thus rendering them ineffective for many patients[6,7]. Cytotoxic T lymphocyte-associated antigen (CTLA)-4-specific antibody therapy targets a co-inhibitory molecule that is expressed by T-cells. The binding of its ligands B7.1 or B7.2 on antigen-presenting cells results in negative regulation of T cell activity. Toll-like receptor 4, a member of the toll-like receptor family of innate immune receptors that recognize molecular patterns of microbes or danger signals derived from tissue damage. Immunotherapeutic regimens are now clearly authenticated their legacy of innovation by exploring PD-1 inhibition and novel combination regimens.

2.2 CAR-T-Immunotherapy as Personalized Cancer Therapy

CAR-T-immunotherapy as personalized cancer therapy is a revolutionary and most promising strategy for some of the most challenging cases of pediatric leukemia and lymphoma. This is a rapidly growing therapy. This is another form of immunotherapy based on modifying the body's own T-cells, a type of immune system cell that chases and destroys abnormal cells, such as cancer cells. This approach of treatment is also known as the adoptive transfer of CAR-T treatment. CD19 is the most frequent target for treatment of B-cell malignancy. However, multiple targets, universal CAR-T cells are on intense exploration.

This therapy approach requires functional tumor-specific antigens on the cell surface of cancer cells to empower targeting the therapeutic administration of CAR-T therapy

among patients with solid tumors. CAR-T therapy is also well-equipped to manage any potential side effects. Only a 9% overall response rate has been observed among the tumors which often do not express such antigens[8-10]. In-depth clinical trials are desirable to assess higher precision of engineered CAR T-cells, clinical administration, their efficacies assessments of tissue penetrance, targeting, potency, and dosing.

2.3 Allogeneic Natural Killer T-Cell Cancer Immunotherapy:

This is another vibrant shifting approach from CAR-T to CAR-NK cells immunotherapy for acute lymphoblastic leukemia (ALL). This CAR-NK cells therapy is composed of CARs (genetically engineered transmembrane receptors) and effector cells (NK cells)[11]. This allogeneic natural killer cell immunotherapy is combined with irreversible electroporation for stage IV hepatocellular carcinoma thus revealing a better survival outcome[12]. Allogenic NK cell immunotherapy involves the intravenous infusion of immune cells that have been expanded and activated ex vivo, treating tumors by directly killing the tumor cells or stimulating the patient's immune response.

3 TARGETED CANCER THERAPY

Recently innovated molecular-guided therapy in oncology is a proactive approach to treatment and has the potential to reduce the time, and minimizes adverse events, thus increasing the patient's duration and quality of life. There is a dramatic shift in cancer management options in the past decades. As such, opened a new era of cancer therapeutics designed to interfere with a specific molecular target usually a protein that has a potential association with tumor growth or progression. Traditional cytotoxic chemotherapy continues as the first line of the treatment of choice for several malignancies.

Targeted therapies are now a module of treatment for many types of cancer, including breast, colorectal, lung, and pancreatic cancers, as well as lymphoma, leukemia, and multiple myeloma[13]. Discovery of molecular signatures as representatives of promising treatment decision as targeted therapy designed to inhibit cancer cell growth by blocking molecular targets essential for cell growth and tumorigenesis[14].

Many targeted drugs such as anti-epidermal growth factor receptor (EGFR) agents and anti-vascular endothelial growth factor and endothelial growth (VEGF/VEGF-R) receptors agents have been approved for cancer treatments, but limitations include rapidly developing resistance and serious adverse effects[15,16]. While both conventional and newly developed treatments have significantly improved cancer survival rates, cancer recurrence and drug resistance remain challenging and indicate the urgent need for new therapeutic strategies. This therapy should not be administered in combination with non-effective chemotherapy, as this may increase the toxicity without adding any benefit. However, its effect can be intensified by the combined use of different targeted therapeutic agents that have different functions, or with the addition of at least partially effective chemotherapy.

Bevacizumab (anti-VEGF) to chemotherapy that consisted of fluorouracil + oxaliplatin + leucovorin known as FOLFOX4 in previously treated patients with metastatic colorectal cancer improved their survival[17]. Similarly, the addition of erlotinib (anti-EGF) to gemcitabine in patients with advanced stages of pancreatic cancer gave better survival than gemcitabine alone[18]. In principle, each tumor has to be studied for its contents of cytokines and growth factors before the initiation of targeted therapy. Identifying one factor and targeting it therapeutically may prove non-beneficial[19], as such tumors may have several cytokines and growth factors.

4 CANCER NANOMEDICINE

Advances in recent years catalyzed the emergence of powerful cancer nanomedicine which is transitioning into a potential combination' of immunotherapies. Nanomedicine is unique and distinctive in their clinical applications as nanomedicine have a high surface-to-volume ratio that enables them to bind, penetrate, and transport small biomolecules like DNA, RNA, drugs, proteins, and other molecules to the targeted site and thus enhance the efficacy of the therapeutic agents. Smart nanoparticles (NPs) are designed through immune engineering, which mimic targeted immunotherapies. Nanotechnology can enhance the selectivity and potency of biological strategies for eliminating cancer cell death while minimizing collateral toxicity to nonmalignant cells. In recent past years, multiple nanotherapeutics have been approved for patients with cancer, but their effects on survival have been uncertain and, in some examples, less than those of other approved therapeutics.

Indeed, nanomedicines can reduce tumor burden to a great extent but do not eliminate the risk of certain life-threatening toxicities. Thus, the combination of these therapeutic classes is of intense research interest. The tumor microenvironment (TME) is a major cause of the disastrous initiatives of both nanomedicines and immunotherapies that not only limits delivery but also can compromise efficiency, even when agents accumulate in the TME. Combined nanomedicine based TME normalization and immunotherapeutic strategy are designed to benefit from immunotherapy[20].

5 NEXT-GENERATION CRISPR SYSTEMS IN CANCER THERAPEUTICS

This technology has advanced our understanding of the genetic basis of disease through better modeling and drug target discovery, opening new avenues for the development of gene-targeted cancer therapies. The advent of innovative

CRISPR/Cas9 technology is widely used to study gene expression and protein function, becoming a tool for editing genes. However, many of these methods are inaccurate, problematic can be an inconsistent, unpredictable process with varying levels of success, thus, resulting in low editing efficiencies. CRISPR engineered cells with desired gene knockout or insert target sequence can be used directly in disease modeling, target validation, and elucidating gene function.

6 OLIGONUCLEOTIDE CANCER THERAPEUTICS

Oligonucleotide cancer therapeutics are an emerging drug option, which comprises modified or unmodified short nucleic acid molecules, and includes antisense oligonucleotides, small interfering RNA, microRNA, aptamers, and DNA zymes. These oligonucleotides may identify a specific mRNA fragment of a given sequence or protein and interfere with gene expression as molecular-targeted agents[21,22].

However, some of the known hurdles such as the poor stability against extra- and intracellular, inefficient intracellular delivery to target cells or tissues, inadequate affinity toward the intended target sequence, as well as possible off-target/toxicity effects have been observed. Additionally, immunostimulation has also been a matter of concern[23].

7 GENE THERAPY IN CANCER TREATMENT

Efficient gene therapies are being explored through innovative genetic science and advanced viral vector as delivery tools. A promising future therapy can permanently treat genetic diseases by replacing a missing or mutated gene with a functional copy. Gene therapy strategies are easing to re-establish or interrupting of disturbed pathways. However, there are huge challenges on the complexity of cell and gene therapies, combined with limited regulatory model, to develop these therapeutics. Combative approaches are being explored to take advantage of advanced vector technologies integrating CRISPR systems thus enhancing gene therapy with targeted therapies and immunotherapies.

8 ADVANCING NEXT-GENERATION EPIGENETIC TARGETS FOR CANCER THERAPIES

There is an established relationship of underlying epigenetic with the drug resistance. The latest pre-clinical and translational development of small-molecule, and other epigenetic modulators of gene expression, provided crucial insights to develop the next generation of clinically important cancer therapeutics. Translational advancements in therapeutic interventions would be aiming all areas of epigenetic machinery including DNA methylation, histone post-translational modifications, chromatin remodeling, and non-coding RNAs.

9 TARGETED CANCER RADIOPHARMACEUTICALS

Molecular imaging technologies using radiopharmaceuticals are some of the most progressive radio-imaging technologies, providing valued information in the assessment and extent of disease. Nuclear medicine is a decisive tool when evaluating cardiovascular, oncology, neurology, and many other disease states. In modern radiation cancer therapy, a radionuclide is systemically or locally delivered to target and deliver radiation to cancer cells while minimizing radiation exposure to untargeted cells[24]. Radiopharmaceuticals with undisclosed tumor-targeting technology are on a great horizon[25]. There is an explosion of research and clinical trials evolving next-generation radioligands known as Targeted Radiopharmaceuticals. Next-generation alpha emitters targeted radiotherapies such as Lutathera (177Lu-DOTATATE), a lutetium-tagged somatostatin analog that is recently approved for radioligand for treating neuroendocrine tumors of the gastrointestinal tract or pancreas.

10 PROSPECTS OF CYTOKINES IN CANCER THERAPIES

Recent insights in signaling transduction pathways in futuristic targeted cancer therapies which are linked with the genesis and progression of most types of human cancers. This has opened a new era to develop a newer cytokines/interleukin based therapeutic intervention in cancer.

Numerous growth factor receptor kinases are the main components for signal transduction pathways which lead to a diverse array of cellular functions including proliferation/cell cycle, differentiation, migration and invasion, angiogenesis, and survival/apoptosis including response to the microenvironment. Mutation in certain kinases can lead to the development and progression of cancer. Aberrant expression or activity of kinases frequently occurs in many human cancers. Identifying the active cytokines and growth factors will provide vital clues on the role of molecular targets associated with the progression of cancer thus facilitating newer strategies for the development of potential cancer therapeutics.

Immunotherapy with cytokines is being explored as an advantageous approach for the treatment of various human malignancies. This exploration has demonstrated as a potential therapeutic option to activate host immune cells in particular malignant cells while sparing normal cells. Cytokines are endogenously produced hormones in the body that support regulating host immune modulation. These soluble factors can perform in a slightly contradictory manner to protect the host against disease or to contribute to inflammatory processes that aggravate the disease. Some cytokines and growth factors function as autocrine and/or paracrine factors in tumor growth, invasion, and angiogenesis

in some human cancers. The identification of autocrine and paracrine factors involved in complex signaling network, elimination of immune suppressive factors by regulatory T cells or CTLA-blockade for immune tolerance in human cells, as well as identifying specific target kinase for cell surface receptors will mutually facilitate envisaging newer paradigms in potential targeted cancer therapeutics[26-29].

So far, there are 138 drugs where the interleukin component has undergone molecular engineering. There is a recent surge of new pre-clinical/clinical trials of engineered interleukins/cytokines such as interleukin (IL)-2, IL-12, and IL-15 to explore the discovery of drug targets associated with disease indication.

11 CONCLUSION

There has been a most exciting mission and historic development of translational strategies shaping the emergence of next-generation drugs with their potential challenges and opportunities in cancer medicine. Despite of previously mentioned enormous advancements in PCM, there are immense challenges encountering patient selection, unlocking rationale in combination strategy, tumor heterogeneity and plasticity in cancer cells focusing on resistance and toxicities, exploring the optimization of biomarker use.

Therefore, PCM has not yet been fully operationalized in the health care as there is a lack of standard outcomes to define clinical benefit. Such hurdles demand aggressive research for the discovery of a more efficacious targeted immunotherapies across different treatment options, differentiating drugs, forecasting the future and gaps of unmet need. Indeed, the successful development of a strategic product may occur and to create a path to commercialization that will ensure accessibility to the patients.

Newly invented targeted radiopharmaceuticals are also getting immense attention in the development of next generation radioligand medicine for targeted cancer therapies. Numerous fast-paced pharmaceuticals are striving to identify and validate new targets, the patient selection strategies to explore the possibilities of combining targeted radiopharmaceuticals with immunotherapy. For a most efficacious and successful immunotherapy option, adjusting one signal or hitting one druggable target will not eliminate the tumor. However, it can only be achieved by adjusting multiple signals or installing combinational cancer therapies.

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Conflicts of Interest

The author declared no conflict of interest.

Author Contribution

Sharma BK designed and wrote the manuscript, and approved the final version.

Abbreviation List

ALL, Acute lymphoblastic leukemia
CAR, Chimeric antigenic receptor
CAR-T, Chimeric antigenic receptor T-cell
CRISPR, Clustered regularly interspaced short palindromic repeats
CTLA, Cytotoxic T lymphocyte-associated antigen
IL, Interleukin
EGFR, Epidermal growth factor receptor
NPs, Nanoparticles
PCM, Precision cancer medicine
PD-1, Programmed death protein 1
TME, Tumor microenvironment
VEGF, Vascular endothelial growth factor

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