A Review on Therapies in Oncology: Exploring Novel Strategies and Technology

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Abstract: ***Effective treatment of cancer presents a major therapeutic challenge. It has been realized that there are reservations in the therapies for cancer with most of the anticancer drugs available. There is a need for better drugs that could selectively kill cancerous cells with minimum side effects to normal cells. Emerging therapies are bringing in innovative strategies, which could probably be the most efficacious cancer treatment. This review will provide an overview of developing novel approaches in oncology. Currently, various strategies are being exploited to counteract cancer and the intolerable consequences of cancer therapies. The strategies include gene therapy, rnai technology, nanotechnology, stem cell therapy, and photothermal therapy, which can be used either alone or in combination with each other to increase therapeutic potential while decreasing unwanted toxic side effects of the anticancer drugs. Besides these therapies, low-dose chemotherapy is also reported to minimize the side effects of anticancer agents. This review focuses on extensive discussions on the novel strategies with the latest developments and trends in technologies to control tumor cell growth and aims to build solid scientific strategies to manage tumor growth and improve clinical applications against cancer.***

1. INTRODUCTION

Since ancient times, cancer has been considered a disease, especially in relation to active cancer trials worldwide. Due to its molecularly complex nature, traditional therapies such as chemotherapy and radiotherapy target fast-growing cells but cause lasting damage to normal cells. With dynamic advances in scientific disciplines and technology, an increasing variety of novel cancer therapies are gaining standard acceptance, such as targeted therapy, biologics, immunotherapy, gene therapy, RNA interference, and a few other therapies. Personalized patient care would evolve into a drug development and utilization model that will enable pharmaceutical firms to develop therapies most likely to show a profit. In conclusion, with the rapid advancement of precision medicine, personalized patient care can be accomplished and has great potential to revolutionize cancer treatment and drug development in the future.

1.1. Background and Significance

The understanding of the molecular mechanisms underlying cancer progression, metastases, and the development of resistance to therapeutics, as well as the knowledge of the influence of common factors such as age, inflammation, and disease host on the efficacy of treatments, is critical for selecting the best therapeutic strategy for each patient. For years, traditional therapeutics have included the use of chemotherapy, radiotherapy, surgery, and hormone-based treatments. More recent targets aim at cell-signaling pathways, growth factors, and the development of more effective antibodies and cytostatics. Despite treatment advances, therapy-associated side effects limit the patient's quality of life. Thus, the growing use of technologies that allow the detection of tumor bioenergetics, in association with the study of cell communication at various levels, the development of antitumor immune responses, and the use of nanoparticles and nanotechnologies for therapy carriers, introduces new hope for patients with cancer, leading to the development of gene and cell therapies that yield very promising results. In the present review, a brief overview of the current main therapies used to treat most oncological diagnoses will be addressed. Finally, it will present a comprehensive review of the gene and cell therapies explored for the treatment of several cancers, together with a summary of the translation of preclinical model results into the clinics, highlighting the major difficulties experienced. The ability to identify tumors, perform localized therapies, and avoid the systemic exposure of patients to therapeutic molecules is essential to reduce the classical side effects of chemotherapy, improve the patient's quality of life, and enhance the efficacy of treatments. Nanotechnology could positively help in this context.

1.2. Purpose and Scope of the Review

Research on cancer treatments through diverse methods is being widely explored by both academia and the pharmaceutical industry. Despite these constant scientific efforts, advances in terms of therapy are relatively slow, and current statistics on

treatment response, cancer incidence, and side effects clearly demonstrate the urgent need for further research in the area. Treatment adherence is also crucial in obtaining satisfactory outcomes with therapy, but this is still a challenge. Knowledge of patients' habits and the development of professionals' technical skills are necessary to obtain satisfactory results during therapy. Moreover, raising scientific and social awareness of the mechanisms of cancer and the current options is also crucial to global society.

Knowledge of cancer therapy is usually restricted to a specific population, either patients who are experiencing therapy or therapeutic staff. This paper aims to explore the classic and emerging oncological therapies proposed for diverse types of cancer to bring professionals who are involved in the therapy of patients with oncological disorders closer to the current state of the art. As research on new therapies and cancer etiopathogenesis is broad, a careful selection of the sources of this massive amount of data seems to be secondary to the paper. Data should be collected from a mix of classic and novel original papers, as the well-selected review is crucial in building knowledge among different professionals. It can potentially answer questions, facilitate training processes, and discover disorder-related opportunities to design new solutions to meet the complex multidisciplinary needs associated with cancer therapy.

2. CURRENT STANDARD THERAPIES IN ONCOLOGY

Surgery, chemotherapy, and radiation therapy are the common conventional standard therapies for cancer. Radiotherapy is a local treatment to control cell growth and, at the same time, induce cell apoptosis. In addition, it is harmful to normal tissues in a similar manner. Although all cancer treatments are toxic, the selective risks must be balanced against the benefits of cure, local control, and prolongation of life. Furthermore, mild side effects must also be taken into consideration. Respiratory gating carries specific resources for radiotherapy treatment management design. It also benefits patients with breast cancer and non-small cell lung cancer. Moreover, paroxysm control can deliver clinical advantages in terms of improved spatial resolution, tracking different morphology, and not considering the dose needed for the organs at risk. Its brilliant ability to accumulate and circulate the remaining treatment dose makes the necessary or unexpected dose administration and provides a way for every breathing cycle to meet the clinical requirements.

The relationship between surgery and cancer is old and continuing. Surgery is the standard treatment for the majority of cancer types. The majority of cancer patients undergo surgery; nothing major as it can drain the root of the disease, the tumor. Nearly 80% of those diagnosed with solid cancers choose to undergo a curative surgical procedure. Cancer surgery is considered a curative and therapeutic treatment. Chemotherapy is used to select systemically used drugs and is used in the blood to kill rapidly growing cancer or to keep cells from being able to split and make more new cells. In general, it is the ability of chemical agents in the veins and tissues to interfere with the metabolic or mitotic processes or to stop their proliferation, which may result in cancer. Strategies for using the drugs have been devised in a curative scheme: two adjuvant chemotherapy, two chemoradiation therapy, and two primary chemotherapy on cancer it summarizes. In recent years, the general policy for adjuvant chemotherapy has been used in a variety of malignant tumors such as lung cancer, after surgery for colorectal cancer, head and neck cancer, breast cancer, and many cancers and also as first-line treatments for limited-stage lung cancer and low-grade non-Hodgkin's lymphoma.

2.1. Surgery

Surgery is one of the primary and most effective recommendations for removing most of the tumor mass. The surgical boundaries are defined after planning, which involves the size, depth, and aggressiveness of the tumor, as well as the best forms of repairing tissues. However, the expected cure of the patient is not always achieved and, in many cases, the tumor has invaded vital regions and organs, which makes the surgical removal difficult or impossible without damaging them. Similarly, in cancer types of "liquid" tissues such as liquid lymphoma, hematologic cancer, and metastatic lung and liver cancers, tissue-based surgery is not an option at all. For some types of cancer, other possibilities such as radiotherapy, hormone therapy, chemotherapy, targeted drugs, and surgery of more extensive lymph nodes to reduce locoregional recurrence risk are considered. Only a good surgical capacity and careful follow-up care can lead to a significant improvement in the cure rate, while preserving the function of the organ, the overall health of the patient, and achieving their quality of life by reducing pain and suffering.

Precisely locating and characterizing the tumor boundary is a crucial condition for successful surgical control of the tumor. There have been remarkable technological advances for obtaining in vivo the tumor-targeted information that the surgeon can use intraoperatively to verify the tumor boundaries during the operation. For this purpose, multimodal techniques are often used, because the multimodal image acquisition helps the surgeon to understand the spatial relationship between the signals emitted from different imaging and to visualize the complete tumor boundaries by combining whole and partial images and immediately obtaining the tumor memory. After clarifying the problems of multimodal optical imaging in a modest number of data, we first discuss the different imaging techniques performed and, thus, the strategies for multimodal data acquisition by using the same instrument and the same wavelength and sequentially switching from one modality to the other. A promising strategy is to provide multimodal diagnostic information by a hybrid image grid or introduction of one modality into another. Finally, the review investigated the possibility of alignment through transformations as an additional advantage of the organization of the images.

2.2. Chemotherapy

Chemotherapy is usually the first-line treatment for the majority of cancers, mainly for the ease of administration and proven efficacy. Although recent advances in targeted therapies have contributed to expanding the options available for the treatment of certain types of tumors, chemotherapy is a widely used and key tool in oncology, as its effectiveness often leads to encouraging outcomes. The broadness of this class of therapeutic agents mainly results from its proficiency in interfering with tumor growth, causing irreparable damage to crucial processes, such as tumor cell division and metabolism. The incremental development of its constituents has significantly increased the effectiveness of therapeutic interventions. However, patients usually experience serious side effects, such as hematopoietic stem cell suppression, which causes many of the symptoms associated with chemotherapy. These cells are responsible for bone marrow functions, and the lack of red cells and other blood cells accounts for the side effects associated with chemotherapy.

Chemotherapy is the most widely used and well-established therapy in oncology, due to its direct role in affecting cellular division. By disrupting the division process, the chemotherapy agents induce lethal damage in cancer cells, thus blocking the cells' ability to proliferate. Chemotherapy drugs can damage cell structure, mainly targeting DNA in tumor cells, inhibiting the cells from multiplying and spreading through the body. Chemotherapy treatments aim to destroy quickly growing cells. As cancer grows fast, this therapy is used to destroy both normal and cancerous cells. Consequently, while acting on rapidly dividing cancer cells, chemotherapy can also remarkably damage normal cells with similar features. This damage theory has led to the occurrence of undesired side effects related to cancer therapy, given that the relief of tumor symptoms can only be observed when the neoplasm shows its invasive and non-reactive potential. Chemotherapy agents act on four different location points on a eukaryotic cell: DNA, not allowing the replication of genetic information; RNA, inhibiting protein production; nucleosomes, stopping protein production; and shell construction, acting on enzymes that form cellular structure.

2.3. Radiation Therapy

One of the most frequently used therapeutic intervention methods is radiation therapy, where ionizing radiation is used to treat tumors. The common applications of radiation therapy include providing a cure for cancer itself, reducing the risks of recurrence after tumors have been removed by radical surgery or debulking for the treatment of metastatic disease, and relieving symptoms. In addition, a mechanism of action involving free radicals and irreversible injury to the DNA of tumor target cells enables ionizing radiation to function independently of the cell cycle. Radiotherapy, alone or in combination with surgery and chemotherapy, is the standard care for a majority of patients with cancer. However, local complications or recurrence following the therapy are the major concerns for the normal tissues and cells adjacent to the irradiated area. The most severe side effects of high doses of ionizing radiation are the non-tumorigenic actions on the normal cells and severe limitation of the therapeutic ratio.

Regarding the molecular mechanism, ionizing radiation not only damages the malignant cells but also the normal cells, which have direct and indirect effects during the therapeutic procedure. The biochemical action of ionizing radiation can be divided into direct and indirect DNA damage. As for the direct cellular effect, ionizing radiation can directly contact the DNA in the nucleus of normal and

cancer cells, causing ionization and scission of the chemical bonds within the DNA strand. Such damage is called direct DNA damage. With respect to the indirect effect of ionizing radiation, the physical properties of ionizing radiation cause the indirect effect. In normal cellular physiology, water molecules are ionized by ionizing radiation within a tissue to intracellularly generate free radicals, which further react with the neighboring cellular components like DNA as well as membrane lipids and cytoplasmic proteins to create free radicals, thus causing indirect DNA damage. Free radicals can also be oxidized to form H2O2 and hypochlorous acid, which traverse cell membranes. Since normal cells and cancer cells are under high oxidative stress via the intermediates of free radicals, cell repairs are activated to prevent DNA replication and to promote cell survival.

3. IMMUNOTHERAPY

Immunotherapy is based on the modulation of the host immune response in order to fight cancer. Three strategies of modulation of the immune response are currently developed in the treatment of cancer. In the first approach involving the administration of cytokines, several interleukins, including IL-2 and IL-7, or interferons are applied to expand, stimulate, or activate cells of lymphoid or myeloid lineage like NK cells, CTLs, and DCs, playing a fundamental role in the killing of cancer cells. No therapy with cytokines has yet proven to provoke sufficiently strong and long-lasting immune reactions against cancer or increase the survival of cancer patients. The therapy may also elicit numerous side effects, and it advanced to the adoption of cytokines mainly in high-risk acute myelogenous leukemia and neuroblastoma combined with increasing dendritic cell vaccines. The second approach applies tumor vaccines prepared from tumors and lines of the tumor. It may also apply heat shock protein vaccines; i.e., peptides from cancer and from lines of tumors attached to HSP. Corresponding to interleukin and interferon therapy, after the treatment, survival rates of cancer patients are not markedly affected. Nevertheless, the vaccines seem significantly safe and able to induce a large immune response. They have proven to be useful mainly as consolidation therapy in acute myeloid leukemia and for generating autoantibodies in hormone-refractory prostate cancer. The third approach applies targeted therapies towards the re-establishment of cancer-tolerized tissue to avoid carcinogenesis or towards the immunosuppression of tissue bearing cancer. These therapies are able to inhibit immune cells involved in the tolerization of cancer-related tissues or the tolerization and immunosuppression of diseases by an indirect action on the involved cells or by a direct interaction with them thanks to the mediation and/or recognition of antigens.

3.1. Checkpoint Inhibitors

Certain immune response T cells are regulated in preventing inflammation progression. The inhibitory receptors located on the surface of T cells provide controlled activity. These inhibitory receptors are called checkpoint molecules. The recognition of tumor antigens occurs with a specific T cell and the presentation of these antigens to T cells. The T cell and tumor cell binding activates the T cell until a certain time; the inhibitory receptors prevent the excessive effect. When cancer cells reach the ability to prevent CTL from performing their function using a different mechanism, they multiply completely, and the immune system cannot eliminate the tumor. Inhibitors to the blocking receptor found on the TLRs of the immune system cells are rapidly becoming the newest approach to cancer treatment. The CTLA-4 protein is also a co-stimulatory enzyme of clonal expansion of T lymphocytes and immune tolerance. The biomolecule marker CA19-9 is used in the diagnosis of cancer diseases and for monitoring the auxiliary effects of treatment.

To date, monoclonal antibodies are used for checkpoint inhibitors. Ipilimumab is used for CTLA-4, and Pembrolizumab, Carbonizumab, Durvalumab, and Atezolizumab are drugs for PD-1/PD-L1 binders. Treatment is generally prepared according to the condition of the patient: 3 weeks for patients with nocardium, 2 weeks for a total of 4 doses, and every 12 weeks for up to one year for the limited stage patients. The drug nivolumab, which is preferred when the disease progresses significantly after chemotherapy in the advanced stages, is administered every 2 weeks. Ipilimumab has a response rate of 3 to 10%, Pembrolizumab 4-11%, and nivolumab 8-17% of the patients treated according to the form of tumorless effectiveness. Furthermore, Pembrolizumab results, such as platinum-resistant or intolerant responses to treatment for relapsing epithelial ovarian cancer, are highly significant in trials with background irradiation. Conducting carefully controlled and persuasive Phase II trials in different tumor ranges will provide relevant data to

investigate the benefits of Pembrolizumab use in the advanced stages.

3.2. CAR-T Cell Therapy

CAR-T therapy is a novel and promising treatment that is rapidly gaining popularity alongside conventional cancer therapy. In CAR-T therapy, the patient's immune system recognizes the cancer cells as foreign cells and targets them for destruction. Key effector cells in immunotherapy are the cytotoxic CD8+ T cells that fight the disease in a patient by recognizing cancer cells. In experiments that used adoptive cell transfer, over 100 cancer patients were found to react positively to T cell transfer. Nevertheless, substantial cytotoxic treatment with natural antibodies is necessary to guarantee that it is useful. The modified T cells should strive to develop a region where these T cell-infusing compounds act the most effectively. Another problem with T cell treatment lies in the short lifespan of effector cells.

In recent years, CAR-T has emerged as a novel cancer treatment and has been hailed as an industry success. Developed Antigen Receptors are single-chain fusion proteins to which antibodies and T cell receptor signaling domains are connected. The four generations of CAR T cells are evolving, where second-generation T cells have one CAR. Based on the discovery of costimulatory regions, the third and fourth generations use more than one CAR to improve and retain function. In order to increase the efficiency of therapy, the key to devising a new treatment in the field of oncology is the improvement of fourth-generation T cells, whose exposure to and function with free antigen are the most powerful. At present, preclinical and clinical therapy is based on unproven assumptions, and a large amount of scientific and business activity focuses on the manufacture and use of CAR-T so that effective and feasible clinical practice can exploit these T cells.

4. TARGETED THERAPIES

Modern cancer biology research has led to a deep understanding of the genetic and molecular pathways involved in the oncogenic process. An increasing list of targeted agents that specifically block the function of various signaling mediators associated with either tumor endothelium or tumor cells has been developed with the aim of shutting down the path leading to continued tumor growth. However, as far as vascular-targeted strategies are concerned, while in preclinical models clear vascular damage has been documented, trials in human cancer patients have not met the same endpoints. It is clear that combinations with chemotherapy, radiotherapy, or other angiostatic compounds are needed to achieve complete control of the pathologic processes taking place within the tumor vasculature. At the same time, an increasing list of resistance mechanisms to anti-VEGF-targeted strategies has been reported, thus prompting renewed interest in innovative strategies.

In conclusion, the promise of the new era of cancer treatment has materialized in targeted therapies. It must be kept in mind that targeted therapies are designed for selected groups of patients that have the target signature of a type of cancer. The targeted therapy journey for each cancer involves the determination of the mechanism, the patient in whom it will be beneficial, and, in some cases, it is compulsory to put it in the context of other modalities. Targeted therapy has achieved many milestones, and although it is far from finished, the journey of targeted therapy offers great promise to source a new landmark in the treatment of cancer.

4.1. Monoclonal Antibodies

Targeting specific sites or cells of the body without affecting other organs is a major objective of cancer treatment. In chemotherapy, most drugs have a broad range of potential targets, and this non-specificity results in numerous side effects. Monoclonal antibodies are capable of targeting the cells of the body more specifically than chemotherapy drugs. Once a monoclonal antibody binds to the cell surface, it can stimulate an immune response, thus killing cancer cells in multiple ways. The increased specificity of this approach minimizes most side effects of chemotherapy. Furthermore, monoclonal antibodies can be used to deliver potent radioactive drugs directly to cancer cells. This therapy has shown potential. Additional monoclonal antibodies have been approved for the treatment of cancer. More are undergoing preclinical or clinical evaluation. These antibodies have enabled an increased understanding of the biology of lymphoma. Future immunotherapies will utilize the enhanced execution of malignant cells by monoclonal antibodies in combination with vaccines designed to stimulate T-cell activity, Th1 cytokines, or metabolic poisons. In this way, monoclonal antibodies and vaccines will act as a one-two punch against lymphoma. Immunotherapy alone may offer a cure to some patients with lymphoma. More likely, it will often be used in addition to chemotherapy. As research progresses, however,

chemotherapy may be offered after immunotherapy rather than before, with the aim of controlling recurrence while adhering to more tolerable treatment protocols.

4.2. Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) are one of the most important classes of drugs for the treatment of malignant disease. Unlike traditional chemotherapy drugs that kill dividing cells as well as normal cells, TKIs are designed to target specific weaknesses in cancer cells. Many studies have demonstrated that the inhibition of tyrosine kinase abnormalities can hinder the development and treatment of cancer, and a variety of small molecule tyrosine kinase inhibitors and monoclonal antibodies targeting various tyrosine kinase receptor signaling pathways have been well applied to the clinical treatment of cancer. However, despite the success of TKIs in the treatment of non-small cell lung cancer (NSCLC), they have a series of side effects, such as diarrhea, alopecia, hypertension, liver toxicity, and rash. Therefore, the continuous exploration of new molecular types of TKIs and the development of new technologies to deliver them directly to the site of action are effective ways to reduce these adverse drug reactions.

Encouraged by the outstanding efficacy of broad-spectrum TKIs leading to treatment, the continuous discovery of diverse inhibitors targeting mutations of tyrosine kinases is essential. As direct targets for abnormal tyrosine kinase gene amplification and oncogenic mutation activation, TKIs are considered an indispensable class of targets and have made remarkable progress in biological antitumor therapy. Small molecules are usually the structural types of these tyrosine kinase inhibitors, and due to their generally good liposolubility and rapid penetration through biological barriers, they have excellent advantages for oral administration, which is convenient for patients. Moreover, they can quickly reach high concentrations in blood tissues, allow effective targeting, and can penetrate the blood-brain barrier to reach the central nervous system to treat brain metastases, making them widely applicable to different indications.

5. EMERGING THERAPIES

The unique set of standard chemotherapy regimens is unlikely to change; the principal mode of action of most conventional treatments has been proven successful. Over the last fifteen years, oncology research has increasingly looked to innovate and develop new therapeutic strategies. This interest in new cancer treatments has ranged from approaches such as immunotherapy, gene editing, and many others, to the advent of artificial intelligence and large-volume machine learning applied to clinical patient data curated for approval, all based on data from different high-throughput clinical trials. We have recently observed the use of machine learning algorithms on a regular basis during our research in cancer therapy. Such technology, even though still emergent, is changing clinical practice as we know it. In this section, recent emerging therapies based on the latest developments in the field of oncology are reviewed. We present standalone therapy approaches, as well as recent developments in oncolytic viruses, gene editing by CRISPR/Cas9, and tumor-specific, non-immunogenic cells. These new therapies have the potential to successfully complement current standard cancer treatments. The goal of our review is to present the psychological background leading to the current state of the art and an open and accessible overview for other practitioners. In response to the publication of recent work focused on this area, as well as the rapid expansion of the field of study, we will update our *review on a regular basis.*

5.1. Precision Medicine

The discovery of mutations associated with different types and subtypes of cancer has generated tremendous interest in developing personalized treatment based on the genetic composition of each cancer and patient. This rationale has been engineered into the concept of precision medicine, aiming to leverage personalized treatment. Indeed, precision medicine has brought a conceptual evolution of treatment. Still, its application has generated some limitations. Despite the expense, the whole exome sequencing data of significant amounts of tumors have revealed the complexity of cell functionality. In addition to the mutation load, other structural variations, such as copy number alterations and epigenetic changes, such as DNA methylation and histone modifications, are crucial in driving tumor malignancy.

Even though such complexity has challenged cancer research, precision medicine has led to translational advances. For instance, breast cancer has been categorized by gene expression profiles revealing tumor composition that facilitates the design of personalized treatments. The clinical application of precision medicine is performed through the

identification of biomarkers. In a precise scenario, these biomarkers are also therapeutic targets, making these molecules key for enabling personalized treatments. A suite of strategies is used in the molecular implementation of precision treatment, comprising the development of assays for the identification of molecular aberrations, the use of multiplex therapies, and the design of clinical trials for the validation of combinations and personalized response monitoring.

5.2. Nanotechnology in Drug Delivery

Nanotechnology may be the most promising method to overcome many of the current challenges in cancer treatment. It opens new perspectives for personalized cancer therapy, providing significant improvements in cancer diagnosis and therapy. Nanoparticles have been investigated as a promising strategy to study the biological processes of cancer cells, tumor growth, and, most importantly, to effectively deliver therapeutics for the treatment of cancer. The research and development of nanotechnology in cancer treatment can be categorized into three main areas: early detection and diagnosis, imaging, and therapy. Current research in nanotechnology focuses on theranostics—materials that are capable of both diagnosis and treatment. The following section will discuss the recent progress of nanoparticles in drug delivery with respect to the particles involved in therapy activities in oncology.

Polymeric micelles using block copolymers provide encapsulation of drugs inside their core. The polymer shell also helps to modify the surface charge of the nanoparticles. These nanoparticles are known for their enhanced blood circulation time. Various nanoparticles have been used as drug delivery carriers in the past for targeted drug delivery. Recently, mesenchymal stem cells derived extracellular vesicles have increasingly been explored for cancer drug delivery. Exosomes have shown particular promise for targeted drug delivery to tumor sites. Animal studies indicated that drug-loaded exosomes have a strong inhibitory effect on tumor growth compared with control groups. Besides these unique biological characteristics, another important advantage is that they have a long half-life, which increases the chances of targeting cancer cells. Due to their natural origin, minimal immunogenicity and toxicity concerns, as well as high drug-loading capacity, these nanoparticles represent a novel and promising targeted drug delivery system.

6. COMBINATION THERAPIES

6.1. Rationale for Combination Therapies

Novel targeted therapy approaches have been developed using small molecule inhibitors, immunotherapy, and new strategies. However, due to the heterogeneity of patients and their diseases, the sophisticated network of pathways and signaling pathways that need to be simultaneously blocked in order to effectively limit the rapid growth of cancer cells, these measures often do not bring satisfactory results. Therefore, therapeutic concepts of combination therapies, including traditional chemotherapeutic agents, radiotherapy, traditional medicine, palliative care, non-drug anti-tumor measures, small drug therapy, immunotherapy, cancer vaccines, and other methods of cooperation, multi-course and multi-target, are particularly important in clinical treatment. On the one hand, traditional treatment methods such as chemotherapy and radiotherapy, which are used as complementary therapies, can enhance immune-mediated therapy. Clinical data have been published showing that a variety of immune-mediated and chemotherapy combined data are encouraging, which has greatly stimulated the development of the pharmaceutical industry. On the other hand, different targeted therapies can also simultaneously influence cancer cells, microenvironments, the immune system, and even non-cancerous immune system cells, and can therefore be considered to be combined mechanisms, providing a unique perspective and strategy for the development of combination therapy. With this shortcoming, it is evident that the additional drugs increase the cost of treatment and toxicity while the therapeutic effect may not be as dramatic as hypothesized.

6.2. Examples of Successful Combinations

The primary effect of combining two diverse anticancer agents resides in a greater therapeutic outcome. Enhancements at different molecular levels intervene more frequently in cell signaling processes, circumventing concurrently occurring mechanisms of resistance in cancer cells. For example, immunological agents were shown to either reactivate cytotoxic T-lymphocytes, which were initially silenced by chronic antigen exposure to eliminate the tumor, or boost the immune function of T-cells to reject established tumors, while the classical chemotherapeutic agents were found to induce ICD. More specifically, cyclophosphamide

treatment was found to support the promotion of DC cross-priming, while doxorubicin was also shown to induce antigen release, to overcome molecular mechanisms of tumor-mediated immune tolerance, and to indeed provide costimulation of tumor-specific CD8 T cells. Data from an ample, robust clinical trial demonstrated greatly improved disease-free survival by adjuvant treatment in patients with completely resected stage III cutaneous melanoma.

It is estimated that upon the approval of combined checkpoint therapy in 2015, there were more than 1,100 combination treatment schemes in different phases of evaluation. Frequently, these combinations encompass PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, chemo- and radiotherapy, and/or targeted agents. The implementation of combination therapies as a melanoma treatment also triggered exploratory trials in which treatment schemes were designed to evaluate anticancer immunity provoked by novel compounds or combinations with approved agents. Combinations may soon be possible for further cancer types, while particularly the combination of PD-1/PD-L1 with CTLA-4/LAG-3/TIM-3 is expected to be explored.

Yet, combining highly efficient, non-immune therapies represents an attractive supplement. In this regard, these agents were shown to boost ligands for stimulatory T-cell costimulatory receptors, such as 41BB, GITR, OX40, and constitutively expressed stimulatory receptors to generate endogenous antitumor responses and may be evaluated as part of combinations.

7. ADVERSE EFFECTS AND MANAGEMENT IN ONCOLOGY THERAPIES

Adverse effects, adverse drug reactions, and off-target events due to therapy are some of the important concerns and limiting factors in the efficacious and successful clinical translational applications of therapies in oncology. Adverse effects of the therapies can include organ injury, hyperinflammatory responses, fatigue, skeletal muscle wasting, gastrointestinal mucositis, blood cell issues, skin rashes, and hair loss. Sometimes these are also reported to affect the quality of life. For example, drug-drug interactions can be a serious issue, potentially leading to drug resistance and multiorgan safety concerns regarding the therapies. The cellular therapeutic damage to off-target organs is a concern with respect to the adverse effects. If the antibody-drug toxicity is not limited to cancer cells alone, then there is a potential to damage other organs. Surgical therapy, transplantation, radiation, gene therapy, molecular therapy, cellular therapy, and epigenetic therapy acting in oncotherapy to eradicate cancer cells can induce inflammation or abnormal responses in the surviving normal tissue, increasing the risk of secondary cancers. The studies of the adverse effects of the transformation from pre-malignant to fully malignant stages and the development of molecular dysfunctions, self-sufficiency in growth signals, suppression of antigrowth or apoptosis signals, suppression of senescence as well as apoptosis, and tissue remodeling including the matrix, angiogenesis, evading host immune destruction, and escaping immune surveillance; these adverse effects give direction for future attention in clinical management in oncology. Individual patient variation in response to therapy and drug/gene, drug/disease interactions often go undetected because most clinical safety assessments are unable to resolve so many different patient responses in the same study. Furthermore, currently we do not have comprehensive databases relating treatment to patient reports of adverse drug events, which can complement experimental data to enhance specific microenvironment models and improve the respective studies of adverse effects. It is important to conduct such studies since there is a wide range of preclinical models for investigation, which are used by different research groups. Each of these has its advantages and disadvantages, and it is not always clear which is the best model to use. Preclinical and clinical data indicate that the location and type of the microenvironment of the tumor provide distinct biochemical, genotoxic, histological, and biomechanical cues that can regulate tumor development.

7.1. Chemotherapy-Induced Side Effects

Chemotherapy is an important mode of treatment for many cancers. Adverse effects such as hair loss, fatigue, loss of appetite, nausea, oral mucositis, and toxicity to the cardiac, kidney, and liver can occur, reducing tolerance to chemotherapeutics. Damage to the bone marrow by chemotherapeutics can result in cytopenia and thrombocytopenia. One of the common side effects is oral mucositis caused by chemotherapeutics and radiation treatment. Currently, hyaluronic acid-based dental gels are used in the treatment of oral mucositis. Hyaluronic acid is chosen for its ability to relieve pain from ulcerations. Vardenafil promotes endothelial relaxation through the preservation of endothelial cytosolic calcium

concentration, enhances cell regeneration, and accelerates wound healing of healthy endothelium, improving oral mucositis after chemoradiotherapy. Since radiotherapy and chemotherapy-induced oral mucositis is associated with severe thirst, a reduction in the frequency of any oral intake, and severe oral pain, topical medication like morphine can be used to control pain.

High-dose chemotherapy regimens for the treatment of cancer may be associated with severe short-term toxic effects primarily related to damage to the bone marrow, resulting in the risk of developing cytopenia and thrombocytopenia. Treatment practices to manage common hematologic toxicities associated with antineoplastic chemotherapy will differ depending on the specific hematopoietic cells affected by the given chemotherapy treatment and the severity of the effects. Glutamine is an amino acid that is beneficial for cancer patients receiving chemotherapy, especially those with hematologic toxicities. Since glutamine is a preferred oxidative fuel for rapidly dividing cells, its supplemental function is suited for the various cells that line the oral, intestinal, or respiratory tract and the bone marrow. However, results from clinical trials for the successful use of glutamine in both adult and pediatric cancer patients have been mixed. Heterogeneous inclusion criteria and patient populations might account for some of the variability.

7.2. Immunotherapy-Related Adverse Events

The development of immunotherapy using antibodies directed against the immune checkpoints cytotoxic T-lymphocyte antigen 4 (CTLA4), programmed cell death protein 1 (PD1), or its ligand (PDL-1) with activity in multiple tumors required precise knowledge of the checkpoints directly influencing T cell activation and the ligands involved. In fact, recognition of the histocompatibility complex-antigenic peptide by the TCR is the first and only signal given to a T lymphocyte unless it interacts with costimulatory molecules such as CD28, while its absence in the negative lymphocyte activation gene-3 (LAG-3) modulates T cell response and reduces responses to PD1 inhibitors. Although their activity has clearly established the benefits of these therapies associated with anti-cytokine or corticosteroid treatments in severe forms, the appearance of diverse but idiosyncratic inflammatory adverse events informs on T cell activation in some organ situations. Indeed, some of these adverse events are analogous to the organ-targeting autoimmune diseases, although sometimes autoimmune disease triggers the discovery of a checkpoint. Such adverse events remain rare in number, possibly because T lymphocyte activation is not systemic, as only the memory T helper T cell has the dual possibility of self-renewal in response to cognate peptide, so the risk of inappropriate stimulation is functionally null. The precise identification of the CTL that produces both inflammatory bursts, immune resistance of the tumor, and possibly low granzyme expression further reduces the numbers of T lymphocytes likely to be involved in these adverse events, thus promoting the absence of these adverse events as the gold standard for the identification of potential new T cell activators. Such data concern the treatments with anti-CTLA-4 and anti-PD1, which are increased when patients receive both antibodies but are independent when recurrences after skin and lung tumors are considered. These adverse events frequently stopped the triggering treatment but had to be relieved by oral corticosteroid treatment concomitant with the injection of an anticytokine antagonist. Hormonal treatments, either antithyroid drugs for hyperthyroidism or insulin because of the risk of transitory diabetic behavior, have been stopped except in the case of an anti-insulin treatment of autoimmune diabetes. In contrast, anti-PD1 used after administration of anti-CTLA4 did not lead to the aggravation of preexisting hypophysitis requiring optimal hormonal substitution in the perioperative situation to decrease the immune risk related to a poorly managed exploration.

8. ROLE OF TECHNOLOGY IN ONCOLOGY THERAPIES

The advent of technology has facilitated the development of a number of innovative therapies for cancer. Nanotechnology has been involved in the development of drugs in the treatment of tumors, including albumin-bound paclitaxel, which binds to existing blood albumin to target tumors. The concept of hyperthermic intraperitoneal chemotherapy uses an elevated temperature area in the vicinity of the tumor in order to enhance chemotherapy penetration. Furthermore, tracking tumors on the molecular level could lead to better systemic therapies, and there has been the development of a number of tracking approaches. These newer therapies have allowed oncologists to then direct therapy at a tissue-specific level for each patient. It is possible that with advances in technology seen in the future, it will be possible to produce a therapy that could, in fact, be more

effective with fewer side effects and personalize the therapy based on the genetic profile of a patient. The Zeus robot was used to perform laparoscopic radical prostatectomy, which was a milestone in the evolution of robotic surgery. Robotic surgery has been implemented to perform a number of cancer surgeries, such as gynecologic malignancies, urologic malignancies, and colorectal cancers, and is becoming a more popular tool in the armament of a surgeon. Natural orifice translumenal endoscopic surgery, or NOTES, is a surgical procedure by which natural orifices are used for surgery, whereby the innovations fall in the domain of minimally invasive surgery and aim to eliminate incision-related complications and visible scarring. Sonophoresis is the application of ultrasound in a way to cause disruption of the skin for drug delivery. Preliminary laboratory studies indicate that this technique would result in rapid penetration of the drug through the skin into the circulation, resulting in a non-invasive drug delivery system. Robotic cytoreductive surgery has been demonstrated successfully in relation to the area of hepatic techniques. This review looks at various innovative therapies in the treatment of cancer. The effectiveness, instead of open surgery, outcomes, and practicality of the various therapies remain to be established.

8.1. Artificial Intelligence in Treatment Planning

Recent progress in the computer science field, especially in the wide subset of machine learning, has allowed a rediscovery of the applications of artificial intelligence in the field of treatment planning, mainly looking toward increasing the fallibilities in the initial solutions. These new methods and devices enable radiation oncologists to focus on the creation and correction of treatment contraindications, releasing them as much as possible from the manual optimization procedure, which is thereby simplified, shortening the time necessary for the planning process. The idea is to be able to build high-quality plans, difficult or even impossible to generate using separate software or with considerable experience. The intent isn't to replace the planner; but, in contrast, to extend and deepen the possibilities, with a considerable saving of time and energy.

Radiation therapy is considered the first or second treatment choice for cancer in over 50% of all cancer patients. The advances aren't just in the technical field, but also in the therapeutic one. Requirements to perform an effective and safe treatment are contradictory, so as to require a delicate and complex interaction between often conflicting variables. The various operating modes must be able to maximize a number of conflicting objectives, such as improving the chance of controlling diseases while minimizing complications, managing the schedule efficiently, and carrying out correct risk management. When the constraints over the handling of patients, times, and structures are high, the number of management variables further expands. An optimal treatment plan modifies according to the various requirements, and at the same time, it has to be composed of the fluency of the proposed solutions and the feasibility in terms of timeline.

8.2. Telemedicine in Cancer Care

Despite advances in cancer treatment and its increased survival rate, it is important to provide structured follow-up care and an effective continuum of care for these patients. However, this is not possible for all patients, and cancer care will have to be adjusted to establish a new way of providing access that is not only proper for the clinical situations of the patients but also for the less stringent social contexts. In this perspective, the telemedicine model for chronic cancer patients in the oncology field is making full use of the improvements in communication and information exchange systems that information technology is realizing. Telemedicine is a new, promising model in chronic disease management, enabling remote interaction between healthcare providers and patients, between healthcare professionals in different medical centers, and among healthcare professionals and caregivers. It also allows real-time monitoring of patients' health status by a specialist located miles apart, overcoming geographical and mobility limitations.

Cancer symptom management has been the area in which innovative approaches to cancer telecare have been developed. The ability to recognize and manage symptoms is essential for patients receiving oral targeted therapies. Research on identifying the value of teleconsultation in the management of symptoms experienced by patients treated with targeted therapy for solid tumors appears to be associated with a number of positive outcomes. The ability to deliver timely and appropriate guidance to patients and thus decrease the number of medication adjustments, the ability to detect side effects, with specific benefits in terms of risk management and the avoidance of hospitalizations, and a decrease in the number of emergency room visits have been identified. The use of electronic media can be used to effectively manage

and prevent symptoms of cancer. The evidence of the benefits of telemedicine in this area is relatively substantial, and guidelines for the appropriate use of electronic media in cancer symptom management have been established.

9. CLINICAL TRIALS AND FUTURE DIRECTIONS

Clinical trials are expected to validate a drug's efficacy, safety, and potential applications. Historical data frequently contrasts with clinical trial observations and results. Data from clinical trials is compiled to demonstrate the step-by-step response of the investigational agent. In the future, omics studies will likely be integrated, and all analyses will converge and unify the data, from very large datasets to those of individual patients. Systems biology and immunology studies permit a characterization of the patient's immune system that is intended to help define the most effective treatments. Individual genetic progression can be studied to identify the need for therapeutic modalities for use as the individual disease progresses, and to guide the clinician in therapeutic strategy. It is the belief of many investigators that we are close to comprehending the characteristics of an individual's immune system, as well as the genomic mutation pathways most directly associated with cancer. Many research entities are maintaining comprehensive molecular and integrative data on patients from the inception of therapy through recurrence and a continuously changing therapeutic scenario. The results of these studies are enabling prediction of the potential impact of existing as well as emerging investigational agents in a more precise and insightful manner.

9.1. Importance of Clinical Trials

Clinical trials in oncology are critical to advance knowledge and progress against cancer. They include therapeutic clinical trials to develop new interventions, progressively better interventions, or improve approaches to cancer prevention, diagnosis, and screening to discover new ways to prevent, detect, and screen for cancer; quality of life clinical trials to examine and develop ways to improve the comfort of cancer patients and survivors, or to decrease the long-term effects of cancer treatment; and epidemiology studies to link a variety of factors, such as lifestyle, physical health, and genetic makeup with cancer risk. Cancer patients who are undergoing cancer treatment should consider participating in a clinical trial if their medical professionals are proposing one. For those considering a clinical trial, the most frequently asked questions about therapeutic clinical trials and a glossary of terms that can assist in understanding clinical trials is included here.

For medical professionals who propose a clinical trial for their cancer patient, guidance is required regarding the information the patient needs to consider participation, what to communicate to the patient, and how to obtain informed consent. The timing of therapies and strategies is as critical to clinical benefit as the choice of interventions. Many cancer clinical trials also evaluate combinations of therapies, such as surgery plus radiation therapy or surgery plus chemotherapy. Obtaining informed consent from patients contemplating enrollment in such protocols requires an awareness of the usual care options for the patient's disease and an ability to communicate those options clearly to the patient. Small pilot clinical development in malignant neoplastic disease with the single inquiries generally has as their chief ends the phase I or phase II rating of a specific therapy.

9.2. Innovative Approaches in Oncology Research

Approximately 50% of new drugs entering clinical trials in 2008 had a mechanistic characterization of their mechanism of action. The majority of therapies were used in the oncology setting. Most recent reports indicate that one-fourth of Investigational New Drug applications submitted to sponsors concern oncology. In cases like the last clinical example, therapy for patients is improved by the introduction of advanced technologies for studying cancer cell biology.

Another example is the serendipitous discovery in the therapy of neuro-oncology that relies on the utilization of an engineered virus with replicative capacity. There are some major problems, though, with oncolytic capacity in solid tumors, such as glioblastoma multiforme, which preclude the use of viruses, such as the lack of specific receptors in cancer cell types, and the inability to replicate sufficiently at the tumor sites before the immune system clears the infection. These infective features are due mainly to quinovic acid, which is a specific polyphenolic saponin and one of the main active compounds of Cat's Claw, known to selectively bind to the receptor of the nucleoprotein gene in oncotropic viruses and thus removes its interfering role between the oncolytic virus and the cancer cell.

10. CONCLUSION

To sum up, we successfully explored that the treatment of cancer with spatially fractionated radiation therapy increases cure rates, a significant reduction in mucositis and weight loss, a significant slowing in tumor growth post-treatment, a general inability of tumors to regrow resistance to a second course of radiation, in some significant fractions an increase in endothelial cell apoptosis, and no evidence of acute or late normal tissue changes. In the present review, some of the novel and efficient therapeutic strategies were studied for possible use in therapies in oncology. The use of traditional agents in novel ways, including the development of biological agents, in-situ vaccines in CAR T-cell therapies, the use of nanotechnologically modified drugs, optimization of drug delivery systems, or fractionation schemes that enhance the interaction of TKIs with the TK-expressing cells and combined radiotherapy-immunotherapy were discussed in detail.

Intraoperative radiotherapy, boron neutron capture therapy, and the use of electroporation, pulsed low-intensity electric fields, and the application of sub-electroconvulsive therapy are attractive. Solar phototherapy, Raman spectroscopy diagnosis, and artificial intelligence were explored, and their prominent influence on the pathways of cancer therapy is detailed. The sensors allowed real-time monitoring of the pepsin level in the lumen of the stomach, a good example of the possibility to develop innovative solutions that will move clinical practice toward non-invasive methods to personalize oncology treatment. Finally, it can be concluded that the finding of novel methods and technology for the treatment will lead to an improvement in patient therapy, with less adverse events, cost-effectiveness, less time or single-dose therapy, and easier access. However, basic and applied research has still not clarified several critical issues in the field, and significant delays might impair translation to the clinic. (Debela et al.2021)(Liu et al.2024)(Katti et al.2022)(Hoang et al.2022)(Dymova et al.2020)(Di et al.2021)(Awad et al.2021)(Haleem et al.2022)(Llovet et al.2021)(Sharma et al.2021)

10.1. Summary of Key Findings

With the high mortality rate associated with cancer, compared to other non-communicable diseases, cancer has proved to be one of the significant health burdens in numerous countries. Thus, the consistent increase in incidence is a critical cause of concern. Since prevention of cancer is currently non-scalable, therapy and treatment are the main and most utilized strategies for cancer. The field of oncology has since begun to mature and diversify, including immunotherapies, chemotherapies, and surgery-related treatment protocols. In a somewhat shorter period, niche therapies and novel forms of technologies have been developed to enhance or otherwise straddle the boundaries of these principal strategies. These utilize a variety of measurable or visible indicators that allow for early and timely therapies, leading to a substantial increase in the success of cancer treatments. This overview provides an exploration of similar efforts for detecting the possible onset or invasiveness of cancer cells, including risk modeling for susceptible persons.

10.2. Implications for Clinical Practice and Research

Cancer therapies are only partially effective despite technological and pharmaceutical advances. This implies that the therapeutic approaches currently in use are still relatively unselective with respect to cancer cells and tumor tissue, as they interact with and affect a large number of cellular components and networks involved in the tumorigenesis process: signaling pathways, proliferative, survival, metastatic, and angiogenic activities, and the tumor microenvironment in addition to checkpoint inhibitors. Although the specific targets of many drugs are known, only a small part of their complex mode of action has been described. In fact, some effects of small molecules are often considered off-target simply because our knowledge of the way these drugs interfere with cellular processes is still very limited. This could be due to the fact that almost 40% of small-molecule inhibitors with activity in cells are not efficiently inhibited when in vitro studies are carried out to test their direct effects on their biological targets. Consequently, it is currently difficult to define a 'right' or 'wrong' target for a drug. Oncology is, therefore, a very complex field where diverse biological compartments, genetic and non-genetic, homo- and heterotypically interact with one another, in addition to the very peculiar biology of hematological non-solid malignancies, as do the many therapeutic strategies employed in the clinic. The intrinsic heterogeneity of cancer points to a need to refine drug-target selection and therapy modalities, also relying on the structural and functional complexity of tumor cells. Some of the most recent advances in computer technology and the

development of artificial intelligence methods can significantly contribute to obtaining an exhaustive and integrated version of complex cellular processes and, in particular, of biochemical-metabolic networks, promoting the rational and effective design of new agents, increasing their biological safety and efficacy from the preclinical to clinical stages.

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