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Review Article

Reviewing the Main Cancer Therapies: Virotherapy Has a High Potential for Cancer Treatment

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Abstract

In 2020, around 10 million deaths worldwide were attributed to cancer, making it one of the leading causes of mortality globally. On the other hand, a lot of money, time, and energy is spent on the treatment process of this disease. In fact, cancer is a big challenge that we have been facing for years, but there is still no method that can definitively cure this disease. For years, we have mainly used surgery, chemotherapy, and radiation therapy to treat cancer. Although many advances have been made in these methods, these methods are not a definitive cure for all types of cancer and also have many complications and impose high costs on patients. By virtue of the remarkable effectiveness of CAR-T cell therapy in the treatment of leukemia, hopes for effective treatment for various types of cancer increased, but by testing this method in solid tumors, it was found that this method has low efficiency in solid tumors. In this review article, I consider the challenges and mechanisms that cancer cells apply to resist different main therapies, and finally, by comparing the challenges of different therapies, I conclude that virus therapy has a higher potential than other methods to end the problem of cancer and become a definitive cure for cancer.

Keywords: Surgery; Chemotherapy; Radiotherapy; Various Immunotherapy Methods; Virotherapy; CAR T-cell Therapy

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Introduction

The first documented case of human cancer in history back to 2700 years ago, by Hippocrates (1). Indeed the word "cancer" came from Hippocrates (a Greek physician and the father of medicine). He described tumor by the Greek words carcinos and carcinoma; therefore called cancer "karkinos". Hippocrates thought a tumor resembled to crab; for this reason, he used Greek idioms were used to describe a crab. Although Hippocrates probably named the disease "cancer," the history of cancer actually begins much earlier and he was not sure the first one to face the disease. Humanity has been plagued by cancer since prehistoric times, and in recent decades, its prevalence has significantly increased in tandem with rapidly aging populations, the general public's rising risk-taking behavior, and the increased presence of carcinogens in consumer products and the environment (1). In 2020, around 10 million deaths worldwide were attributed to cancer, making it one of the leading causes of mortality globally. The process by which cancer cells travel to other organs is known as metastasis. Cancer cells have a quicker rate of growth than normal cells. The primary factor in cancer-related deaths is metastases. Chemotherapy, radiotherapy, and surgery are three commonly used cancer treatment options (2). Another method is immunotherapy which is a developing and promising method. In addition, there are unusual and creative methods, such as using an electric field to disrupt the mitotic spindle in cancer cells that prevent them from dividing (3) (4). In the following, I review the main methods of cancer treatment.

Surgery

It is one of the most common methods for treating solid tumors (5). Because of the progress and improvement of surgical procedures, surgical side effects and mortality have been significantly reduced (6); but there are still many risks to patients. Although primary or even metastatic cancers can be removed surgically to preserve or extend a patient's life, it has long been known that surgery might hasten or trigger a tumor relapse (7).

Surgery Leads to the Development of a Novel Metastatic Disease

For a cancer cell to successfully spread to a distant organ, a complicated series of events must take place (7, 8). A cancer cell must enter the circulatory system, overcome the host's defense mechanisms, and then become imprisoned at a local or remote location before invading and thriving at the new metastatic site. Circulating tumor cells are typically seen in patients with primary malignancies. However, metastasis is typically a wasteful process, and most cancer cells that enter the bloodstream are quickly eliminated (7, 8). Nevertheless, all tissue trauma, including the sterile incision made by surgeons, causes a chain reaction of cellular and humoral inflammation on the local, regional, and systemic levels that has the ability to engulf the cancer cell and encourage its survival and metastatic growth (7). It has been established that tumor cells are shed into the blood and lymphatic circulation as a result of the unavoidable damage to the patient's tissues during the incision and manipulation of the tumor that is cut out and its vasculature (7, 9). Circulating tumor cells could increase at least 10-fold as a result of treatment for the tumor (7, 10). In addition, it has been shown that the quantity of cancer cells in the blood before and after surgery is a reliable indicator of relapse (7, 11). Numerous postoperative modifications let the cancer cells survive in circulation and raise the probability of distant implantation in addition to aiding in the spread of circulating cells (7). The removal of cancer cells from the bloodstream and the avoidance of metastasis formation are both significantly aided by natural killer (NK) cells and macrophages (7, 12, 13). According to the size and extent of the operation, decreased NK cell cytotoxicity and abnormal macrophage activity were observed in experimental animals, along with an increase in tumor growth (7, 12, 13).

Surgery Promotes the Residual Disease and Growth of Micro metastatic

Early in the course of the primary tumor's growth, metastatic cancer cells may depart, organizing clinically invisible micrometastases at distant sites. The balance between cellular death and proliferation can persist in these islands of clinically undetected micrometastases (7, 14). Surgical trauma-related systemic and local inflammatory processes may unexpectedly unleash their growth potential (7, 14). Furthermore, surgery can cause the adaptive immune response to be downregulated afterward, which can lead to immunological evasion (7).

Perioperative Risk Factors for Cancer Recurrence

Numerous perioperative factors, such as anesthetic administration, hypothermia, blood transfusions, and the progression of postoperative

problems, can alter the oncological outcomes in addition to the alterations previously discussed that are directly related to surgical treatment (7). For these reasons, radiation therapy or chemotherapy is usually used in addition to surgery to bridle the complications of surgery and cure cancer in the patient.

Chemotherapy

Chemotherapy is a low-targeted treatment which damages both healthy and cancer cells; for this reason, it has many side effects such as hair loss, Decreased ability of the body to fight infections**,** Anaemia, Bruising and bleeding, Sore mouth, Nausea, and vomiting, etc. **.** However, by advances in drug delivery, this treatment has improved.
Chemotherapy is the use of medications or chemicals to kill cancer cells, and it has systemic effects. Based on their mechanisms of function, anticancer medications fall into a number of distinct categories, including (5):

1) Alkylating substances (that damage DNA)

2) Anti-metabolites (which substitute the regular building blocks of DNA and RNA)

3) Antibiotics (which interfere with the enzymes involved in DNA replication)

4) Inhibitors of topoisomerase (which inhibit either topoisomerase I or II; these are the enzymes involved in unwinding DNA during transcription and replication).

5) Inhibitors of mitosis (which inhibit mitosis and cell division)

6) Corticosteroids (that are used for the treatment of cancer and to mitigate the negative effects of other medications)

Cancer cells can resistant to chemotherapy. The bulk (over 90%) of fatalities in cancer patients receiving conventional chemotherapy or novel targeted medicines are caused by multidrug resistance (MDR) (15). Cancer cells use different MDR mechanisms during chemotherapy that can be including genetic factors (epigenetic alterations, gene mutations, and amplifications), increased drug efflux, increased xenobiotic metabolism, increased DNA repair capability, growth factors, epithelial-mesenchymal transition, drug degradation, altered cell surface receptors, active stroma, escape from apoptosis, and immune system evasion; each of these mechanisms can reduce the therapeutic efficacy of applied drugs, making the treatment of tumors more difficult (15-22). Furthermore, the ongoing development of tumor cells from cancer stem or progenitor cells that already exist and the persistence of cancer stem or progenitor cells following chemotherapy are two additional processes that play a significant role in cancer drug resistance (21, 22).

A significant issue with chemotherapy outcomes is drug resistance. A recurrence occurs in around 80% of patients with advanced ovarian cancer a few months after chemotherapy, and these tumors are frequently resistant to conventional chemotherapy (21, 23, 24). Expression of MDR1 in some ovarian cancers following conventional chemotherapy (paclitaxel and a platinum compound) causes cancer recurrence (25, 26). Also, the majority of chemotherapy medications are frequently ineffective against liver cancer, and no combination (the most popular combos include doxorubicin and/or cisplatin) is better than a single medication. Numerous drug combinations used to treat liver cancer are linked to high toxicity (21, 27).

In addition to the cancer cells' resistance to chemotherapy, patients who receive it may experience harmful side effects. Numerous anti-cancer medications, such as vinca alkaloids, platinum-based medicines, proteasome inhibitors, taxanes, and angiogenesis inhibitors, are to blame for chemotherapy-induced peripheral neuropathy (CIPN). High morbidity, including ataxia, depression, and sleeplessness, is associated with long-term CIPN (28).

Peripheral and central neurotoxicity brought on by anti-cancer medications may persist for years following the end of therapy and significantly lower functional capacity and quality of life in cancer survivors (28).

Radiotherapy

This method is more targeted than chemotherapy as well as one of the most economical aspects of cancer treatment is radiation (29, 30). High radiation dosages are used in this procedure to destroy cancer cells and reduce tumor size. Ionizing radiation (high energy) used in radiotherapy damages the DNA of the cancer cells in the treated area, killing them. Healthy cells are also affected by radiation. By irradiating malignant tissues in methods that increase tumor control and by reducing doses to healthy tissues to reduce treatment problems, technological advancements aim to improve cancer outcomes in two main ways (31). Radiation therapy advancements have

improved long-term outcomes for cancer patients (31). For instance, in the United States, the 5-year survival rate for cancer has grown to approximately 83% for children and 68% for adults (31, 32). Long-term survivors are more likely to experience treatment-related side effects such as infertility issues (33), radiogenic second malignancy, cardiovascular (34, 35), and central nervous system (36, 37) disorders, as well as a wide range of other toxicities (38, 31). These challenges could be brought on by a disease (such as damage from a primary cancer) or by treatments including chemotherapy, surgery, and radiation therapy. These will continue to manifest in many people even after the main malignancy has been treated. For instance, among those who survived childhood cancer, the risk of morbidity and mortality remained elevated past the age of 40 (39, 31). There are currently significant knowledge gaps in the following areas: a) the issues with long-term health that long-term cancer survivors have, particularly ten years or more after exposure; b) dose, quality, modality, and fractionation of radiation and their impacts on the risk of late effects; c) the application of risk models created from radiation exposures to healthy populations with low doses to groups of cancer survivors with high-dose fractionated exposures; d) the usefulness of population-based hazard models for specific patients, whose sensitivity to radiogenic late effects can vary depending on their genetic profile and other circumstances; and e) the incidence, severity, and economic implications of late side effects following modern technology radiotherapies (31). It will take new research infrastructure, tactics, and methodologies to close these gaps.

Usually, radiotherapy is followed by the unavoidable development of cancer cells that are resistant to radiation exposure (30, 40, 41). One of the biggest challenges in treating cancer is radiotherapy resistance (RR), which is defined as a decrease in the efficacy of anti-tumor therapy (42). Radiotherapy resistance either results from the cancer microenvironment shielding cancer cells from the treatment or happens within cancer cells when cancer cell genes or phenotypes are altered in response to radiation exposure. External resistance refers to the former, and internal resistance to the latter (30, 43). RR leads to poor treatment response, cancer recurrence, poor prognosis, increased disease treatment burden, and reduced quality of life. In addition, rectal bleeding, radiation-related diarrhea, and radiation dermatitis are a few of the symptoms caused by radiotherapy resistance, which damages healthy tissues next to cancer and disrupts their biochemical and physiological processes (30, 44), as well as a grown risk of later secondary cancer (30, 45, 46) or persistent noncommunicable illnesses including cardiovascular diseases or type II diabetes (30, 47). In the past century, numerous studies have been conducted to examine the regulatory genes, chemicals, and signaling pathways linked with RR in order to build radiation sensitizers and understand the fundamental mechanisms of RR (30, 48).

Increased RR in cancer cells is caused by a variety of causes, including membrane signaling sensors, the local cancer microenvironment, the patient immune system, nutritional status (49), gut microbial community (50), and mental health status (51). The most important operator in the response to radiation exposure and the orchestration of the subsequent cascade of DNA repair response signaling pathways to control cancer cell cycle arrest and cell fate, i.e., survival or death, is DNA damage, which is a primary and intrinsic factor among the discovered and reported factors (52). Therefore, the DNA damage response (DDR) of tumor cells and their capacity to repair DNA damage are crucial in deciding the outcome of cancer cells. In other words, the ability of radiation to control cancer is mostly dependent on radiation-induced DNA damage (RIDD). (30).

In response to an IR insult, DNA damage initiates a series of biochemical processes, signaling a variety of cellular responses. How DNA damage is detected and how cascade signaling of ensuing biochemical reactions is initiated, however, are the key issues. Recognizing DNA damage requires the use of primary signal transducers and DNA damage sensors (53). The ideal DNA damage sensors are the first proteins that recognize damage signals and initiate cell signaling transduction as soon as they come into contact with DNA damage locations (54). Additionally, DNA damage sensors have the ability to attract DDR proteins to DNA damage sites (55). Signal transducers frequently collaborate with DNA damage sensors as functional partners (56). Since signal transducers and DNA damage sensors frequently coexist, it is challenging to classify them. Signal transducers, however, have kinase activity, which impels the chemical signal of DNA damage to cause biochemical modification reactions and activate downstream effectors (30).

Repair of DNA damage caused by IR

Through the induction of DSBs (double-strand breaks) in cancer cells' genomic DNA, IR de-

stroys cancer cells by causing apoptosis, genomic instability, postmitotic death, or changes to the cell cycle checkpoint. Cancer cells create and adapt unique DNA damage repair mechanisms to protect themselves from IR insults during IR therapy in order to survive (57). "Hormesis" is the term for the induction of DNA mechanisms needed to recognize IR effects (58). It has been shown that three distinct major pathways—NHEJ, the HR-based pathway, and alternative end joining—evolved to execute DSB repair. These repair pathways are designed to address various DNA lesions, removing DSBs while maintaining genomic integrity in the process. (30, 59).

Understanding the fundamental processes by which DNA damage is repaired in cancer cells following IR treatment would help combat RR (60). For example, radiation-induced DSB repair in non-small-cell lung cancer (NSCLC) cells was significantly delayed by the active quassinoid (eurycomalactone), which was isolated from *Eurycoma longifolia Jack* (61). According to research by Koval et al. (58), chronic exposure to γ-rays increased the expression of the mus210, mus219, and mus309 genes in Canton-S flies even 56 days after exposure. They also showed that cancer cells could activate a protective system in response to IR, increasing their resistance to subsequent exposure to IR. The detailed mechanism of cancer cell defense in IR-induced hormesis is still unknown, despite the development of genome-wide sequencing technologies enabling scientists to recognize the molecular mechanisms of the radiation-induced adaptive response, including the Notch, tumor growth factor-β, mammalian target of rapamycin, and Wnt signaling pathways (30).

DSB repair mechanisms for DNA

The HR pathway was the first to be discovered in the study of the DSB repair pathway (62). Due to the close proximity of homologous strands during mitosis, the HR pathway received its name. Particularly in cells in the later S and G2/M phases, HR is triggered (63). The DNA end-joining pathway, the second DSB repair process, was discovered in the 1980s. Unlike HR, NHEJ is activated both in the G2/M and G0/G1 phases (64). NHEJ is thought to predominate in mammalian cells, as opposed to microorganisms, though (65, 66). The second discovered pathway was called to as NHEJ since the idiom homologous had already been employed in the HR pathway via radiobiological community (67, 68). Some radiobiologists, however, disagree with the naming strategy and have proposed the existence of additional DSB repair pathways because studies have shown that the HR and NHEJ pathways exist in cancer cells with high radiotherapy sensitivity, indicating that additional repair pathways are probably active as well (30).

For cancer survivors, radiotherapy treatments are associated with significant side effects that might lower their quality of life. Modern radiation oncology procedures have helped to lessen some of the negative effects, but further in-depth research is needed to reduce RT-induced negative effects. General oncologists and other healthcare professionals should carefully assess and manage any side effects of radiation therapy (RT) (69).

Immunotherapy

Immunotherapy uses our immune system to fight cancer cells and tumor. Although immunotherapy is a promising and developing treatment, an important challenge to this approach is the controlled modulation of the immune system because it has side effects including nonspecific inflammation and autoimmunity. There are various types of immunotherapy as follows:

Monoclonal Antibodies

Monoclonal antibodies (mAbs or Moabs) can either directly kill cancer cells or stimulate the immune system to attack cancer cells. Of course main goals of many monoclonal antibody therapies is to block growth factor receptor signaling. The body can react to mAbs and causes side effects, including: fever, chills, weakness, headache, nausea, vomiting, diarrhea, low blood pressure, rashes. Nevertheless, they have fewer side effects than conventional chemotherapy (70). Currently, mAbs are applied in a variety of ways to treat cancer, including: targeting pro-tumorigenic compounds in the microenvironment, immune checkpoint inhibitors, bispecific T cell engagers (BiTEs) as well as antibodies can be conjugated to drugs (ADCs), radionuclides, protein toxins, cytotoxic organic compounds, immunomodulators such as cytokines (71, 72). Although mAbs have been shown to have successful therapeutic effects in the treatment of cancer, the instability of these drugs and their clinical resistance to mAbs, poor tumor tissue penetration, heterogeneous distribution (failure to deliver efficacious doses throughout the tumor may resulting in treatment failure and the development of acquired resistance mechanisms) are important challenges that hamper the clinical efficacy of mAbs. The stability of mAbs is improved by making changes in

their molecular structure and engineering them, but not completely, in fact their instability is still a matter of concern (73). Most patients become disease resistant within a year, and few individuals will react to mAbs (71, 74, 75). There are two types of therapeutic resistance: innate (primary) and acquired (secondary). Typically, innate resistance results from mutations that were present in the tumor cells prior to therapy whereas the result of immune selection pressure and tumor immunoediting during treatment is acquired resistance. Preclinical models and clinical trials of mAb therapy have discovered a numerous of mechanisms of resistance, including mutations of the antibody target, epithelial to mesenchymal transition (EMT), induction of alternative growth signaling pathways, and impaired effector cell responses (71).

Physical barriers in the tumor microenvironment, most notably a markedly elevated hydrostatic pressure, prevent macromolecules from penetrating the tumor following systemic administration (70). As a result, due to a reduction in the overall amount of antibody molecules that reach the target tissue as well as the exposure of difficult-to-penetrate tumor regions to marginal antibody dosages, acquired antibody resistance and treatment failure result (70, 76). In fact, due to the relatively limited efficacy of mAbs, they are commonly administered in combination with chemotherapy (70, 77).

Therapeutic mAb must overcome physical barriers in order to penetrate and distribute uniformly all over the tumor (70). Damaged lymphatic drainage in solid malignant tumors brought on by a sparse network of lymphatic vessels generates a buildup of macromolecules in the interstitial tissue, which raises hydrostatic pressure (70) (78). Convection and extravasation of macromolecules from the vascular lumen into the tumor are therefore constrained by the altered pressure differential from the vascular vessels to the interstitial compartment. In addition, cellular internalization and subsequent endocytic clearance at the tumor edge ("binding-site barrier") impede extravasation and antibody distribution further, resulting in poor penetration and regions of marginal antibody concentrations (70, 79). The binding-site barrier demonstrates that higher antigen expression and higher affinity, especially at the tumor edge, can delay mAb tumor penetration and damage homogeneous distribution (70). One solution to improve diffusion is to use smaller antibody fragments. However, though these agents distribute more, the clearance amounts for smaller fragments is significantly higher than full-size antibody molecules (70, 80, 81).

Checkpoint Inhibitors

The immune system uses checkpoints to distinguish normal cells from abnormal or foreign ones. In fact, checkpoints can enable or disable the immune response. However, malignant cells express some of immune-checkpoint proteins to dysregulate the antitumor immunity and help the growth and development of cancer cells (82, 83). Checkpoint inhibitors don't eliminate cancer cells directly; they help the immune system to attack and kill cancer cells. Checkpoint inhibitor is a type of drug that targets and blocks proteins called checkpoints that are expressed by some cancer cells and some types of immune system cells, such as T cells. T cells can kill cancer cells better following blockade of these checkpoints. Checkpoint proteins detected on cancer cells or T cells include PD-1, PD-L1 and CTLA-4. Side effects of this type of treatment may include the following: diarrhea, fatigue, cough, nausea, skin rash, poor appetite, constipation, muscle and joint pain, as well as more serious side effects take place less often, including: infusion reactions (chills, fever, flushing of the face, itchy skin, rash, wheezing, feeling dizzy, and trouble breathing) and autoimmune reactions (life-threatening problems in the intestines, lungs, liver, kidneys, hormone-making glands, or other organs).

Anti-PD-1/PD-L1 antibodies are most well-known immune checkpoint inhibitors (ICIs). It has been estimated via a review that the objective response rate (ORR) for patients who treated with Pembrolizumab (a type of anti-PD-1/PD-L1 antibody) in esophageal cancer (10%), head and neck squamous cell carcinoma (17%), urothelial carcinoma (29%), renal cell carcinoma (RCC) (36%), non-small cell lung cancer (NSCLC) (42%), melanoma (52%), and Hodgkin lymphoma (72%) (84). Furthermore, some of responders after treatment with ICIs will become non-responders. For instance, 20% of responders with reactive melanoma who received anti-PD-1 inhibitor treatment achieved a complete response (CR), whereas 55% of them achieved a partial response (PR) and afterward developed acquired resistance (85). Acquired resistance to ICIs can be due to the following reasons:

1. Signaling pathways:

Changes in canonical cancer pathways such as the WNT-β-catenin, PI3K-AKT-mTOR, and MAPK (mitogen-activated protein kinase) pathways are related to increased resistance to Im-

mune checkpoint blockade (ICB). Inactivation of the PI3K (phosphoinositide 3-kinase) and MAPK pathways, via alterations such as PTEN (phosphatase and tensin homolog) loss, are related to a decrease in tumor infiltrating lymphocytes (TILs) and reduced expression of pro-inflammatory cytokines in the tumor mutational burden (TME). On the other hand, activation of the IDO1 (indoleamine 2,3-dioxygenase) and WNT-β-catenin pathways lead to suppression of NK (natural killer) cells and T cells in the TME. Also, Induction of TGFβ, and LoF (loss of function) changes in the JAK-STAT pathway, by change of the immune response directly, increase resistance to immune checkpoint therapy (86).

Although IFN-γ can be used as an immunomodulatory agent in the treatment of certain malignant tumors, it plays a paradoxical role in regulating anti-tumor immunity (85, 87, 88). In fact, imbalance of the IFN-γ signaling pathway due to ICI treatment assists to the development of acquired resistance (85).

2. Gene mutations in tumor cells

3. Blockade of the antigen presentation process

4. Loss of tumor neoantigens

5. Epigenetic alterations in tumor cells:

The epigenetic alteration (histone enzyme modification and DNA methylation) affects the expression amounts and presentation of tumor antigens, the abundance of myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and the functions of T cells including regulatory T cells (Tregs) and CD8+T (85, 89).

6. Tumor microenvironment:

Tumor microenvironment can affect ICI therapy by increase of suppressor T cells and decrease of effector T cells, Up-regulation of ICs, angiogenesis, EMC remodeling (85, 90-96).

Despite the fact that ICIs therapy is frequently more well-tolerated than conventional chemotherapy, clinical benefits are only seen in a small percentage of cancer patients. Additionally, some patients who initially react to treatment frequently experience relapses brought on by cancer resistance (82).

Vaccines

Cancer vaccines assist the immune system in locating and eliminating cancer cells. Cancer vaccines can both help treat cancer and prevent recurrence after other treatments, as well as help prevent certain cancer (Prophylactic vaccines include hepatitis B virus (HBV) vaccine and human papillomavirus (HPV)). Some cancer vaccines are used to treat cancer are made up of pure antigens (specific proteins on cancer cells), parts of cancer cells, or cancer cells. In order to create a vaccine and boost and improve the immune response against the cancer cells, it is occasionally necessary to remove the patient's immune cells and expose them to these substances in a lab. Cancer vaccines are often combined with other cells or substances called adjuvants to help elevate the immune response. In fact, an adjuvant is a product that modulates or increases the immune response against an antigen. The perfect adjuvant, according to this widely accepted definition, should increase the effectiveness of the immune response while remaining safe and non-toxic (97). Therapeutic cancer vaccines (TCVs) due to use of adjuvant and antigen engage both innate and adaptive immunity to stimulate an innate and adaptive response (98). Through pattern recognition receptors like Toll-like receptors that recognize and react to damage- or pathogen-related molecular patterns, non-specific innate immune responses are triggered (98). Engagement of these receptors activates transcription factor nuclear factor κB (NF-κB), triggers chemokine and cytokine production, and recruits and activates lymphocytes (98, 99). To trigger adaptive CD8+ cytotoxic T cell lymphocyte-mediated anti-tumor responses, TCVs must help in (a) presentation and recognition of immunogenic tumor antigens via antigen-presenting cells (APCs); (b) employment, antigen processing, and maturation of APCs; (c) induced expression of T cell co-stimulatory signals and cytokines via APCs; (d) interaction of APCs with the adaptive immune system to activate CD8+ T cells; and, finally, (e) localization of these components to the tumor (98, 100-102). Nevertheless, TCVs have rarely met the requirements for the variety of biological processes that must be activated for a TCV to be effective (98). Numerous pivotal studies and hundreds of TCV clinical trials have all failed to clearly demonstrate a therapeutic advantage (98, 103, 104). This is probably caused by a combination of factors not limited to (a) lack of effective adjuvants, (b) poorly immunogenic platforms, (c) suboptimal antigens, and (d) an inadequate number of CD8+ cytotoxic T cell lymphocytes (CTLs) entering the tumor caused by immunosuppression associated with high disease burden, an immunosuppressive tumor microenvironment, or poor immune fitness (98, 105, 106). In addition, other factors can affect the effectiveness of

cancer vaccines, including: (a) The patients that will receive the vaccines have an impaired immune system (or immuno-compromised) due to, for instance, impaired mechanisms of antigen presentation, non-responsiveness of activated T cells and increased inhibition of self-reactivity via regulatory T cells. (b) The tumor antigen (Ag) are usually self-derived and are, thus, poorly immunogenic. (c) Tumors develop evasion mechanisms to avoid the immune system, such as tumor editing, secretion of suppressive cytokines and low or non-expression of MHC I molecules. (d) It has been proven cell-mediated immunity leading T cells toward tumor-specific antigens is difficult. (e) Interpatient heterogeneity affects the immunogenicity of TCVs (97, 98).

Cytokines

Proteins called cytokines are essential for regulating the activity and development of immune system and blood cells. Cytokines signal the immune system to perform its duty as they are released. The development and growth of all blood cells as well as other cells that support the body's inflammatory and immunological responses are affected by cytokines. Furthermore, by sending signals, they assist to boost anti-cancer activity that can assist make healthy cells live longer and unhealthy cells perish. In fact, immune cells use molecules called cytokines as molecular messengers to communicate with one another in order to establish a strong, well-coordinated, yet self-limited immune response to a particular antigen (107). Cytokine signaling is crucial to a variety of biological processes, including aging, cell growth, and tissue repair, in addition to serving as an important immune system mediator (108). Side effects of cytokines can be as follows: flu-like symptoms (including: headache, fever, chills, fatigue, vomiting, nausea, loss of appetite), low white blood cell counts (that increase the hazard of infection), thinning hair, skin rashes; these side effects may be severe. Of course, the majority of negative effects are short-lived when treatment ends; however, nerve injury is a rare long-term side effect (including the spinal cord and brain).
The main characteristic of cytokines as regulators of the immune system response is having a considerable degree of pleiotropism that means cytokine regulates various types of the immune system cells that can support both pro-tumor and anti-tumor responses (109). In addition, the pleiotropic feature of cytokines allows a cytokine to affect a variety of cell types to mediate diverse and sometimes conflicting effects (107). The degree of redundancy in cytokine signaling—the fact that several cytokines have the same functional effects—is another important aspect of the process (107). Because one cytokine's modification can be made up for by another, this redundancy makes manipulating cytokines for therapeutic purposes somewhat difficult (107). Cytokines play complex and often conflicting roles in the host defense, development of the immune system, and tumor immunobiology (107). Therefore, the mechanisms of action and biological activities of cytokines are very important that must be considered in cytokine-based therapies and drugs for cancer treatment. Pro-inflammatory cytokines (e.g., interferon (IFN)-α, interleukin (IL)-2, IL-15, IL-21, IL-10, IL-12) can play a role in cancer immunotherapy and acting on every stage of the cancer immunity cycle (110-112). Therefore, cytokines can make better antigen priming, increase the number of effector immune cells in the tumour microenvironment (TME) and increase their cytolytic activity (112). Nevertheless, the vast redundancy and pleiotropism of cytokines, and the dual function of multitude cytokines in both immune suppression and immune activation, poses substantial challenges to reach significant anti-tumor responses without causing treatment-limiting toxicities-a dilemma that by the low response rates and infamous toxicities of IL-2 is well demonstrated (107). In fact, despite the biological importance of cytokines and their clinical application in the treatment of cancer, cytokine-based therapies have intrinsic challenges that limit their therapeutic potential including: the short half-life and poor circulation, systemic toxicity of high doses of cytokines (which are necessary to obtain a considerable response in cancer patients) prompt pro-inflammatory and autoimmune reactions, and low tissue- or cell-specificity (108, 109). For this reason, scientists through improve targeting of cytokines, alter their pharmacokinetics, and engineer cytokines, try to overcome the challenges of cytokine therapy and increase their therapeutic potential. However, because they are significantly pleiotropic and under normal physiological conditions, they are commonly produced and function very locally in tissues, may systemic administration can result in severe side effects that it has been caused the clinical application of cytokines limited (113). On the other hand, intratumoral injection of cytokines does not prevent their systemic leakage. (113, 114). Many of the side effects of cytokines are due to the release of downstream cytokines (i.e., the cytokine cascade) (113). The cytokine cascade can prompt

autoimmune disorders, affecting thyroid activity and sometimes resulting in psychiatric disorders such as depression (113, 115). It is difficult to stop immune activation without also stopping the expression of downstream cytokines (113). Furthermore, although the downstream cytokines may result in toxicities, they may also take part in the therapeutic effect. For instance, IL-12-mediated toxicities are associated with induction of high amounts of systemic IFN-γ (113, 116).

Other cancer therapies may be used in combination with cytokines to increase therapeutic efficacy and reduce cytokine toxicity. However, these combination therapies may be encountered with challenges due to the complexity of the effects and functions of cytokines, as follows:

Aberrant cytokine signaling direct the formation of stromal blood vessel networks, and the proliferation of tumor cells that both of them support progressive tumor growth (117). Cytokines are responsible for a number of physiologic processes (including: cell migration, inflammation, apoptosis, and angiogenesis) that are strongly associated with tumor growth, metastasis and tumorigenesis (117). There is an evidence that cancer cells and their related stroma secreted cytokines that play a crucial role in drug resistance so that probably primary diagnosis of cancer drug resistance may finally be made during chemotherapy by monitoring alterations in circulating cytokine levels (117).

Chronic inflammation prompted caused by the tumor microenvironment (TME) lead to cancer initiation, proliferation, progression, metastasis, and therapeutic resistance (118). TME induces the secretion of diverse cytokines, in various types and stages of cancers (118). These cytokines may prevent tumor growth, but they may also contribute to persistent inflammation, which promotes tumor growth and has been linked to poor cancer treatment outcomes (118).

Furthermore, the effects of cytokines on tumor formation are frequently dependent on one another due to the complexity of the TME, the variety of cytokines, and the presence of pleiotropic regulatory networks among them (119-122).

These data demonstrate that the complexity of cytokine signaling pathways, the intertwined relationship that cytokines have with each other, dual and contrasting functions of cytokines, and the importance of their effects on body physiology and cancer treatment may hinder high effects of combination therapies with cytokines.

Oncolytic viruses

Oncolytic virotherapy (OVT) uses viral particles that replicate within the cancer cell that lead to cell death that has the potential to be effective against metastatic cancers (123). OVT uses oncolytic viruses (OVs) in order to kill cancer cells (124). The advantage of OVs is their capability to infect and replicate in cancer cells without harming healthy cells that causes few side effects because OVs by genetic engineering and modification, are lack the thymidine kinase gene, which causes viruses to replicate only in cells that up-regulate the RAS pathway, such as cancer cells (124, 125). Virotherapy is considered as a highly tolerable cancer treatment for most patients and its side effects are limited. The severe and minor side effects may include an inflammatory response to the treatment and flu-like symptoms (such as fever, nausea, chills, and muscle aches) respectively. OVs can create long-lasting immunological memory, thus preventing metastatic recurrence and spread. In fact, viruses can induce the process that is a particular form of apoptosis in which the death of cancer cells is capable to trigger an effective anti-tumor response (i.e. immunogenic cell death (ICD)). For this reason, OVs through infecting tumor cells, they are capable to trigger an inflammatory reaction (124). On the other hand, the main anti-viral response of the cells is IFN pathway but in case of cancer cells, IFN pathway is often dysfunction. In fact, tumor cells reduce several specific mechanisms applied by host cells to respond to viral infection (e.g. type I IFN pathway) thus, viruses can replicate successfully in tumor cells (124, 126). As a result, OVs are capable to infect cancer cells easily and accomplish their function. Despite the characteristics of oncolytic viruses, their antitumor efficacy is limited and have been successful in a small number of clinical trials (124, 127).
Challenges that virotherapy encounters generally include the following:

1. The patient's immune system response to virotherapy can lead to rapid clearance of the virus and ineffective treatment.

2. Tumor microenvironment:

Other than cancer cells, solid tumor masses contain diverse and complex compounds of noncancerous cells and matrix components, including: resident stromal cells like endothelial and fibroblast cells, immune cells, extracellular matrix (ECM) proteins, and cancer-associated fi-

broblasts (CAFs) which these factors collectively are referred to as the tumor microenvironment (TME) or tumor stroma (128, 129). Cancer cells form a “cold” immunosuppressive tumor microenvironment and use numerous mechanisms to escape and suppress anticancer immune responses (130). In other words, interactions between components of the TME and the cancer cells forms an immunosuppressive network, which extremely affects tumor development, progression, and metastasis as well as immunosuppression in the TME may lead to a resistance to treatment and deficient therapeutic response (128,131). Oncolytic viruses have demonstrated able to transform a cold TME into an inflamed one, as a result of that, they can reawakening antitumor immune responses (130). However, viruses in the tumor microenvironment encounter challenges that can include the following:

α) One of the main challenges of virotherapy is the large size of the tumor that can hinder OVs access to the tumor core (124). In fact, solid tumors contain many physical barriers, such as fibroblasts, that can cause heterogeneous and incomplete spread of viruses in the tumor. The extracellular matrix (ECM) may also act as a snare for virus binding and absorbing viral particles, thereby hindering infection of tumor cells. In addition, the extracellular matrix can act as a molecular sift; in other words, whiles the movement of large particles (~150 nm diameter) such as herpes viruses is impeded, smaller nanoparticles (~20 nm) spread out more easily throughout the matrix (132, 133).

β) tumor-associated interferon-mediated resistance (134)

χ) Increased pressure gradients and the interstitial pressure of solid tumors within the tumors can repel viruses and hindering them from entering and spreading in the tumors (132). Even considerably increased internal pressure in solid tumors and nodules cause an obvious hurdle for delivery and diffusion of other types of macromolecules (132).

δ) In areas of the tumor where hypoxic conditions are prevalent, it can reduce the replication of viruses (132).

ε) Immune system cells and antibodies can prevent the spread of viruses in the tumor microenvironment and clear them.

ϕ) Tumor cells may eliminate virus receptors by modifying their cell membranes to prevent the virus from entering tumor cells.

γ) Some tumor cells may escape destruction by hiding in connective tissue (132).

Chimeric Antigen Receptor (CAR) T-cell therapy

CAR T-cell therapy apply T cells taken from the patient's blood that altering them in the lab to fight cancer cells. In fact, these T cells are engineered by adding a gene for a receptor is called a chimeric antigen receptor or CAR. Afterward, CAR T cells will be given back to the patient once they have been made enough of them. Chimeric antigen receptor (CAR) assists the T cells attach to a specific cancer cell antigen. Of course, the patient may get chemotherapy a few days prior to the CAR T-cell injection to help reduce the amount of other immune cells, which offers the CAR T cells a better chance to become activated to fight cancer. Because CAR T cells function best while there are still cancer cells to assault, this chemotherapy is typically not very intense. The CAR T cells multiply when they attach to cancer cells and can help even more eradicate cancer cells. CAR T-cell therapy is sometimes referred to as a form of cell-based gene therapy since it involves changing the genes within T cells to assist them to attack cancer cells.
Although CAR T-cell therapy has shown high results in the treatment of refractory blood malignancies, only a small number of patients with solid tumors and brain tumors respond fully to this treatment.

Side effects of CAR T-cell therapy may include the following:

1. Cytokine release syndrome (CRS): high fever and chills, trouble breathing, (severe vomiting, nausea, and/or diarrhea), feeling dizzy or lightheaded, headaches, fast heartbeat, feeling very tired, muscle and/or joint pain

2. Nervous system problems: headaches, changes in consciousness, confusion or agitation, seizures, shaking or twitching (tremors), trouble speaking and understanding, loss of balance

The main challenges of this type of treatment include the following:

1. Expression of heterogeneous antigens in solid tumors:

One of the reasons CAR T cells are so effective in treating blood disorders is that cancer cells commonly express specific markers, but solid tumors often do not express one tumor-specific marker (135). The markers that are targeted, may also be expressed on the patient's healthy and non-cancerous cells, which causes toxicity in the patient, even if these markers are slightly expressed on healthy cells. In fact, solid tumors incline to express a significant level of antigen heterogeneity and due to most tumor cells are of epithelial origin, the presence of specific antigens, which are not present on normal epithelial cells, is rare that leading to toxicity (135, 136).

2. Low ability of CAR T cells to infiltrate and enter the tumor effectively:

Tumors comprise multiple cells and connections, such as blood vessels, extracellular matrix, and fibroblasts, which prevent high doses of CAR T cells from reaching cancer cells inside the tumor (137, 138). In addition, conditions inside the tumor, such as low pH, low oxygen, and low nutrient conditions, make therapeutic delivery considerably difficult as well as immuno-factors secreted by solid tumors , including growth factors, cytokines, and chemokines, can hindering CAR T cells from infiltrating within the tumor (137, 139).

3. Tumor microenvironment (TME) conditions:

As I mentioned, due to the physical barriers and the tumor microenvironment (TME) conditions, an insufficient dose of CAR T cells penetrates the tumor, then this insufficient dose of CAR T cells is exposed to significant amounts and diverse types of immune suppressive checkpoint molecules and cytokines, as well as exposed to a multitude of metabolic stresses, all of which these factors affect the efficiency of CAR T cells and as a consequence can render these cells anergic, exhausted, or apoptotic (136).

The TME is hypoxic and also lacks essential nutrients required for T cell proliferation (140). Moreover, considerable metabolic end products exist in the TME that are immunosuppressive; for instance, R-2-hydroxyglutarate in tumors with isocitrate dehydrogenase 1/2 mutations (140-143). In fact, tumor cells are extremely metabolically active due to increased glutaminolysis and glycolysis and these metabolic pathways lead to accumulation of different metabolites in the TME which can affect CAR T-cell function; for instance, prostaglandins that are obtained by prostaglandin E2 synthase and cyclooxygenase (COX)-1/2-mediated catabolism of arachidonic acid, can suppress T-cell function or lactate is a metabolite obtained by the glycolytic pathway that is extremely produced by tumor cells and can also directly suppresses proliferation, cytokine production, and effector function of human cytotoxic T lymphocytes (136, 144, 145); for this reason, metabolites are known as crucial immune-modulatory molecules by themselves (136). On the other, the TME contains reactive oxygen species (ROS) and reactive nitrogen species (RNS) that hinder T cell function as well as the TME has raised concentrations of immunosuppressive electrolytes; for instance, potassium (136, 140).

The T-cell function can also be suppressed by a number of amino acid-degrading enzymes, which are primarily expressed in the TME. These include nitric oxide synthase (NOS) and arginase-1 that degrade l-arginine, and tryptophan-2,3-dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO) that degrade tryptophan (136). T-cells have been shown to be particularly sensitive to the reduction of these amino acids, leading to hindered proliferation and effector function of T-cell and increased T-cell apoptosis (136, 146-149). Furthermore, the catabolites of tryptophan degradation such as 3-hydroxyanthranilic acid and l-kynurenine have also been shown to be immunosuppressive (136, 150, 151).

4. Hindering the function of CAR T cells in killing cancer cells:

CAR T cells mediate tumor killing through three procedure: (a) Fas and FasL: Targeting antigen-negative fraction; (b) Cytokine secretion: Stromal cell sensitization; (c) Perforin and granzyme: Targeting antigen positive fraction (152). The primary mechanism of redirected target cell killing carried out by CAR T cells is thought to be the cytolytic degranulation of perforin and granzymes (152-155). Blocking released perforin through egtazic acid (EGTA) that is a calcium ion chelator, was demonstrated to abrogate most CAR T cell-mediated killing (152, 156).

There are several different approaches that have been suggested to improve efficiency and lessen the side effects of CAR T-cell treatment, such as modifying and engineering the genome of CAR T cells, modifying the different components of CAR T cell receptor, inducible safety switches; However, challenges and high toxicity still strongly affect this type of treatment, and CAR T-cell therapy efficiency is still limited in treatment of solid tumors.

Discussion

Cancer is a complex disease because it is the result of extensive mutations, and the behavior of cancer varies from patient to patient; in fact, it does not have a clear and consistent pattern in all people and can progress rapidly. On the other hand, most of the treatments available for cancer are more effective in the early stages of the disease than in the malignant form of the disease; that's why some researchers are trying to come up with methods that can diagnose cancer in early stages and quickly. In fact, our biggest challenge is malignant cancer. So, we have to use the experiences we have gained during the past years to consider the general characteristics of cancer cells and the strategies cancer cell use for neutralize different treatments to find a way to definitively treat different types of cancer. At first we must note that cancer cells, such as viruses and bacteria, are not external agents; rather, they are the result of changes in our normal cells, so they can use our genetic information and the facilities that healthy cells use to deal with external factors, to neutralize various treatments. Due to cancer cells can intrinsically and acquiredly resist to different therapies, scientists try to counteract this feature of cancer cells by combining different therapies. On the other hand, combination therapies usually have fewer side effects than single therapies. However, in general, this idea has not been very effective in treating cancer. In fact, we are dealing with a disease that learns the lessons from our therapies and can counteract our therapies by evolving and adapting itself because our genetic information is in its hands; so we have to deal with it by a treatment method that cancer cell has limited and few solutions to neutralize it and also has few side effects.

Cancers are able to employ multiple mechanisms in order to hinder therapies chemical molecule-, drug-, and ion-based. Cancer stem cells, canals and pumps surface of cancer cells, repair mechanisms as well as genetic and epigenetic alterations are factors that strongly counteract this type of treatment. On the other hand, physical barriers and the tumor environment conditions, prevent therapeutic agents from easily reaching the cancer cells within the tumor. Even if targeted therapeutic agents are delivered at tumor cells, they may do not demonstrate a high efficiency in treating various types of cancer because strategies of cancer cells against these therapies, are diverse. In addition, increasing the dose of this type of therapeutic agents to elevate their efficiency and therapeutic effect is dangerous for the patient; because these agents are inherently toxic and can cause serious side effects.

Another number of therapies help the immune system without modifying and engineering the immune cells to kill cancer cells. The tumor microenvironment employs a vast range of cytokines and immune checkpoint molecules to inactivate and suppress immune cells; on the other hand, small amounts of immune cells can infiltrate into the tumor microenvironment. These two factors collectively cause these types of therapy not become a definitive solution to the cancer problem. Furthermore, it seems that immune cells cannot very affect cancer without engineering. For this reason, CAR T cell therapy has demonstrated higher efficiency.

Although CAR T cell therapy has been very successful in treating leukemia, solid tumors pose substantial challenges for this type of therapy. One of the major reason for preventing CAR T cell therapy from succeeding in solid tumors is the large size of CAR T cells because the physical barriers in the tumor microenvironment are abundant and dense that CAR T cells have little infiltration into Inside the tumor; as a result, a small dose of these cells reach the cancer cells inside the tumor. As I mentioned previously, even nanometer-sized viruses have difficulty penetrating solid tumors due to the high density of barriers in the tumor microenvironment, and nanoparticles that are 20 nanometers or less are easier to infiltrate. On the other hand, the tumor microenvironment conditions pose substantial challenges for them so that the low infiltrating dose of CAR T cells cannot overcome these conditions. In addition, cancer cells can counteract the perforin and granzyme released by CAR T cells.

Oncolytic virotherapy, like other therapies, faces a number of challenges. Nevertheless, viruses have the potential to through engineering and modifying them, they may be able to counteract most tumor cell strategies. Unlike immune cells, viruses are so small that they can infiltrate the tumor more easily. In addition, by engineering them, viruses can only replicate in certain cells, such as tumor cells; for this reason, they often do not cause severe side effects. On the other hand, viruses can be engineered to both counteract tumor-associated interferon and increase their replication rate in tumor cells that all of these, leading to further spread of viruses in the tumor

microenvironment. Due to the evolution of tumor cells during treatment, combination therapies are sometimes used to enhance the therapeutic outcome; While viruses can not only kill tumor cells by themselves, but also they can effectively stimulate the immune system to kill cancer cells, a feature that can serve as a combination therapy. The major challenge of virotherapy is their rapidity clearance after administration. However, more research on virus capsid can reduce the sensitivity of capsid to antibodies so that increase their half-life in the blood and slowing their clearance in the blood; As a result, more doses of viruses reach the tumor and can subsequently spread further into the tumor microenvironment. Viruses have the potential to evolve so that interact with the immune system and do not stimulate it extremely. This feature of viruses is exemplified in the gut microbiome bacteriophages well.

conclusion

Finally, although the clinical efficacy of virotherapy is still limited, with further research on this type of therapy, it is hoped that oncolytic virotherapy will become a highly effective treatment for a variety of cancers.

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