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INNOVATIVE DRUG DELIVERY SYSTEMS FOR CANCER: CURRENT TRENDS AND A REVIEW OF CURRENT ADVANCEMENTS

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ABSTRACT

Cancer is expected to be the world's biggest cause of death in 2020, accounting for 10 million deaths and 19.3 million new cases worldwide. Conventional techniques, including as radiation, chemotherapy, and surgery, can damage healthy cells and result in drug resistance. Stem cell therapy is an advanced cancer treatment that uses undifferentiated bone marrow cells to differentiate into various body cells, which makes it a safe and effective therapeutic option. In 2006, developments in cell biology made headway, eschewing moral conundrums related to embryonic death. While mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) are employed to treat primary and metastatic breast cancer as well as other malignancies, adult stem cells (ASCs) are necessary for tissue regeneration and repair. Molecularly focused cancer therapies, commonly referred to as targeted medication delivery, impede growth molecules in order to stop the growth and spread of cancer. The TM circumstances of the tumor dictate its initiation and progression; hence a crucial field of study is targeted therapy. Because conventional chemotherapy mimics normal cells, it is difficult to treat. Protein kinase B and serine/threonine kinase are examples of angiogenic factors that are blocked by enzyme inhibitors like Avastin, which target cells that control cell survival. One useful method for addressing gene silence and interfering with the creation of proteins is RNA interference, or RNAi. Three methods of administration are being studied: chemical modification, lipid encapsulation, and conjugation with organic molecules. Cells secrete microscopic particles

called exosomes, which contain compounds that encourage the spread of disease, and have been linked to a number of disorders, including cancer. The microbiome and the human immune system are closely related, and IgA antibodies are essential for protecting the environment and getting rid of pathogens. Tumor-specific antigens (TAA) are the goal of cancer vaccines, which seek to enhance immune responses against cancer. Cancer vaccination platforms come in four varieties: peptide-based, viral-based, nucleic acid-based, and cell-based. Tumor cell targeting has shown effective with oncolytic virus immunotherapy, peptide-based vaccinations, nucleic acid-based vaccinations, DNA and mRNA-based vaccinations, and customized vaccines like NeoVax.

KEYWORDS: Cancer, Therapy, Exosome, Immunotherapy, Vaccines.

INTRODUCTION

In 2020, there will be 10 million fatalities and 19.3 million new cases of cancer worldwide, making it the leading cause of death in the world. Radiation therapy, chemotherapy, and surgery are among the available treatment options. Treatment possibilities have been enhanced by recent developments in combinatorial techniques and targeted pathways. Drugs, biological molecules, and immune-mediated therapy are some of the novel techniques being utilized to lower metastatic cancer death rates and increase survival times.[1]

Treatment for neoplastic cancer depends on certain features and mechanisms. Chemotherapy is a commonly utilized treatment that produces reactive oxygen species by genotoxically attacking tumor cells. Hormonal therapies, which are regarded as cytostatic, prevent tumor growth by reducing growth factors, blocking hormone receptors, and reducing the production of adrenal steroids.[2]

The article emphasizes the significance of novel anti-cancer treatments by highlighting advanced cancer therapies, research strategies, and clinical strategies to overcome the limitations of current therapy.[3]

Cancer Treatment Modalities

There are two types of cancer therapy modalities: traditional and advanced. Approximately half of all medical trials conducted globally are focused on cancer treatments. Modern treatments include hormone therapy, anti-angiogenic, stem cell therapies, immunotherapy,

and dendritic cell-based immunotherapy; traditional methods include surgery, chemotherapy, and radiotherapy.[4]

Conventional Cancer Therapies

Chemotherapy, radiation, and surgical excision are common cancer treatment approaches. Early disease progression is best treated with surgery, although radiation can harm healthy cells. Chemotherapy lowers morbidity and death, but it can also harm healthy cells—especially those that divide and develop quickly. One of the main problems with chemotherapy is drug resistance, which is the result of diminished drug uptake and greater efflux in cancer cells. There are drawbacks to traditional chemotherapy techniques, such as dose selection challenges and deleterious side effects.[5]

Advanced Cancer Therapies

Treatment for cancer, and symptom reduction are greatly hampered by drug resistance and delivery system issues. Tumor pathology and structural anomalies decrease the effectiveness of conventional cancer treatments, even with a plethora of approved medicines. Innovative and cutting-edge cancer treatments include advantages as well as drawbacks.[6]

Stem Cell Therapy

Undifferentiated bone marrow cells called stem cells have the ability to differentiate into other bodily cells, making them viable and safe cancer treatments. Mesenchymal stem cells (MSCs) derived from bone marrow, adipose tissues, and connective tissues are being employed in experimental clinical trials for tissue regeneration.[7]

Pluripotent Stem Cells Therapy

In cell biology, pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) are utilized to generate effector T cells, natural killer cells, and the manufacturing of anti-tumor vaccines. Cell biology made strides forward in 2006 with the discovery of Yamanaka factors, which avoided the moral dilemmas associated with the death of embryos.[8]

Adult stem cells therapy

Tumor therapy employs adult stem cells (ASCs), such as neural stem cells (NSCs), mesenchymal stem cells (MSCs), and hematopoietic stem cells (HSCs). MSCs are essential for tissue regeneration and repair, while HSCs, which are present in bone marrow, can develop into adult blood cells. While NSCs self-renew and produce new neurons and glial

cells to treat primary and metastatic breast and other malignancies, MSCs are employed in conjunction with other treatments.[9]

Target Drug Delivery

Precision medications, sometimes referred to as molecularly focused cancer therapies, are medications that obstruct growth molecules to prevent the growth and spread of cancer. The TM of an atypical tumor, which includes endothelium, pericytes, smooth muscle, fibroblasts, inflammatory, dendritic, and CSCs, determines the start and course of the tumor. The use of TM conditions to facilitate efficient targeting strategies for cancer therapy is the main area of emphasis for research.[10]

Because it resembles normal cells, conventional chemotherapy is difficult to cure. Interventions can be made by cellular mechanisms such as cell cycle arrest, activation of apoptosis, restriction of proliferation, and metabolic reprogramming. Two efficacious ways for treating cancer include targeting and modifying tissue for drug delivery. Drugs used in targeted therapy specifically target cancer cells while causing the least amount of harm to healthy cells.[11]

The rate of survival for some diseases, like advanced pancreatic cancer and chronic myeloid leukemia, has dramatically increased thanks to targeted therapy. The therapy of breast cancer and renal cell carcinoma has been transformed by enzyme inhibitors, which stop the enzyme signals that cancer cells need to proliferate. These medications can be categorized according to their target site or mode of action.[12]

Drugs that cause apoptosis specifically target cells that regulate cell survival, like protein kinase B (PKB/Akt) and serine/threonine kinase. By stopping the blood supply and blocking angiogenic factors like VEGF or its receptors, these medications stop tumor growth. According to a study, administering Avastin (bevacizumab) in conjunction with 5-fluorouracil-based chemotherapy extended the survival time of patients with advanced colorectal cancer by several months.[13]

Types of Cancer Target Agents

Monoclonal antibiotics - Artificial immune system proteins called antibodies are employed to combat cancer cells. They enlist the aid of the host's immune system, interfere with vital functions, and transport deadly payloads like poisons or radioactive materials. A monoclonal

antibody specific to CD-33 called gemtuzumab is used to treat AML. An anti-CD20 called ibritumomab tiuxetan is being developed for clinical use. Monoclonal antibody target agents also transport prodrug activation enzymes, toxic chemicals from chemotherapy, and active therapies.[14]

Small molecular inhibitors- These proteins are easier to ingest orally since they are smaller than monoclonal antibodies and can easily pass through plasma membranes. Their primary function involves disrupting cellular processes by interfering with tyrosine kinases' intracellular signaling.[1] This results in the inhibition of tyrosine kinase signaling and sets off a molecular cascade that can inhibit angiogenesis, migration, proliferation, and cell growth in malignant Small molecule inhibitors include gefitinib and erlotinib, which block the EGFR kinase and EGFR in patients with non-small cell lung cancer (NSCLC), respectively. EGFR/Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2) for ERBB2-positive breast cancer and VEGFR kinase in renal cancer are also inhibited by lapatinib and sorafenib.[15]

RFA Therapy- RFA can be used in conjunction with other traditional cancer treatments and is a successful treatment for tiny tumors less than 3 cm in diameter. It can treat medium tumors after employing multiple-electrode systems or deployable devices.[16]

Gene Therapy

Inserting a healthy copy of a damaged gene is known as gene therapy, and it is used to treat some diseases. When the ADA gene was introduced to T cells in SCID patients in 1990, it all started. There are now 2900 active gene therapy clinical trials, of which 2/3 are for cancer. Oncogene targeted silencing, wild-type tumor suppressor genes, proapoptotic and chemosensitizing genes, and other strategies are under evaluation.[17]

Thymidine kinase gene delivery is effective for ganciclovir administration, activating expression and causing specific cytotoxicity. Recently, p53 tumor suppressor gene vectors have been assessed for clinical use. ONYX-015 and Gendicine, recombinant adenoviruses, have shown high response rates in NSCLC patients and complete disease regression in head and neck squamous cell cancer.[18]

The obstacles associated with gene therapy include the need to carefully choose the conditions and delivery method, limited effectiveness in some patient populations, and a significant risk of immune system neutralization. RNA interference (RNAi) is a highly

effective technique that can be used to cleave messenger RNA, target gene silencing, and disrupt protein production. This technique, which depends on siRNA-mediated gene suppression of anti-apoptotic proteins, transcription factors, or cancer-mutated genes, disables desired targets, inducing cell proliferation and metastatic invasion.[19]

Drugs based on siRNA have several benefits, including minimal production costs, safety, high specificity, efficiency, and few side effects. They may, nevertheless, occasionally have unintended consequences or trigger innate immune reactions. Three delivery strategies are being investigated: conjugation with organic compounds, lipid encapsulation, and chemical modification.[20] Through straightforward electrostatic interactions, cationic liposomes can make transfection simple. In order to assess the safety of Eph receptor A2 targeting 1,2-dioleoyl-snglycero-3-phosphocholine (DOPC) encapsulated siRNA, a Phase I clinical investigation is now accepting participants. Concentrations of SiRNAs can be found in cationic polymers such polyethyleneimine (PEI), cyclodextrin, and chitosan. Conjugating to aptamers, peptides, and antibodies increases the stability of siRNAs during circulation and boosts their uptake by cells. The pharmacokinetics, targeting specificity, biodistribution characteristics, and stability of siRNA have all enhanced with the introduction of nanocarriers. However, individual differences and dose correction.[21]

Application of Exosome Research in Cancer Therapy

Exosomes are tiny, 50–150 nm particles that have lipids and proteins on their surface. They are secreted by cells. They include useful substances like as proteins, mRNAs, and microRNAs. Exosomes are linked to a number of illnesses, including cancer, because they carry chemicals that promote the spread of the disease. Cancer exosomes, for instance, have the ability to alter gene expression, stimulate angiogenesis, and breach the blood-brain barrier, all of which can lead to brain metastases. Moreover, exosomes cause cancer cells to become dormant, and which prolongs the course of the disease and increases its chance of reoccurring.[22]

Cancer cells secrete exosomes, which can be utilized for both cancer diagnosis and treatment. Exosome secretion can be stopped, which can stop signal transduction and stop tumor microenvironments and pre-metastatic habitats from forming.[24] Blood and urine are bodily fluids that contain exosomes, and identifying these particles can reveal sickness. But it's important to distinguish between exosomes linked to cancer and those that are normal. In order to use exosomes for cancer diagnosis, specific biomarkers are required. Exosome

detection techniques are now being developed for use in the serum and urine of patients with pancreatic and colorectal cancer. Exosome research has a major impact on our knowledge of cancer invasion, growth, and metastasis as well as cancer diagnosis and treatment strategies.[23]

Microbiome in Cancer Therapy

Numerous microorganisms, such as bacteria, viruses, and fungus, can be found inside the human body. Bacteria are abundant in variety and quantity, with approximately 100 trillion individual cells and perhaps 1000 different species found in the digestive system alone. The whole population of bacteria, or the intestinal flora, is known as the microbiota or Microbiome.[25]

Our knowledge of the four phyla that make up the gut microbiome—Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria—has improved as a result of recent advances in NGS technology. The two most prevalent species are Firmicutes and Bacteroidetes. The diversity of microbiomes differs with age and race.[26] Illnesses such as inflammatory bowel disease, colorectal cancer, obesity, diabetes, and allergy illnesses have been related to dysbiosis, a condition that decreases microbiome diversity. A particular microbiome may be linked to the early stages of colorectal cancer development, which could help with early cancer identification.[26]

Research has indicated a robust association between the human immune system and the microbiome. An essential part of the intestinal immune system, the IgA antibody plays a role in both preserving the environment and getting rid of infections. Pathogenic bacteria and toxins are identified, eliminated, and neutralized while preserving a symbiotic interaction with the host's microbiome. The generation of IgA antibodies is decreased in mice devoid of a microbiome. W27IgA antibodies have been found in recent research to bind to a variety of bacteria, including E. coli, but not to suppress microorganisms that cause enteritis, such as lactic acid bacteria and bibidobacteria. This emphasizes the function of the microbiome in systemic and internal immunity.[27]

Current State of Cancer Immunotherapy

Immune checkpoint inhibitor therapy- Over the past ten years, the FDA has approved immune checkpoint inhibitors (ICI) as a promising cancer immunotherapy treatment for over nine different forms of cancer. T cells bearing negative regulatory markers that serve as

activation checkpoints are used in ICI therapy. When these markers attach to co-stimulatory ligands, which are increased by T cells, cytotoxic T-cell activation is inhibited, which results in tumor development and immune suppression. When cancer cells are targeted and destroyed by ICI, which is released during treatment, a variety of resistant tumors can be successfully treated. When used in conjunction with traditional cancer therapy, ICI (Interferon-β) has demonstrated notable effectiveness in treating patients who had previously had poor outcomes. It has been used to treat a variety of illnesses. Ipilimumab, a therapeutic anti-CTLA4 antibody, was the first ICI to receive FDA approval. Another anti-CTLA antibody, tremelimumab, was ineffective in late-stage trials for metastatic advanced melanoma.[28]

The first FDA-approved treatments for refractory and incurable melanoma were two human IgG4 anti-PD-1 checkpoint inhibitors called pembrolizumab (pembro) and nivolumab. When compared to standard-of-care chemotherapy, Pembro has demonstrated a higher overall response rate (ORR) in patients with melanoma and NSCLC. Anti-CTLA4 + anti-PD-1 combination therapy has greatly increased ORR for metastatic melanoma, reaching 58%. The problem of increased toxicity to combination treatment still exists, though. In some cancer subtypes, the degree of PD-L1 expression is employed as a biomarker for ICI indication, and it has been associated with better responses to pembro. Crucial is the scoring scheme employed. Anti-PD-L1 antibody therapies have shown promise in treating a variety of cancer types.[29]

Examples of these include atezolizumab for urothelial carcinoma and durvalumab and avelumab for solid tumor malignancies. Defective DNA mismatch repair proteins lead to microsatellite instability, which has been associated with better outcomes in ovarian and colorectal cancer, among other cancer subtypes. The first medication to demonstrate appreciable improvements was pembro, which was licensed for use in disease-agnostic settings. Dostarlimab demonstrated 100% clinical ORR and no recurrence in a recent clinical study.[30]

While ICI is a successful cancer treatment, approximately 20–30% of patients experience a meaningful improvement. It is essential to recognize and target new checkpoint pathways in order to remedy this. Novel ICI drugs, including T-cell immunoreceptor with immunoglobulin (Ig) and ITIM domains (TIGIT), V-domain immunoglobulin T-cell activation suppressor (VISTA), and T-cell immunoglobulin and mucin-domain containing-3

(Tim-3), are being studied in ongoing clinical trials. These medications have demonstrated potential in the treatment of MDS and AML. Anti-Tim-3 ICI increases antitumor T-cell activity by specifically targeting AML cells that express Tim3. Although immune checkpoint blockade has demonstrated efficacy, problems such as non-responsive patients and side effects still exist. Future success depends on more research on tumor escape factors and alternate paths.[31]

CAR T- Cell Therapy- Three methods are used in adoptive cellular treatment (ACT): chimeric antigen receptor (CAR)-modified T cells, genetically modified T-cell receptor therapies, and TIL infusion. The most effective ACT is CAR T-cell therapy (CART), which has FDA-approved indications for a number of hematologic malignancies. Since its initial description in 2011, CAR T cells have demonstrated a notable level of clinical effectiveness in treating leukemias, multiple myeloma expressing B-cell maturation antigen, and B-cell lymphomas that express CD19. Future research areas and challenges include CAR-M, CAR T-cell treatment, and other immune cell types.[32]

Diffuse large B-cell lymphoma (DLBCL), a prevalent subtype of non-Hodgkin's B-cell lymphoma (NHL), has demonstrated notable response to CART. However, results are not good in DLBCL that has relapsed or is refractory. For patients with R/R DLBCL, ZUMA-1 and JULIET were pivotal studies for an autologous anti-CD19 CART (CAR19) product. CAR19 yielded a complete response rate of 40–54%, an extraordinary ORR of 54–82%, with a median overall survival of five years or more.[33]

Targeting BCMA, CART has demonstrated efficacy in treating R/R Multiple Myeloma (MM), with high response rates seen with Idecabtegene vicleucel and Ciltacabtagene autoleucel. However, a retrospective investigation discovered that patients receiving therapy other than CART had inferior outcomes. Additional clinical trials are required to ascertain the ideal date.[34]

The FDA has approved the use of two anti-BMCM CART medicines and four CAR19 medications for the treatment of hematologic cancer. However, the majority of patients relapse after failing therapy as a result of initial progress or reaction. Remissions in children acute lymphoblastic leukemia (ALL) have been shown, but because adult relapse rates are so high, most patients need allogeneic stem cell transplantation beyond CAR19.[42]

The processes underlying CART resistance, which can be brought on by host-intrinsic factors, CAR T-cell product-specific mechanisms, or tumor-intrinsic factors, require further investigation. To combat antigen loss, alternative antigen and multi-antigen treatments are being developed.[35]

Clinical performance may be impacted by CAR T-cell product intrinsic defects that result in poor expansion and function. Low-quality donor T cells, unfavorable growing conditions, and manufacturing errors can all contribute to these problems. Improving patient condition and production procedures is essential to resolving these failure modes. Novel approaches to the production of CAR T cells, such as point-of-care manufacturing and variable culture duration, can enhance therapeutic outcomes. Promising outcomes when employing IL7 and IL15 for CART culture expansion have been shown in recent research.[36]

Tumor-associated macrophage (TME) and infused CAR T-cell product interact to cause tumor, host, and CAR T-cell interactions. Interactions between immunosuppressive TMEs and host inflammation and tumor load can both decrease growth and enhance tiredness. High tumor volume, inflammatory markers, and extranodal disease locations are risk factors for CAR T-cell failure. To get beyond TME-mediated CART inhibition, researchers are looking into new bridging and conditioning regimens as well as radiation therapy.[37]

Before leukapheresis, bruton's tyrosine kinase inhibitor (BTKi) enhances CAR T-cell growth and activity in CLL, reduces exhaustion, and lessens toxicity. Richter's Syndrome patients at the Ohio State University Comprehensive Cancer Center were able to achieve CR and long-term disease-free status by using ibrutinib. TAM-induced upregulation of PD-L1 is linked to worse CART results.[38]

Due to increased toxicity and lack of efficacy in clinical trials, CART's effectiveness in treating solid tumors is still quite low. Tumor function is compromised by the strong and immunosuppressive TME seen in solid tumors. Even with the success in hematologic malignancies that express CD19 and BCMA, more research is required to improve tumor identification, TME infiltration, and anti-cancer efficacy.[39]

Cancer Vaccines- Tumor-specific antigens (TAA) are the goal of cancer vaccinations, which strengthen immune responses in an effort to produce long-lasting anticancer immunity. However, because of the possibility of autoreactive immune responses, generating TAAs is

difficult. Potential targets for the immune system include neoantigens, which are produced from gene alterations connected to carcinogenesis. There are four types of cancer vaccination platforms: peptide-based, viral-based, nucleic acid-based, and cell-based.[40]

By utilizing adenovirus and Herpes simplex virus vectors, oncolytic virus immunotherapy induces anticancer responses while specifically targeting tumor cells. The FDA has approved T-VEC, a first-generation vector, for the treatment of recurring, incurable melanoma. Both BCG-unresponsive bladder cancer and HER2+ breast cancer have responded well to adenovirus vectors. Strong immune responses are elicited by peptide-based vaccinations against tumor antigens like DSP-788.[41]

Vaccines containing nucleic acids enhance immunity, elicit a robust CD8+ T-cell response, and encrypt whole tumor antigens. Vaccines based on DNA and mRNA have the ability to kill tumor cells and release antigens, which increases response rates. Personalized vaccines such as NeoVax have demonstrated tumor infiltration and the long-term persistence of T lymphocytes specific to neoantigens in patients with glioblastoma and melanoma. In immunotherapies such as ICI, an elevated load of tumor mutations results in strong immune responses and enhanced therapeutic effectiveness. Neoantigens exhibit individual variability, which propels the use of tailored therapy. To create cancer vaccines that work, further immunologic research is required, taking into account the different types of tumors and neoantigen analysis.[42]

CONCLUSION

Cancer is the leading cause of death worldwide, with 10 million fatalities and 19.3 million new cases expected in 2020. Novel techniques, such as drugs, biological molecules, and immune-mediated therapy, are being used to lower metastatic cancer death rates and increase survival times. There are two types of cancer treatment modalities: traditional and advanced. Traditional methods include surgery, chemotherapy, and radiotherapy. Advanced cancer therapies, such as stem cell therapy, pluripotent stem cells, and adult stem cells, offer both advantages and drawbacks. Mesenchymal stem cells (MSCs) are being used in clinical trials for tissue regeneration, while pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) are used to generate effector T cells, natural killer cells, and anti-tumor vaccines. Target drug delivery is a method of cancer treatment that focuses on obstructing growth molecules to prevent the growth and spread of cancer. It is a method that focuses on modifying tissue for drug delivery, allowing cancer cells to be targeted while minimizing harm to healthy cells.

This approach has significantly increased the survival rates for certain diseases, such as advanced pancreatic cancer and chronic myeloid leukemia. Target agents include monoclonal antibiotics, small molecular inhibitors, and RFA therapy. Gene therapy involves inserting a healthy copy of a damaged gene to treat certain diseases. Exosomes, tiny particles secreted by cells, carry chemicals that promote the spread of diseases, including cancer. Exosomes can be used for cancer diagnosis and treatment, but specific biomarkers are needed. The microbiome, a diverse population of bacteria, viruses, and fungi, is crucial in cancer therapy. Recent advances in NGS technology have improved our understanding of the gut microbiome, with Firmicutes and Bacteroidetes being the most prevalent species. The first FDA-approved treatments for refractory and incurable melanoma were two human IgG4 anti-PD-1 checkpoint inhibitors called pembrolizumab (pembro) and nivolumab. CAR T-cell therapy (CART) is the most effective ACT for hematologic malignancies, with CAR T cells showing notable clinical effectiveness in treating leukemias, multiple myeloma expressing B-cell maturation antigen, and B-cell lymphomas that express CD19. Cancer vaccinations aim to strengthen immune responses against cancer by targeting tumor-specific antigens (TAA). There are four types of cancer vaccination platforms: peptide-based, viral-based, nucleic acid-based, and cell-based. Oncolytic virus immunotherapy, peptide-based vaccinations, nucleic acid-based vaccines, DNA and mRNA-based vaccines, and personalized vaccines like NeoVax have shown success in targeting tumor cells.

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