An Overview on Emerging Therapy for Cancer

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ABSTRACT - Cancer is a global health problem responsible for one in six deaths worldwide. Treating cancer has been a highly complex process. Conventional treatment approaches, such as surgery, chemotherapy, and radiotherapy, have been in use, while significant advances are being made in recent times, including stem cell therapy, targeted therapy, ablation therapy, nanoparticles, natural antioxidants, radionics, sonodynamic therapy, and ferroptosis-based therapy. Current methods in oncology focus on the development of safe and efficient cancer nanomedicines. Stem cell therapy has brought promising efficacy in regenerating and repairing diseased or damaged tissues by targeting both primary and metastatic cancer foci, and nanoparticles brought new diagnostic and therapeutic options. Targeted therapy possessed breakthrough potential inhibiting the growth and spread of specific cancer cells, causing less damage to healthy cells. Ablation therapy has emerged as a minimally invasive procedure that burns or freezes cancers without the need for open surgery. Natural antioxidants demonstrated potential tracking down free radicals and neutralizing their harmful effects thereby treating or preventing cancer. Several new technologies are currently under research in clinical trials, and some of them have already been approved. This review presented an update on recent advances and breakthroughs in cancer therapies.

Keywords: Cancer, treatment, stem cell, targeted drugs, natural antioxidants, gene therapy.

1.INTRODUCTION

Cancer is a global health problem responsible for one in six deaths worldwide. In 2020, there were an estimated 19.3 million new cancer cases and about 10 million cancer deaths globally. Cancer is a very complicated sequence of disease conditions progressing gradually with a generalized loss of growth control. There were only a few options of cancer treatment for patients for many decades which include surgery, radiation therapy, and chemotherapy as single treatments or in combination. But recently, many pathways involved in cancer therapy progression and how they can be targeted has improved dramatically, with combinatorial strategies, involving multiple targeted therapies or "traditional" chemotherapeutics, such as and platinum compounds, being found to have a synergistic effect. New approaches, such as drugs, biological molecules, and immune-mediated therapies, are being used for treatment even if the excepted therapy level has not reached that resists the mortality rate and decreases the prolonged survival time for metastatic the creation of a new revolution in neoplastic cancer or targeting drugs depends on the pathways and characteristics of different tumor entities. Chemotherapy is considered the most effective and widely used modality in treating cancers as used alone or in combination with radiotherapy. Genotoxicity is how chemotherapy drugs target

the tumor cells mainly producing reactive oxygen species that largely destroy tumor cells Hormonal treatments are also widely used for cancer malignancies and considered as cytostatic because it restricts tumor development by limiting the hormonal growth factors acting through the direction of hypothalamic–pituitary–gonadal axis (HPGA), hormone receptor blockage, and limiting of adrenal steroid synthesis.[1]

In this narrative review, a general overview of the most advanced and novel cancer therapies was provided. In addition, also new strategies currently under investigation at the research stage that should overwhelm the drawbacks of standard therapies different strategies to cancer diagnosis and therapy and their current status in the clinical context, underlining their impact as innovative anti-cancer approaches.Standard treatments available for curing cancer includes surgery, Radiotherapy, Chemotherapy, Gene therapy, Hormone therapy, Bone marrow transplant, Cryosurgery, Immunotherapy, Photodynamic therapy, Peripheral stem cell transplant. Usually, all cancer cases require surgical treatment of cancerous mass or chemotherapy, hormonal therapy or radiation therapy, but in some extremely rare cases of kidney cancer or melanoma, the cancer cells vanish on their own by shrinking. Targeted therapies such as small molecule tyrosine kinase inhibitors and monoclonal antibodies (MABs) are also being used to treat cancers. Since cancer cells mutate and also results in modification of expression of various genes so targeted therapies are of great help as they can be aimed at a class of molecular targets or a particular single molecular target in cancer cells.[1]

2.Cancer treatment modalities

We can see cancer treatment modalities by dividing them into conventional (traditional) and advanced or novel or modern categories. In this era worldwide, over half of all ongoing medical treatment trials are focusing on cancer treatments. Entities, such as the type of cancer, its site, and severity, guide to select treatment options and its progress. The most widely used traditional treatment methods are surgery, chemotherapy, and radiotherapy, while modern modalities include hormone therapy, anti-angiogenic, stem cell therapies, immunotherapy, and dendritic cell-based immunotherapy.[1]-[2]

Cancer Conventional therapies:

The most recommended conventional cancer treatment strategies include surgical resection of the tumors followed by radiotherapy with x-rays and/or chemotherapy. Of these modalities, surgery is most effective at an early stage of disease progression. Radiation therapy can damage healthy cells, organs, and tissues. Although chemotherapy has reduced morbidity and mortality, virtually all chemotherapeutic agents damage healthy cells, especially rapidly dividing and growing cells. Drug resistance, a major problem with chemotherapy, is a phenomenon wherein cancer cells that initially were suppressed by an anti-cancer drug develop resistance to the drug. This is caused primarily by reduced drug uptake and increased drug efflux. Limitations of conventional chemotherapeutic modality, such as dosage selection difficulty, lack of specificity, rapid drug metabolism, and mainly harmful side effects.

Advanced and innovative cancer therapies:

Among the obstacles of cancer, drug resistance and its delivery systems are the most problem in cancer cure and decreasing signs and symptoms; but currently, there are many approved treatment approaches and drugs. The efficiency of conventional cancer is reduced due to tumor pathology and architectural abnormality of tumor tissue blood vessels. The following are the advanced and innovative cancer therapy types with their benefits and challenges.[2]

3.Treatments and Prevention

Not always abnormal growth of cells giving rise to tumor formation can be termed as cancer, some tumors do not spread to other parts of the body and are hence called Benign tumors. By performing Biopsy report of a tumor also,

one can determine whether it is benign or malignant. The exact cause of benign tumor is unknown but some causes may include unhealthy lifestyle, excessive stress, consumption of toxins etc. usually these tumors are removed by performing surgery. Whereas the malignant tumors are termed as cancer. They do not show any symptoms in the early stage that is why detection in early stage is tough. Sometimes no signs or symptoms is found even in the last stage. A few local symptoms can be seen for example, if the growth of mass is present in the brain, then it affects brain functioning, if the growth of mass occurs in the breast, then a lump can be felt thus it indicates breast cancer. If a person observes difficulty in breathing followed by a series of respiratory disorder, then it might be a symptom of lung cancer because in such case the growth of mass has taken place in lungs, blocking the bronchus. Apart from these the commonly observed symptoms might include night sweats, unintentional weight loss, unexplained fevers, bleeding, fatigue, bowel changes etc. [3]-[4]

Treatment For Cancer:

Standard treatments available for curing cancer includes:

1. Surgery.
2. Radiotherapy.
3. Chemotherapy.
4. Gene therapy.
5. Hormone therapy.
6. Bone marrow transplant.
7. Cryosurgery.
8. Immunotherapy.
9. Photodynamic therapy.
10. Peripheral stem cell transplant.

Cancers can be treated by performing surgery and removing the localized tumor or in some cases the whole organ itself. It is used for non-hematological cancers only and also can treat those cancers which has not metastasized to other parts of the body. Even if a single cancer cell has metastasized to different part of the body it can lead to the formation of a new tumor. The chance of recurrence of cancer is determined by biopsy test. Staging of cancer can be done by examining the presence of healthy tissues and cancerous tissues in the surgically removed tissues. Surgery is performed to treat cancers like, mastectomy of breast cancer, liver cancer, lung cancer, prostatectomy for prostate cancer, kidney cancer etc. [4]

Recent advances in treatment:

The standard therapy methods do cure cancer but along with that they pose serious threat to normal healthy cells as well and have side effects. Due to this reason, new treatment methods are being adopted. Tumor microenvironment allows to look into clinical trials tests, several treatment types like new drugs, new perspective in respect to treatment methodologies using radiation therapy, chemotherapy, surgery or combination of some treatments. The conventional treatment methods have a number of disadvantages for example, vascular structures of the tumor are leaky and excessively perplexed. The tumor becomes immune to radiation because its core experiences lack of oxygenation. Due to these reasons, tumor microenvironment and a successful therapeutic method for diagnosis and treatment of

cancer are much required. Since past decades, immunotherapy has rapidly transformed treatment methods for many types of cancer. One more encouraging step towards cancer immunotherapy is the use of personalized vaccines. Neoantigens play major role in helping the body to make an immune response against cancer cells. It can activate CD4+ and CD8+ T cells to produce an immune response. Thus, these have a very high probability to become new targets of tumor immunotherapy. The advancements in bioinformatics and sequencing technologies are adding great value to working efficiency of neoantigen vaccines.[5]

4.Stem cells therapy

Stem cells are undifferentiated cells present in the bone marrow (BM) with an ability to differentiate into any type of body cell. Stem cell therapeutic strategy is also one of the treatment options for cancer which are considered to be safe and effective. Application of stem cell is yet in the experimental clinical trial; for example, their use in the regeneration of other damaged tissue is being explored. Mesenchymal stem cells (MSCs) are currently being used in trials that are delivered from the BM, fat tissues, and connective tissues.[5]-[6]

Pluripotent stem cells:

Embryonic stem cells (ESCs) isolated from the uniform inner mass cells of the embryo possess the flexibility to administer rise to any or all kinds of cells except those within the placenta. In 2006, the invention of Yamanaka factors to induce pluripotent stem cells (iPSCs) from physical cells in a culture marked a breakthrough in cell biology. Avoiding ethical issues from embryo destruction, iPSCs and ESCs have the same characteristics. Hematopoietic embryonic stem cells (HESCs) and iPSCs are currently used for the induction of effector T cells and natural killer (NK) cells, and anti-tumor vaccine preparation.

Adult stem cells:

Adult stem cells (ASCs) groups often used in tumor therapy include hematopoietic stem cells (HSCs), MSCs, and neural stem cells (NSCs). HSCs, located in BM, can form all mature blood cells in the body. Currently, only approved by the Food and Drug Administration (FDA) is the infusion of HSCs derived from cord blood to treat multiple myeloma and leukemia. MSCs are found in many tissues and organs, playing important roles in tissue repair and regeneration into cells, such as osteocytes, adipocytes, and chondrocytes. MSCs have special biological characteristics and are used as complimentary with other approaches in treating tumors. NSCs can self-renew and generate new neurons and glial cells and are used for treating both primary and metastatic breast and other tumors.[7]

Cancer stem cells:

Cancer stem cells (CSCs) are generated in normal stem cells or precursor/progenitor cells by the epigenetic mutations process. Their role in tumor treatment includes cancer growth, metastasis, and recurrence, so that it could give promise in the treatment of solid tumors. Stem cells have several action mechanisms in treating the tumor. The homing process is one mechanism which is a rapid migration of HSCs into defined stem cell niches in BM after that the transplants undergo the engraftment process before giving rise to specialized blood cells. This mechanism is dependent on the active interaction between stem cell CXCR4 receptors and requires their interaction with endothelial cells through LFA-1, VLA-4/5, CD44, and the secretion of matrix degradable enzyme MMP-2/9. The second mechanism is the tumor-tropic effect in which the migration of MSCs toward tumor microenvironment (TM) after attraction by CXCL16, SDF-1, CCL-25, and IL-6 secreted by tumor cells and differentiation of MSCs within the tumor cells which contributes to tumor stromal development. Stem cells also act by paracrine factor secretion, including extracellular vesicles (EVs) and soluble materials, and their differentiation capacity, such as transplanted HSCs, can give rise to all blood cell types. Generally, cancer treatment using stem cell therapy by various strategies, including transplantation of HSC,2MSC infusion, therapeutic carriers, generation of immune effector cells, and

vaccine production. several successes, there are challenges, such as therapeutic dose control, low cell targeting, and retention in tumor sites, that should be investigated and overcome in the future. In addition, existing results from stem cell technologies are highly encouraging for tumor treatment but it still needs further efforts to improve the safety and efficacy before they could enter clinical trials.[8]

5.Targeted drug therapy

Targeted cancer therapies are drugs or other substances which are sometimes interchangeably used as "molecularly targeted drugs," "molecularly targeted therapies," and "precision medicines." Those drugs' mechanism of action is by interfering with growth molecules which leads to blocking the growth and spreading of cancer.34 Tumor initiation and progression are determined by the TM of an atypical tumor which comprises endothelial cells, pericytes, smooth muscle cells, fibroblasts, various inflammatory cells, dendritic cells, and CSCs. There are various signaling mechanisms and pathways that TM-forming cells dynamically interact with the cancerous cells which are suitable for sustaining a reasonably high cellular proliferation. So, it is the area of research interest using TM conditions to mediate effective targeting measures for cancer there

Types of target agents:

Monoclonal antibodies: Antibody drugs are man-made versions of immune system proteins administered intravenously to attack certain targets on cancer cells. They contain a more proportion of human components than murine components. Their attack mechanisms of action are recruiting host immune functions to attack the target cell, binding to ligands or receptors thereby interrupting essential cancer cell processes, and carrying a lethal payload, such as radioisotope or toxin, to the target cell. Gemtuzumab is an example of a CD-33- specific monoclonal antibody currently used for AML treatment by conjugating with calicheamicin. In addition, ibritumomab tiuxetan is an anti-CD20, a 90Y metal isotope-based is developed in clinical therapy. Delivery of active therapeutics, prodrug activation enzymes, and chemotherapy toxins are also another use of target agents of monoclonal antibodies.

Small molecule inhibitors: These are smaller protein in size (⩽500Da) than monoclonal antibodies, so that they can simply translocate through plasma membranes and can be taken orally. Their main function is interrupting cellular processes by interfering with the intracellular signaling of tyrosine kinases which leads to the inhibition of tyrosine kinase signaling and initiates a molecular cascade that can lead to the inhibition of cell growth, proliferation, migration, and angiogenesis in malignant tissues. Examples of small molecule inhibitors are gefitinib and erlotinib which inhibit epidermal growth factor receptor (EGFR) kinase and EGFR in non-small cell lung cancer (NSCLC) patients, respectively. There are also lapatinib and sorafenib which act on the inhibition of EGFR/Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2) for ERBB2-positive breast cancer and VEGFR kinase, in renal cancer.[9]-[10]

Natural antioxidants

Day to day, the anatomy undergoes many exogenous insults, such as ultraviolet (UV) rays, pollution, and tobacco smoke, that end in the assembly of reactive species, particularly oxidants and free radicals, liable for the onset of many diseases, together with cancer. These molecules can even be made as a consequence of clinical administration of medication. Vitamins, polyphenols, and plant-derived bioactive compounds are natural antioxidants used as preventive and therapeutic drugs against these molecules that damage the body due to their anti-inflammatory and antioxidant properties. Studies added to cancer therapy after appreciating their antiproliferative and proapoptotic properties. Compounds, such as vitamins, alkaloids, flavonoids, carotenoids, curcumin, berberine, quercetin, and others, are examples of natural antioxidants screened.

Limited bioavailability and/ or toxicity is one of the challenges of natural drugs while their translation into clinical practice. Curcumin has cytotoxic effects in different kinds of tumors, such as the brain, lung, leukemia, pancreatic,

and hepatocellular carcinoma,80 while sparing normal cells at effective therapeutic doses. The curcumin's biological properties, treatment duration and efficient therapeutic doses are under

Berberine is an alkaloid compound that has been studied to be effective against different cancers as a chemo preventive agent, modulating many signaling pathways. Different nanotechnological strategies have been developed to facilitate its delivery across cell membranes due to their poorly soluble in water. [9]-[10]

6.Gene therapy

Gene therapy is the insertion of a normal copy of a defective gene in the genome to cure a specific disorder. The first application dates back to 1990 when a retroviral vector was exploited to deliver the adenosine deaminase (ADA) gene to T cells in patients with severe combined immunodeficiency (SCID). Approximately, about 2900 gene therapy clinical trials are currently ongoing, two-third of which are related to cancer. Strategies, such as expression of proapoptotic and chemosensitizing genes, expression of wild-type tumor suppressor genes, expression of genes able to solicit specific anti-tumor immune responses, and targeted silencing of oncogenes, are under evaluation for cancer gene therapy. Thymidine kinase (TK) gene delivery is effective for the administration of prodrug ganciclovir to activate its expression and induce specific cytotoxicity. The p53 tumor suppressor gene which is vectors carrying has been assessed for the clinical purpose very recently. ONYX-015 has been tested in NSCLC patients and gave a high response rate when given alone or combined with chemotherapy. Gendicine, a recombinant adenovirus carrying wild-type p53-induced complete disease regression in head and neck squamous cell cancer had similar success when combined with Some challenges that have been faced with gene therapy are the selection of the right conditions and the choice of the best delivery mechanism. Identified drawbacks of this therapy are genome integration, limited efficacy in specific subsets of patients, and high chances of being neutralized by the immune system. Basic research and medical translation used RNA interference (RNAi) as an efficient technology that able to produce targeted gene silencing. RNA-induced silencing complex (RISC) mediates the targeted gene silencing process by cleaving the messenger RNA (mRNA) and interference with protein synthesis. A siRNAs can be designed to block desired targets, involving cell proliferation and metastatic invasion; hence, precise molecular mechanisms are a triggering factor for tumor formation. This method relies on siRNA-mediated gene silencing of antiapoptotic proteins, transcription factors (i.e. c-myc gene), or cancer mutated genes (i.e. K-RAS).[11]

Advantages of siRNA-based drugs are safety, high efficacy, specificity, few side effects, and low costs of production. However, occasionally, they can induce off-target effects or elicit innate immune responses, followed by specific inflammation. Delivery methods currently under are chemical modification (insertion of a phosphorothioate at 3' end, introduction of a 2' O-methyl group, and modification by 2,4-dinitrophenol) and lipid encapsulation, or conjugation with organic molecules (polymers, peptides, lipids, antibodies, small molecules) efficiently target to spontaneously cross cell membranes of naked siRNAs. Interaction of cationic liposomes with negatively charged nucleic acids facilitates easy transfection by simple electrostatic interactions. They can be constituted by 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) and N-[1-(2,3-dioleoyloxy) propyl]-N, Ntrimethylammonium methyl sulphates (DOTMA). Currently, a Phase I clinical trial is recruiting patients for evaluating the safety of Eph receptor A2 (EphA2) targeting 1,2-dioleoyl-snglycero-3-phosphocholine (DOPC) encapsulated siRNA (siRNA-EphA2-DOPC) in patients with advanced and recurrent cancer. siRNAs can be concentrated in cationic polymers, such as chitosan, cyclodextrin, and polyethyleneimine (PEI). CALAA-01 is one of the cyclodextrin polymers conjugated with human transferrin is being entered a Phase I clinical trial.

PEI has been used as an anti-cancer by forming small cationic nanoparticles and loading with human epidermal growth factor receptor 2 (HER-2 receptor)-specific siRNA. Phase II clinical trial has been started to evaluate Local Drug Elute (siG12D LODER) directed to mutated Kirsten rat sarcoma (K-RAS) oncogene for the treatment of advanced pancreatic cancer. Conjugating to peptides, antibodies, and aptamers improves stability during

circulation and enhances cellular uptake of siRNAs. The introduction of nano carriers has largely improved siRNAs stability, pharmacokinetics and biodistribution properties, and targeting specificity. Polyallylamine phosphate nanocarriers have been developed to release siRNAs in the cytoplasm after disassembly at low endosomal PH. [12]

Dose correction and variabilities between individuals and different stages of disease are challenging issues on clinical translation of the siRNA-based approach. In the future, the needed research is on setting up the best-personalized therapy and toward controlled release to reach only specific targets on treating the tumor. Current methods in oncology focus on the development of safe and efficient cancer nanomedicines. Targeted medical care helped rising the biodistribution of recent or already tested chemotherapeutical agents around the specific tissue to be treated; different methods, such as sequence medical care, siRNAs delivery, therapy, and inhibitor molecules, supply new potentialities to cancer patients. Gene therapy acts by direct in situ insertion of exogenous genes into benign tumors. Noticeably, stem cells can be used as regenerative medicine, therapeutic carriers, drug targeting, and generation of immune cells because of having unique biological actions on other cells.22 On the opposite hand, thermal ablation and magnetic hyperthermia are promising alternatives to the growth surgical process. Finally, radionics and pathomics approaches facilitate the management of huge knowledge sets from cancer patients to enhance prognosis and outcomes. [12]

Conclusion

The history of cancer dates back to more than 200 million years ago, although earlier it was not that common. Since the last couple of decades, cancer cases have increased dramatically, but at the same time due to advancement in science and technology, the mortality rate is decreasing. The conventional treatments like surgery, chemotherapy, radiation therapy etc are useful but have negative impact on the healthy tissues of the body, hence it is important to find more effective techniques. Immunotherapy, targeted therapies like small molecule tyrosine kinase inhibitors, MABs and gene therapy are some recent advancements in cancer treatment. Also, studies are being conducted on the usage of personalized vaccines for cancers. A perfect cure for this deadly disease is still awaited and many more research work needs to be conducted for improving the survival rate and quality of lives of cancer patients.

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