RECENT ADVANCES AND NEW TECHNIQUES IN CHEMOTHERAPY

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ABSTRACT: One in every six fatalities globally is caused by the global health issue of cancer. The procedure of treating cancer has been quite difficult. Aside from recent significant advancements in stem cell therapy, targeted therapy, ablation therapy, nanoparticles, natural antioxidants, radionics, chemodynamic therapy, sonodynamic therapy, and ferroptosis-based therapy, traditional treatment modalities like surgery, chemotherapy, and radiotherapy are still in use. Oncology practises today concentrate on creating effective and secure cancer nanomedicines. Targeting both primary and metastatic cancer foci, stem cell treatment has demonstrated remarkable success in regenerating and repairing sick or damaged tissues, and nanoparticles have introduced novel diagnostic and therapeutic possibilities. The development and spread of particular cancer cells can be prevented by targeted treatment, which also protects good cells from harm. Ablation treatment has become a less invasive method for freezing or burning tumours without performing open surgery. Natural antioxidants have shown promise in locating free radicals and counteracting their damaging effects, perhaps treating or preventing cancer. Clinical trials are being conducted on a number of innovative technologies, some of which have already received approval. An update on current developments and discoveries in cancer therapy was provided in this review.

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

INTRODUCTION
Globally, there will likely be 10.3 million cancer deaths and 19.3 million new instances of the disease in 2020. Cancer is a highly complex chain of symptoms that develops over time with a broad lack of growth inhibition. [1–3] For many years, patients had just a few alternatives for cancer treatment, which included surgery, radiation therapy, and chemotherapy either individually or in combination. [4],[5] Combinatorial strategies, involving multiple targeted therapies or “traditional” chemotherapeutics, such as the taxanes and platinum compounds, have been found to have a synergistic effect. However, recently, many pathways involved in cancer therapy progression and how they can be targeted have improved dramatically. [6] Despite the fact that the accepted therapeutic level has not been achieved that reduces the death rate and lengthened life times for metastatic cancer, new techniques, such as medications, biological molecules, and immune-mediated treatments, are being employed for treatment.

The development of a fresh revolution in neoplastic cancer or medications that target specific tumour entities rely on those pathways and traits. [7] Whether used alone or in conjunction with radiation, chemotherapy is thought to be the most efficient and often employed treatment option for cancer. Chemotherapy medications target tumour cells primarily by creating reactive oxygen species, which primarily kill tumour cells. [8] Hormonal therapies are also frequently used for cancer malignancies and are regarded as cytostatic because they inhibit the growth of tumours by limiting the hormonal growth factors that act via the hypothalamic-pituitary-gonadal axis (HPGA), blocking hormone receptors, and limiting the production of adrenal steroid hormones. [9] A basic summary of the most cutting-edge and cutting-edge cancer medicines was given in this narrative review. Also included are various approaches to cancer diagnosis and treatment, their current status in the clinical setting, underscoring their impact as cutting-edge anti-cancer approaches, as well as new strategies that are currently being studied at the research stage and should outweigh the drawbacks of conventional therapies.

Cancer treatment modalities
By categorising cancer therapy options into conventional (traditional) and advanced or new or modern categories, we may examine how they differ from one another. Almost half of all currently running medical treatment trials globally focus on cancer therapies today. [7] Factors such the type of cancer, where it is located, and how severe it is influence the treatment options and its course. Surgery, chemotherapy, and radiation are the most often used conventional treatment modalities. Modern modalities include hormone therapy, anti-angiogenic, stem cell treatments, immunotherapy, and immunotherapy based on dendritic cells. [10]

Conventional cancer therapies
The standard cancer treatment approaches that are most frequently advised involve surgically removing the tumours, followed by radiation using x-rays and/or chemotherapy. [11] Surgery is the one of these treatments that works best while the illness is still in its early stages. Radiation therapy has the potential to harm healthy tissues, cells, and organs. Despite the fact that chemotherapy has decreased morbidity and death, almost all chemotherapeutic drugs harm healthy cells, particularly those that divide and expand quickly. [12] A significant issue with chemotherapy is drug resistance, which occurs when cancer cells that were originally inhibited by an anti-cancer treatment start to become resistant to the agent. Reduced drug absorption and increased drug efflux are the main...
contributors to this. [13] limitations of traditional chemotheray, including difficult dose selection, lack of selectivity, quick drug metabolism, and mostly negative side effects. [14]

ADVANCED AND INNOVATIVE CANCER THERAPIES

Drug resistance and its delivery mechanisms are the biggest barriers to treating cancer and reducing its symptoms, yet there are presently several authorised therapy modalities and medications. Due to aberrant blood artery architecture and tumour biology, traditional cancer is less effective than it formerly was. [15] The following are examples of cutting-edge and creative cancer therapies, along with their advantages and drawbacks.

Cancer stem cells

Epigenetic alterations cause normal stem cells, precursor/progenitor cells, or cancer stem cells (CSCs) to develop. They play a part in the development, metastasis, and recurrence of cancer, which suggests that they may be effective in treating solid tumours. [23]

There are several ways that stem cells can cure tumours.

### Table 1. Licensed stem cell therapies.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Stem cell therapies</th>
<th>Examples</th>
<th>Authority</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Pluripotent stem cells</td>
<td>iPSC (sipuleucel-T)</td>
<td>FDA</td>
<td>Prostate cancer[19]</td>
</tr>
<tr>
<td>02</td>
<td>Adult stem cells</td>
<td>MSC-INFβ</td>
<td>FDA</td>
<td>Ovarian tumor[32]</td>
</tr>
<tr>
<td>03</td>
<td>Cancer stem cells</td>
<td>Venetoclax</td>
<td>FDA</td>
<td>AML[33]</td>
</tr>
</tbody>
</table>

AML: acute myelogenous leukemia; FDA: The US Food and Drug Administration; iPSC: induced pluripotent stem cell; MSC-INFβ: mesenchymal stem cells with interferon beta.

One method involves the HSCs quickly migrating into specific stem cell niches in the bone marrow (BM), after which the transplants go through the engraftment phase before producing specialised blood cells. The production of the matrix degradable enzyme MMP-2/9,22 and the contact of the stem cell CXCR4 receptors with endothelial cells via LFA-1, VLA-4/5, and CD44 are also necessary for this pathway. The second mechanism is the tumor-tropic effect, in which MSCs migrate into the tumour microenvironment (TM) after being drawn there by the tumour cells' secretions of CXCL16, SDF-1, CCL-25, and IL-6, and then differentiate within the tumour cells to aid in the growth of the tumour stroma. [24] Extracellular vesicles (EVs) and soluble substances, as well as paracrine factor secretion, are other ways that stem cells function. [25] and they have the ability to differentiate, much like transplanted HSCs, to produce all various types of blood cells. [26]

Cancer is typically treated with stem cell therapy employing a variety of techniques, such as HSC transplantation, MSC infusion, therapeutic carriers, creation of immune effector cells, and vaccine development. [31] The following adverse effects were seen with the stem cell cancer treatment strategy: Tumorigenesis, unfavourable outcomes after allogeneic HSC transplantation, medication toxicity and treatment resistance, heightened immunological responses and autoimmunity, and viral infection are among the possible side effects. [22] Despite these achievements, there are still problems that need to be looked at and resolved in the future, including therapeutic dosage management, low cell targeting, and retention in tumour areas. Also, while early results from the use of stem cell therapies to treat tumours are very promising, more work needs to be done to increase their safety and effectiveness before they can be used in clinical trials. Table 1 summarized the licensed list of stem cell therapies.

**Adult stem cells**

Hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and neural stem cells are adult stem cell categories that are often employed in tumour treatment (NSCs). All adult blood cells in the body can be formed by HSCs, which are found in BM. Only the infusion of HSCs produced from cord blood is currently authorised by the Food and Drug Administration (FDA) to treat multiple myeloma and leukaemia. [20] MSCs are present in a variety of tissues and organs and are crucial for tissue regeneration into osteocytes, adipocytes, and chondrocytes as well as for tissue repair. MSCs are employed in conjunction with other methods of treating malignancies due to their unique biological properties. [21] NSCs are employed to treat both primary and metastatic breast and other malignancies since they can self-renew and produce new neurons and glial cells. [22]

**Pluripotent stem cells**

The embryo's homogenous inner mass cells, known as embryonic stem cells (ESCs), can give birth to every type of cell, with the exception of those found inside the placenta. A breakthrough in cell biology occurred in 2006 with the development of Yamanaka factors, which allowed physical cells in a culture to become pluripotent stem cells (iPSCs). [17] Because iPSCs and ESCs have the same traits, there are no ethical concerns associated with embryo destruction. For the development of an anti-tumor vaccination as well as the stimulation of effector T cells and natural killer (NK) cells, hematopoietic embryonic stem cells (hESCs) and iPSCs are being utilised. [19]

**Stem cells therapy**

In the bone marrow (BM), stem cells are undifferentiated cells with the capacity to develop into any kind of body cell. Another cancer therapy method that is thought to be both safe and efficient is the use of stem cells. The use of stem cells is yet in the exploratory stage of clinical trials; one potential use is the regeneration of other damaged tissue. BM, fat, and connective tissue-derived mesenchymal stem cells (MSCs) are now employed in clinical studies. [16]
Targeted drug therapy

Drugs or other chemicals that are "molecularly targeted," "molecularly targeted treatments," or "precision medicines" are considered targeted cancer therapy. These medications work by interfering with growth molecules, which prevents cancer from developing and relocating. [34] The TM of an atypical tumour, which is made up of endothelial cells, pericytes, smooth muscle cells, fibroblasts, different inflammatory cells, dendritic cells, and CSCs, controls the genesis and growth of the tumour. The TM-forming cells actively engage with the malignant cells through a variety of signalling pathways and processes that are suited for supporting a moderately high level of cellular growth. Hence, employing TM circumstances to mediate efficient targeting strategies for cancer therapy is the field of study focus. [35]

It is challenging to selectively target cancer cells with traditional chemotherapy because they resemble normal cells. Cellular processes, such as cell cycle arrest, induction of apoptosis, suppression of proliferation, and interference with metabolic reprogramming by targeted pharmacological treatment agents, intervene in order to address these issues. [36] Two tactics that can be employed for the treatment of cancer include altering TM and targeting TM for medication delivery. [37] Drugs used in targeted therapy do differ from those used in traditional chemotherapy in the manner they attack cancer cells while causing less harm to healthy cells, which is the programming that distinguishes cancer cells from healthy, normal cells. [38]

The addition of erlotinib to regular chemotherapy boosted the survival rate for some illnesses, bringing it from 17% to 24% in patients with advanced pancreatic cancer. Rituximab, sunitinib, and trastuzumab have all altered the treatment of renal cell carcinoma and breast cancer, respectively. Imatinib has had a significant impact on chronic myeloid leukemia. [39]

Based on how they operate or where they target, we may categorize the agents that target cells. Some enzymes act as growth signals for cancer cells. Some targeted medicines block the growth-stimulating enzymes that cancer cells use as signals. Enzyme inhibitors are the name of these medicines. By suppressing these cell signals, cancer can be prevented from developing and spreading. [40]

Because they directly target the cell components that determine whether cells survive or die, certain targeted treatments are known as apoptosis-inducing medications. Examples include protein kinase B (PKB/Akt), which increases cell survival, and inhibitors of this enzyme are now in the preclinical stage of development. [41]

These substances prevent tumors from forming new blood vessels, which helps to cut off the tumors' supply of blood and prevent tumor growth. Additionally, they halt the growth of tumors by reducing the amount of blood that reaches the tumor by blocking the activity of angiogenic factors like vascular endothelial growth factor (VEGF) or its receptors. According to the study, individuals with advanced colorectal cancer had their lives prolonged by months when Avastin (bevacizumab) was combined with chemotherapy that used the drug 5-fluorouracil. [42]

TYPES OF TARGET AGENTS

Monoclonal antibodies

Drugs called antibodies are synthetic copies of immune system proteins that are injected into the body to assault specific targets on cancer cells. They have a higher percentage of human than murine components. [43] Their assault strategies involve inducing the host immune system to attack the target cell, attaching to ligands or receptors to stop vital cancer cell operations, and delivering a deadly payload to the target cell, such as a radioisotope or poison. [44] By conjugating with calicheamicin, the monoclonal antibody Gemtuzumab, for instance, targets CD-33 and is now utilized to treat AML. [45] Ibritumomab tiuxetan is also a clinically developed anti-CD20 that is based on a 90Y metal isotope. [46] Targeting agents of monoclonal antibodies can also deliver active medicines, prodrug activation enzymes, and chemotherapeutic toxins. [47]
Small molecule inhibitors

These proteins are smaller in size (500Da) than monoclonal antibodies, making it easier for them to cross plasma membranes and be ingested. Their primary purpose is to disrupt cellular processes by interfering with tyrosine kinase intracellular signaling, which inhibits tyrosine kinase signaling and sets off a chain of events that can stop cell growth, proliferation, migration, and angiogenesis in malignant tissues.\(^48\) Gefitinib and erlotinib, two examples of small molecule inhibitors, block the kinase and EGFR, respectively, in patients with non-small cell lung cancer (NSCLC). Additionally, for ERBB2-positive breast cancer and for renal cancer, there are lapatinib and sorafenib, which operate to suppress EGFR/Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2) and VEGFR kinase, respectively.\(^49\)

Ablation cancer therapy

The surgical alternative is not recommended for tiny tumors that are less than 3 cm in size, thus ablation is a therapy method that eliminates tumors without removing them. For bigger tumors, embolization and ablation are combined. Due to the possibility of killing part of the normal tissue surrounding the tumor, this method may not be recommended for treating tumors that are close to major blood arteries, the diaphragm, or major bile ducts.\(^50\)

Thermal ablation

In this method, a focused zone inside and surrounding the tumor is targeted for destruction using intense heat or hypothermia. Similar to surgery, thermal ablation eliminates the tumor along with a margin of tissue that seems to be normal but is really destroyed in situ before being absorbed by the body. The technique is administered frequently using a percutaneous or non-invasive route, but is identical to surgery when performed via an open, laparoscopic, or endoscopic approach. The method will depend on the type of tumor, the location, the doctor's preference, and your health.\(^51\)

Currently, clinical settings utilize cryoablation, high-intensity focused ultrasound, radiofrequency ablation (RFA), and microwave ablation. In order to cause tissue damage via a freeze-thaw process against others, cryoablation employs a hypothermic modality. Except for cryoablation, all of these therapies work on the basis of hyperthermia. Cryoablation has the greatest potential to cause a post-ablative immunogenic response of any ablation procedure.\(^52\)

Recent research has shown that RFA and cryoablation, which are used as treatments for TM and in systemic circulation, can affect the immune system in addition to causing tissue disturbance. Ablation methods have been demonstrated to impact carcinogenesis because of the local inflammatory response that creates an immunogenic gene signature.\(^53\)

The benefit of this method over surgery is that it offers a minimally invasive (e.g., laparoscopically or percutaneously) or non-invasive approach to cancer therapy and attracts attention as a substitute for conventional surgical therapies.\(^54\)

Cryoablation

Cryoablation is one of the ablation methods that destroys large amounts of tissue by freezing it to fatal levels, followed by liquid formation. The majority of original tumors treated with this treatment are both benign and malignant.\(^55\) After experimenting with the use of low temperatures by salt and ice solutions for the formation of local numbness before surgical procedures in the nineteenth century, James Arnott found that the freezing temperatures can affect cancer cell survival. He recommended cryoablation as an appealing treatment choice that improved a patient's chance of survival.\(^56\)

The basis for cryoablation techniques is the Joule-Thomson effect, which was extensively researched in the 1930s. It was found that using liquid CO2 under high pressure, liquid air, and liquid oxygen could produce ice crystals, which could then be used to treat lesions, warts, and keratosis. However, Allington took the position of liquid N2 for the treatment of many skin lesion conditions after 1950.\(^47\)

RFA therapy

RFA is a minimally invasive method that uses high-frequency electrical currents to create a hyperthermic environment to kill cancer cells. Needle electrodes are guided into a tumor cell using imaging techniques including ultrasound, computed tomography, or magnetic resonance imaging (MRI). RFA is often the best method for treating small-size tumors with a diameter of less than 3 cm. RFA can be used with other traditional cancer therapy modalities.\(^57\) RFA can treat medium tumors after deploying deployable devices or numerous electrode systems. (up to 5cm diameter).\(^58\)

Gene therapy
In order to treat a particular condition, a faulty gene is replaced with a healthy copy in a process known as gene therapy. The adenosine deaminase (ADA) gene was originally introduced to T cells in individuals with severe combined immunodeficiency in 1990 using a retroviral vector. (SCID). Two-thirds of the over 2900 active clinical studies for gene therapy are focused on cancer. For cancer gene therapy, methods including the production of proapoptotic and chemosensitizing genes, wild-type tumor suppressor genes, genes able to elicit certain anti-tumor immune responses, and targeted silencing of oncogenes are being considered.[47]

![Figure 3: Workflow of Gene Therapy](image)

For the injection of the prodrug ganciclovir to stimulate its expression and produce particular cytotoxicity, thymidine kinase (TK) gene delivery is efficient.[59] The p53 tumor suppressor gene, which is carried via vectors, has recently been evaluated for therapeutic use. When taken alone or with chemotherapy, ONYX-015 demonstrated a good response rate in NSCLC patients.[60] When paired with radiation, gendicine, a recombinant adenovirus containing wild-type p53, caused full disease regression in head and neck squamous cell carcinoma.[61]

The correct circumstances and the finest delivery method to use are two issues that have been encountered with gene therapy. The therapy's genomic integration, limited effectiveness in some patient subgroups, and significant risk of immune system neutralization have all been identified as downsides. The effective method of RNA interference (RNAi), which may result in targeted gene silencing, has been applied in basic research and medicinal translation.[62] The RNA-induced silencing complex (RISC), which cleaves messenger RNA (mRNA) and interferes with protein synthesis, mediates the targeted gene silencing process. [63] It is possible to create siRNAs to inhibit specific targets, such as cell proliferation and metastatic invasion; as a result, particular molecular processes are a catalyst for tumor development. This approach depends on antiapoptotic proteins, transcription factors (such the c-myc gene).[64],[65] or cancer-related genes being silenced by siRNA. (i.e. K-RAS).[66]

Safety, excellent effectiveness, specificity, few adverse effects, and inexpensive production costs are benefits of siRNA-based medications.[67] Sometimes, though, they can cause off-target effects or innate immune reactions that cause particular inflammation.[68] There are several delivery strategies being investigated right now, including lipid encapsulation, conjugation with organic molecules (polymers, peptides, lipids, antibodies, small molecules), chemical modification (insertion of a phosphorothioate at the 3' end, introduction of a 2'-O-methyl group, and modification by 2,4-dinitrophenol), and spontaneous cell membrane translocation of naked siRNAs.[69] Simple electrostatic interactions between negatively charged nucleic acids and cationic liposomes make transfection simple and effective.[70] They can be made up of N-[1-(2,3-dioleyloxy) propyl]-N', N-trimethylammonium methyl sulfate and 1,2-dioleoyl-3-trimethylammonium propane (DOTAP), (DOTMA).[71] In order to assess the safety of Eph receptor A2 (EphA2) targeting 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) encapsulated siRNA (siRNA-EphA2- DOPC) in patients with advanced and recurring cancer, a Phase I clinical trial is now enrolling patients.[72] Cationic polymers including chitosan, cyclodextrin, and polyethyleneimine can be used to concentrate siRNAs. (PEI).[73] One of the cyclodextrin polymers coupled with human transferrin is entering a Phase I clinical study, and its name is CALAA-01. By creating tiny, cationic nanoparticles containing the human epidermal growth factor receptor 2 (HER-2 receptor)-specific siRNA, PEI has been employed as an anti-cancer agent. [74] The evaluation of Local Drug EluteR (siG12D LODER), which targets the mutant Kirsten rat sarcoma (K-RAS) oncogene, for the treatment of advanced pancreatic cancer has begun as part of a Phase II clinical study. Enhancing cellular absorption of siRNAs by conjugating to peptides, antibodies, and aptamers increases stability throughout circulation.[75] With the addition of nanocarriers, siRNAs' stability, pharmacokinetics, and biodistribution characteristics, as well as their targeting specificity, have been significantly enhanced. Polyallylamine phosphate nanocarriers have been created to disassemble at low endosomal pH and release siRNAs into the cytoplasm.[76]

The siRNA-based approach's clinical translation faces difficult problems with dose adjustment, individual variability, and disease stages. Future research will focus on developing the best customized therapies and on controlled release to only treat the tumor's specific targets. Based on their mode of action and induction, Table 2 provides a summary of the gene therapy medications.

**Natural antioxidants**

Daily exposure to several external insults, including ultraviolet (UV) rays, pollution, and cigarette smoke, causes the body to produce reactive species, mainly oxidants and free radicals, which are responsible for the development of a number of illnesses, including cancer.
including cancer. These molecules can also be produced as a result of the therapeutic administration of drugs, but they are also produced spontaneously by mitochondria and peroxisomes in our cells and tissues, as well as by the metabolism of macrophages during classic physiological aerobic activities.[47]

### Table 2. Summary of gene therapy approaches.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Gene therapy</th>
<th>Mechanism of action</th>
<th>Category</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zalmoxis</td>
<td>Enhances immune reconstitution</td>
<td>Allogeneic hematopoietic stem cell transplantation (allo-HSCT)</td>
<td>Hematopoietic malignancies</td>
</tr>
<tr>
<td>2</td>
<td>Oncolytic virotherapy (OV)</td>
<td>Directly lyses tumor cells and introduces wild-type tumor suppressor genes into cells</td>
<td>Naturally occurring or genetically modified viruses</td>
<td>Tumor immunotherapy</td>
</tr>
<tr>
<td>3</td>
<td>Oncorine (rAd5-H101)</td>
<td>Causes oncolysis</td>
<td>Replicative, oncolytic recombinant ad5</td>
<td>Refractory nasopharyngeal cancer</td>
</tr>
<tr>
<td>4</td>
<td>Imlygic</td>
<td>Causes apoptosis of tumor cell</td>
<td>Genetically modified oncolytic HSV-1</td>
<td>Non-resectable metastatic melanoma</td>
</tr>
<tr>
<td>5</td>
<td>Gendicine</td>
<td>Induces the expression of p53, restores its activity, and destroys the tumor cells</td>
<td>Non-replicative adenoviral vector</td>
<td>Neck and head squamous cell carcinoma</td>
</tr>
<tr>
<td>6</td>
<td>Rexin-G</td>
<td>Inhibits cell cycle in the G1 phase</td>
<td>Replication-incompetent retroviral vector</td>
<td>Metastatic cancers</td>
</tr>
<tr>
<td>7</td>
<td>Kymriah</td>
<td>Initiates the anti-tumor effect through CD3 domain</td>
<td>CAR T cell-based gene</td>
<td>Relapsed B-cell acute lymphoblastic leukemia</td>
</tr>
</tbody>
</table>

By causing damage to DNA and other bio-macromolecules, oxidative stress and radical oxygen species can drastically alter how transcription factors are regulated.[77]

Due to their inherent anti-inflammatory and antioxidant capabilities, vitamins, polyphenols, and bioactive chemicals produced from plants are utilized as preventative and therapeutic medications against harmful molecules that harm the body.[78] Studies that recognized their proapoptotic and antiproliferative effects were added to cancer treatment. Natural antioxidants that have been tested in vitro and in vivo include vitamins, alkaloids, flavonoids, carotenoids, curcumin, berberine, quercetin, and other substances.[79]

One difficulty in using natural medicines in clinical settings is their low absorption and/or toxicity.[47] In several tumor types, including those of the brain, lung, leukemia, pancreas, and hepatocellular carcinoma, curcumin exhibits cytotoxic effects while preserving normal cells at therapeutically effective doses.[80] Studies are being conducted on the biological characteristics of curcumin, the length of therapy, and effective therapeutic dosages.[80] About 27 clinical trials on curcumin are being completed now, while another 40 are being researched. As a chemopreventive drug, berberine, an alkaloid molecule, has been shown via research to be effective against several cancers by modifying a number of signaling pathways. Due to their limited solubility in water, many nanotechnological techniques have been developed to help in their distribution through cell membranes.[81] Six clinical trials are being investigated, and two have already been finished.

Another natural substance from plants, quercetin, has been shown to be helpful both on its own and in conjunction with chemotherapeutic drugs in the treatment of several malignancies, including lung, prostate, liver, colon, and breast cancers.[82] The way quercetin works is by attaching to cellular receptors and disrupting various signaling pathways.[83] Six clinical trials are being investigated at the moment, and seven investigations have been finished.

**Current clinical trials**

Recent advancements in the study of clinical trials have been made in the analysis of cancer medicine in the direction of less intrusive, more precise, and practical cancer therapies. (Figure 4).
The terms stem cell, targeted treatment, immunotherapy, and gene therapy are now the most often used entries concentrating on cancer therapies in the database of clinical trials (www.clinicalTrials.gov), as they are extremely promising and successful. The possible benefits and drawbacks of the novel treatment modalities are presented in Table 3. The approaches to advanced cancer treatments and their corresponding delivery methods are compiled in Table 4 with examples.

Table 3. Comparison of advantageous and disadvantageous of new cancer therapies.

<table>
<thead>
<tr>
<th>S. no</th>
<th>Treatment approach</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Stem cell therapy</td>
<td>Safe and effective Can be combined with other strategies Decreases tumor volumes and extend survival</td>
<td>Treatment not durable Potential tumorigenesis</td>
</tr>
<tr>
<td>02</td>
<td>Targeted therapy</td>
<td>High specificity Reduced adverse reactions</td>
<td>Long-term side effects in question</td>
</tr>
<tr>
<td>03</td>
<td>Ablation therapy</td>
<td>Precise treatment Possibility to perform along with MRI imaging (magnetic hyperthermia)</td>
<td>Efficiency mainly to localized areas Low penetration power Needs skilled operator</td>
</tr>
<tr>
<td>04</td>
<td>Gene therapy</td>
<td>Expression of proapoptotic and chemosensitizing genes Expression of wild-type tumor suppressor genes Expression of genes able to solicit specific anti-tumor immune responses Targeted silencing of oncogenes and safety (RNAi)</td>
<td>Genome integration Limited efficacy in specific subsets of patients High chances to be neutralized by the immune system Off-target effects and inflammation (RNAi) Need for ad hoc delivery systems (RNAi) Setup of doses and suitable conditions for controlled release (RNAi)</td>
</tr>
<tr>
<td>05</td>
<td>Natural antioxidants</td>
<td>Easily available in large quantities The exploitation of their intrinsic properties</td>
<td>Limited bioavailability Possible toxicity</td>
</tr>
</tbody>
</table>

MRI: magnetic resonance imaging

Table 4. Advanced therapy approaches and delivery systems.

<table>
<thead>
<tr>
<th>S. no</th>
<th>Types of therapy</th>
<th>Delivery system</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Stem cell</td>
<td>Nanoparticles84</td>
<td>Hyaluronic acid (HA) Polyvinyl alcohol</td>
</tr>
<tr>
<td>02</td>
<td>Immune therapy85</td>
<td>Nanoparticles Scaffolds Hydrogels</td>
<td>Antigen-TLR agonist fusion vaccines Porous 3D scaffolds Anti-PD-1 mAbs</td>
</tr>
<tr>
<td>03</td>
<td>Gene therapy86</td>
<td>Viral gene delivery Non-viral gene delivery</td>
<td>Polysaccharides Polyethyleneimine (PEI) Lipid Naked DNA</td>
</tr>
<tr>
<td>04</td>
<td>Natural antioxidants</td>
<td>Nano delivery systems87</td>
<td>Solid nanocrystals Nanoemulsion Nanoliposomes</td>
</tr>
</tbody>
</table>
CONCLUSION

Oncology practices today concentrate on creating effective and secure cancer nanomedicines. Different approaches, such as sequence medical care, siRNAs delivery, treatment, and inhibitor compounds, provide new potentialities to cancer patients. Targeted medical care helped increase the biodistribution of current or already tested chemotherapeutical medicines around the target tissue to be treated. Direct in situ insertion of foreign genes into benign tumors is how gene therapy works. Because of their distinct biological effects on other cells, stem cells are particularly useful for regenerative medicine, therapeutic carriers, drug targeting, and the production of immune cells. [22] On the other hand, intriguing alternatives to the growth surgical procedure include thermal ablation and magnetic hyperthermia. In order to improve prognosis and outcomes, radionics and pathomics methods make it possible to handle enormous knowledge sets from cancer patients. Personalized therapeutics must be improved by further research and improvement of medication delivery technologies. To improve treatment results, drug delivery methods must be developed and improved further.

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