An Overview of Common Cancer Treatments

Shivaani Kumara Venkatesh

Abstract

Cancer, an extremely debilitating disease characterized by uncontrolled cell growth and development, causes millions of deaths annually despite significant research efforts and advances. This paper will cover some of the most promising therapies for cancer outlined in several studies such as gene therapy, surgery, stem cell therapy, radiotherapy, and chemotherapy. They will be summarized, with a brief overview of each method and further detail on the different techniques and approaches (Mathur, et al., 2015).

Introduction

Though a variety of therapeutics exist, none have proven to be versatile and effective enough as a treatment that works in all instances or for all patients. For example, standard approaches such as surgery and chemotherapy or radiotherapy damage healthy cells and tissue. A major obstacle on the path to finding a suitable treatment is drug resistance, or when cancer cells develop resistance to a suppressor drug. In recent years, however, more treatments have been clinically tried and approved. Most of the current therapeutics, especially within the realm of chemotherapy, focus on apoptosis, in order to induce cell death and slow proliferation. However, gene therapy aims beyond, also targeting angiogenesis inhibitors, suppression and inhibition of oncogene and tumor genes, and strengthening the immune response through CAR-T cell therapy. More clinically advanced forms of radiotherapy are now able to target tumors and avoid critical organs through more advanced computer scanning and imaging systems. Additionally, stem cell therapy holds promise for replacing damaged cells, including blood cells (Debela, et al., 2021).

Surgery

For years, surgery has been the most common treatment for cancer, and is often paired with radiation or chemotherapy as one of the most successful treatments. Different situations call for varied methods, based on the aim of the operation, the progression of the cancer, and the health of the patient (Mintzer, 1999). It has been considered a highly effective tool for diagnosis, treatment, and prevention of cancer, and is the best method in early stages of disease progression. Generally, surgeons would remove the tumor from the body, along with surrounding tissue or lymph nodes that would be tested for cancer cells (Debela, et al., 2021). Recently, however, surgical methods have been abandoned in favor of less invasive techniques, such as the following (Mintzer, 1999).

Chemotherapy

This method of treatment uses drugs to prevent the proliferation of cancer cells. Compared to normal tissue, cancerous cells are more easily and efficiently killed by such toxic substances. However, even a small change in chemical structure can alter the effectiveness of the drug. Many different variations of the treatment exist, including changing the function of cellular proteins, interacting with hormones, and altering biological pathways. The combination of drugs is dependent on the variety of the cancer and how far it has spread, and extremely harmful effects on surrounding tissue have been recorded based on the dosage and frequency. Exposure over long periods of time has been observed to have detrimental effects on the patient's health, in addition to the cancer cells developing drug resistance.
Different approaches of chemotherapy exist, chosen depending on the patient and the cancer. Additionally, most of the drugs are centered around slowing or inhibiting proliferation (Anand, et al., 2023).

Alkylating agents cause the change in structure of DNA, often by creating intrastrand crosslinks, which inhibits the synthesis of new DNA (often during S-phase) (Bukowski, et al., 2020).

Antimetabolites are divided into several groups, and use a false replacement instead of the nucleotide needed in the genetic sequence (Bukowski, et al., 2020).

Mitotic spindle inhibitors cause cell death by altering the formation of the mitotic spindle during metaphase of mitosis, eventually preventing the cell from dividing (Bukowski, et al., 2020).

Topoisomerase inhibitors cause the DNA to become overly wound up, inducing cell death. Generally, this is prevented by the topoisomerase enzyme, which creates single or double stranded breaks to unwind the DNA (Bukowski, et al., 2020).

Tyrosine kinase inhibitors block cell proliferation signaling pathways (Bukowski, et al., 2020).

Proteasome inhibitors cause a buildup of misfolded proteins by halting degradation, eventually causing the cell to undergo apoptosis (Bukowski, et al., 2020).

Antibiotics are generally given alongside chemotherapy to lower the risk of infection (Bukowski, et al., 2020).

Radiotherapy

Approximately 50% of cancer patients receive radiation therapy through ionizing radiation. This name is due to the manner in which it works, by depositing ions within cancer cells that cause genetic changes which, in turn, cause the cell to die. Cancerous cells have a lower rate of recovery from such treatment compared to regular cells, however, there is still a risk of damage to other organs. Radiation therapy is most commonly done alongside other treatments, such as chemotherapy, immunotherapy, and surgery (Baskar, et al., 2012). Radiation doses are separated into individual sections (fractions) (Chaput, et al., 2021).
The aim of neoadjuvant radiation therapy (before surgery) is to shrink the tumor, while the adjuvant goal (postoperative) is to destroy miniscule leftover cells (Baskar, et al., 2012).

Radiation is measured in grays (Gy), where a Gy represents one joule of energy per a kilogram of tissue. Two methods are used to deliver the radiation: external beam radiotherapy (EBRT), and brachytherapy (internal radiation) (Chaput, et al., 2021). The first method uses a high-energy beam, such as photon or particle radiation, focused on the tumor from outside the body. The latter uses radioactive sources, such as catheters, from inside the body itself. Generally, photon radiation is divided into x-rays and gamma rays. Neither transfer much energy as they penetrate the cells, and hence are called 'linear energy transfer' rays, or LET. X-rays are created by the excitation of electrons, in machines such as cathode ray tubes or linear accelerators, while gamma rays are generated by the decay of several radioactive substances such as radium, cobalt-60, and cesium. Particle radiation is also separated, into electron, proton, and neutron beams. They are high LET rays and are capable of inflicting more damage to the cell, however, they have proven to be more effective, especially with radioresistant cancer types (Baskar, et al., 2012). In the EBRT method, an imaging technique is used to determine the dosage and fractions necessary for the patient's treatment before the therapy begins (Chaput, et al., 2021). Several other different, specific approaches are used in radiation therapy (Baskar, et al., 2012).

IMRT
This method avoids critical organs while conforming radiation doses to the tumor, made possible through a combination of software planning and computer-controlled radiation (Baskar, et al., 2012).

3DCRT
By replacing 2-D X-ray methods with CT scans, the 3DCRT method for accurate and precise treatment of the tumor with a small margin for microscopic tumor extension, or CTV (clinical target volume) (Baskar, et al., 2012).

SBRT
This technique utilizes highly concentrated radiation over fewer fractions and has shown promising results, particularly for non-small-cell lung cancer in patients for whom surgery is not feasible. Though nearby tissue may be dangerously damaged due to the high radiation, there is a relatively low risk due to the small amount of normal tissue present in the area (Baskar, et al., 2012).

IGRT
This method makes it possible to detect potential error and prevent damage to critical organs. This is done through pre-radiotherapy procedures, such as CT scans (Baskar, et al., 2012).

Gene therapy

Gene therapy has been shown to have a high potential for treating a plethora of medical conditions, including cancer. The main aims of this treatment would involve either activating therapeutic genes, switching off unwanted or mutated ones, providing lacking genes, or replacing mutated genes with a functional version. This is done by introducing the genes *in vivo* via a viral or non-viral vector. Targets of gene therapy are sorted into inhibition of oncogene,

tumor suppressor activation, immunotherapy, suicide gene therapy, and antiangiogenic gene therapy (Cesur-Ergün, et al., 2023).

Inhibition of oncogene:
Oncogenes are cancer-causing cells, created by mutated proto-oncogenes, or genes that help with normal growth and division of cells. This disrupts the balance between proto-oncogenes and tumor suppressors. One method to suppress the over-expression of oncogenes in tumors utilizes antisense oligonucleotides (ASOs). ASOs are short DNA or RNA pieces that bind to a sequence of RNA in order to prevent it from functioning. Short oligodeoxyribonucleotides also function in a similar manner, by blocking gene expression, specifically by binding to the DNA sequences containing oncogenes (Cesur-Ergün, et al., 2023).

Tumor suppressor activation:
The most well-known tumor suppressor genes are the Rb gene, BRCA-½, CDK inhibitors, and the most widely-studied, p53. These genes control the proliferation of cells by inducing apoptosis or blocking certain stages of the cell cycle. The use of an adenoviral vector for the p53 gene as well as treatment through chemoradiotherapy has been evaluated to have promising results. Through several studies, the effects of other tumor suppressive genes have been shown. p21 transfection (introduction by a means other than a viral vector) had tumor-shrinking effects on breast cancer in rats, while p14ARF blocked prostate cancer cells blocked from apoptosis, respectively. Additionally, cisplatin, a chemotherapy drug, is proven to be enhanced when combined with gene therapy treatments for p53, p16, and PTEN genes in bladder cancer (Cesur-Ergün, et al., 2023).

Immunotherapy:
Many gene therapy studies for immunotherapy utilize enhancement of the human immune system to recognize and fight cancer cells. Though cancer cells have identifiable molecules called antigens, they have found ways to evade destruction, such as hiding their antigens, weakening immune responses, and reducing the expression of major histocompatibility complexes (MHCs), which are molecules that aid the immune system in detection of these cells. Many approaches aim to deliver immunostimulants, MHCs, and molecules that support the function of T-cells (costimulatory molecules). It has been suggested that immunotherapeutic treatments focused on T-cells have more importance than those of B-cells due to their higher risk of being affected by cancer cells and the key role they play in the immune response. An example of a treatment is the introduction of a gene that encodes cytokines, which are heavily involved in the functions of T-cells. Non-viral vectors also seem to show promise, especially the interleukin-12 transfection which has been shown to activate various parts of the immune system.
Chimeric antigen receptor T-cell (CAR-T) therapy focuses on genetically modifying T-cells in order to improve their function. This is done by the addition of a receptor, which consists of four parts:
Target binding domain: binds to cancer cells using antibodies or cytokines.
Hinge region: provides flexibility and recognition for the CAR.

Transmembrane domain: attaches the receptor to the membrane of the T-cell.
Intracellular signal domain: sends signals to the T-cells and causes it to attack cancer cells. It also contains costimulatory and activation molecules.
The T-cells are removed from a patient, modified in a laboratory, and re-introduced to the body. Each variation of therapy targets different cancer antigens. There are currently five generations of CAR-T therapy (Cesur-Ergün, et al., 2023).

Suicide gene therapy:
The aim of suicide gene therapy is to slow cell proliferation by inducing apoptosis. An inactive but toxic prodrug is given to cells, along with genes that encode a specific enzyme. This enzyme is used to activate the prodrug, which will then kill the cell due to its toxicity. The thymidine kinase/ganciclovir system is a prodrug system that uses the *Herpes simplex* virus as its vector. The enzyme, thymidine kinase, acts as a catalyst for the phosphorylation of ganciclovir, causing it to turn to ganciclovir monophosphate, and eventually ganciclovir triphosphate due to other enzymes in the cell. It binds to DNA, halting the replicative process and causing cell death. Additionally, many other suicide therapy methods and systems exist, utilizing different enzymes and pathways (Cesur-Ergün, et al., 2023).

Antiangiogenic gene therapy:
Angiogenesis, or the creation of blood vessels, is highly necessary for the spread and development of tumors. Initiated by hypoxia, angiogenesis allows for the tumor to have access to oxygen and nutrients. The main method of antiangiogenic gene therapy focuses on inhibiting inducers of angiogenesis, such as angiopoietin and VEGF, or utilizing inhibitors such as angiostatin, endostatin, IL-12 and p53 (the most well-researched tumor suppressor gene) (Cesur-Ergün, et al., 2023).

Stem cell therapy

Stem cells carry many capabilities, including influencing other cells, self-renewal, differentiation, and directional migration, and have the potential to replace cells damaged through cancer. Stem cell therapy has the ability to target tumors with high accuracy and improve the results of other therapeutic techniques, as well as the ability of having fewer off-target effects (OTEs). The use of stem cells in therapy depends on their classification. Stem cells can be split into two categories: pluripotent stem cells (PSCs) and adult stem cells (ASCs). The former is characterized by being able to differentiate into any cell type. They include ESCs (embryonic stem cells) and iPSCs (induced pluripotent stem cells), which can be generated directly from a somatic cell through the help of Yamanaka factors. The latter, adult stem cells, are either multipotent or unipotent, meaning their range of differentiation is rather limited. Several varieties within ASCs exist for cancer treatment, and the utilized option depends on factors such as the target cancer. There are different categories of ASCs:
Hematopoietic stem cells (HSCs) are located in bone marrow and can form any mature blood cell in the body. At the moment, HSC infusion from the blood of the umbilical cord is the only FDA-approved treatment for multiple blood disorders including leukemia.

Neural stem cells (NSCs) originate from the central nervous system and are able to differentiate into neurons and glial cells. They have been shown to treat breast, lung and prostate cancers in mice.
Mesenchymal stem cells (MSCs) are found in many types of tissue and are used as support for many other therapies by modulating the immune response, promoting tissue repair, or delivering therapeutic agents. ASCs are preferred in many clinical settings due to ethical concerns surrounding embryonic stem cells, but PSCs are also used in research and some experimental therapies.
In some cases, chemotherapy damages blood-forming cells, and patients receive a transplant of HSCs, which then form blood cells (Dinh-Toi, et al., 2020).

Conclusion

Many methods of cancer treatment today aim to induce apoptosis in cancer cells. While some of these therapies have been researched and used to treat patients more than others, all of them show a high level of potential in the future. Immunotherapy, specifically through gene therapy, can be used in order to heighten immune cells' ability to detect cancerous cells. Other treatments focused on gene editing target the regulation of tumor suppressors, apoptosis, and cell proliferation.
Radiotherapy, though its various forms, shows promise to accurately affect specific cells without too many off-target effects. Chemotherapy in its multiple variants effectively induces regulated cell death, whereas stem cell therapy can compensate for the loss of healthy cells, including blood cells. Additionally, surgery, especially when combined with other methods, can be effective in the treatment of localized tumors.

References

1.
Mathur, G., et al. (2015). Cancer: an overview. *Academic Journal of Cancer Research, 8(1)*, 1-9. 10.5829/idosi.ajcr.2015.8.1.9336

2.
Debela, D.T., et al. (2021). New approaches and procedures for cancer treatment: current perspectives. *SAGE Open Medicine, 9*. https://doi.org/10.1177/20503121211034366

3.

Mintzer, D. (1999). The changing role of surgery in the diagnosis and treatment of cancer. *The American Journal of Medicine, 106(1),* 81-89.
https://www.amjmed.com/article/S0002-9343(98)00373-8/fulltext

4.
Anand, U., et al. (2023). Cancer chemotherapy and beyond: current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes & Diseases, 10(4),* 1367-1401. 10.1016/j.gendis.2022.02.007

5.
Bukowski, K., et al. (2020). Mechanisms of multidrug resistance in cancer chemotherapy. *International Journal of Molecular Sciences, 21(9)*. *https://doi.org/10.3390/ijms21093233*

6.
Baskar, R., et al. (2012). Cancer and radiation therapy: current advances and future directions. *International Journal of Medical Sciences, 9(3). 10.7150/ijms.3635*

7.
Chaput, G., et al. (2021). Radiotherapy: Clinical pearls for primary care. *Canadian Family Physician, 67(10)*, 753-757. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8516179/

8.
Cesur‐Ergün, B., et al. (2023). Gene therapy in cancer. *The Journal of Gene Medicine*, *25.* https://doi.org/10.1002/jgm.3550

9.
Dinh-Toi, C., et al. (2020). Recent progress of stem cell therapy in cancer treatment: molecular mechanisms and potential applications. *Cells, 9(3).* https://doi.org/10.3390/cells9030563