How Can We Stop Cancer?

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Abstract
Cancer is a disease that humans have been struggling to combat for centuries. It originates from the accumulation of several mutations over the life of a cell that causes it to evade cell death and multiply rapidly. It can affect any tissue in the body and can spread to other parts of the body through metastasis. Cancer comes in numerous shapes and sizes with different levels of aggression, growth speeds, and health risks. Many treatments for cancer exist today, three of the most popular being surgery, chemotherapy, and radiation therapy, which can be used in combinations with other treatments to best fight cancer. Verma et al. (2019) showed that when surgical resection is used before chemotherapy, a significant decrease in postoperative hospitalization lengths and 30-day mortality rates occurs, with correlation to trends that show increased overall survival and decreased 90-day mortality rates as well. Kim et al. (2018) approached treating surgery with a targeted therapy called anti-angiogenesis using the prodrug TA, which provided successful results in combating cancer cells by inducing apoptosis in cancer cells themselves as well as the endothelial cells that nourish tumors. This research can be taken into account by oncologists and physicians when prescribing certain treatment methods in fighting cancer, as these treatment options may have similar effects in treating and preventing other cancers, neoplastic diseases, and infections that leach nutrients from the body.

Keywords
cancer, anti-angiogenesis, cancer treatment, radiation therapy, radiotherapy, chemotherapy, surgery, resection, induction chemotherapy, neoadjuvant chemotherapy, vascular endothelial growth factor, VEGF, prodrug, topoisomerase I, COX-2
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What is Cancer?

Cells are the smallest subunits of life. Some can live on their own, while others work together to make up multicellular organisms. Together, cells build the tissues, organs, and organ systems that make up a multicellular organism. Each cell must go through the cell cycle to duplicate itself to produce offspring. In unicellular species, this makes up a whole other organism, but in multicellular species, this is the way that tissues grow. The cell cycle can be broken up into five different phases: $G_1$ (growth phase), $S$ (duplication of genetic information phase), $G_2$ (duplication of other cellular parts), mitosis (separation of cellular nuclei and their genetic contents), and cytokinesis (separation of the cells themselves).

Checkpoints exist between each phase of the cell cycle that cells must pass to continue living. When a cell is stopped at a checkpoint due to the accumulation of mutations or other genetic damage, the cell either goes through the process to repair itself or enters another phase of the cell cycle, called the $G_0$ phase. In the $G_0$ phase of the cell cycle, the cell undergoes apoptosis, or programmed cell death. This system keeps the organism healthy on a cellular level by eliminating cells that get too old or acquire too many mutations to continue living a normal life.

Cancer is defined as a group of diseases characterized by the uncontrollable growth and division of cells that have accumulated a significant number of mutations and have the ability to spread to other parts of the body. These cells hinder normal organ functions and take over the nutritional and gaseous supply to a body region. This occurs when a cell is able to bypass the checkpoints that would normally send it into apoptosis, which is usually caused by a mutation(s) that a cell misses during self-assessment (National Cancer Institute, 2015, A).

History of treatment

Cancer is usually categorized by size, abnormality, and invasiveness. Not all tissues that grow at a faster rate are considered cancerous metastases because they are unable to spread to other parts of the body. These growths are called neoplasms and typically result in benign tumors (National Cancer Institute, 2015, A). Neoplasms can be broken down into hyperplasias and dysplasias. When a normal tissue exhibits signs of cell proliferation and faster cell division, but still maintains normal cell organization, the growth is called hyperplasia, and usually results in a single-layered benign tumor with the suffix “-oma;” the prefix comes from where the tumor is found. Dysplasia is a more serious condition because it exhibits more abnormality and less organization among the proliferation of cells. If the tumor the state of dysplasia produces becomes large enough to have multiple layers of cells, but still doesn’t invade nearby tissues, the tumor is called in situ. This form of neoplasm is usually treated because it is the last version of tissue proliferation before cancer (National Cancer Institute, 2015, A).

Cancer occurs when tumors progress and become invasive to nearby tissues. Invasive tumors are typically named by their location and the types of cells they originate in. The most common type of cancer is a carcinoma, which forms from epithelial cells in the body. Invasive tumors may break off and migrate to other parts of the body, usually by the circulatory or lymphatic system. When this happens, the tumor is said to be malignant, and the piece of tumor that broke off and migrated is called a metastasis. Malignant cancers are much more difficult to treat because they affect multiple parts of the body and are usually spread to an unknown extent (National Cancer Institute, 2015, A).
Since its first recognition by the ancient philosopher and physician Hippocrates near 400 BC, many ways to treat cancer and other neoplastic diseases have developed. Most of the advances in cancer therapy have been developed within the last 100 years due to breakthroughs in technology and medicine. Oncologists - doctors who specialize in cancer treatment - continue to expand this field of medicine through extensive research in strategies to fight cancer.

Surgical resection is the oldest type of treatment for cancer. This involves the use of scalpels, lasers, hyperthermic conditions (sometimes using cauterization techniques for burning off abnormal cells), photodynamic therapy (the use of drugs activated by light that kill surrounding tissues), or the application of liquid nitrogen or argon gas (to freeze and destroy abnormal tissue). Surgery usually requires the use of local, regional, or general anesthetics to cause loss of feeling for pain in small parts, large parts, and the entire body, respectively. Under general anesthesia, patients lose consciousness and exhibit symptoms similar to a deep sleep, which allows the surgeon to operate safely. Surgical resection can be performed by extracting a tumor and nearby tissues through a large cut in open surgery, or can be done through multiple small cuts, extracting small parts of the tumor multiple times using tools and monitors in minimally invasive surgery. Due to the fact that the surgeon is unable to see the inside of the body through small cuts in minimally invasive surgery, they use a laparoscope (a small tube with a tiny camera on it to project video of the inside of the body to a monitor for the surgeon to see) to complete the resection. Minimally invasive surgery requires less time to recover because smaller incisions are used than during open surgery, which tend to heal at a faster rate. Surgical resection can also be performed for multiple purposes: curative surgery aims to remove the entire tumor to cure the patient of cancer; preventive surgery involves the removal of tissue that has the potential to become cancer, such as dysplasia or in-situ tumor; diagnostic resection takes one part of a cell growth out of the body to study for cancerous properties; debulking resection extracts a large part of a tumor to minimize its size; palliative care includes the use of surgery to ease pain caused by cancer; supportive therapy aims to help other cancer treatments work more effectively; restorative surgery is used to rebuild a patient’s body through plastic surgery to restore normal bodily characteristics (National Cancer Institute, 2015, B). Marinho et al. (2018) performed a study that recorded cancer patients’ qualities of life before surgery and quality of recovery after, finding 31 out of 138 surveyed patients having poor quality of recovery. Patients who had a poor quality of recovery also had significantly poor qualities of life, frailness, and high cardiac risk factors, which are all characteristics that oncologists need to consider when recommending surgical resection as a treatment for cancer. Despite this, surgical resection remains the preferred treatment type because of its diversity, conformity, and ability to be used in conjunction with other methods to treat cancer.

Chemotherapy, or chemo, is the second most common way to treat cancer. It involves the use of drugs to stop or slow cancer growth. This can help oncologists treat cancer by curing it, lessening its chance of return, or reducing the size of tumors that cause pain or other symptoms. Chemotherapy is typically used in conjunction with other forms of therapy. When it is used before another form of treatment (mainly to decrease the size of a tumor), it is called neoadjuvant chemotherapy. Conversely, adjuvant chemotherapy is defined as chemotherapy used after another form of cancer treatment. It can be administered in a multitude of ways depending on cancer type, drug conformity, and medicinal accessibility: oral (by mouth), intravenous (directly into a vein), injection (by a hypodermic needle), or topically (by rubbing it into the skin). Chemotherapy is a non-invasive treatment but has other side effects because it does not differentiate between healthy and cancer cells. This typically affects normal cells in the body that divide fast, such as cells that make up hair and the linings of the mouth, stomach, and intestine, causing hair loss, mouth sores, ulcers, and nausea. Fatigue is another side effect common with chemotherapy treatment because healthy body cells slow their rates of growth.
activity and do not perform at optimal metabolic capacities (National Cancer Institute, 2015, C).

Another common way to treat cancer is through radiation therapy, or radiotherapy. This is the exposure of the body to high levels of radiation to reduce tumor sizes and destroy cancer cells. Radiation therapy can be performed by using an external beam of radiation to deliver concentrated doses of radiation to a localized area or by using an internal source of radiation. External beam radiation can be delivered by two methods: conventionally fractionated radiation therapy and stereotactic ablative radiation therapy. Conventionally fractionated radiation therapy uses a broad, low-powered beam of radiation administered in multiple doses to destroy cancer cells while stereotactic ablative radiation therapy involves the use of a highly accurate, high-powered, concentrated beam of radiation to eliminate cancer cells (National Cancer Institute, 2015, D). Verma et al. (2018) concluded that no significant difference exists in the overall survival rates between patients who received either treatment for inoperable stage I small cell lung cancer. Although, stereotactic ablative radiation therapy is the favored external form of radiotherapy because it is more cost-effective, conformative, and convenient than conventionally fractionated radiation therapy while producing relatively equal results of treatment. On the other hand, internal radiation therapy also has two forms: brachytherapy and systemic radiation therapy. Brachytherapy uses a solid source of radiation that is implanted in the body near or in the tumor to release radiation over time, while systemic radiation therapy involves the introduction of a radioactive liquid into the system through ingestion, hypodermal injection, or intravenous solution, to travel through the blood to reach and destroy cancer cells. Radiation therapy is very similar to chemotherapy in regards to side effects, frequency of being combined with other treatments, and that it also affects healthy tissues within the area of treatment, but is different in that it has the ability to be more localized and is associated with lifetime dose limits to avoid the development of other health issues in areas that are treated with radiation more than once (National Cancer Institute, 2015, D).

Among the three main ways to treat cancer described above, many other treatment options exist that are relatively new. Immunotherapy is a cancer treatment that aids the immune system in battling cancer. Targeted therapy treats cancer by targeting its methods of growing, dividing, and spreading. Hormonal therapy blocks the body’s ability to produce hormones that some cancers use to grow. Virotherapy uses oncolytic viruses that have had their virulence factors removed to attack cancer cells while ignoring normal cells (National Cancer Institute, 2015, E). Virotherapy works very well when paired with immunotherapy because defects in immune signaling within tumors can be used for oncolytic viruses to target for destruction and self-replication (Kadia, 2016). Another supportive treatment of cancer includes stem cell transplants, which replace the stem cells in a patient’s body that have been destroyed by other treatments (National Cancer Institute, 2015, E). Cancer treatments are constantly being developed and tested by oncologists around the world in the international fight against cancer.

As with any disease, one of the most effective ways to combat cancer is to prevent it. A scientific review published by Colditz et al. (2012) shows the potential for our society to prevent cancer to be at a level that could cut cancer cases by more than half (54.5%). Ways to prevent cancer include quitting smoking, implementing healthier diets, increasing exercise, avoiding obesity, acquiring vaccinations against cancer-causing viruses, avoiding UV and other ionizing radiation, decreasing irresponsible consumption of alcohol and prescription medications, and decreasing pollution. Obstacles for the success of such prevention include societal skepticism of the preventability of cancer, the lack of research in cancer prevention (rather than treatment), and the absence of an infrastructure that can be held accountable to educate the public.

In this work, I examine and review studies that address the different treatments to help cure the family of diseases called cancer and keep it from returning. Using an approach that compares overall survival rates, postoperative hospitalization lengths, 30/90-day mortality
rates, and 30-day readmission rates between cancer patients treated with induction chemotherapy and then surgical resection versus up-front resection followed by postoperative chemotherapy, Verma et al. (2019) showed that patients who received up-front surgical resection followed by postoperative chemotherapy had significantly shorter postoperative hospitalization and lower 30-day mortality, as well as correlation to increased median overall survival and decreased 90-day mortality. In addition, Kim et al. (2018) used targeted therapy through the injection of a hypoxia-responsive, anti-angiogenic prodrug ($TA$) into strains of normal and cancerous cells under normoxic and hypoxic conditions in vitro to show that, when activated in hypoxic cancer cells, $TA$ causes a reduction in topoisomerase I, COX-2, and VEGF gene expression, leading to significantly increased toxicity and decreased cancer cell viability while normal cells were left relatively unaffected. Taken together, these studies both contribute to the eradication of cancer and suggest successful ways to fight and end cancer, as well as other neoplastic diseases, while increasing overall survivability for patients.

**R/PC may be a more successful combination of treatment methods**

In the past 50 years, it has become very common for surgical resection and chemotherapy to be used together to treat cancer. If neoadjuvant chemotherapy is administered before surgery, the treatment combination is called induction chemotherapy followed by surgical resection, which is regularly abbreviated as IC/R. Advantages of this method would be having the ability to reduce the size of a tumor before its extraction, which also may minimize how invasive the surgery after chemo is. Up-front resection followed by postoperative chemotherapy, or R/PC treatment, involves the use of adjuvant chemotherapy after surgical resection. The advantages of this procedure include the ability to prevent cancer from returning using chemotherapy after the surgery removes the majority - if not the entirety - of the tumor. In addition, it is more typical to provide weaker, less harmful chemotherapy medication in R/PC treatment than in IC/R treatment because IC/R treatment relies more heavily on the use of chemotherapy to remove cancerous tissue (Verma 2019).

To determine the best treatment or combination of treatments to fight cancer, Verma et al. (2019) examined the data for two different combinations of treatments for patients with malignant pleural mesothelioma (IC/R and R/PC). Malignant pleural mesothelioma is an aggressive and deadly form of cancer that resides in the mesothelium, which is a thin layer of tissue that covers most internal organs in the thoracic and abdominal cavities. It is caused by the inhalation and migration of asbestos fibers from the air to the pleural lining, causing inflammation, tissue damage, and scarring. Since asbestos is considered a carcinogen, it has the capacity to cause mutations in the tissues that are exposed to it, posing a greater risk for the development of cancer. In addition, the asbestos can also cause nearby tissues to have similar symptoms to those of the mesothelium and trigger the development of cancers in the lung, peritoneum, and pericardium. Comparative analysis techniques were used to study the overall survival rates, lengths of postoperative hospitalization, 30/90-day mortality rates, and 30-day readmission rates between IC/R and R/PC treated patients that were documented in the National Cancer Database.

Of the 361 malignant pleural mesothelioma patients, 182 were treated using IC/R and 179 were treated using R/PC techniques. R/PC patients were found to have a correlation to increased median overall survival and decreased 90-day mortality rates. In addition, R/PC patients had significantly decreased postoperative hospitalization lengths (6 days vs. 7 days, $p = 0.001$) and 30-day mortality rates (0.0% vs. 3.3%, $p = 0.020$) on 95% confidence intervals. There was no statistical difference in 30-day readmission rates for patients between each treatment combination. Therefore, R/PC is a more successful treatment combination than IC/R for treating malignant pleural mesothelioma (Verma 2019), and may show increased success in treating similar cancers.
Anti-angiogenic prodrugs significantly decrease Cancer viability

The circulatory system is a vital body system in multicellular organisms. It serves many functions, including the transport of nutrients, ions, gases, metabolites, and metabolic wastes around the body through blood vessels. Angiogenesis is the formation of blood vasculature throughout the various tissues of our body to aid in the delivery and removal of the molecules that are vital to many life processes. It is stimulated by growth factors and hormones throughout the development of an organism to maintain vascular coverage through the entirety of the body. This is important to prevent the starvation or buildup of toxic substances in local areas of the body. Without the circulatory system, the internal cells of many multicellular organisms would never acquire essential molecules for life and, in turn, would starve or accumulate metabolic wastes that would not be transported away from internal tissues.

As with any body cell, cancer cells need vital nutrients essential to life to continue to grow and divide. They also require the removal of waste products. To grow inside a multicellular organism, tumors must acquire nutrients and get rid of metabolic wastes using blood vessels. They attract blood vessels and induce angiogenesis by releasing a growth factor called VEGF (vascular endothelial growth factor). This growth factor stimulates the formation of new vasculature towards the tumor and capillaries to grow around it. The constant flow of nutrient, oxygen-filled blood to the tumor allows it to obtain nutrients from the body to grow and divide. The blood also cleanses the cancer cells by removing metabolic waste buildup, further supporting it. Finally, blood vessels that connect to the tumor provide a route for the tumor to metastasize and travel to other parts of the body and form other cancerous growths (Kim 2018).

Anti-angiogenesis is a form of targeted therapy that aims to starve cancerous tumors by cutting off their supply lines, inhibiting angiogenesis locally to prevent tumors from siphoning nutrients and oxygen from the body and leaving it with metabolic wastes. Like chemotherapy/radiation therapy, many chemicals involved with anti-angiogenic therapy are toxic to neighboring normal cells (Wang 2015). Kim et al. (2018) employed anti-angiogenic techniques to destroy cancer cells in their experiment by injecting a hypoxia-induced, anti-angiogenic prodrug (denoted as TA) into strains of normal and cancerous cells under normoxic (21% O2) and hypoxic (1% O2) conditions in vitro. They observed the differences in cell viability (by cytotoxicity) and gene expression levels to determine the effect TA had on the injected tissues.

Under hypoxic conditions (when TA becomes active), the gene expression of topoisomerase I, COX-2, and VEGF was decreased in cancer cells. This contributes to the apoptosis of cancer cells themselves and the vascular tissue surrounding the tumor. Topoisomerase I is a protein that aids in the rewinding of DNA during replication, and without it, cancer cells aren’t able to live, grow, and divide. Therefore, decreased levels of topoisomerase I show that TA contributes to cell death in cancer cells when activated by hypoxic conditions. In addition, COX-2 (a gene associated with inflammation and vascular growth) and VEGF (growth factor associated with vascular development) also exhibited decreased levels in hypoxic conditions when exposed to TA, supporting the idea that TA contributes to anti-angiogenesis. Other data from Kim’s experiment suggest that TA only produces lethal effects in hypoxic cancer cells, not harming hypoxic normal cells in any significant way. Hypoxic cancer cells significantly dropped in viability from 100% to 40% with just a 10 micromolar concentration of TA, as well as decreasing by a factor of two with each incremental increase in TA concentration, while hypoxic normal cells only decreased to a minimum of 90% viability (p < 0.05). In this experiment, TA shows that it is successful in combating cancer using its apoptotic and antiangiogenic effects on cancer cells while leaving normal cells virtually untouched (Kim 2018). This may also hold true in human cancers, and should be explored more.
The most successful ways to combat cancer

Cancer is a disease that humans have been struggling to combat for centuries. Recently, the treatments that have already been developed by oncologists to fight cancer have been used in combinations with other treatments to best fight cancer. This popular treatment method implements the use of drug cocktails and multiple treatment plans to attack cancer through various mediums. Verma et al. (2019) showed that when surgical resection is used before chemotherapy, a significant decrease in postoperative hospitalization lengths and 30-day mortality rates occurs, with correlation to trends that show increased overall survival and decreased 90-day mortality rates as well. This type of study helps oncologists and physicians decide what the best combination of treatment options is so an educated decision can be made before choosing to randomly mix multiple therapies.

Research into novel treatment methods is very important as well. Kim et al. (2018) approached treating surgery with a new targeted therapy involving anti-angiogenesis using the prodrug TA, which provided successful results in combating cancer cells in vitro by inducing apoptosis in cancer cells themselves as well as the blood vasculature that nourishes tumors. This experiment was very significant for the development of this new therapy type, which will be very helpful if/when approved for testing in vivo in human bodies someday. Since no universal intervention exists for all cancers yet, research into new ways to destroy cancer is conducive to the progression of the field of study. When paired with other new or old treatment methods, novel therapies like anti-angiogenesis could someday lead oncologists to the cure for cancer.

Lastly, the results from the aforementioned studies, along with the findings of other oncological researchers, can be taken into account by physicians and oncologists when prescribing certain treatment methods or combinations for treating cancers, neoplastic diseases, or other infections that leach nutrients from the body, as these treatment options may have similar effects in treating and preventing these types of medical issues. Studies like these promote the use of Western medicine and support the advancement of our biological and medical understanding of the human body.
References


