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CRISPR in Cancer Treatment

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ABSTRACT

Cancer, a disease which is often lethal, has had a drastic impact on society. Despite the tireless work being done towards producing a cure for cancer, the main methods being used to treat cancer remain the same. Radiation therapy, chemotherapy, surgical resection, and immunotherapy can be a great help to cancer patients; however, they also come with their own side effects which can make the fight against cancer even more difficult. In order to avoid these side effects, scientists have developed a tool which allows them to efficiently target cancer cells themselves in order to stop them before the cancer progresses to a level in which medical professionals are no longer able to help. This tool is called CRISPR, and it holds the key to the future of cancer treatment due to the efficiency and convenience which it offers.

Introduction

Over the years, mankind has been able to overcome a variety of formidable illnesses that plagued us- influenza, for example was once the cause of death for over 50 million people. However, today we are not as wary of the disease as getting vaccines every year helps us prepare our immune systems in the event that we catch it. Throughout the COVID-19 Epidemic, we have seen this culture of medical innovation working in real time as scientists fought to create a vaccine to combat this virus as soon as possible. However, there is one disease that has been present since the beginning of time and yet we do not yet have a cure. This disease is cancer. Every year, over 10 million lives are claimed by cancer, and yet we are not able to treat it. Currently, treatment options include chemotherapy and radiation, surgical resection, and immunotherapy depending on the type of cancer. Despite the clear advances that have been made in the area of cancer treatment as shown in the graph portraying the steady improvement of colon cancer survival rates, we still are not able to provide a definite cure for cancer. Depending on the stage and type of cancer a patient has, these treatment options can vary in effectiveness significantly. However, as we delve deeper into our understanding of cancer, scientists have been able to bring the process of gene editing into cancer treatment, which opens up a world of new possibilities. By bringing CRISPR, an easy to use tool for gene editing, to the list of usual options of treatment for cancer patients, we will be able to better combat this ailment and possibly even cure it.

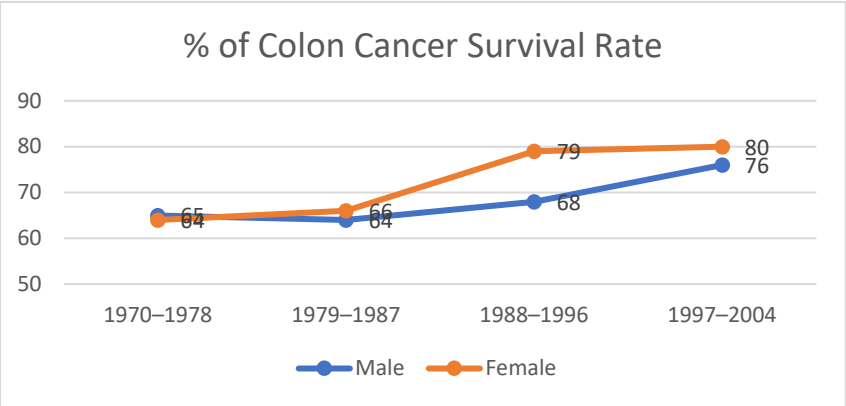


Figure 1. Chart showing the percentage of survival for patients recovering from colon cancer. As time moves on, the survival rate continues to increase with the emergence of new cancer treatment methods and improvements in the healthcare system.

What is Cancer?

Every person on this Earth has been impacted by cancer in some way. Whether they fought cancer themselves or watched someone close to them go through it, cancer has had a major impact on everyone's lives. When hearing the diagnosis of cancer, we often believe that it is an automatic death sentence for the person who has been diagnosed with it. This however may not necessarily be the case. Cancer is a disease that results from the uncontrolled growth of certain cells within the body. In a cancerous cell, the cell is unable to cease multiplying. This results in the cell continuing to multiply, eventually forming a cancerous mass of cells. Cancer cells can have incredibly adverse effects on the human body as they can spread to other parts of the body. This process is known as metastasis. When this occurs, the cancer cells can spread to other organs and begin forming tumors that can hinder the original function of the organ and cause those afflicted to go into organ dysfunction. When this occurs, the cancerous masses need to be taken out of the body before they result in organ failure, which would be fatal for the patient. When cancer forms, it is important to catch it before it has the chance to metastasize to other parts of the body so that it can be easily treated.

Current Cancer Treatments

Today, the treatments that are most prevalent in cancer treatment include chemotherapy, radiation, and surgical resection.

Chemotherapy

In chemotherapy, the patient is given cytotoxic agents which causes damage to the cancer cells, rendering them unable to divide further. Chemotherapy's main objective is to prevent the metastasis of cancer cells to other parts of the patient's body. Chemotherapy goes straight to the root of the disease by hindering the uncontrolled cell division of cancer cells. In other words, chemotherapy ensures that cancer cells are unable to invade other parts of the body. In theory, this seems like the ideal treatment for a disease that is just the uncontrolled division of cells. However, the cytotoxic agents that are released into the patient's body don't just impact cancer cells; an unspecialized treatment, also impacts the healthy cells in a patient's body. In addition, some cytotoxic agents administered during chemotherapy can be toxic to the liver and the kidneys, which metabolize and filter them. In some cases, these toxins can result in organ dysfunction and even failure. Chemotherapy also results in a vast array of side effects for those undergoing treatment. Side effects include "nausea, vomiting, diarrhea, alopecia,

fatigue, sterility, infertility… [and] furthermore, there is an increased risk of infections due to immunosuppression" (Cancer Chemotherapy).

Radiation Therapy

Another treatment option commonly used is radiation therapy. Unlike chemotherapy, which is more of a chemical agent, radiation therapy is a physical agent which "damages [the] genetic material… of cells and thus [blocks] their ability to divide and proliferate further" (Cancer and Radiation Therapy: Current Advances and Future Directions). Radiation therapy can be used differently in different situations: it can be used as neoadjuvant therapy or adjuvant therapy. When used as neoadjuvant therapy, radiation therapy is used before surgical resection of the tumor to shrink it in an attempt to make it more manageable. When used as adjuvant therapy, radiation therapy is used after surgical resection in order to target any cancer cells that may have been left in the body to prevent a tumor from forming again. Much like chemotherapy, however, radiation therapy is a non-specialized treatment which impacts both the target cancer cells and surrounding healthy cells. Despite this, healthy cells are able to "repair themselves at a faster rate and retain [their] normal function status than… cancer cells" (Cancer and Radiation Therapy: Current Advances and Future Directions).

Surgical Resection

Yet another widely used cancer treatment is surgical resection. The most promising cure for solid tumors, surgical resection is often accompanied by chemotherapy and radiation before and after the procedure in order to shrink the tumor to a manageable size so that the surgical team can resect it, as well as to ensure that any remaining cancer cells that may have been left behind after the resection do not begin to multiply again and begin the cancerous process all over again. Within surgical resection, there are two types: standard resection and radical resection. In standard resection, the surgeon only removes the affected tissue or organ. In radical resection, the surgeon also removes any surrounding tissue that has the potential to become infected.

Immunotherapy

One last common cancer treatment is immunotherapy. A biological therapy, immunotherapy helps the patient's immune system respond more efficiently to cancer cells. Even without immunotherapy, the immune system is able to hinder the growth of cancer cells. However, cancerous cells have adapted ways to avoid being affected by the immune system. Some of the traits they have adapted in order to continue to be able to thrive include mutations that make them less likely to be detected by the immune system, developing proteins on their surface which hinder the function of immune cells, or mutating the healthy cells surrounding the cancerous mass in order to interfere with the response of immune cells against the cancer cells. Immunotherapy is used to help the immune system overcome the challenges put forth by the adaptations of the cancer cells.

Overall, chemotherapy, radiation therapy, surgical resection, and immunotherapy are all used in different ways and have various different pros and cons. These options are all different and have different positives and negatives within a specific patient. Despite this, these three treatment methods are most often used in a combination depending on the status of the patient who is receiving treatment. There are a few factors which go into deciding what treatment a patient will get, including the type of cancer and the stage that it is in. The graph below is an example of this shown in relation to Non-Small Cell Lung Cancer. In this, you can see the different treatment methods and how they vary from stage to stage. For example, treating the cancer using only surgical resection is very common in Stages I and II of the disease. However, when we look at the statistics for

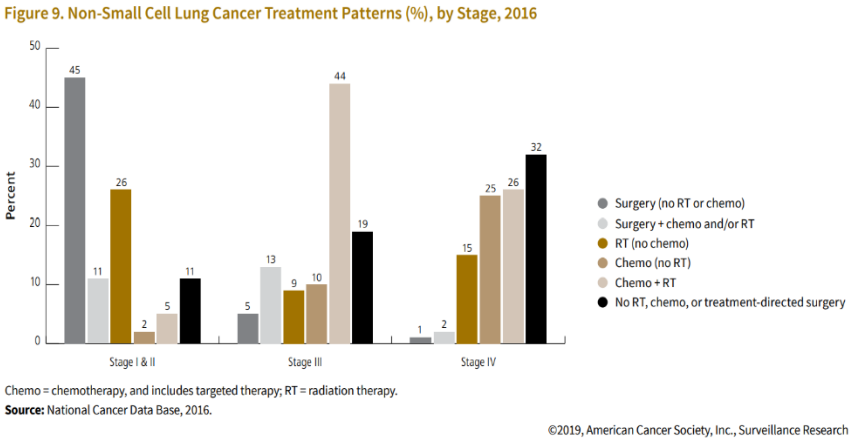


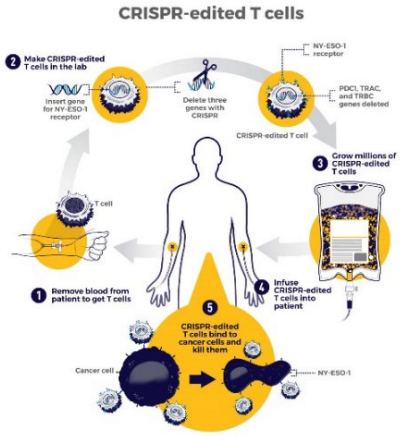
Figure 2: Graph showing treatment methods preferred during different stages of non-small cell lung cancer. The different treatment methods pictured are surgery alone, surgery, chemo, and/or radiation therapy, radiation therapy without chemotherapy, chemotherapy without radiation therapy, chemotherapy and radiation

Stage IV Non-Small Cell Lung Cancer, this treatment method is almost obsolete.

CRISPR

In the human body, the immune system acts as the guards against foreign bodies that might pose a threat, including viruses and diseases. By taking this function, scientists are now testing a type of immunotherapy for cancer by genetically modifying a patient's immune cells to better target and respond to the cancer cells in the patient's body. After the realization was made that cancer results after a change in the DNA of the cell, scientists began thinking of applying the new technology of gene editing as a new treatment for cancer. In gene editing, you can manipulate the DNA of a cell. However, this technology never became easily applicable in the world of cancer as it was not easily accessible. However, "a game changer occurred in 2013, when several researchers showed that a gene-editing tool called CRISPR could alter the DNA of human cells like a very precise and easy-to-use pair of scissors" (how CRISPR is changing cancer research and treatment). The technology is so easily accessible that according to Alejandro Chavez, M.D., Ph.D., "'Before, only a handful of labs in the world could make the proper tools [for gene editing]. Now, even a high school student can make a change in a complex genome' using CRISPR" (How CRISPR is changing cancer research and treatment). An incredibly versatile tool, CRISPR can be used to edit almost any given section of DNA. CRISPR consists of 2 main components- a guide RNA and a DNA-cutting enzyme, commonly referred to as CAS-9. Then, scientists "design the guide RNA to mirror the DNA of the gene to be edited" (how CRISPR is changing cancer research and treatment). The guide RNA leads Cas9 to the target strand of DNA, and after the guide RNA binds to the target DNA, much like the "easy-to-use pair of scissors" mentioned earlier cuts the DNA. There are also a variety of different

applications of CRISPR. In some cases, the gene is inactivated after the DNA is scrambled during the reparation.



Credit: National Cancer Institute

Figure 3. The figure depicts the process of combating cancer cells using CRISPR technology in order to modify T-cells so they specifically target cancer cells.

However, in others, scientists can add new segments of DNA to replace that which was cut or even so precise as to edit single letters of DNA. Not only this, but CRISPR can be used to detect specific targets, which is where this technology begins to tap into the realm of cancer treatment; it can be used to detect the DNA of viruses known to result in cancer as well as the DNA from cancer cells themselves. CRISPR is still in the development and testing stages, and does require some more tweaking before it can be used to treat cancer patients in a clinical setting, it still shows more promise than the current methods of treatment: chemotherapy, radiation therapy, and surgical resection. As mentioned before, all of these methods have positives and negatives when being used to treat a cancer patient, and they all have different uses and instances in which they need to be used. However, they do put the patient through a lot of grueling side effects which can render them so weak that a simple cold could be their cause of death. These current treatment methods also are not guaranteed to work. As CRISPR continues to be improved on and developed, however, there is great hope that in the future CRISPR may enable us to bypass these unfortunate side effects in the process of treating cancer. In the process of genetically modifying the T-cells, or immune cells, that are used to create the cancer killing cells, one gene is added while 3 others are deleted. CRISPR is used to add a gene which serves to give the cell "a claw like protein… that 'sees' NY-ESO-1, a molecule on some cancer cells" (How CRISPR is Changing Cancer Research and Treatment). This protein is called a receptor. After this addition is made, CRISPR is used to remove 2 genes "that can interfere with the NY-ESO-1 receptor and another that limits the cells' cancer killing abilities" (How CRISPR is Changing Cancer Research and Treatment). First and foremost, scientists wanted to find out if this treatment would be safe to use in cancer patients. In a clinical trial, this treatment was tested in 2 patients afflicted with advanced multiple myeloma and one with metastatic sarcoma. Multiple myeloma is a type of cancer which begins in the white blood cells that produce antibodies, and sarcoma is "a type of cancer that begins in bone or in the soft tissues of the body, including cartilage, fat, muscle, blood vessels, fibrous tissue, or other connective or supportive tissue" (National Cancer Institute). After carrying out the treatment, researchers have determined that the use of CRISPR to treat cancer patients is safe. In addition, the treatment proved to have an impact on the sarcoma patient and one of the multiple myeloma patients; the second multiply myeloma patient did not see any effects from this treatment. Though this treatment did not have a major impact on the cancer of any of the patients it was tested on, it still is an incredibly important advancement in the realm of cancer treatment as according to Edward Stadtmauer, M.D., "Solid tumors have been a much more difficult nut to crack with cellular therapy" and it did prove to have an impact on the sarcoma patient.

Further Research Being Done

CRISPR shows a great amount of promise in the realm of cancer treatment. Despite this, as it is still a relatively new technique, there are still some issues that need to be resolved before CRISPR can become a widespread cancer treatment. As a gene editing tool, CRISPR is becoming a go-to for scientists. However, because of some of the issues with it, scientists are unsure of what the implications could be of using it on a person. There are a number of ethical concerns being raised about CRISPR, including limitations of the technology as of now. These include limited on-target efficiency, incomplete editing, and inaccurate targeting. According to the National Cancer Institute, "Scientists are worried that such unintended edits could be harmful and could even turn cells cancerous, as occurred in a 2002 study of a gene therapy" (How CRISPR is Changing Cancer Research and Treatment). In this 2002 study, "several individuals with X-Linked SCID were treated by gene therapy… while 9 out of 10 patients were successfully treated, 4 of the 9 developed T-cell leukemia 31-68 months after gene therapy" (Insertional Oncogenesis in 4 Patients After Retrovirus-Mediated Gene Therapy of SCID-X1). In this trial, gene therapy was being used in order to add a gene to these patients that they had previously been missing that contributed to their disease- the IL2RG gene. In 5 patients, this did not lead to any adverse effects. However, as stated beforehand 4 patients developed leukemia, a type of cancer. This is a prime example of how the use of gene editing to cure a disease from its origin can go wrong when being used in a widespread manner. As CRISPR continues to be improved upon however, the ability to simply alter the DNA of a cancerous cell to make it so that it is no longer able to multiply and create more cancerous cells would be a much more ideal technique to all the grueling hours of chemotherapy and radiation, and maybe even surgical resection, that patients today have to go through.

Not only this, but the process of gene editing as a whole is one which scientists are unsure of whether it is ethical or not. After editing the genes of an individual, it is unknown if these genes will then be passed onto offspring and affect the DNA of future generations.

Conclusion

Cancer today is still a disease that is filled with uncertainties. Once a person is diagnosed with cancer, you can never be completely certain whether they will recover or not. Because of its unpredictable and complex nature, the pathways to cute cancer are not yet ones that we can walk. Continuing on throughout other diseases that have plagued and passed, cancer is still unbeatable, quite a formidable foe for the scientists and researchers fighting for a cure. With the new advancements we have made in the field of gene editing has come an easily accessible tool, CRISPR. Likened to a pair of scissors, CRISPR is simple and efficient and cuts straight to the root of the cancer problem by enabling scientists to alter the genetic material, or DNA, of target cells. Because cancer is a result of a genetic mutation, this advancement shows great potential in the field of cancer treatment. As of today, we use chemotherapy, radiation therapy, surgical resection, and immunotherapy overwhelmingly to treat those afflicted with the disease of cancer. As discussed, each of these treatment methods have their positives and negatives, ranging from the destruction of healthy cells to the weakening of the immune system of the patient. These current treatments are not guaranteed to work for every patient, and sometimes can do nothing but cause more discomfort for those undergoing them. With CRISPR, medical professionals can bypass ineffective, inefficient treatments and go straight to the source of the problem.

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