

Pace University

DigitalCommons@Pace

Honors College Theses

Pforzheimer Honors College

2020

Gene Editing in Healthcare as it Relates to Oncological Practices

Jennamarie Scanlon

Follow this and additional works at: https://digitalcommons.pace.edu/honorscollege_theses

 Part of the [Nursing Commons](#)

Gene Editing in Healthcare as it relates to Oncological Practices

Jennamarie Scanlon

Pace University, College of Health Professions, Lienhard School of Nursing

Advisor: Dr. Esmā Paljevic EdD, RN, CPNP

Pforzheimer's Honors College Director: Dr. Len Mitchell, Ph.D

Presentation Date May 5, 2020

Graduation May 2020

Abstract

Gene editing is defined as a group of biotechnological techniques used to make changes to specific DNA sequences in the genome of a living organism. By altering the DNA at the amino acid level, this technology has the ability to pinpoint certain mutations and to make alterations that prove advantageous to the organism. This technology has become a major focus in the world of medicine as it is a feasible technique to treat certain diseases. Specifically, the field of oncology has become one of the more prominent fields that has adapted these techniques to treat, and in some cases, even prevent certain cancers. Gene editing can also be used in eugenics, customizing fetal features, and preventing or treating non-cancerous diseases. As I aspire to become a pediatric oncology nurse in the future, this technology is important as it is the future of cancer treatment. A nurse's responsibility to stay up to date on the latest medicinal practices that have the possibility of helping their patients is essential to their advocacy role. This paper will specifically discuss how gene editing affects cancer research and immunotherapy. It will also focus on the impact of immunotherapy on patients and patient diagnoses and outcomes.

Keywords: gene editing, genome, oncology, immunotherapy, nursing

Table of Contents

Abstract	2
Gene Editing in Healthcare as it relates to Oncological Practices	4
Eugenics and Genome Editing	4
Treating Non-Cancerous Disease	6
Literature Review	8
Immune Checkpoint Therapy	11
Cancer Vaccines	14
CAR T Cell Therapy	17
Nursing Considerations	21
Nursing's Advocacy Role	24
The Ethics behind Gene Editing	25
Methodology	27
Conclusion	28
References	30

Gene Editing in Healthcare as it relates to Oncological Practices

Gene editing has quickly become one of the more promising technological advances used to treat and cure certain diseases. Gene editing, as a technological advancement, offers numerous benefits and although it is in its early stages, it proves hopeful as the prominent therapy in cancer treatment. Cancer is one of the leading causes of mortality across the world. Researchers are working tirelessly to uncover the pathology behind tumor growth and to investigate various methods for tumor lysis and tumor suppression. Gene editing has become the foundation of immunotherapy in cancer treatments and has proven its efficacy in treating certain cancers. While there has been success using this therapy, there is a question of consistency. The question lies in its precision since this practice has yet to be perfected. The hope is that if gene editing can improve precision and accuracy of these targeted therapies, immunotherapy can be used more broadly.

Eugenics and Genome Editing

Understanding gene editing lies in careful study of its origins. This begins with the study of eugenics. Eugenics is the beginning of the gene editing movement that began with the overarching idea to select specific human characteristics to enhance a species. Eugenics is defined as “the practice or advocacy of controlled selective breeding of human populations to improve the population’s genetic composition” (“Eugenics”, 2019). There are two different types of eugenics: positive and negative. Understanding the difference between positive and negative eugenics is essential to one's opinion on the morality of gene editing. Negative eugenics is described as discouragement of reproduction by persons having genetic defects or presumed to have inheritable, undesirable traits. Positive eugenics is described as the encouragement of

reproduction by persons presumed to have inheritable and desirable traits. Studies in eugenics became infamous during the Nazi regime and in prisons around the world. Even in the United States, there are cases of coerced sterilization in women's prisons. The goal of this movement was to stop the reproduction of traits deemed unfavorable that these inmates were perceived to have, due to their believed inherent criminal tendencies. These methods made it difficult for those deemed 'unfit' breeders to reproduce. In Nazi Germany, Adolf Hitler's regime used the principles of eugenics to remove any non-Aryan race members from society. His misguided belief that the Aryan race was superior and should reproduce to create an "elite" population was the motivation for encouraging breeding in select humans. In relation to positive eugenics, those who Hitler believed were the most fit, were encouraged to reproduce, while others were inhibited from reproducing.

Upon the introduction of computers, scientific technology advanced exponentially. This advancement coupled with the philosophy of eugenics, introduced the process of genome editing. Genome editing allows scientists to change the genomic makeup of living things. Gene editing "allows genetic material to be added, removed, or altered at particular locations in the genome" (Genetics Home Reference, 2020). Gene editing has been developed with the hopes of eradicating certain diseases that can be tested for and manipulated at the level of nucleic acids in DNA and RNA. Gene mapping was introduced and enabled the discovery of locating all genes in the human body. This project was labeled The Human Genome Project (HGP), and their goals were first articulated in 1988. The "ultimate product of the HGP has given the world a resource of detailed information about the structure, organization, and function of the complete set of human genes. This information can be thought of as the basic set of inheritable 'instructions' for

the development and function of a human being” (National Human Genome Research Institute, 2018). Without the discovery of the genome map, gene editing would not have been able to progress to where it is today.

The two different types of gene editing are germline and somatic. Germline editing refers to the editing of genes in reproductive cells, so that the modified DNA will be passed onto future generations with the desired trait. Somatic editing is the editing of somatic cells, or cells other than reproductive cells. In treating disease, germline editing has been researched thoroughly. For example, Alzheimer’s disease, a progressive degenerative disease resulting in memory loss and loss of function, shows a strong inheritance pattern in certain families. Scientists are looking for ways to edit germline cells to prevent the proliferation of offspring who possess the nucleic acid sequence that correlates to the progression of this disease. This method has the ability to potentially create an immunity to Alzheimer’s disease. Somatic gene editing is predominantly looked at in cancer research to treat current disease by altering the cells of the immune system to launch an attack against the invading cancer cells.

Treating Non-Cancerous Disease

Genome technology was originally created to try to pinpoint the nucleic acid sequences which code for proteins that form the basis of genotypes, specifically related to disease processes. This technology was created with the intent of developing an immunity for children for certain inheritable diseases. It could also help cure diseases in the individual, once they have already presented with the disease by altering the somatic cells’ genome. One of the predominant gene editing techniques in the field is referred to as CRISPR, also known as clustered regularly interspaced short palindromic repeats. These repetitious base sequences were found to have

protective characteristics in prokaryotes against viruses. CAS 9 is the protein associated with CRISPR and functions as “molecular scissors, capable of cutting strands of DNA” (Vidyasagar, 2018). This tool allows scientists to use the CAS 9 protein to slice DNA and insert or delete nucleic acid bases to change the protein being coded. A change in the nucleic acid base sequence can alter the genotype of an organism and concurrently drastically alter the phenotype.

Blood disorders are one of the groups of diseases that could also be impacted by this technology. A trial using CRISPR has been initiated in treatments for sickle cell disease. In this trial, scientists use CRISPR to make bone marrow stem cells that produce fetal hemoglobin, which has a higher oxygen carrying capacity than adult hemoglobin. CRISPR also has the ability to pinpoint and to mutate sequences to either prevent or cure cases of genetic blindness. An epidemic that has been facing the country for years is the rise of HIV and AIDS. An approach that has recently been examined in China, would allow the technology to pinpoint and utilize the mutation that some people have on the CCR5 gene which creates a natural resistance to HIV. It has been proposed that CRISPR could be used to “cut the DNA of the HIV virus out of its hiding place in the DNA of immune cells [...] which could be used to attack the virus in its hidden, inactive form, which is currently the aspect of the virus that is stopping scientists from completely curing the disease” (Fernandez, 2019).

People around the world today have been facing the global pandemic of the 2019 novel coronavirus outbreak (COVID-19). Although varying strains of the coronavirus have been exposed to the population before, this particular strain known as severe acute respiratory syndrome coronavirus (SARS- CoV-2), “has high variability of disease presentation” (Tu, et al., 2020). It has proven to have deteriorating effects on the respiratory system, resulting in Covid-19

related pneumonia. Many patients are ending up ventilators because the virus has weakened the immune system to the point that they can no longer breathe on their own. Multiple modalities have been tested to treat the symptoms of this virus and some of those modalities have foundations in immunotherapy. The drugs being tested in clinical trials are described in the following ways:

The therapies can be divided into two categories depending on their target. One is acting on the coronavirus directly, either by inhibiting crucial viral enzymes responsible for genome replication, or by blocking viral entry to human cells. The other is designed to modulate the human immune system, either by boosting the innate response, which has a particularly important role against viruses, or by inhibiting the inflammatory processes that cause lung injury. (Tu, et al., 2020)

By altering the genes of the cells responsible for performing the actions listed above, the results may prove to be beneficial in potentially treating coronavirus patients. Immunotherapy use is becoming more prevalent and is being relied upon to treat complex diseases plaguing the world today.

While there are some diseases where it may be seemingly easy to manipulate genes, such as cystic fibrosis and muscular dystrophy as well as the ones previously mentioned, other diseases are much more challenging, like cancer. In many cancers there are multiple genes that play a role in its presentation. If multiple genes are responsible for controlling a condition or disease, scientists must be extremely cautious not to manipulate the cells around the targeted ones (“off target cells”), as that could result in severe adverse reactions and even fatal events. These complex disease processes make the act of gene editing more difficult and require more precision. However, due to the complexity of the editing tools as well as human error, scientists could end up creating situations less desirable than the original disease itself. In terms of cancer research, “CRISPR/Cas9 promises to accelerate cancer research by providing an efficient

technology to dissect mechanisms of tumorigenesis [and] identify targets for drug development” (Zhan et al., 2019). This development has led the way for various immunotherapies.

Literature Review of Immunotherapy

Gene editing has found its way across the medical field and has broken the barrier into the field of oncology. It has created the foundation for immunotherapy in treating cancer patients worldwide. CRISPR technology has pioneered cancer research “by providing an efficient technology to dissect mechanisms of tumorigenesis, identify targets for drug development, and possibly cells for cell-based therapies” (Zhan, et al., 2019). Immunotherapy is defined as, “a form of cancer treatment that uses the immune system to attack cancer cells, in much the same way that it attacks bacteria or viruses” (“Immune Checkpoint Therapy”, n.d). It is important to understand the relationship between the immune system and cancer cells before any therapies are explained in order to understand exactly how immunotherapy enhances the innate immune response to kill cancer cells at a more effective pace.

In a healthy body, the immune system has an innate mechanism that recognizes abnormal cells and attacks them before any damage is done to the surrounding normal tissue. Antigens are protein fragments found on the surface of cells that serve as markers for other cells to recognize them. These antigens signal the body’s white blood cells, more specifically, T- cells, to attack foreign cells. The presence of tumor cells means the presence of tumor specific antigens attached to these cells. T- cells have claw-like protein receptors on their surface that can recognize antigens and latch onto cells. Normally, the T-cells will recognize the abnormal tumor specific antigens, latch onto those antigens, and then the T-cell will activate and inject toxins to kill the tumor cell. This process signals other immune cells to the area to help destroy the remaining

tumor cells. This innate process is the same one that allows your body to fight off the common cold, measles, the flu, and many other diseases and viruses.

There are some definitions that are important in understanding the various components of the immune system that play a role in tumor suppression. Two of the most abundant and useful cells in the immune system that attack tumor cells are CD8+ T cells and CD4+ T cells. CD8+ T cells are, “T cells that can be cytotoxic (“killer” cells) or secretors of cytokines (and other molecules). They are triggered by recognition of peptide-MHC class I complexes on the surface of cells” (Butterfield, 2015). CD4+ T cells are defined as, “T cells that generally secrete cytokines to support (or “help”) T cells and B cells” (Butterfield, 2015). There are also tumor infiltrating lymphocytes (TILs) that are “generally CD8+ and CD4+ T cells that spontaneously infiltrate tumor deposits. TILs may also include B, natural killer, or suppressive cells” (Butterfield, 2015).

Although this natural process is very successful attacking other viruses, a major question in science remains, “How do tumors avoid attack from the immune system?” Abnormal cells are able to develop methods to evade the protective mechanisms of the immune system. According to research:

Tumor development can be controlled by cytotoxic innate and adaptive immune cells; however as the tumor develops from neoplastic tissue to clinically detectable tumors, cancer cells evolve different mechanisms that mimic peripheral immune tolerance in order to avoid tumoricidal attack. (Gonzalez, Hagerling, Werb, 2018)

In other words, tumor cells can “outsmart” immune cells to avoid detection and destruction.

There are a few ways that cancer cells can bypass the T-cell’s surveillance. One way is to disguise themselves as healthy cells so that the T-cell does not recognize it as foreign, latch on and release toxins. Tumor cells can also produce an excess amount of antigens on the surface,

preventing T-cells from mounting an effective attack against them. Lastly, the tumor cell finds ways to turn off the body's immune response against them. The immune response will eliminate some of the foreign cells, especially the tumor cells that are very immunogenic and observable to the T-cells as abnormal. Immunotherapy is medicine's counter-attack against cancer cells that evade natural immune responses. Immunotherapy uses the body's natural response directly to fight cancer cells. There are different types of immunotherapy that can be used depending on type and stage of cancer, progression of disease (POD) and efficacy of current treatments. Three types of immunotherapy will be discussed, beginning with checkpoint inhibitors.

Immune Checkpoint Inhibitor Therapy. Immune checkpoint inhibitor (ICI) therapy has shown success in treating certain cancers, most popularly, advanced metastatic melanoma. A checkpoint is a surface protein that acts as a "brake" in the immune response. It causes the T-cell to become inactive and prevents the accidental damage of healthy cells. Some tumor cells are able to activate this checkpoint protein and stop the white blood cell from carrying out the immune response against them. Checkpoint inhibitor drug's mechanism of action is to release the brakes on the T-cell so that it can continue the immune response. This therapy is called immune checkpoint blockade because, "the molecule that acts a brake on immune cells- the checkpoint- is blocked by the drug" (Immune Checkpoint Inhibitor Therapy, n.d). ICI is able to disable cells from evading CD4+ T-cell destruction by preventing them from disguising as normal cells. They take away the ability of these cells to manipulate checkpoint inhibitors and bypass the immune system's response to certain antigens. Research that has uncovered "how antibodies target cancer cells, has helped to revolutionize the methods used to treat cancer" (Bayer, et al., 2017). Different drugs have the mechanism of action to affect different checkpoint proteins. The

following four drugs have been approved by the Food and Drug Administration (FDA) are currently being used in practice today. Ipilimumab is a drug that targets a checkpoint protein named cytotoxic T-lymphocyte antigen-4 (CTLA-4) and is used to treat melanoma. A uninhibited “CTLA-4 pathway suppresses T-cell activation by binding to ligands, molecules that bind to other molecules” (Bayer, et al., 2017). Ipilimumab prevents “T-cell inhibition and promotes the activation and proliferation of effector T- cells” (Darvin, et al., 2018). T -cell production is increased and an antitumor response is started. Other drugs, such as Pembrolizumab and Nivolumab, target checkpoint protein, programmed death- 1 (PD-1). Atezolizumab targets checkpoint protein PD-L1. PD-1 primarily affects T-cells in the peripheral pathways. When bound to ligands, PD-1 inhibits an effective antitumor response. These drugs “showed promising results in melanoma and non-small cell lung carcinoma (NSCLC) patients, with an objective response rate of 40-45%” by enhancing the antitumor response of T-cells before the pathways can become inhibited by tumor cells” (Darvin, 2018). All of these drugs are administered intravenously over the course of thirty to sixty minutes at a frequency individually determined by the oncologist. The frequency is dependent upon reaction to treatment, stage of disease when therapy is initiated, as well as the checkpoint inhibitor that is being targeted for specific cancers.

Unfortunately, only a small percentage of cancer patients are able to benefit from the immune checkpoint inhibitor (ICI) therapy due to “severe-immune related adverse events” (Darvin, 2018). Although most side effects are mild and can be managed with adjuvant drugs, some emerge more severely. Therefore, one of the more serious concerns regarding immunotherapy is the severe adverse effects that have the potential of occurring. In order to

improve this therapy, managing those side effects and more accurately predicting if this treatment will be successful for each individual will help doctors develop a more individualized course of treatment. One of the ways to accomplish this is through research on biomarkers. A biomarker refers to, “a broad subcategory of medical signs- that is, objective indications of medical states [...] which can be measured accurately and reproducibly” (Strimbu & Tavel, 2010). Currently, there are ongoing studies that are using biomarkers in patient’s blood to predict whether ICI therapy will be successful. In this case, the biomarkers being used are peripheral blood absolute lymphocytes, also known as the absolute lymphocyte count (ALC). This is a measure of white blood cells in the body. The results showed that, “patients with a 1.35 fold increase in their ALC values from baseline in the first 2 weeks of treatment had significantly higher overall survival” (Darvin, 2018). This is proven to be a good predictive indicator of success during early stages of therapy. Other lab values that have served as biomarkers have also had an impact in predicting success of the ICI therapy:

In ipilimumab-treated patients, overall progression-free survival was associated with a low serum lactate dehydrogenase value ($LDH \leq 1.2$ -fold), a low absolute monocyte count ($AMC < 650$ cells/ μ L), a low myeloid-derived suppressor cell count ($MDSCs < 5.1\%$), a high absolute eosinophil count (eosinophils ≥ 50 cells/ μ L), a relative lymphocyte count $< 10.5\%$ and baseline $CD4+CD25+FOXP3+$ Tregs $\geq 1.5\%$ in the peripheral blood. Multiple studies validating the applicability of LDH as a predictive biomarker showed that patients with elevated levels of LDH also responded to ICIs. (Darvin, 2018)

The above mentioned biomarkers, although predictive, do not guarantee success and are currently still being researched. If researchers can use these biomarkers to predict efficacy of the therapy, severe adverse events could potentially be avoided, preventing systemic autoimmune responses that could result in fatal events. While these therapies are promising and have shown some success, it is important to note that these do not apply for all cancer cases. For example,

“initiation of mainstream checkpoint therapy to treat cancers is obstructed by the low response rate and immune related adverse events in some cancer patients” (Darvin, 2018). In relation to checkpoint immune inhibitors, different cancers have responded differently to different drugs. As mentioned earlier, “melanoma, and non-small cell lung carcinoma [had] an objective response rate of 40-45%” when treated with Pembrolizumab and/or Nivolumab (Darvin, 2018). Other studies reported the following response rates:

Additionally, urothelial bladder cancer patients treated with PD-1/PD-L1 inhibitors showed an increase in overall response rate, between 13 and 24%. In triple-negative breast cancer (TNBC) patients, the response to PD-1 inhibitors was relatively moderate (19%). In contrast, in relapsed or refractory Hodgkin’s lymphoma, nivolumab showed an objective response rate of 87% with 17% complete response. (Darvin, 2018)

Clearly, the results are variable depending upon stage of disease, type of cancer, and personal response to drug immunotherapy. Unlike other therapies, such as CAR T-cell therapy discussed later on, ICI therapy works primarily on solid tumors. However, the evidence shows enough success to continue hundreds of clinical trials to continue research in this type of immunotherapy incorporating solid and hematological malignancies. ICI therapy poses several challenges to nurses in terms of management. In order to properly control symptoms, nurses must be prepared to complete focused assessments, continually monitor lab values, and be aware of atypical symptoms that could be indicative of a larger problem (Bayer, et al., 14).

Cancer Vaccines. Cancer vaccines are given to patients to enhance their immune system in their fight against cancer. The vaccines are created with two basic ingredients: antigens and an adjuvant. The antigen protein comes from the cancer cell and help the immune cells recognize and attack the cancer cells. A tumor associated antigen (TAA) is a “protein expressed by a tumor that can be immunogenic” (Butterfield, 2015). An adjuvant is defined as, “non-antigen specific

triggers of the immune system that increase the immune response to an associated antigen.

Adjuvants can include components of infectious agents, immune cell growth factors, and tissue damage signals” (Butterfield, 2015). The adjuvant acts as a chemical “red flag” that will alert the immune system that a TAA is present. By exposing the body to the identification antigens that are attached to the tumor cells, the immune system will be able to recognize and attack more of those cells at a more effective rate.

Currently, sipuleucel-T, also known as Provenge, is a cancer vaccine used to treat metastatic prostate cancer. Metastasis is the process of “cancer cells break[ing] away from the primary tumor, travel[ing] through the blood or lymph system, and form[ing] a new tumor in other organs or tissues in the body” (National Cancer Institute, n.d). Metastasis is common in later stages and makes the cancer more difficult to treat as it spreads throughout the body, requiring multiple modality approaches. This FDA approved vaccine, “rallies the immune system’s disease-fighting forces in men who already have prostate cancer. Provenge is created by removing some immune cells, exposing them to a molecule from prostate cancer cells, and then infusing them back into the body” (Memorial Sloan Kettering Cancer Center, n.d). This vaccine has shown to lengthen the life expectancy of men with metastatic prostate cancer. Other vaccines that are listed under cancer vaccines are used as a method of primary prevention. Doctors want to administer the vaccine prior to evidence of a disease process in order to prevent the disease process from initiating. For example, the hepatitis B vaccine is administered to decrease chances of developing liver cancer. The human papillomavirus (HPV) is given to prevent occurrence of cervical cancers as well as head and neck cancers, particularly in women.

In order to specify the cancer vaccine to target the tumor cells, scientists must personalize the vaccine. Cancer formation occurs when there is a mutated genetic composition of cells. In the human genome, each protein is coded for from the amino acid sequence. A mutation can occur in any part of this process, creating a mutated amino acid sequence and therefore producing an abnormal antigen on the surface of cells. The “sequence-altered proteins are termed neoantigens, and their mutated epitopes that are recognized by T-cells are called neoepitopes. Neoepitopes are absent from normal tissues and new to a given individual’s immune system” (Sahin & Tureci 2018). Genetic engineering is the basis for cancer vaccine therapy as it is so individualized for each patient. Each mutation in cancer is unique and not the same for all patients regardless of similar cancer diagnoses. In order to discover the ingredients for the cancer vaccine, the specificity of proteins of the tumor cells must be determined. This occurs with “next generation sequencing (NGS) [which] allows rapid sequencing of genomes at low costs. Together with bioinformatics tools, NGS enables comprehensive mapping of all mutations in a cancer [...] and prediction of binding neoepitopes” (Sahin & Tureci, 2018). Through genetic sequencing, scientists can determine the exact amino acid mutations that have developed in the cancer cells by comparing the sequences to healthy tissue sequences extracted from the patient. Therefore, they can create a vaccine that targets the exact neoantigens on those tumor cells. Determining the time and circumstances surrounding the delivery of the vaccine is also important in predicting its success. For example, “a therapeutic vaccine most likely works particularly well in the adjuvant or minimal residual disease settings, where tumor load is low and immune-suppressive mechanisms are not firmly established. Efficient control of a larger tumor load may require combination immunotherapies” (Sahin & Tureci, 2018). Combination immunotherapy may be

beneficial to those with large tumor loads as to attack the tumor in various ways creating a stronger attack.

There are some uncertainties when developing this therapy that can affect success. The extraction of the nucleic acid is done with, “fresh, frozen and formalin-fixed paraffin-embedded tissues” (Sahin & Tureci, 2018). However, this extraction is only collected from a single tumor in a small biopsy, “therefore sequence data may not be representative of the tumor’s full clonal spectrum” (Sahin & Tureci, 2018). Another aspect that is still currently under investigation, relates to the possibility of erroneous mutation determination. Although NGS is considered mostly reliable, there is still a possibility of error when determining sequence of nucleic acid mutations, resulting in the erroneous formation of antigens in the vaccine and the inability of the new vaccine antibodies to recognize the correct specific tumor antigen.

CAR T Cell Therapy. Chimeric antigen receptor (CAR) T-cell therapy is at the forefront of genetic engineering in the field of immunotherapy. Genetically engineering CD4⁺ T and CD8⁺ T cells is a promising technique that allows for the prompt recognition of tumor specific antibodies and the attachment of these customized domains to the TAA. Through the engagement of two domains, T-cell proliferation is initiated, prompting a forceful attack on the abnormal cells detected. CAR T-cells are created in the laboratory and give immune cells the ability to recognize cancer in the patient once they are reintroduced into the bloodstream. The immune cells, consisting of mostly CD4⁺ and CD8⁺ T- cells, are first harvested from the patient in a process called leukapheresis, which mimics a blood donation. They are then brought to the lab where chimeric antigen receptors are added to the surface in either murine or humanized forms. These CARs give the T-cell the ability to latch onto specific antigens of the tumor cells

and release the cytokines to destroy them. They are able to do this with the attachment of synthetic receptors “composed of single chain variable fragments that serve as the targeting moiety” (Newick, et al., 2017). These modified immune cells are capable of recognizing the tumor specific antigen based off of the specific nucleic acid sequence identified mutation that has led to the formation of the abnormal cells. The specificity of the binding complex between the CAR T-cell and tumor specific antigen has led to increased avidity and therefore, increased effectiveness. Another advantage involves T-cell memory, which occurs when a T-cell recognizes an abnormal antigen, kills it with cytokines and remembers the antigen so that in the future, it can recognize and attack the same cell quicker to avoid relapse infection. This T- cell memory has the capability of surveillance. Surveillance is the ability to monitor or survey for the memorized antigen so that it cannot build up in the system before the immune cells have a chance to act. T-cell memory and surveillance provide hope that immunotherapy can potentially create an immunity to certain cancers. The body will be able to recognize the malignant cell and kill it, before it is able to multiply in the body. This therapy has shown significant effectiveness in B- cell acute lymphoblastic leukemia (B-ALL), B-cell Non-Hodgkin’s lymphoma (B- NHL), chronic lymphocytic leukemia (CLL), and Hodgkin’s Lymphoma (HL). Successful CAR T-cell therapy is dependent upon factors relating to the TAA type and amount:

The first step in successful adoptive T cell therapy is selecting an optimal TAA for CAR T cell targeting. The ideal target should meet at least two criteria. First, the TAA needs to be selectively expressed on tumor cells at high levels but not be expressed on the surface of important normal tissues (or, if expressed, it should be at a very low level). Second, the ideal TAA would be expressed on 100% of the tumor cells. Because the CAR can only attack cells having the targeted antigen, success would be unlikely unless almost all the tumor cells expressed the TAA (Newick, 2017).

The aforementioned factors will determine the success rates, tumor response, and if both criteria are present, the rates of remission will increase in patients. B-cell malignancies are the primary cancers associated with success because almost all B-cell malignancies contain the same TAA, CD-19, in high amounts. Out of the 6,000 cases diagnosed of acute lymphoblastic leukemia (ALL) in the United States, about 3,000 of those are found in children and adolescents. In the treatment of ALL, B-cells would be targeted by the synthetic CAR T-cells. In this case, CD-19 is targeted and with this therapy, “CART-19 cells are capable of high proliferative potential and can overcome large tumor burdens” (Callahan, et al., 2017). This is the main reason that CAR T-cell therapy has proven itself hopeful in the treatment of ALL. CAR T-cell therapy has also become a hopeful option for many patients suffering from other malignancies, particularly other leukemias and lymphoma. This therapy:

has yielded unprecedented efficacy in B cell malignancies, most remarkably in anti-CD19 CAR T cells for B cell acute lymphoblastic leukemia (B-ALL) with up to a 90% complete remission. However, tumor antigen escape has emerged as a main challenge for the long term disease control of this promising immunotherapy in B- cell malignancies. (Wang, et al., 2017)

While this therapy has proven to be effective in control over specific cancers, there is significant difficulty in translating this therapy to be effective against solid tumors as well.

Researchers are attempting to translate this modality from hematologic disorders to work against solid tumors. There are certain differences between solid tumors and hematological malignancies that are proving to be difficult in overcoming this transition. For example, “finding specific tumor antigens that are highly and uniformly expressed has been difficult” (Newick, 2017). Another obstacle facing this transition includes the difficulty of having the newly infused CAR T-cells introduced through the bloodstream, “infiltrate the stromal of solid tumors in order

to elicit TAA- specific cytotoxicity” (Newick, 2017). Although it is difficult, one of the targeted proteins for research in CAR T-cell therapy in solid tumors is mesothelin. Mesothelin is a “glycoprotein whose overexpression in mesothelioma and in ovarian and pancreatic carcinomas, combined with low expression on peritoneal, pleural, and pericardial surfaces, has made it an attractive target for CAR therapy” (Newick, 2017). Although this seems promising, one of the more important factors to consider is an “on-target, off-tumor” reaction. This occurs when the protein targeted is present in low levels on surfaces other than the tumor itself. This can result in cell death of healthy tissue. This has the potential to become a fatal event when enough CAR T-cells are infused into the patient as they cannot be specifically removed if an adverse event occurs. Another side effect is B-cell aplasia. CAR T-cells do not have the ability to distinguish between leukemic and healthy B-cells, resulting in destruction of all B-cells. This condition is easily treatable with immunoglobulin replacements and counteracts negative effects of this specific therapy.

Nurses require continued education on the topic to know what to do in each situation they will face with a patient receiving this transfusion. During the administration of CAR T-cells, nurses are responsible for all aspects of the infusion process as it directly relates to the status of the patient. Nurses must be accountable for, “administering premedications, monitoring vital signs pre and post CAR T-cell infusion, and monitoring for allergic reactions” (Bayer, et al., 2017). Patients should stay local for the six weeks that they are receiving treatment so that they can be carefully monitored by the doctors heading the infusion. This includes the week of chemotherapy needed to deplete the immune cells and prepare for the CAR T-cells infusion, then the infusion week, followed by four weeks of monitoring. In determining response to treatment

and longevity of CAR T-cells, multiple procedures are completed. The response is evaluated at day 28 after infusion:

with a bone marrow aspirate, biopsy, and diagnostic lumbar puncture. Those procedures are repeated every three months for the first year to examine the presence of CART-19 cells and disease remission. CART-19 cells are found in the peripheral blood, bone marrow, and cerebral spinal fluid (even in patients without central nervous system disease). (Callahan, et al., 2017).

It is important to keep track of patients well beyond the conclusion of therapy in order to examine long term benefits of the therapy and to test how it affects remission and relapse rates.

The techniques of immunotherapy are profound and are being tested in hundreds of clinical trials. In some cases, immunotherapy alone is not sufficient in tumor suppression. Although it aids in fighting tumor cells, it is often combined with chemotherapy or radiotherapy to achieve maximum efficacy. Chemotherapy is usually induced before immunotherapy to deplete the immune system of its immune cells in an attempt to reintroduce more powerful immune cells to the system. Immunotherapy can be used to fight off remaining cancer cells and provide support for long term remission while chemotherapy and radiation are used as initial treatment methods. Surgery is also indicated in some cases, with adjuvant chemotherapy and/or radiation to follow, in order to ensure that the body is completely rid of all the cancer cells.

Nursing Considerations

The nursing profession is constantly changing and evolving as new technologies are brought to the forefront. Nurses are constantly being taught new skills, given new drugs to administer, and ordered new interventions for their patients, specifically those in the oncology sector. While many hospitals provide in-services that offer quick learning opportunities for anything new required by the nurse, in the end, it is the nurse's responsibility to remain

competent in all aspects of the profession and to keep up to date with the new therapies being offered. It is important to remain knowledgeable so that the nurse can competently and confidently care for each individual patient. In oncology nursing, each patient's diagnosis is very specific to the type and stage of cancer, demanding treatment in an individualized manner. Each course of treatment will vary depending upon the progression of disease, patient tolerance to treatment, and adverse effects encountered, as well as patient preference. Although there are many ongoing clinical trials as well as established immunotherapy treatment plans, this therapy is still in the beginning stages. Aside from not knowing all the possible adverse events that could potentially occur with each specific therapy, each individual will tolerate and react differently to the therapies. The individual's reaction will be unpredictable because, typically, their bodies have never experienced anything remotely close to these interventions.

The recommendations and guidelines for administering immunotherapeutic agents are constantly evolving as new developments are recorded. The Oncology Nursing Society (ONS) is an organization consisting of experienced oncology nurses that publish literature on various aspects of oncologic nursing. According to the ONS, nurses should, "have a fundamental knowledge of the class of immunotherapy the patient is receiving, as well as knowledge of specific agents and protocols to follow, and apply this knowledge to administration and monitoring for efficacy and adverse events during the treatment trajectory" (Wiley, et al., 2017). It is fundamentally important to have a solid knowledge of immunotherapeutic agents, as they are associated with very individualized and potentially life threatening complications. The ONS suggests that the immunotherapeutic agents be handled with the "same level of care and vigilance as other neoplastic agents" (Wiley, et al., 2017). While administering

immunotherapeutic agents, just as with chemotherapy or blood products, it is important to “ensure that independent checks between two professionals deemed competent in immunotherapy administration are verifying and documenting critical components of administration orders, such as patient identifiers, drug name and dose, route and rate of administration, and dosing calculation variables” (Wiley, et al., 2017). With advancing medicine comes increased knowledge on the most effective courses of treatment against cancer. In nursing, it is crucial to have the “knowledge of anti-neoplastic principles in conjunction with, rather than in isolation of, one another” (Ginex, et al., 2017). One of these treatment courses include multimodality treatments, also known as combination therapy. This therapy incorporates multiple therapies into one patient’s care. For example, chemotherapy, radiation, and immunotherapy agents, used in various combinations with each other to increase the chance of success in suppressing the tumor.

Nurses are on the frontlines and log the most hours of direct patient care compared to all members of the care team. Therefore, it is crucial to the development of a successful care plan and, ultimately, a positive patient outcome that nurses assess, document, and manage symptoms of patients. Nurse’s firsthand experience with the symptoms associated with any therapy and are crucial in determining how to properly manage those symptoms. Symptom management is one of the most important methods of increasing quality of life, not only in the inpatient setting, but also patient education of how to manage symptoms at home. Quality assessment and documentation can help predict and manage symptoms more effectively in the cancer patient population.

Nursing’s Advocacy Role

It is very important to develop the skill of therapeutic communication to properly care for these patients. Communication is required to create a trusting and honest relationship with the client as well as to effectively develop a care plan with the care team consisting of doctors, therapists, psychiatrists, physical therapists, and occupational therapists. By communicating effectively, nurses can become advocates for their patients and their families. Nurses are oftentimes considered the extension of the patient to the care team and advocates for the patient's needs, wants, wishes and preferences to the physicians. It is important to remain knowledgeable about the current therapies available so that the nurse can act appropriately and in the best interest of the client while advocating.

Nurses have more of an autonomous role in the medical field today than they did years ago, and medical professionals are more receptive to nurse's opinions than ever before. However, with this increased role comes greater responsibility. Nurses must understand and be comfortable with their own values, beliefs, and morals before they can help guide others through their journey. It is also extremely important for nurses to be knowledgeable about immunotherapy as it is becoming increasingly popular. It is important for nurses to be aware of new technology in the field so they can fully and accurately answer questions from patients. In order to be well-informed advocates for their patients, nurses must be updated on the latest immunotherapeutic agents. It is important to be able to hold conversations about disease treatment options and for oncology nurses in particular, conversations about chemotherapy, radiotherapy and immunotherapy are extremely common.

Advocacy also comes in the form of caring for your patient in the best possible way. According to ONS, "understanding the mechanisms of action is essential in determining

potential risks to the patient, their family and caregivers, and healthcare providers” (Wiley, et al., 2017). Nurses must be aware of these potential side effects, potential reasons for contraindication of therapies so they can care for their clients appropriately before, during, and after chosen therapy is induced. Competency is maintained through constant learning, researching, and developing. It is imperative to hold a certain competency level while caring for vulnerable populations. Gene editing is an effective and world changing technology that could change how society functions. This technology leaps out of the medical world and enters fields such as psychology, sociology, ethics and genealogy. It is important that scientists anticipate as many possible effects of using this technology as possible so that we can prepare for the future scenarios that science has not yet seen. In terms of ethics, we need to decide if each action we take is of high moral quality and meets the ethical standards of good practice.

The Ethics behind Gene Editing

The largest debate surrounding the discussion of gene editing and eugenics involves ethical principles and whether this technology infringes upon them or upholds them. With regards to immunotherapy, most people argue that gene editing has been used in a manner that will help individuals maintain a quality of life. However, from this growing technology comes the other technologies that sprout from it. For example, one of the major ethical dilemmas associated with gene therapy is the argument of designer babies. Gene editing has been proposed to be used in the ability to change the genetic makeup of one’s unborn baby to choose certain traits you would like the baby to possess. It has been discussed that if science starts using the genetic engineering techniques to treat current disease and prevent onset of new disease, a door

would be opened that would allow scientists to play a larger role in evolution than they should be allowed.

The ethical principle at the forefront of this discussion is autonomy. Autonomy is defined as, “the ability to make your own decisions without being controlled by anyone else” (“Autonomy”, n.d). It is an individual's right to practice autonomy and decide what treatments they will undergo or refuse. Specific to the cancer population, the right to autonomy also deals with the right to palliative care and the decision to die with dignity if the decision to forgo treatment is made. Although it becomes a discussion between the client and the care team, ultimately the decision of whether or not to undergo immunotherapy lies with the client. It is within the role of the nurse to advocate for and help guide the client through their journey.

Another ethical consideration in the argument is related to nonmaleficence and beneficence. Nonmaleficence is the basic “ethical principle of doing no harm” (“Nonmaleficence”, n.d). Nonmaleficence is evident in the argument of, “whether the technology is, or will ever be, sufficiently safe for clinical use. The most obvious safety hazard currently related to CRISPR is the risk of unintended edits” (Gumer, 2019). There has been evidence that this therapy has inflicted harm upon patients. Although this has been unintentional, it is still potentially dangerous. According to Gumer (2019), “scientists are working to improve the precision of CRISPR such that the risk of off-target edits is likely to decrease” (2019). If the precision of genetic editing can be enhanced, the rates of success among immunotherapy recipients may increase.

As previously mentioned, as nurses, we need to ensure that we are advocating for patient safety. Nonmaleficence falls in conjunction with beneficence. The desire to do good is directly

related to doing no harm. This technology challenges this idea because while we have the ability to do good for a lot of people, we could also potentially do harm due to the fact that “most diseases and disabilities are influenced by a complex interplay of numerous genes” (Gumer, 2019). This would make using the therapy more difficult, because the likelihood of error increases when multiple genes are involved.

Lastly, the bioethical principle of justice is explained in relation to gene editing. Is it justifiable that immunotherapy is used on only certain populations? Is it ethical to edit germline cells when future generations have no say? Is it justifiable to allow the elite and wealthy to use this technology while the less wealthy can't afford it, thereby creating greater disparity between classes? These questions hinder the progression and advancements of CRISPR gene editing. In the argument relating to genome editing in the germline cells, is it justifiable that parents choose the traits of their child? Who gets to decide what traits are desirable and which traits are undesirable? These are ethical dilemmas related to principles upon which individuals base their everyday decisions. It is extremely important for nurses to understand their own beliefs, and values and to come to terms with their opinions on gene editing before being able to non-judgmentally care for others.

Methodology

In the process of researching the current methods of gene editing in healthcare as it relates to oncological practices, a mixed methods review was done to analyze current data in the field. Most of the information sourced is from scholarly journals, The Oncology Nursing Society, and information provided by Memorial Sloan Kettering Cancer Center website. The journals were found through the Pace Library Database using PubMed and CINAHL. Through analysis of

these resources, a full and complete thesis was created to explain the varying methods of gene editing in today's medical field as it relates to oncology. Search words were used to filter results and obtain the most specific resources available. Some of the search words used were: immunotherapy, genome editing, eugenics, ethics, cancer treatment. However thousands of results were found. To further specify the search, the following words and phrases were added: chimeric antigen receptors, cancer vaccines, patient outcomes related to cancer immunotherapy, gene editing and immunotherapy, immune checkpoint inhibitors, and cancer remission rates. The data was collected from clinical trials, systematic reviews and within a time period of ten years. The time period was determined based on the fact that this therapy has greatly evolved over the past 20 years so evidence from that time kept its relevance. While incorporating the data into this thesis, content analysis was performed. The process of defining key words and phrases to better understand and explain the topic was crucial. Thematic analysis was also performed to understand how each therapy related to one another as well as how it fit into the overarching theme of cancer therapies and the role of nursing in those therapies.

Conclusion

The process of gene editing has taken the medical field by storm and has drastically improved cancer research. It continues to give hope to increasing remission rates with the potential of creating an immunity to certain cancers. Immunotherapies such as immune checkpoint inhibitors, cancer vaccines, and chimeric antigen receptor T-cells have been thoroughly explained. The pathophysiology behind each therapy as well as nursing considerations and patient outcomes were analyzed and interpreted. None of these therapies would be possible without the technology of genome editing. Gene editing provides the

foundation in which one's own immune cells are manipulated at the nucleic acid level to enhance the immune system's response against foreign invaders. Although gene editing is in the beginning stages of treating non-cancerous disease, the types of immunotherapy discussed are specific to the cancer population. When caring for patients with this chronic illness, it is important to recognize that "cancer is not one disease but hundreds—each with its own unique features, treatment challenges, and vulnerabilities" (Ginex, et al., 2017). Therefore, care must be individualized to maintain the highest quality of life achievable for these patients at all stages of the disease process. This individualized nature of the disease makes immunotherapy a prime choice due to its capacity to be specified to the RNA and DNA of each individual cell. By improving immunotherapy, finding new cancer weaknesses, and using combined drug therapy, this method can greatly alter the future of cancer research. Gene editing has changed the way that scientists and doctors have thought about medicine and will continue to pave the pathway for future treatment modalities across all medical fields.

References

- American Psychological Association. (2010). *Publication Manual of the American Psychological Association* (6th ed.)
- Autonomy (n.d). Retrieved from
<https://dictionary.cambridge.org/us/dictionary/english/autonomy>
- Bayer, V., Amaya, B., Baniewicz, D., Callahan, C., Marsh, L., McCoy, A. (2017). Cancer Immunotherapy. *Clinical Journal of Oncology Nursing* 21(2) pp. 14-21. <https://doi.org/10.1188/17.CJON.s2.13-21>
- Butterfield L. H. (2015). Cancer vaccines. *BMJ (Clinical research ed.)*, 350, h988.
<https://doi.org/10.1136/bmj.h988>
- Callahan, C., Baniewicz, D., Ely, B. (2017). Car T Cell Therapy. *Clinical Journal of Oncology Nursing* 21(2) pp. 22-28 <https://doi.org/10.1188/17.CJON.S2.22-28>.
- Cancer Vaccines. (n.d.). Retrieved April 19, 2020, from
<https://www.mskcc.org/cancer-care/diagnosis-treatment/cancer-treatments/immunotherapy/cancer-vaccines>
- Checkpoint Inhibitors. (n.d). Retrieved April 19, 2020, from
<https://www.mskcc.org/cancer-care/diagnosis-treatment/cancer-treatments/immunotherapy/checkpoint-inhibitors>
- Darvin, P., Toor, S.M., Sasidharan Nair, V. et al. (2018). Immune checkpoint inhibitors: recent progress and potential biomarkers. *Exp Mol Med*, 50, 1–11.
<https://doi.org/10.1038/s12276-018-0191-1>

Eugenics. (n.d). Retrieved from <https://www.merriam-webster.com/dictionary/eugenics>.

Fernandez, C. R. (2019). 7 Disease CRISPR technology could cure. Retrieved from

<https://www.labiotech.eu/tops/crispr-technology-cure-disease/>

Genetics Home Reference (2020, April 15). *What are genome editing and CRISPR CAS 9?*

<https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting>

Ginex, P. , Brassil,K., Ely, B. (2017). Immunotherapy. *Clinical Journal of Oncology Nursing*

21(2) pp. 9-12. <https://doi.org/10.1188/17.CJON.s2.9-12>

Gonzalez, H., Hagerling, C., & Werb, Z. (2018). Roles of the immune system in cancer: from

tumor initiation to metastatic progression. *Genes & development*, 32(19-20), 1267–1284.

<https://doi.org/10.1101/gad.314617.118>

Gumer, J. M. (2019). The wisdom of germline editing: an ethical analysis of the use of

CRISPR-Cas9 to edit human embryos. *The New Bioethics*, 25(2), 137–152.

<https://doi:10.1080/20502877.2019.1606151>

Newick, K., O'Brien, S., Moon E., and Albelda, S.M. (2017). CAR T Cell therapy for solid

tumors. *Annual Review of Medicine*. 68(1), 139-152.

<https://doi.org/10.1146/annurev-med-062315-120245>

National Cancer Institute (n.d). *Metastasis*.

<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/metastasis>

National Human Genome Research Institute (2018, October 28). *What is the Human Genome*

Project? <https://www.genome.gov/human-genome-project/What>

Nonmaleficence (n.d). Retrieved from

<https://medical-dictionary.thefreedictionary.com/nonmaleficence>

- Sahin, U., & Türeci, Ö. (2018). Personalized vaccines for cancer immunotherapy. *Science*, 359(6382), 1355–1360. <https://doi: 10.1126/science.aar7112>
- Strimbu, K., & Tavel, J. A. (2010). What are biomarkers? *Current opinion in HIV and AIDS*, 5(6), 463–466. <https://doi.org/10.1097/COH.0b013e32833ed177>
- Tu, Y.F., Chien, C.S., Yaramishyn, A. A., Lin, Y.Y., Luo, Y.H., Lin, Y.T., ... Chiou, S.H. (2020). A review of SARS-CoV-2 and the ongoing clinical trials. *International Journal of Molecular Sciences*, 21(7), 2657. <https://doi: 10.3390/ijms21072657>
- Vidyasagar, A. (2018, April 21). *What is CRISPR?* Liveu Science. <https://www.livescience.com/58790-crispr-explained.html>
- Wang, Z., Wu, Z., Liu, Y., & Han, W. (2017). New development in CAR-T cell therapy. *Journal of Hematology & Oncology*, 10(1). <https://doi: 10.1186/s13045-017-0423-1>
- Wiley, K., LeFebrve, K., Wall, L., Baldwin-Medsker, A., Nguyen, K., Marsh, L., Baniewicz, D (2017). Immunotherapy Administration. *Clinical Journal of Oncology Nursing* 21(2) pp. 5-7. <https://doi.org10.1188/17.CJON.s2.5-7>
- Zhan, T., Rindtorff, N., Betge, J., Ebert, M., Boutros, M. (2019). CRISPR/Cas9 for cancer research and therapy. *Seminars in Cancer Biology*, 55, 106-119. <https://doi.org/10.1016/j.semcancer.2018.04.001>