Is Gene Therapy a Viable Option for Cancer Treatment?

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Abstract

The use of gene therapy as a medical treatment option was first introduced to the world in 1990, when a four-year-old girl became its first patient. Since then gene therapy has met great success but also severe drawback. Incidences with severely negative outcomes on patients gave gene therapy a bad name and many began skeptical towards its use, but the constant work and progress on the safety and effectiveness of gene therapy is making it a more viable route of treatment. This paper focuses on gene therapy as a form of cancer treatment. Viral insertion of the modified genetic material is the most effective method of insertion, targeting a large number of cells, although physical insertion may be safer and more economical. The mechanism by which many gene therapies work is suicide genes, genes that cause the cell they enter to lyse. The paper goes on to discuss the H-19 locus on the genome, which plays a significant role in cancer development and conversely, treatment. BC-819 is a plasmid that is synthetically produced to treat cancer based on targeting the H19 locus. Research and test models of the BC-819 show promising results for many cancer patients.

Introduction

Cancer is the second leading cause of death worldwide, taking the lives of over 8.2 million people every year. The standard cancer treatments, such as chemotherapy and radiation therapy, are often inadequate and debilitating, destroying healthy fast-growing cells in the process of treatment. Over the past decade, gene therapy has become a more prevalent option for treating cancers. Gene therapy avoids targeting healthy cells, selecting only cancerous cells for treatment. There are three approaches to gene therapy immunotherapy: stimulating a patient's immune system to recognize and attack cancer cells, oncolytic virotherapy, which generally uses viruses to infect and kill cancer cells, and gene transfer, which is the insertion of genetic material into the cancerous cells. This paper aims to consider the viability of gene transfer therapy. Gene transfer therapy is an exciting new technology that is shifting the paradigm of cancer treatment. It involves inserting a foreign gene directly into the cancerous cells or surrounding tissue's genome (Cross, Brumester 2006). With all the strides and progress made in gene transfer there are still problems that need to be rectified. In early safety test cases, gene transfer scared many by causing the death of a patient (Raper, et. al. 2003). Also, in some cases, gene transfer methods have promoted leukemia in their attempt to cure the patient of his disease (Thomas, et. al. 2003). Additionally, there is still plenty of research yet to be done in this area due to its relative newness. This paper will assess how much of an option gene therapy is for cancer patients, taking into account its numerous benefits and sometimes severe drawbacks.

Methods

Research literature for this paper was obtained through the Touro College Online library. Searches done on the Touro College Online library led the student to Proquest and Pubmed, where majority of the articles were obtained. Articles found on other scholarly sites were also used. The articles discussed experimental studies done and the thorough analysis of these articles allowed for the assessment of gene therapy's practicability. Review articles also assisted in composing the formal analysis.

Discussion

The standard treatment method for cancer today is chemotherapy. Chemotherapy can cause an array of both short term and long term side effects. Short term side effects are side effects that are present during the time of treatment and are often reversible, while long term side effects cause more severe and permanent damage. Short term side effects include hair loss, nausea, and vomiting, which can sometimes hinder patient compliance. Long term side effects such as arthritis, appendicitis, and thyroid damage have less of a probability of occurring, but do occur in some patients (Ramirez, et. al. 2009). The above mentioned are general side effects, but each patients' individual circumstance can pose other possible risks. If patients could be assured that chemotherapy would remove the cancer in totality, undergoing chemotherapy would be more tolerable, yet in many cases the chemotherapy fails to rid the body from the cancer and therefore, is often not a preferable option.

In this paper, gene therapy will be analyzed to assess whether it is a better option of treatment for cancer patients or whether it is yet another treatment method that provides partial results and causes severe side effects. How efficient gene therapy is in treating cancer, what side effects it includes and what the severity of the side effects are all questions that need to be addressed.

Insertion Approaches

There are two approaches to gene insertion; it can be done by means of either a viral or a non-viral vector (Amer, 2014). A viral insertion uses a virus as a vector to harbor the drug. A non-viral vector, which generally uses naked DNA or toxic material for the cell as a vector, can be inserted either chemically or physically. Physical insertion can be done by a gene gun or ultra sound. Another physical approach is that of electroporation, which uses high voltages of electricity to disrupt the cell's membrane, allowing the drug to enter the cell (Baranyi, et. al. 2013).

Viral Insertion

Viruses have long been a choice for a vector because of some important properties they contain. Viruses are small pathogenic particles that contain either DNA or RNA encoded in a protein coat. Some viruses also contain a lipid bilayer surrounding the protein coat. The mechanism in which a virus infects a cell is by implanting itself on the host cell's membrane and inserting its viral DNA into the host cell. The host cell then transcribes and translates the viral DNA, which codes for the creation and

assembly of more viral particles. These new viruses cause the cell to burst and proceed to infect more cells. The mechanism by which the virus operates is useful, for genetic material that will lead to cancer cell death or degeneration can be placed in a virus vector, which is essentially the outer protein coat of the virus deprived of its viral genome, and then infect the target tissue area. Before using it as a vector, the virus has to be rendered non replicative so it no longer behaves as a pathogen. Viral vectors are advantageous since they can be produced in high concentrations and have minimal side effects (Amer, 2003).

The most popularly used viral vector is the adenovirus. The adenovirus is favored since it can be made in high titers and can infect both dividing and non-dividing cells. When using a viral vector such as the adenovirus, steps must be taken to ensure that the virus will not reproduce in the host's body like it naturally would. Prevention of the adenovirus replication can be achieved by removing early regions of the adenovirus vector's genome (Pulkkanen, et. al. 2005).

Comparing Adenovirus to Retrovirus

A comparison of the efficiency of the adenovirus and the retrovirus as vectors for gene transfer was done. Ten patients with malignant glioma, a spreading brain tumor, were treated with a beta galactosidase gene via retrovirus and adenovirus vectors. This was done by inserting a catheter into the tumor and injecting the patient with retroviruses and adenoviruses for three consecutive days. This was followed by resection of the tumor one to two days later. X-gal staining was then used to highlight the beta galactosidase gene and to evaluate its efficacy in gene transfer. Findings showed that beta galactosidase was well tolerated with both vectors. In all but two patients, no systemic or tissue complications were apparent. The gene transfer was successful, with an efficacy between <.01- 4% for the retrovirus and an efficacy <.01-11% for the adenovirus. The adenovirus was thus more efficient then the retrovirus as a gene transfer vector (Puumalainen, et. al. 1998).

Malignant Glioma Adenoviral Gene Therapy

Although adenoviral vectors have some of the highest efficacies of gene transfer amongst other viral vectors, they still fall short of producing significant effects on the treatment of tumors. A study of the treatments of malignant glioma was conducted with the aim of evaluating the safety of the adenoviral vector as well as determining the maximum possible dose that would be tolerated. Fourteen patients with relapsed malignant glioma were treated with adenoviral vector containing the Herpes simplex virus thymidine kinase (HSV-tk) and its promoter (IG.Ad.MLPI.TK), and were then treated with ganciclovir, an antiviral drug. Prior to this the retrovirus had been used as a vector for HSV-tk gene therapy treatment. However, the adenovirus was used in this study because of its advantages of high titer production and efficacy of gene transfer.

The patients underwent as much debulking of the tumor as was considered safe. The wound bed was then infiltrated with around 50 evenly spaced injections of the HSV-tk gene. The patients were treated with different dose levels and then monitored for any adverse events. The patients reported either adverse events or serious adverse events. From surgery until completion of the ganciclovir treatment, 27 adverse events and 5 serious adverse events were reported. However none of the adverse events or serious adverse events were from the adenoviral vector.

After surgery, the patients were kept in strict isolation in the ICU, and viral cultures were taken until there were two consecutive days of negative culture results. None the cultures taken were found to be positive, indicating that the viral vector did not shed during its administration and did not pose a hazard to the environment.

The adenovirus was thus considered to be a safe vector internally and externally. However, in regard to the results of the patients' tumor responses, the adenovirus does not appear as promising. Unfortunately, none of the tumors responded to the successful gene transfer. Overall the patients did not fare well. The median survival time was four months, with four patients surviving for over a year. The median survival time attained in this study with the injection of the adenoviral vector was no better than the survival time in respective studies of malignant glioma with no gene therapy treatment. According to the study, even the survival of patients with the favorable prognosis was most likely due to the nature of the tumor and not the gene transfer.

It is clear that the adenoviral vector used in this study is a safe method of choice but not significantly effective in diminishing the tumor growth. It is not definitive from this study if the adenoviral gene transfer had even any effect on the tumor. (Smitt, et. al. 2003).

In contrast to viral vectors, non-viral vectors are generally more economical and easier to produce in large quantities. They also have limited immunogenicity which allows for re-dosing. There is no concern of a gene recombination causing the virus to become competent and pose a danger to the body (Amer, et. al. 2014).

Physical Insertion

Physical insertion involves injecting naked DNA or liposomes directly into the target cell through a breach in the membrane made by rapid needle or jet injections, particle impact, electric pulse, laser radiation, or ultrasound. A novel method of physical insertion is the Jet injection, which was first introduced in 1947 as an alternate to needle injections. Jet injection uses a pressurized gas, like carbon dioxide, to drive an ultrafine high speed stream of DNA into the target tissue in the form of plasmids. Comparisons done between jet and needle injections demonstrated that gene expression was fifty times greater when

done by jet injection than it was done by the standard needle injection.

A phase I study was conducted to determine the safety and feasibility of jet injection on patients with skin metastases from melanoma and breast cancer. Seventeen patients received five jet injections of B-galactosidase, a LacZ- expressing DNA plasmid, into a single cutaneous lesion. To monitor the clearance of the plasmid in the blood stream, real time quantitative PCR of blood samples was done throughout the study. After two to six days, the lesions were resected and a series of tests were performed to determine the efficiency of the plasmid uptake, as well as the transcription of DNA to mRNA and translation to a protein.

All the patients responded well to the jet injections. Four weeks after jet injection, all the patients were alive and none showed any adverse effects from the jet injection. Within forty-eight hours any small bleeding and jet penetration at the injection site disappeared. Additionally, the LacZ plasmids were successfully taken up by all the tumors, with variation in amounts detected in each tumor (Wolfgang, et. al. 2008).

Because this was a phase I study, research was taken to determine the safety of the jet injection and did not cover the efficacy of jet injection in reducing cancerous growth. The LacZ gene did not have any association to reduction of cancerous growth, but rather served as a marker to determine if jet injection was a viable method of gene transfer. Research on humans using jet-injection-based gene transfer as antitumor therapy is limited and quite recent. There have been studies done on mice, though, with encouraging results.

A study was conducted on mice containing human colon carcinoma to test the effectiveness of gene transfer jet injection in its ability to inhibit tumor growth. The mice were injected four times with a suicide gene, Escherichia coli cytosine deaminase, and then after forty-eight hours treated with 5-flurocytocine, an antifungal drug. Tumor volumes were monitored, and starting on day five, there was a significant decrease in the size of the tumors treated with the jet injected suicide gene in comparison to the control groups' tumors. Additionally, protein and mRNA levels revealed that the suicide gene was sufficiently expressed (Walther, et. al. 2005).

Although this study was not conducted on humans, it still has significant findings, chiefly that non-viral jet injection of suicide genes is an alternate method to injection via viral vectors, with comparable therapeutic response. Though there are studies, as mentioned above, of successful adenoviral vector gene transfers, the adenoviral vector does have limitations that the jet injection does not. When using the adenovirus as a vector, there is always the concern that it may have a pathogenic effect on the patient, or that the patient's immune system will respond to the viral proteins and inhibit the vector in completing its task. Jet injection looks promising for cancer treatment, but it is only useful for subcutaneous cancerous growths, like that of melanoma and breast cancer, since it cannot penetrate very deep.

Suicide Genes

Once the genetic material is successfully transferred into the host cancer cells and incorporated into the nuclear genetic DNA, there are a few methods by which it represses tumor growth. A key method being the injection of suicide genes, which are genes that cause apoptosis, or cellular death, when expressed. These genes are usually transcribed by various promoters found within the host cell. The H19 RNA gene is an example of one such promoter. The H19 gene locus was the first imprinted non-coding RNA identified. Recently, extensive study has been done on the role of the H19 gene and tumorigenesis. It is found that there is an abnormal expression of the H19 RNA gene in many cancerous cells, causing cancer cell proliferation, genetic instability, vascular angiogenesis, and tumor metastases. In a number of studies, blocking the H19 gene led to tumor regression and necrosis (Amer, et. al. 2014).

H19 Locus and tumorigenesis

The H19 RNA gene is greatly expressed in fetal organs but is rapidly turned off at birth. In tumor cells, the H19 gene becomes highly expressed or shows an abnormal expression pattern when compared to normal non-cancer cells. In cancer cells, the H19 gene expression can be activated by a combination of various transcriptional modulators and regulators that have malfunctioned. The interplay of the H19 gene locus and the modulators in tumorigenesis is highly complex, involving many regulatory factors that rely on many other regulatory factors (Matouk, et. al. 2013).

Hypoxia and H19

One such approach to the H19 gene's upregulation in cancerous cells is through hypoxia. Hypoxia is the loss of oxygen to areas of cancerous growth, and is considered a major trigger for metastasis, tumor angiogenesis, and chemotherapy resistance. Hypoxia is also considered to increase H19 expression in tumor cells. A study was done to investigate the relation between hypoxia and H19 upregulation in tumor cells. Carcinoma and Hepatocellular carcinoma cell lines were placed in an Aneropack rectangular jar and supplemented with Gaspak to create a hypoxic environment. Some cells where left with normal oxygen conditions as a control. The cells were then monitored by a hypoxic indicator. After twenty-four hours, the cells were examined and RNA from each cell was extracted and amplified through PCR. Viewed on the gel, the cells under anaerobic conditions expressed the H19 RNA significantly more than the cells under normal oxygen conditions.

In a similar study, mice were injected with Hep3B, cells containing hepatitis B, which caused the proliferation of Hepatocellular carcinoma on their dorsal side. A group of those mice were then injected with siRNA, a H19 gene knockout. The results showed that the mice that were treated with the siRNA showed

a significant retardation of tumor growth of 82%. Thus, from this study it is clear that H19 plays a large role in tumor growth, and is activated by hypoxia, which is common in cancerous growths (Matouk, et. al. 2007, Matouk, et. al. 2005).

c-Myc and H19

Another factor that induces H19 transcription is the c-Myc transcription factor. C-Myc is a transcription factor that, together with its obligate partner, protein Max, another transcription factor, binds to E-boxes, which are enhancer sequences on the DNA that initiate transcription. C-Myc then promotes gene transcription by initiating chromatin remodeling on the DNA or RNA polymerase clearance. To assess the role of c-Myc in tumor cells with increased H19 expression, a study was designed in which c-Myc was inserted into breast and glioblastoma cell lines. Cells inserted with c-Myc showed a seven-fold to ten-fold increase of H-19 expression based on Real-time PCR readings. Breast and lung cancer cell lines were also used to determine the correlation between elevated levels of c-Myc and H19 and tumor growth. The cell lines containing elevated levels of H19 and c-Myc were treated with siRNA to knock down H19 expression. The cells with knockdown H19 exhibited significant retardation of tumorigenesis. Thus, c-Myc was established as another factor that induces H19 upregulation and thereby increases tumor growth (Barsyte, et. al. 2006).

E2F1 and H19

Another basis for increased H19 expression in cancer cells is the E2F1 regulatory factor. E2F1 belongs to the E2F protein family that regulates DNA by binding to promoters. E2F1 binds to the H19 promoter and initiates its transcription. E2F regulation is based on the stages of the cell cycle. E2F1 is considered a key factor in the transition from G1 to S in the cell cycle, as it promotes the transcription of genes whose protein products are necessary for the progression of the cell cycle and for imitating DNA duplication. Thus, increased E2F1 expression when it is not the appropriate cell stage or time for cell replication can lead to cancerous growths.

A study conducted assayed the correlation between increased E2F1 and H19 gene expression in the S phase, as well as E2F1's impact on tumor growth. First, epithelial breast cells were transfected with a luciferase reporter gene, a selectable marker gene that, when expressed, causes the cells to emit a bioluminescence. Half of the cells were transfected with a luciferase reporter gene carrying the wild type H19 gene and the other half with a mutated promoter site of an H19 gene, so E2F1 binding is inhibited. The breast cells were then serum starved, and after twenty-four hours, some cells were placed in a fresh medium to stimulate their entry into cell cycle. After a set time, the cells were then compared using FACS analysis, a fluorescent strength intensity test, because the luciferase reporter that was used contains bioluminescence. Results showed that serum-starved cells had very little H19 expression, while cells in S phase had remarkably increased levels of H19. The cells transfected with the mutated promoter site had low H19 expression compared to the wild type cells that had overall increased H19 expression, especially at S phase (Fig. 1).

The correlation between H19 and E2F1 binding to its promoter is demonstrated when the comparison between the wild type and mutated transfected cells are noted. The cells with wild type H19 promoter sites showed a higher concentration of luciferase activities, since E2F1 was able to bind to the promoter site and activate transcription, while the cells with the mutated promoter sites exhibited a lower concentration of luciferase activities since E2F1 was not able to bind to the mutated promoter site. Additionally, H19's and E2F1's definite role in G1/S phase is observed by the fact that the greatest percentage of cells were recorded during the S phase of the cell cycle.

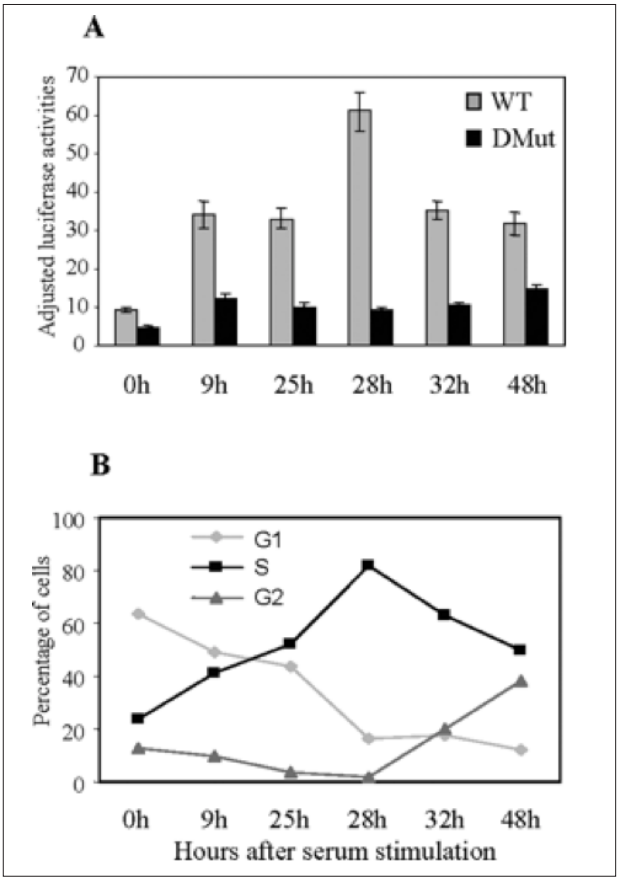

Figure 1: A. Cells were treated with luciferase reporter gene with either wild type (WT) H19 promoter sites or H19 promoter mutated in two E2F sites (DMut). The cells with the wild type promoter exhibited the higher concentration of luciferase activities than the mutated cells.
B. Shows the percentage of cells distributed throughout the cell cycle. Note the elevated S phase line. (Berteaux, et. al. 2005)

The second step of the study was to examine the roles of H19 and E2F1 in cancer proliferation. Breast cancer cell lines were obtained and the levels of E2F1 mRNa and H19 RNA were calculated. Normal breast cells were used as a control. The data showed that the expression of E2F1 and H19 were generally corresponding. In the healthy breast cells there were low levels of both E2F1 and H19 expression, while most of the cancer cells showed notable activation of E2F1 and H19 gene. In one line of cancer cells however, the E2F1 expression was high but the H19 expression was comparatively low. This discrepancy was attributed to heterogeneity of breast tumors. In general, there is a correlation between E2F1 and H19 upregulated gene expression in cancerous tissue (Berteaux, et. al. 2005).

Based on the studies discussed above, increased H19 expression is regulated by a number of regulatory factors, such as c-Myc and E2F1. Their upregulation is also triggered by environmental stress conditions such as hypoxia and S phase induced cells after serum starvation. However, cells under normal conditions do not demonstrate significant H19 expression (Ayesh, et. al. 2002). These findings reinforce the evidence that H19 is upregulated in many cancer cells, for hypoxia and serum starvation are considered normal stages in tumor growth. Thus, the tumor's growth causes its further proliferation. As it outgrows its blood supply, some portions of the tumor lack sufficient oxygen and reside in hypoxic microenvironments, which in turn triggers the increased expression of H19, further promoting cancerous growth.

Some of the explanations of H19 gene upregulation in tumor cells have been presented, and the therapeutic methods involving the H19 locus will now be discussed.

BC-819 Gene Therapy

In the past couple of years, BC-819, a plasmid involving a suicide gene and the H19 promoter, has been developed and has successfully improved treatment of a number of cancers. BC-19 is a double-stranded DNA vector that contains Diphtheria toxin A sequence, which isused to destroy the cancer cell, and an H19 promoter sequence. It is mixed with Polyethylenimine transfectant (PEI), which allows for easier entry of the plasmid into the rapidly dividing tumor cells. In some cases, PEI is not used and BC-819 is injected intratumorally or by hepatic artery infusion (Matouk, et. al. 2013).

Once BC-819 is in the cancer cell, the H19 promoter is activated and transcribed continuing with the Diphtheria toxin A sequence, which causes cell death by disrupting protein synthesis. BC-819 can actively select tumor cells to destroy, since only tumor cells have increased levels of H19 transcriptional factors. BC-819 will enter healthy cells as well, but since they lack the H19 regulatory factors, they will not transcribe the plasmid and the cells will not be destroyed. BC-819 is an ingenious development that acts as a 'search and destroy' unit by only killing cells that contain H19 transcriptional factors thereby triggering their own demise (BioCanCell, 2017). BC-819 has been semi-successful at treating bladder, pancreatic and ovarian cancer patient (Fig. 2)s.

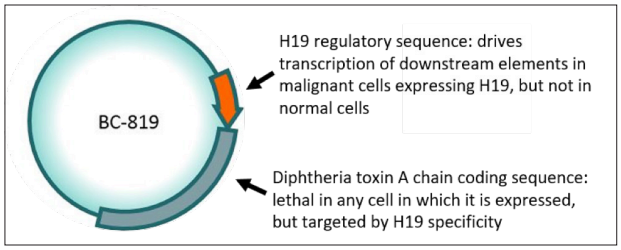

Figure 2 (BioCanCell, 20170

Bladder Cancer

In the United States, bladder cancer is the fourth most common cancer in men, with an estimated 74,000 annual incidents. Around 70% of bladder cancer patients suffer recurrence within five years. A chief goal of battling bladder cancer is in preventing its recurrence. For decades, the standard care option was the BCG vaccine but the vaccine included drawbacks such as recurrence, resistance to the treatment, and negative side effects (Matouk, et. al. 2013).

A phase 2b study was conducted testing the efficacy of BC-819 treatment of bladder cancer. Patients who had confirmed recurrent bladder cancer and for whom BCG and chemotherapy had failed were recruited and BC-819 with PEI was administered to them. First, they were given six weekly treatments of BC-819, and at week nine, safety and efficiency of transfer were assessed. In cases of no toxicity or recurrence therapy was discontinued in patients and follow up maintenance therapy was given for the duration of the year. From the first cohort, nine out of eighteen patients had complete resolution of the target lesion within eight to ten weeks. Overall, 63% of patients had recurrence-free tumors for the first three months after treatment and 48% had tumors for a year after treatment. Additionally, the patients tolerated the treatment well with only mild to moderate adverse effects.

Reports of Phase III trials have not yet been published but trials are in progress as of the year 2016.

Pancreatic Cancer

The eighth leading cancer cause of death in the United States is pancreatic cancer, with a poor prognosis of five year survival. The standard treatment for pancreatic cancer is gemcitabine, a chemotherapy drug. However, gemcitabine has limited effect because of its poor intracellular metabolism. Other methods have been tried in combination with gemcitabine in the hope of a more effective treatment, but none proved worthwhile. Recently, BC-819 and gemcitabine were tested together on pancreatic patients in a phase 2b study that showed more promising results. Patients received four week treatments of gemcitabine

and were then administered with BC-819 through endoscopic ultrasound. Continued treatment with gemcitabine and BC-819 was done for as long as the cancerous growth did not progress. After three months, nine out of eleven patients showed encouraging results. Two had partial recovery and seven reached a point of stable disease. There were several adverse events mostly relating to liver function, but it was concluded that the adverse events were not related to the BC-819 , but were rather due to the advanced stage of the cancer that all the patients had (Matouk, et.a. 2013).

Ovarian Cancer

For women, ovarian cancer has a high mortality rate and is the fifth leading cause of cancer related death in the United States. Ovarian cancer patients generally have a poor prognosis, because the initial detection of the cancer is usually after it has reached an advanced stage. The typical course of treatment includes surgical removal of the tumor followed by chemotherapy. Unfortunately, most patients with the advanced stage tumor experience relapse after treatment. In the hopes of finding a better alternative treatment course, a phase ½ study testing the efficacy of BC-819 plasmid was conducted on fourteen ovarian cancer patients. All fourteen women had been pretreated with extensive chemotherapy. Different doses of BC-819 were administered to different groups of the patients. The first cohort of patients were treated for three weeks with BC-819, rested for a week, and were then treated for six more consecutive weeks. This was followed by a four week rest period. The second and third cohort were treated with increased dosages for three weeks, with four weeks of rest and then an attempt at repeat treatment when possible. Of the fourteen subjects, only 3 completed the study, while the rest withdrew prematurely due to overall clinical deterioration. There were fifteen reported severe adverse events, yet none were from the drug. There were, however, five adverse events that were possibly related to BC-819 administration. The best outcome of the treatment was a stable disease, with insufficient shrinkage or growth to qualify as either a partial response or progressive disease. The patients in the study all had advanced tumor growth, but the findings suggest that with less advanced stage ovarian cancer, BC-819 treatment would yield a partial response (Lavie, et. al. 2017).

BC-819 shows great promise for cancer patients. Although not every patient treated in the studies mentioned above had a positive outcome from the treatment, no one's medical state was worsened. The study of the BC-819 treatment is still in progress. The studies mentioned above are phase one or two studies, which means they are being done to determine the maximum tolerable dose of the drug, its safety, and efficiency. A phase three trial is generally the final test performed before the drug can be open to the public. A phase three trial is presently ongoing for bladder cancer, and a phase one/two has been completed for ovarian and pancreatic cancer.

Based on the various studies presented, gene therapy appears to be a viable option for cancer treatment. Although in each study there were some patients who did not fare well with this form of treatment, as an overall option, gene therapy looks like a promising alternative for cancer patients for whom standard treatment is insufficient.

Gene Therapy and Leukemia

However, there have been studies that have shown that in its attempt to rid the patient of his illness, gene therapy can actually promote one of the deadliest cancers, leukemia.

In 2002, a group of infants with severe combined immunodeficiency (SCID) were treated with gene therapy, but four out of the nine patients developed leukemia within the next five years. This alarmed many patients and researchers, and was a major setback in the advancement of gene therapy.

SCID is caused by a genetic mutation, making a patient with it lack the IL-2 receptor γ (IL2RG) gene. To restore the absent gene, the infants in the study were treated with a therapeutic gene via a retroviral vector. However, the retroviral vector works by inserting its genome near a transcription start site in the host genome, allowing the virus' long terminal repeats, which are repeated identical sequences of DNA that enable insertion into the host genome, to unintentionally turn on transcription of other nearby sites. In these infants with SCID, the LMO2 oncogene site was found near the insertion site and was turned on, promoting leukemic growth (Hacein-Bay-Abina, et.al. 2008).

The events of this gene therapy treatment were unfortunate, and did remove some of the enthusiasm for gene therapy at the time. However, the fact that this occurred on SCID patients and not on cancer patients must be taken note of, thus gene therapy might not be the right choice for SCID patient, but that does not rule out cancer patients. Cancer patients may not have an oncogene site near the insertion site for their therapeutic gene, which completely removes the possibility of inducing leukemia. In the research done, no reports have been made demonstrating that gene therapy for cancer patients further induced new cancerous growths.

Conclusion

Although gene therapy as a treatment option for cancer has had some setbacks and inconclusive results, it still provides a large source of hope for cancer patients. The paradigm of treating cancer is slowly shifting due to the ongoing progress of gene therapy. Based on the studies presented above, overall gene therapy, whether administered through a viral vector or a non-viral vector, was successful in treating a portion of the

patients. Additionally, even in the studies done in which small or no substantial recovery was obtained, there were no considerable adverse effects on the patients treated with gene therapy. This greatly contrasts standard treatments like chemotherapy that cause an array of adverse effects on the patient without necessarily providing complete removal of the cancer. Thus, even though gene therapy may not provide a complete cure against cancer, it is a promising alternative to standard cancer treatment. With the constant hard work and progress of medical researchers and physicians that is presently taking place, it is anticipative to say that gene therapy will provide great relief to many cancer patients in the coming years.

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