Pharmacogenomics and Acute Lymphoblastic Leukemia

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer in the United States. It is also a very prominent cancer among adults, mostly as a recurring form from a childhood diagnosis (Hawwa, 2008). Acute lymphoblastic leukemia is the abnormal proliferation of lymphatic cells in the bone marrow (Hawwa, 2008). This specific type of cancer is treated using different forms of chemotherapy. There is a large variation in patient response to the treatments for ALL (Hawwa, 2008). A medication that may be beneficial for one patient could have no effect for another. Pharmacogenomics could be an effective solution to figuring out which medication will work for individual patients.

Pharmacogenomics is the study of how a person's genetic makeup can affect their response to medications. Each individual has a very unique genetic makeup. Genes code for proteins and these proteins are responsible for breaking down medications. If an individual has a genetic mutation, they may not produce the protein necessary to make a certain medication effective. Pharmacogenomics sequences an individual's genome to give information as to which medication may work best for that individual with the least amount of side effects (Relling, 2004). Pharmacogenomics could be useful in the treatment of ALL. It would allow for oncologists to determine which medication would be beneficial for the patient from the very beginning of their treatment. It would avoid the issue of trial and error.

There is already some research being done on the topic. Many say that pharmacogenomics cannot be applied to cancer treatment (Swen, 2007). Chemotherapy is a very intense treatment that takes many proteins to break down. Oncologists speculate that there is not just one specific gene that can determine how a patient will react to a chemotherapy treatment

(Swen, 2007). Many pharmacists argue that if enough information is gathered about the topic, pharmacogenomics can be applied to cancer treatments. The information can be gathered to determine which medication has the greatest probability of being effective for an individual patient (Relling, 2004). This would be a pivotal discovery for the treatment of ALL and many different types of cancer.

Literature Review

Medications can vary in their efficacy on a patient to patient basis. This means that a medication may be effective for one individual, but it could have idiosyncratic or toxic effects for another. Pharmacogenomics is the concept that this variation could be due to one's genetics. Understanding how genetics impacts the metabolism and effectiveness of medications can help prescribers determine effective dosing for the patient. It can also help providers determine which medications will be the most effective for each patient (Relling, 2004). Pharmacogenomics has been a research topic since around 1950 but has only recently begun being used in the clinic (Relling, 2004). One major reason that there has been such a delay in regular usage of pharmacogenomics is due to the lack of scientific evidence to back its effectiveness (Swen, 2007). Although there is significant evidence for a few medications, the number of medications that have been studied is very limited. Another big setback of getting pharmacogenomics into the clinic has been the high price of running the genomic test (Swen, 2007). The price of running the genome of an individual is very expensive. This has kept most providers from using it in their clinic. However, testing prices continue to decrease as time goes on.

The idea that medications can be personalized varying from patient to patient is called individualized medicine. Pharmacogenomics allows for each patient's medications to be personalized based on their genome (Relling, 2004). Variations in genetics can cause several

different reactions to drugs. Pharmacogenomics looks at the efficacy and toxicity of medications. Efficacy refers to how effective the medication is. A drug may have a high efficacy for one patient, but may not be effective at all for a different patient (Relling, 2004). Toxicity refers to the level of and severity of the side effects experienced by the patient. A drug may have no side effects for one patient but could be life threatening for another patient (Relling, 2004). Knowing an individual's genetic makeup can allow providers to prescribe the most effective drug. It can also help providers determine the proper dosing for the patient (Relling, 2004).

Pharmacogenomics has recently become relevant in the treatment of cancer. Cancer is caused by uncontrolled proliferation of cells. Most anticancer medications are meant to stop the proliferation of these cells. Since most cancer medications have a low therapeutic index, they have severe side effects for the patient (University of California, 2008). Pharmacogenomics could help reduce the amount of side effects the patient will experience. Knowing how medications will affect the patient can help their provider to determine the best medication for them. Genetic variations can affect both pharmacokinetics and pharmacodynamics (University of California, 2008). Pharmacokinetics relates to how medications are absorbed by the body. Pharmacodynamics refers to how the medication works on the receptors of the body and how they are transported. Pharmacokinetics and pharmacodynamics can both largely affect how a medication will affect a patient (University of California, 2008). Determining how anticancer medications affect the patient can largely improve their quality of life during treatment.

Understanding how genetics play into medication can help providers maximize the therapeutic benefits of their anticancer treatment (Wheeler, 2007). Maximizing the therapeutic effects can give the cancer the best chance at survival with the least amount of side effects. Cancer is one of the leading causes of death in industrialized countries. Determining how to

maximize therapeutic benefits for each patient can help decrease the death rate significantly (Wheeler, 2012). One of the most effective ways of using pharmacogenomics in cancer patients is to test germline variations. Germline variations are not only present in the cancerous tissues, but they are also present in regular tissue cells as well (Wheeler, 2013). This means that germline variations can alter both pharmacokinetics and pharmacodynamics. Since germline variations are present in all cell types, it means that knowing how these variations work can help alter medications regardless of disease type (Wheeler, 2013). Knowing the germline variation is an effective way to treat several different cancer types. Clinical trials for anticancer medications are an effective place for pharmacogenomic testing to be initiated. Clinical trials are for new mediations and are typically testing for efficacy and toxicity (Wheeler, 2013). Pharmacogenomic testing is also looking to limit toxicity and maximize efficacy, so the similarities make it a good place to start.

Many oncologists argue that pharmacogenomics would not be useful in determining effective cancer treatments. Their argument against it is that chemotherapy is a very intense medication. It can take numerous proteins produced by one's genetics to effectively break down the medication regardless of which one is being used (Swen, 2007). This is a large controversy in the field of pharmacogenomics. Those that are attempting to prove the effectiveness of pharmacogenomics in cancer treatment argue that it is not about finding a medication that is one hundred percent effective for the patient. It is focused on finding the medication that will give the patient the best chance at survival with minimal side effects (Wheeler, 2012). All of the genes that affect the response to a medication are not necessarily needed in order to determine how a patient will react to a medication. As long as there are at least three genetic sequences

determined, an informed decision can be made (Wheeler, 2012). This is a big controversy in the field and provides a good concept of why more research needed to be conducted.

Research Design and Methods

Research Design

This research project is quantitative positivist. It will use a specific group of patients that must match a certain set of requirements. It will be run over a period of four months. Blood will be drawn from the patients at five different times throughout the experiment.

Methods

Study Subjects

Patients were considered for the study if they were a pediatric patient diagnosed with acute lymphoblastic leukemia. This is a cancer that affects the white blood cells of the bone marrow and blood. Patients were only eligible if they had been prescribed AZA or 6-MP for at least one month prior to the beginning of the experiment. Patients also had to have seven consecutive days of treatment with 6-MP to be eligible for this study. A total of 19 pediatric patients that met the requirements were found for this study.

Study Design

Blood samples were taken from the patients with acute lymphoblastic leukemia to measure the concentration of 6-MP. Blood samples were taken at a specific phase of treatment when they had an indwelling cannula (IV) of vincristine therapy at least eight hours after the preceding dose of 6-MP. The blood samples taken were collected in ethylenediamine tetraacetic acid tubes. The tubes were kept on ice until centrifugation. Blood plasma that was separated from red blood cells was frozen. Red blood cells were washed twice with a balanced salt solution. Samples were taken on a maximum of five occasions over a four month span. Other

data collected included age, weight, height, gender, pathology, current treatments, lab results, and any reported side effects.

Assay of 6-MP Metabolites

Red blood cell and plasma concentrations of 6-MP were measured using a reversed high-performance liquid chromatography method. The intraday and interday coefficient of variation for the assay developed was between 1.6 and 3.5%. The lower limit of quantification was 13 pmol per 8 x 10^8 in the erythrocytes.

Genotyping of TPMT, ITPA, and XO

Patients were screened for seven different polymorphisms in enzymes that are involved in the metabolism of 6-MP. The polymorphisms are thought to be involved in the toxicity and side-effects related to 6-MP. The possible polymorphisms include changes in XO, ITPA, and TPMT. Genomic information was extracted from peripheral blood using QIAmp Mini Kit. The DNA concentration that was extracted was measured using Quant-iT PicoGreen dsDNA Quantitation Kit. Single nucleotide polymorphisms were detected using TaqMan genotyping assay obtained from Applied Biosystems. Polymerase chain reactions, a technique for amplifying DNA, were performed in a 96 well plate. The amplification cycle was as follows; 96 degrees celsius for 15 minutes, followed by 50 cycles of 95 degrees celsius for 15 seconds, then 60 degrees celsius for a minute and half.

Practical Considerations

There are some ethical concerns with this research project. The main concern is that it must be done on human subjects. The human genome is unique so animal subjects are not an option. This is not a major concern as no new medications are being tested. An additional concern is finding subjects for testing. This cancer is most prominent in children and the

requirements are specific. The best way to avoid this concern is to find newly diagnosed patients. This will give the most accurate results with the research as well.

This research project will be influential in the treatment of ALL. It will also help with the controversy between pharmacogenomics and cancer treatments. Finding the most effective treatment as soon as possible will give patients the highest chance at survival. It will also be very beneficial in reducing the amount of negative side effects experienced by the patient.

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