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OBJECTIVE: To examine the safety and efficacy of administering the drugs carboplatin and doxil in combination chemotherapy for the treatment of gynecologic cancers, mainly endometrial and ovarian cancer. MATERIALS AND METHODS: Carboplatin and doxil were previously administered intravenously to 6 patients. Each patient received 3 to 8 cycles of chemotherapy. Doses of carboplatin ranged from 310 mg to 665 mg. The doses of doxil ranged from 54 mg to 80 mg. This is a retrospective study. The 6 patient's medical charts were reviewed. Data was extracted and a spreadsheet formatted database was created. RESULTS: Due to the small number of patients the results are not statistically significant. 2 patients showed tumor progression while receiving treatment. All patients tolerated doses very well and experienced minimal toxicities. CONCLUSION: Carboplatin plus doxil combination chemotherapy given intravenously has a potent effect on endometrial and ovarian cancers. Studies using this chemotherapy for the treatment of gynecologic cancers should be conducted on a wider scale to access the statistical significance of the treatment.

CLINICAL INTERNSHIP WITH THE DIVISION OF GYNECOLOGIC ONCOLOGY AT UT SOUTHWESTERN MEDICAL CENTER: CARBOPLATIN AND DOXIL FOR GYNECOLOGIC CANCERS

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THESIS

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By Camitria N. Epps

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INTRODUCTION

Cancer is a concern for many citizens in the United States. This concern may continue to grow as Americans continue to live longer. Many studies have been conducted in an attempt to find the best treatment for cancer. While some treatments have shown great success, improvements in care are still needed. "The relative 5 year survival rate for all cancers is 62%."[19] Thousands upon thousands die from this dreadful disease every year.

Cancer comes in many forms including gynecologic cancers in women. Endometrial cancer is the most common gynecologic cancer. This form accounts for 6% of cancers in women and average age of onset is between 50 and 59 years of age. Ovarian cancer accounts for 4% of cancers in women and average age of onset is between 55 and 59 years of age. Females between birth and age 39 have a 1 in 52 chance of developing cancer, but by the time a woman is 60 her chance has increased to 1 in 5.[14]

The following chapters and information was obtained through literature review conducted as a part of a 5 month internship with the Division of Gynecologic Oncology at UT Southwestern Medical Center. This resulting project was developed to examine the effectiveness of one treatment for endometrial and ovarian cancer. The study was retrospective and involved reviewing the medical charts of patients who underwent the carboplatin plus doxil combination chemotherapy regimen. The information gathered from the patient charts was entered into an excel database.

The primary objective of the project was to determine a tumor's response to carboplatin plus doxil chemotherapy. Determining time to progression and overall survival were secondary objectives.

CHAPTER 1

LITERATURE REVIEW

CANCER: AN OVERVIEW

A cell is the smallest living unit in the body. The life span of the cell is termed the cell cycle. Under normal conditions during the cell cycle, the cell grows, reproduces and eventually dies. This process is controlled at many levels in the body. Cell growth and death are kept in close balance. Cancer is a group of diseases in which there is a loss of control and uninhibited cell growth is seen. In addition, cancer may deprive normal cells of nutrients and lead to their demise resulting in failure of vital organs.

The cause of cancer is unknown. "Cancer is proposed to arise in a two step fashion. Each step requires a mutation (step one) which may be either germinal (inherited) or somatic (acquired). The second mutation (step 2) is almost always somatic."[8]

Cancer begins as an inherited event in which a single cell that possesses malignant potential passes that potential to other cells through reproduction. External factors such as smoking, sunlight, and radiation exposure induce carcinogenic events that lead to the mutation of DNA. The mutation of DNA is the vital step in the formation of cancer because it is DNA that encodes all proteins, building block elements, and behavior of cells.

Certain genes (oncogenes) are present in cellular DNA of all normal cells and are the targets of carcinogens. Similarly, some viruses can use the body's genes by converting proto-oncogenes into cancer causing agents. "Oncogene sequences in normal cells are known as proto-oncogenes."[8] Carcinogenic processes are the result of oncogene activity. They may cause an abnormal production of protein or production of an abnormal product. It is currently not known what occurs to cause the expression of the oncogene. Theories include a change in genes surrounding the proto-oncogene by either incorporating a new gene into a host gene or by translocation. A gene in normal people may be located on a particular chromosome, but those who lack that chromosome may have the gene translocated to a different chromosome. This may place the proto-oncogene under different genetic regulation.[8] Inherited cancers usually exhibit a loss or malfunction of suppressor and repair genes. These genes normally suppress certain activities and repair damage to prevent the mutation usually seen in cancer.[25]

Oncogenes are thought to play roles in cellular behavior, proliferation, and differentiation. They are involved in cell regulation, governing such processes as secretion of growth factors and of growth factor receptors, transmission of signals from membrane to nucleus (second messenger), and even DNA transcription.[8] Carcinogens, cancer-causing agents, act on proto-oncogenes or oncogenes and cause an alteration or mutation leading to the development of cancer. There are 3 phases in this development, initiation, promotion, and progression. During initiation a carcinogen causes an error in the body's normal detoxification system.[41] This results in an alteration of cellular DNA.

The cell has the potential to become cancerous if the altered DNA is not repaired before cell division.[41]

Promotion or phase 2 involves the effect of continued exposure to promoters, such as chemical agents. These promoters may cause a cell that has undergone initiation to become malignant and cause alterations in cellular interaction. It is believed that alteration of the promoter (i.e., smoking cessation) can prevent the development of cancer.[41] Phase 3 or progression is the phase in which the growth invades or metastasizes to other sites.[41]

Uncontrolled cell growth can lead to the formation of a tumor. Cancer cells lack the mechanism that controls cell proliferation. They continuously multiply and they lack a cohesiveness, which can lead to metastasis (or spreading of the cancer cells to other tissues). There are many routes by which tumors may metastasize. They may use the existing vascular system, lymphatic system, or new vessels may form (angiogenesis) to facilitate the spread.

CANCER STATISTICS

Cancer is a leading cause of death in the United States. It is second only to heart disease. It has been estimated that in the U.S. 1 out 4 deaths is from cancer.[14] In the year 2002 over 550,000 Americans died from cancer, while 1.3 million new cases were diagnosed.[19] Cancer can effect people of all ages. Seventy percent of cases however are diagnosed in people 55 and older.[14] The chance of getting cancer increases with age. It can be said that because more Americans are living longer more incidents of cancer may

be seen. "The National Cancer Institute estimates that approximately 8.9 million Americans with a history of cancer were alive in 1997."[14]

Since 1990 about 16 million new cancer cases have been diagnosed. It was estimated that in 1997 1.3 million new cases of cancer were diagnosed and 560,000 Americans died from their disease. This rate of diagnosis has held constant from 1997 to 2002. The majority of cancer related deaths is due to tobacco use, alcohol use, or poor nutrition and lifestyle.[14]

Between 1997 and 2002 the number of cancer related deaths remained constant. Tobacco related deaths totaled 170,000-175,000. Alcohol related deaths totaled 19,000-20,000, and 1/3 of cancer deaths were linked to poor nutrition, lack of physical activity, and lifestyle in general.[14] The 5 year survival rate in 1997 was 56% for all cancers. There has been a slight increase in this rate. In 2002 the 5 year survival rate was 62%.[14] This increase may be due to earlier detection and better treatment options.

Cancer is not only costly in terms of lives but also in dollars. The overall cost for cancer was estimated to be $156.7 billion in the year 2001. Direct medical costs were $56.4 million. Lost production due to illness or indirect morbidity costs were $15.6 billion. Lost production due to death or indirect mortality costs were estimated to be $84.7 billion.[14]

Many Americans must rely on Medicaid and Medicare for medical expenses. Because these are government programs, in the long term we all pay the tremendous cost to treat cancer.

DETECTION AND DIAGNOSIS

Advanced cancer may spread to so many different areas of the body that it is sometimes difficult to determine where the primary tumor began. The identification of the primary or origin of the tumor is critical in determining the appropriate treatment regimen; especially if one is treated with chemotherapy. Diagnosing cancer at an early stage can be beneficial. A method of describing cancer has been developed for medical use worldwide. The system is known as the TNM system. "T" indicates tumor size. "N" indicates if the cancer has infiltrated the lymph nodes. "M" indicates if there is metastasis. The system is further broken down into stages. Staging is used to describe the anatomic spread of cancer.

Staging Cancer (Table 1)	
Stage	Area
Stage 0	In Situ
Stage I	Local Invasion
Stage II	Spread to Lymph Nodes or Tissue in Local Proximity
Stage III	Spread to Lymph Nodes or Tissue not in Local Proximity
Stage IV	Spread to Distant Areas

Tumors are also graded, usually by a pathologist. There is a microscopic examination used to determine the degree of malignancy. Grading is based on cell differentiation.

Grading Cancer (Table 2)	
Grade	Differentiation
Grade 1	Well Differentiated (Resembles Normal Cells)
Grade 2	Moderately Well Differentiated
Grade 3	Poorly Differentiated
Grade 4	Undifferentiated

The least malignant cells (Grade 1) are those that closely resemble normal cells and the most malignant cells (Grade 4) are those that have an appearance very unlike a normal cell. Staging and grading can be different for each cancer but the basis is the same. In general the higher the grade and stage the lower the prognosis of survival.

Cancer may be detected through blood tests. Certain cancers may cause a change in chemical composition of the blood which could be due to cancer's effects on organ function. Some of the biochemical tests are BUN (blood urea nitrogen), SGOT (serum glutamic oxaloacetic transaminase), and bilirubin. Urea is produced in the liver as an end product of protein metabolism. It is usually found in low levels in the serum because it is excreted efficiently by the kidneys into urine. When there is kidney damage or obstruction as may be seen with metastatic cancers, the blood urea nitrogen (BUN) level may increase. Serum glutamic oxaloacetic transaminase or SGOT is an enzyme normally found in the liver and kidneys. An increased level of SGOT in the plasma may signify tissue destruction. Bilirubin is derived from hemoglobin during the breakdown of red blood cells. It is excreted by the liver in bile. There is always some bilirubin in blood but an abnormally high level may be indicative of liver damage which could be caused by cancer or increased red blood cell destruction associated with cancer.[9]

There are tests performed to identify specific cancer antigens such as CA-125 which is often elevated in cases of ovarian cancer. Blood counts may also be performed to assess whether sufficient blood cells are in circulation. Urine studies may also be used to detect abnormalities. Tissue samples are often taken either by biopsy (histology) or exfoliative cytology to look at the cellular level if cancer is present.

There are visualizing techniques such as a MRI, CT scan, x-ray, ultrasound, and endoscopies employed to detect the presence of a tumor.

TREATMENT

"There are three principle goals in the treatment of cancer: cure, control, and palliation. The primary objective is cure, to completely eradicate all cancer. Control is the arrest/slowing of tumor growth, thereby prolonging survival and maintaining quality of life. The third goal, palliation, may not prolong survival but does alleviate pain and discomfort associated with cancer."[9] There are several treatments for cancer. Treatment often depends on type, location, and stage of cancer. Options may include chemotherapy, radiation therapy, hormonal therapy, biological therapy, and surgery. Surgery is the most common treatment for early cancer.[9] Surgery can be used to cure cancer, prevent it, and diagnose it. There are other uses of surgery including staging and reconstruction.

Hormonal therapy employs the use of hormones (i.e. progesterone) to slow or halt cancer cell growth. Radiation therapy uses radiation to shrink or kill cancer cells. This therapy makes use of ionizing radiation which deposits energy that injures or destroys cells in the area being treated by damaging their genetic material, making it impossible for these cells to continue to grow.

Biological therapy utilizes the body's own immune system to boost its response. The immune system is a network of cells that work together to defend against invasion or disease. It can differentiate healthy cells from abnormal cells. It works to eliminate abnormal cells such as cancerous cells. "Biological therapies are designed to repair, stimulate or enhance the immune systems response."[20]

Some therapies may stimulate a particular immune system cell leading to a secondary response, like an increased production of cytokines. Certain other biological therapies utilize laboratory produced agents normally produced during an immune system secondary response, to boost the immune defense or restore ability to fight.[20]

CHEMOTHERAPY

Chemotherapy involves the use of drugs to kill cancer cells. Anti-cancer drugs interfere with the cancer cell's ability to divide and reproduce. The goals of chemotherapy are the same as the principle goals of treatment (cure, control, and palliation). Some chemotherapy drugs are used alone while others are used in combination. When determining drug use it is important to take into account drug efficacy, direct action, and toxicity. Healthy cells may be affected by chemotherapy causing unwanted side effects, but because these healthy cells have intracellular repair mechanisms, chemotherapy affects fast growing cells, and the chemotherapeutic agents are not aimed at them, they should be able to repair the damages.

Chemotherapy may be given following surgery or radiation therapy. This is known as adjuvant chemotherapy. Chemotherapy may be given is several ways; intravenous injection, subcutaneous injection, intramuscular injection, and orally.

Intravenous injection was the route of administration for the carboplatin plus doxil study that forms the basis of this project. Advantages to using IV are that there are no barriers to absorption, rapid onset, one can control drug concentration and large fluid volumes are possible. There are also drawbacks or disadvantages to using intravenous injection. There is usually a high cost, there must be trained personnel and the process is

inconvenient to the patient. Infection is possible and it is irreversible. This form of drug delivery may be one of the best because some factors that affect rate and extent of drug absorption are not an issue. Some these factors are size of the absorbing surface and condition of the absorbing surface.

Chemotherapeutic agents not only differ in method or mode of action, but some agents act on cells in certain phases of the cell cycle. Some drugs attack DNA directly while others inhibit enzyme activity. Drugs may also effect the formation of the spindle apparatus during mitosis.

It is important here to note the specifics of the cell cycle. The cell cycle consists of 5 phases. G_1, G_2, G_0 and S phase are all phases in interphase. M phase is mitosis. RNA synthesis and protein synthesis occur during G_1, S, and G_2. During S phase another very important activity occurs, DNA synthesis. G_0 is just a resting period that may or may not occur.

M phase encompasses mitosis in which there is a nuclear division and a cell division (cytokinesis). There are several stages of mitosis. The specifics of each are listed below.[42]

Prophase · Chromosome condensation and spindle assembly

ProMetaphase · Nuclear envelope breakdown and chromosomes attach to spindle

Metaphase · Chromosomes move to spindle equator and are aligned at metaphase plate

Anaphase · Centromeres split and sister chromatids separate

Telophase · Daughter chromosomes arrive at spindle poles and cytokinesis begins.

The cell cycle proceeds in the following order: G_2, M, G_0, G_1, and S. At the end of S phase the cycle begins again with G_2. This process continues until cellular death.

ENDOMETRIAL CANCER

The most common gynecologic cancer is endometrial cancer.[22] In 2002 there were 35,000 new cases, while 4000-5000 women died from it that year.[22] A consistency in numbers can be seen between 1997 and 2002. In 1997, there were 34,900 new cases and 6,000 women died from endometrial cancer.[22] Endometrial cancer affects the endometrial lining of the uterus. "It develops when cancer cells of the endometrium start to grow rapidly. As these cancerous cells multiply they form masses. Part of the masses die off and pass out of the uterus through the cervix and vagina as abnormal bleeding."[21] Normally the female body produces hormones such as estrogen and progesterone. It has been proposed that when estrogen is in abundance and progesterone is not, progesterone's effects cannot balance the effects of estrogen. This may lead to endometrial cancer.[22] Most endometrial cancers are adenocarcinomas meaning they are glandular in nature. Endometrial cancer is also found more commonly in post-menopausal women.[13] The hormonal imbalance that may be seen with this cancer can be due to obesity, estrogen replacement, and the use of drugs that decrease the risk of other cancers. An example of such a drug is tamoxifen often used to treat breast cancer. It is an anti-estrogen but it behaves as an estrogen in the uterus.[14] Family history may also play an important role in the development of this cancer. Genes are inherited. The PTEN gene is responsible for suppressing tumor growth. It is often inactivated in endometrial cancer.[14] Between 1973 and 1978 there was an increase in incidence associated with estrogen replacement therapy, but since 1988 the incidence has remained fairly constant.[21]

There are certain things that lower the risk of occurrence. Pregnancy causes an increase in progesterone and thus lowers the risk of developing endometrial cancer. Oral contraceptives have been shown to decrease risk, as well as taking progestins. It is crucial that disorders seen as pre-cancerous be treated immediately.

"The incidence of endometrial cancer is 1% to 2% and this incidence peaks between the ages of 60 and 70."[21] "The median age at diagnosis of endometrial cancer is 69 years of age. The largest number of women diagnosed with this cancer is between 50 and 59 years of age. Approximately 2% to 5% of women will be diagnosed before 40 years of age, and 20% to 25% will be diagnosed before menopause."[6]

Early detection methods for endometrial cancer at this point do not exist. Symptoms of the disease include bleeding, discharge, weight loss, pelvic pain, and pelvic mass. A majority of the women with endometrial cancer present with post-menopausal bleeding. "Abnormal bleeding is the most common (90%) symptom of endometrial cancer."[21] In diagnosing endometrial cancer a healthcare professional will want to know family history and medical history. A physical exam is performed. Tests such as MRIs, x-rays, or blood tests may be requested. Endometrial cancer is staged and graded in much the same way as other cancers. The uterus is often removed (hysterectomy) to stage this cancer.

Staging Endometrial Cancer[10] (Table 3)	
Stage	Area
0	In Situ
I	Confined to Uterus
II	Involves Corpus and Cervix
III	Extends Outside Uterus but not Beyond True Pelvis
IV	Extends Beyond True Pelvis or Involves Bladder or Rectum

Grading Endometrial Cancer[10] (Table 4)	
Grade	Differentiation
G1	Highly Differentiated
G2	Moderately Differentiated
G3	Poorly Differentiated

The earlier endometrial cancer is diagnosed the greater the survival rate. "If endometrial cancer is not diagnosed at an early stage, metastasis may be seen. The most common sites of spread are the vagina, lungs, and abdominal cavity."[21] "Prognosis of endometrial cancer depends upon a number of factors including clinical staging, tumor differentiation, uterine size, myometrial invasion, and age."[10]

Prognostic Correlation with Clinical Stage in Endometrial Cancer[20] (Table 5)	
Stage	Five Year Survival Rate
I	90-95%
II	75%
III	60%
IV	15-26%

Endometrial cancer is often treated by the use of surgery, radiation therapy, hormonal therapy, or chemotherapy. At this point the effectiveness of chemotherapy for endometrial cancer is not clear. There is not sufficient evidence to conclude that chemotherapy is an effective treatment for this cancer. Surgery may include a complete hysterectomy or radical hysterectomy.

A complete hysterectomy is the removal of the uterus, ovaries, and fallopian tubes. This procedure can be carried out as a total abdominal hysterectomy (TAH) or vaginal hysterectomy. Performing a TAH in which the incision is made in the abdomen is more beneficial because it allows for a more accurate investigation.

A radical hysterectomy is usually performed when the cancer has spread to the cervix or parametrium. It involves the removal of the entire uterus, tissues next to the uterus, and the upper part of the vagina.

After completion of treatment follow-up visits are crucial. Cancer will often recur, usually within the first 3 years. The risk of recurrence increases with age.

OVARIAN CANCER

More females die from ovarian cancer than any other disease of the reproductive system and it is the 5th leading cause of cancer death in women. This type of cancer accounts for 4% of cancers in women.[19] It was estimated that in the year 2002, 23,300 new cases of ovarian cancer were diagnosed while 13,900 women died from it.[14] In 1997 there were 26,800 new cases and 14,200 women died from ovarian cancer. This small difference could be due to emerging medical science, the development of new treatments, and cancer awareness. The poor survival rate of women diagnosed with this cancer makes it evident that better detection and treatment options are needed. There is currently a lack of methods to prevent the occurrence of ovarian cancer.

The ovaries are located on each side of the uterus. They are ova producing organs of the body. Three forms of ovarian cancer exist. They are classified as stromal tumors, germ-cell tumors, and epithelial carcinoma. Most current knowledge of ovarian cancer is based on the most common type, epithelial carcinoma. Epithelial carcinoma is the 5th most frequent cause of cancer death in women. Classification depends upon the location of the cancerous cells. Epithelial carcinoma involves the epithelial cells covering the surface of

the ovaries. Germ-cell tumors involve the cells, which produce the ova, and stromal tumors involve the connective tissue and cells that produce hormones.[14]

Family history, hormone replacement, and breast cancer are a few of the risk factors for ovarian cancer. Five percent to ten percent of cases are familial.[21] Most women who develop ovarian cancer however, do not have any of the known risk factors. Risk factors increase the odds of getting a disease such as ovarian cancer but do not guarantee it will occur.[14] The cause of ovarian cancer is unknown but it is thought that genetics plays a role. There are more cases of ovarian cancer seen in industrialized countries so environmental factors may also contribute to the development of this cancer.[6] Decreasing the risk of ovarian cancer may include the use of oral contraceptives, pregnancy, tubal ligation, prophylactic oophorectomy, and genetic counseling. It is not known exactly how tubal ligation reduces the risk of ovarian cancer but when performed after childbearing, the chance of developing ovarian cancer is reduced by up to 67%. It has been suggested that when cancer causing agents enter the vagina, they can be prevented from passing to the ovaries by tubal ligation.[14] Genetic counseling can be beneficial since certain tests can be performed to determine if a person is a carrier of genetic alterations, which may increase the chance of developing ovarian cancer.[40] The BRCA1 and BRCA2 genes normally make proteins that keep cells from growing abnormally. These genes are found to be mutated in several cases of ovarian cancer.[14] Prophylactic oophorectomy is usually reserved for women who are at high risk for developing ovarian cancer. Those who have a deleterious mutation in BRCA1 or 2 have an overall 90% reduction in risk if a prophylactic oophorectomy is performed.[14]

"It is estimated that 1 of every 70 women will develop ovarian cancer, with most cases seen in women between 55 and 59 years of age. Only 7% to 8% of ovarian carcinoma occurs in women under 35 years of age."[6] Symptoms of ovarian cancer are vaginal bleeding, abdominal swelling, pelvic pressure, and back pain. Usually symptoms do not appear until after the disease has spread beyond the ovaries. "If the disease is diagnosed before it has spread a 95% 5 year survival rate is seen. Unfortunately, only 25% of cases are diagnosed before metastasis occurs."[19]

Before a treatment plan is decided upon, ovarian cancer, like all cancers, must be staged and graded. Ovarian cancer is staged based on surgical evaluation. Grading is similar to that of enodmetrial cancer.

Staging Ovarian Cancer[35] (Table 6)	
Stage I	Growth limited to ovaries
Stage IA	Limited to one ovary; no ascites. No tumor on external surfaces; capsule intact
Stage IB	Limited to both ovaries; no ascites. No tumor on external surfaces; capsule intact
Stage IC	Stage IA or IB with tumor on surface of one or both ovaries; or capsule ruptured; or malignant ascites present or malignant washings present
Stage II	Growth involving one or both ovaries with extension to pelvic structures
Stage IIA	Extension and/or metastases to uterus and/or tubes
Stage IIB	Extension to other pelvic structures
Stage IIC	Stage IIA or IIB with tumor on surface of one or both ovaries; or capsule ruptured; or malignant ascites present or malignant washings present
Stage III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal nodes
Stage IIIA	Tumor macroscopically confined to the

	pelvis and negative retroperitoneal nodes with microscopic disease in the abdomen except liver parenchyma
Stage IIIB	Tumor macroscopically involving the abdomen but not single nodule measuring greater than 2 cm. Nodes are negative
Stage IIIC	Abdominal implants greater than 2 cm or retroperitoneal or inguinal node involvement
Stage IV	Extra-abdominal disease or parenchymal liver disease. Pleural effusions cytologically positive

As with all cancers it is critical that ovarian cancer be diagnosed at an early stage.

Stage and Prognosis in Ovarian Cancer[20] (Table 7)	
Stage	5 year Survival Rate
I	85%
IA	90%
IB	85%
IC	80%
II	65-70%
IIIA	60%
IIIB	40%
IIIC	30%
IV	20%

Ultrasound, blood tests, x-ray, and MRI are some of the methods or procedures used to detect ovarian cancer. The most accurate method to diagnose ovarian cancer is by examining a tissue sample. Most women with ovarian cancer undergo surgery and one other form of treatment, such as chemotherapy or radiation. Upon treatment completion, follow-up exams are important.

SELECTION OF CHEMOTHERAPY DRUGS AND DOSE DETERMINATION

Once cancer has been diagnosed, staged, and graded a physician will decide upon a treatment plan. If chemotherapy is part of that plan, deciding which drug will be best is a vital task. The type of tumor is considered, in addition to whether a single agent or a combination of agents will be taken into consideration. Toxicity of drugs and the mechanism of action must be considered.

Some tumors respond very well to single agents while others show optimal response to combination chemotherapy. If combination chemotherapy is determined to be the best route of action, agents must be used that do not exhibit the same toxicity. Drugs will be used that have documented clinical activity to a particular tumor. Drugs used in combination should act synergistically or enhance the activity of the other.[9]

It would be ideal to use a large dose to kill as many cancer cells as possible. Such a large dose however, could be lethal to the patient. When taking into account dosing options, that which offers a large enough dose to kill cancer cells while keeping adverse effects to a minimal is a goal. A particular dose depends on a number of things such as the body surface area of the patient, which takes into account height and weight, usually measured in square meters. Overlapping toxicities, previous treatments, pre-existing conditions, and nutritional status are all considered.[9]

RESPONSE TO CHEMOTHERAPY

Chemotherapy is not always a success. In some cases, a tumor may not be sensitive to a drug selected for treatment. A tumor can also become insensitive or resistant to a particular drug. On occasion an appropriate dose (dose at which the tumor is responsive

to) is not given and a tumor will continue to grow. It has been observed that tumor size can play a significant role. A small tumor, usually fast growing, will respond better to chemotherapy than a larger one. Chemotherapy is often a difficult treatment for patients. It may cause a wide range of side effects. The healthier the patient and the higher the morale, the more tolerable this type of treatment may be.[9]

CARBOPLATIN

Carboplatin, also known as paraplatin and CBDCA, is commonly used to treat ovarian cancer. It is dissolved into a clear fluid given as an infusion. Platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0']-, (SP-4-2) is the chemical name of carboplatin. It has the molecular formula $C_6H_{12}N_2O_4Pt$. Carboplatin is an analog of cisplatin. "It contains a platinum atom surrounded by two ammonia groups and two other ligands in the cis position. The exact mechanism of action is unknown, but it undergoes intracellular activation forming reactive platinum complexes which inhibit DNA synthesis by forming inter- and intra-strand cross-linking DNA molecules."[11] Carboplatin is one of the few platinum-containing compounds that can be found in plasma not bound to proteins. The platinum portion however, can become irreversibly bound to plasma proteins. Renal excretion is the main route of elimination. Carboplatin has been approved by the FDA for the following 2 uses: 1) "Initial chemotherapy of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents; 2) Palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin."[17] Carboplatin is a cell cycle non-specific drug.

Adverse Experiences in Patients with Ovarian Cancer (Bristol-Myers Squibb)
Bone Marrow • Thrombocytopenia • Neutropenia • Leukopenia • Anemia • Infections • Bleeding • Transfusions
Gastrointestinal • Nausea and Vomiting • Vomiting • Other GI Side Effects
Neurologic • Peripheral Neuropathies • Ototoxicity • Other Sensory Side Effects • Central Neurotoxicity
Renal • Serum Creatinine Elevations • Blood Urea Elevations
Hepatic • Bilirubin Elevations • SGOT Elevations • Alkaline Phosphatase Elevations
Electrolytes Loss • Sodium • Potassium • Calcium • Magnesium
Other Side Effects • Pain • Asthenia • Cardiovascular • Respiratory • Allergic • Genitourinary • Alopecia Mucositis

Table 8(Information in above table taken from package insert for Carboplatin)

DOXIL

Doxil is also known as liposomal doxorubicin. It has been used to treat metastatic ovarian cancer. It is provided as a dispersion and administered as a light red fluid. Doxil is doxorubicin (HCL) enclosed in a liposome. "There are hair-like strands made of polyethylene glycol coating the liposome, which allows it to avoid detection and destruction by the immune system."[16] It has more time to reach the tumor tissue, where the active medication slowly leaks out.[16] The liposome coat allows this drug to remain in circulation longer yielding a greater effect of the chemotherapy. The chemical name for doxil is (8S, 10S)-10-[(3 amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycol-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride. The molecular formula is $C_{27}H_{29}NO_{11}$•HCL. Doxil binds DNA and inhibits nucleic acid synthesis. The FDA approved use of doxil is the "treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel and platinum based regimens."[17] Doxil is a cell cycle non-specific drug.

Adverse Experiences in Patients with Ovarian Cancer (Ortho-Biotech)
• Neutropenia
• Anemia
• Thrombocytopenia
• Palmar-plantar erythrodysesthesia
• Stomatitis
• Nausea
• Asthenia
• Vomiting
• Rash
• Alopecia
• Constipation
• Anorexia
• Mucous Membrane Disorder
• Diarrhea
• Abdominal Pain
• Paresthesia
• Pain
• Fever
• Pharyngitis
• Dry Skin
• Headache

Table 9 (Information in above table taken from package insert for Doxil)

PAST STUDIES

There have not been many studies to investigate the efficacy of carboplatin plus doxil combination chemotherapy in the treatment of gynecologic cancers. In fact only one study could be found in which only doxil and carboplatin were used. Each drug has shown great success when used alone as well as in combination with other drugs. Previous studies provide insight as to which direction to go when determining dose and cycle length or number.

"Epithelial ovarian constitutes approximately 90% of cases of ovarian cancer and 70% of patients present in advanced stage epithelial ovarian cancer."[27] In one study 48 patients

with epithelial ovarian cancer were treated intravenously and intraperitoneally with carboplatin. An 80% response rate was seen in patients who had received no prior treatment. There was a 3 year survival rate of 92.3%in patients in stage I, and 30% in stage III patients. Tumor recurrence during chemotherapy was 15% in stage I patients and 53.3% in stage III patients.[29]

In another study carboplatin was given to patients with recurrent or advanced endometrial cancer. An overall response rate in those receiving first line chemotherapy was 17%.[38]

"Doxil has a response rate of 25% in platinum-resistant relapsed ovarian cancer."[31] In a phase II study, doxil was given at 50 mg/m2 every three weeks. The overall survival was 1.5 months to more than 24 months in those patients with refractory ovarian cancer. The doxil showed substantial activity and there was minimal toxicity.[34]

Carboplatin and doxorubicin are two of the most active single agents used to treat advanced or recurrent endometrial cancer. Standard of care is usually doxorubicin plus cisplatin which generally yields a response rate of 47-60%.[28]

In a phase I study, carboplatin plus pegylated liposomal doxorubicin was given to 22 patients with advanced solid tumors. The dose of carboplatin was held constant at AUC 5 and doxil was given at 30, 35, and 40 mg/m^2. Three of the 22 patients responded and there were 2 clinical complete responses.[32]

CARBOPLATIN PLUS DOXIL

It is the belief that the use of combination chemotherapy utilizing doxil and carboplatin will be just as successful, if not more than, in treating endometrial and ovarian cancer as currently used methods.

A phase II trial of carboplatin plus doxil for gynecologic cancers was conducted at the University of Texas Southwestern Medical Center. Phase II trials are performed to determine optimal dose and the safety and efficacy of a drug. They have the purpose of determining dose scheduling and the tumor type responsive to the drug. The investigator's goals in this study were to ascertain tumor response, time to progression, quantify toxicity and overall survival. Tumor response could be determined by measuring tumor volume prior to treatment and after treatment. Time to progression was determined by noting the time period between a tumor's absence or small volume and the time of return of the tumor or growth. Overall survival was determined by noting if subjects lived and for how long after treatment. Quantifying the toxicity is more technical. A toxicity is an adverse event which can be definitely, probably, or possibly attributed to a medical treatment. Before treatment began a baseline measurement of laboratory values was obtained. During the course of treatment lab work-ups were repeated. Any deviation from baseline is usually graded by the investigator. Grades may range from 0 to 5.

Toxicity Grading

0-Normal

1-Mild

2-Moderate

3-Severe

4-Life-Threatening

5-Death

Baseline should be collected at course 0. If an adverse event is experienced more than once during a cycle, only the grade associated with the most severe adverse event is reported. Syndromes are graded only when diagnosed by a physician.[20]

Six patients were treated with carboplatin plus doxil. Doses were based on body surface area, prior-treatments, and general health. The carboplatin doses ranged from 310 to 665 mg. The doses of doxil ranged from 54 to 80 mg. All patients were post-menopausal with 2 patients having recurrent cancer. All patients had a total abdominal hysterectomy and a bilateral salpingo-oophorectomy at some time prior to this chemotherapy regimen. Patients were pre-treated with dexamethasone and granisteron to lessen adverse effects, such as nausea that result from chemotherapy. Both are indicated for use in moderate to moderately severe degree of nausea and vomiting.[20] The information pertaining to the patients was taken directly form the medical charts.

CHAPTER 2

RESULTS

Patient #1: Was 69 years of age when diagnosed with stage IV-B uterine cancer. She presented with abdominal distension (x 2 months), weight loss, anorexia, early satiety, vaginal spotting (x 1 week), and occasional nausea and vomiting. Patient underwent surgery. She had an exploratory laparotomy, total abdominal hysterectomy (TAH), bilateral salpingo-ooporectomy (BSO), bilateral pelvic sidewall dissection, omentectomy, appendectomy, debulking and bilateral ureterolysis. Residual disease after surgery was 1 cm in diameter. Patient had first menses at age 10 and began menopause at age 59. Patient had first pap smear in 2002 (time of diagnosis). She began the carboplatin plus doxil treatments March 2002. She underwent 5 cycles. Carboplatin doses ranged from 395 mg to 575 mg and doxil from 56mg to 58 mg. Patient reported having abdominal swelling, chest pressure, difficulty urinating, loss of appetite, and weakness during treatment time span. Patient's last follow-up visit was in September 2002 had not experienced any tumor progression. Estimated 5 year survival rate for stage IV is 15-26%.

Patient #2: Was 61 years of age when diagnosed with endometrial adencarcinoma, stage IV-A. She presented with 6 months of vaginal bleeding and had experienced constipation, nausea, and a 20lb. weight loss. Her medical history included hypertension and diabetes. She had her first menses at age 9 and last at age 60. Patient had an exploratory

laparotomy, TAH, BSO, pelvic and periaortic lymph node sampling, endocervical curettage, endometrial biopsy, and cervical biopsy. Patient also had radiation therapy prior to chemotherapy. There was not any residual disease before chemotherapy began in February 2002. Patient received 5 cycles of carbolatin plus doxil. Carboplatin doses ranged from 350 to 525 mg and doxil from 66 to 68 mg. Patient reported being weak and tired during treatment time span. She also experienced neutropenia (which delayed treatment 4 times) and sinus arrhythmia (which delayed treatment once). The two toxicities are currently un-graded. Her last follow-up visit was in September 2003. Patient did not show tumor progression. Estimated 5 year survival rate for stage IV is 15-26%.

Patient #3: Was 75 year of age when diagnosed with stage III-A endometrial adenocarcinoma. Her condition was recurrent. Patient underwent a TAH and BSO in 1997. Her medical history included diabetes, hyperlipidemia, hypertension, and congestive heart failure. She had her first menses at 12 and last at 45. Patient began carboplatin plus doxil treatments in September 2002. She received 5 cycles with carboplatin doses ranging from 310 to 415 mg and doxil from 62 to 64 mg. There was 1 delay in treatment due to cardiac work-up. Patient reported experiencing dizziness, fainting, and constipation. Patient also experienced an URI, leg edema, and pulmonary edema. In February of 2003 a CT scan revealed disease progression at liver and spleen. Patient then began receiving taxol in March 2003. Her last follow-up recorded in charts was in April 2003. Estimated 5 year survival rate for stage III is 60%.

Patient #4: Was 50 years of age when diagnosed with stage IV-B endometrial adenocarcinoma, with unknown primary, possibly endometrial or ovarian. She presented with vaginal discharge and lower abdominal pain. Her medical history included Hepatitis C, latent secondary syphilis, anemia, adnexal masses, rectal mass, and history of drug use. Patient underwent an exploratory laparotomy, TAH, BSO, descending colostomy, suboptimal debulking, omentectomy, and lysis of adhesions. Residual tumor after surgery was >2 cm in diameter in large bowel. Patient began carboplatin plus doxil treatments in February 2003. She received 8 cycles. Carboplatin doses ranged from 470 to 550 mg and doxil from 54 to 60 mg. No adverse events were recorded in patient's charts. The date of last follow-up was in September 2003. Patient had not shown tumor progression. Estimated 5 year survival rate for stage IV is 15-26%.

Patient #5: Was 54 years of age when diagnosed with stage IV-B endometrial adenocarcinoma. She presented with vaginal bleeding. Her medical history included insulin dependent diabetes, HPV, and morbid obesity. Patient underwent a TAH, BSO, omentectomy, tumor debulking, lysis of adhesions, and umbilical hernia repair. Residual disease after surgery was <1 cm in diameter. Patient began carboplatin plus doxil in October 2002. She received 6 cycles with carboplatin doses ranging from 580 to 665 mg and doxil at 80 mg. She reported experiencing constipation, back pain, nausea, leg pain, and vomiting. March of 2003 patient showed tumor progression with tumor being 2.5 cm in diameter. Patient began receiving taxol which was on-going as of October 2003. Patient's last follow-up was in October 2003. It was not reported if the tumor had regressed or continued to progress. Estimated 5 year survival rate for stage IV is 15-26%.

Patient #6: Was 63 years of age when diagnosed with un-staged endometrial adenocarcinoma. Her condition was recurrent. She presented with abdominal pain, periodic vaginal spotting, increased rectal pressure, leg cramps, and cramping during urination. Patient had a medical history of renal problems and had a right nephrectomy, nephrostomy tube placement, ureteral stint placement, and ureteral cath through renal. Patient had also undergone a TAH and radiation brachytherapy 2 years prior to current diagnosis. Her medical history included hypertension and ureteral obstruction. Patient began carboplatin plus doxil in March 2003. She received 6 cycles by October 2003 and treatment is currently on-going. Her reported carboplatin dose ranges were from 350 to 405 mg and doxil 60 to 61 mg. She had 1 delay in treatment due to neutropenia. Her last follow-up was in October 2003 and there were no reports of tumor progression at that time.

CHAPTER 3

CONCLUSION AND DISCUSSION

This study only involved 6 patients. The small number of patients is not enough to establish statistical significance. As of November 2003 toxicities experienced by patients were being graded and all patients were reportedly alive, however no patient contact had been initiated as of October 2003 to check patient status. Some patient records were missing from the charts and thus it was difficult to ascertain if partial or full responses were seen. Only 2 of the 6 patients showed tumor progression. Four of the six patients reportedly exhibit progression free survival. It is known that 1 patient is still receiving the carboplatin plus doxil treatments and so patient data collection is not complete. Cycle # was limited either by disease progression or it was deemed that no further treatments were needed at the time.

From the results obtained from the medical charts, carboplatin plus doxil seems to be relatively safe and effective. It is difficult at this time to assess whether this treatment is better than other chemotherapy regimens. It does seem however, that it would be worthwhile for this study to be conducted on a grander scale in the future.

The study conducted at UT Southwestern followed no set protocol and finding information in the charts was difficult due to the fact that information was missing or out of order. In the future it is suggested that a larger sample size be used and that patients with a history of nerve conditions, anemia, and CHF be excluded, simply because both

drugs have possibly caused nerve problems and anemia. The carditoxicity effects of doxil are also unknown at this time. It is suggested that a quality of life survey/questionnaire be completed by each patient prior to treatment, between treatments, and after treatment completion to assess how patients feel about their lives and conditions over the course of treatment. It would be beneficial to future studies if after a patient completes treatment that contact be made at least once a year thereafter for 5 years to learn patient condition. It is suggested that a form (case report form or data collection tool) be designed which could be used to record all patient data, tumor data, and treatment information. This would be helpful because all information pertaining to the study could be found in one place without having to shuffle through a mass of papers.

Overall tumor response cannot be reported at this time. Tumor volumes after treatments were not found in the patient's charts. 1 patient showed a 5 month time to progression and another showed a 6 month time to progression. 4 patients were progression free and all patients were reportedly still alive. Toxicities such as neutropenia and sinus arrhythmia are in the process of being graded. It is the belief that this treatment option shows some promise for the treatment of gynecologic cancers.

CHAPTER 4

INTERNSHIP EXPERIENCE

The following information is based on the clinical internship with UT Southwestern. It represents dates and activities taken directly from the intern journal. All dates are in chronological order and it will serve as the methodology section. I performed the following actions for the carboplatin plus doxil study. I began the internship by first performing a literature review on cancer, endometrial cancer, ovarian cancer, carboplatin and doxil. I used the gathered information to put together a research proposal. I then wrote a project summary and submitted it along with some other paperwork to the IRB to get approval to move forward with the carboplatin plus doxil study. Once approval was granted the information was sent to the hospital to gain access to patient's charts. The hospital gave approval and I began collecting information from the charts. I compiled the information into a database. I then began to write the thesis and I constructed the powerpoint presentation.

Journal Entries:

June 25, 2003

I went to tumor board today at Southwestern. It is a meeting where the research staff gets together to discuss patient's conditions and make suggestions on treatments. The meeting started at 7:30 AM. After the meeting I researched my project and began writing it.

June 30, 2003

I went in to Southwestern today to actually do something. I arrived at 1:40 PM. I read different forms pertaining to the IRB. I left at 5:00 PM.

July 8, 2003

Today can be considered my first day. I went in to Southwestern at 10:00 AM. I read a GOG sponsored study protocol, appendices, consent forms, and memos. I began typing a summary of the study to be submitted to the IRB. I left at 4:00 PM.

July 9, 2003

I arrived at Southwestern at 9:00 AM. I finished typing the summary for the IRB. I began trying to reconfigure the GOG consent form to meet the IRB's standard. I left Southwestern at 1:30 PM. I met with Dr. Kaman, the head of my committee, at UNT in Fort Worth at 3:00 PM. We discussed my proposal that I faxed to him the week before.

July 10, 2003

I went to MedTrials at 8:15 AM to speak with Barbara Richardson. We discussed my proposal. I arrived at UT Southwestern at 8:55 AM and finished the IRB consent form. I reviewed forms to be submitted to the IRB and to other sites also conducting the study.

July 11, 2003

I arrived at Southwestern at 9:00 AM. I checked my proposal that I edited last night according to Dr. Kaman's suggestions. I completed my IRB training and received a certificate of completion. Training included ethical principles, federal regulations, and university policies protecting human subjects in research (Belmont Report, 45 CFR 46, M-1304).

July 14, 2003

I arrived at Southwestern at 9:00 AM. All I did today was work on a project summary. I left at 2:00 PM.

July 15, 2003

I arrived at Southwestern at 9:00. We talked about the reasons why a project summary submitted to the IRB was sent back and ways to correct it. I left at 4:30 PM.

July 18, 2003

I arrived at Southwestern at 9:00 AM. My GroupWise and Novell accounts were set up. I typed information for reporting some serious adverse events to be reported to the IRB (Adverse Events Reports). I filled out a modification form because of a change in protocol. The change was specified in an amendment. I left at 5:00 PM.

July 21, 2003

I arrived at Southwestern at 11:45 AM. I finished everything specified by the IRB to perform correct modifications. I redlined deleted information on the approved protocol and highlighted added information on the proposed protocol. I had to include a fresh copy of the proposed protocol. I left at 5:00 PM

July 22, 2003

I arrived at Southwestern at 9:00 AM. I did a project summary and an NR1 form expedited review form for submission to the IRB. I left at 4:30 PM.

July 24, 2003

I arrived at 9:30 AM. I left at 2:00 PM.

July 28, 2003

I had a meeting with Dr. Kaman at 10:00 AM in Fort Worth.

July 29, 2003

I arrived at Southwestern at 9:00 AM. I edited my project summary. I did an NR1 form and NR3 form. I left at 5:00 PM

July 30, 2003

I arrived at Southwestern at 9:00 AM. I left at 5:00 PM.

July 31, 2003

I arrived at 10:00 AM. I waited all day to do my HIPAA training. I left at 5:00 PM and had not my training yet.

August 1, 2003

I arrived at Southwestern at 10:00 AM. I watched and learned how to put together papers and packages to send to the GOG. I left at 5:00 PM.

August 18, 2003

I arrived at 9:00 AM. I left at 2:00 PM.

August 19, 2003

I arrived at Southwestern at 9:30 AM. I filled out some AE reports and I left at 5:00 PM.

August 20, 2003

I arrived at Southwestern at 9:00 AM. I put my paperwork for my study together. The paperwork included a project summary, NR3, NR1, and HIPAA waiver. The papers must be submitted to the IRB. I typed some AE reports. I left at 12:00 PM.

August 21, 2003

I arrived at Southwestern at 10:00 AM. I am waiting for approval to begin my data collection. I left at 1:00 PM.

August 22, 2003

I arrived at Southwestern at 10:00 AM. I edited my NR1 form, NR3 form, and HIPAA waiver. I had a meeting with Dr. Miller today at 1:00 PM. We discussed how my project was going. I finished all the paperwork to submit to the IRB. I left at 5:00 PM.

August 23, 2003

Today is Saturday. I went to UNT in Fort Worth to complete my HIPAA training on UNT's web-site. I finished at 11:23 AM.

August 25, 2003

I arrived at 10:00 AM. I emailed the IRB my NR1, project summary, and HIPAA waiver because Barbara Fitzpatrick said that pre-review may have been necessary. I printed off a GOG protocol and started to work on the project summary. I left at 5:00 PM.

August 26, 2003

I arrived at Southwestern at 10:00 AM. I finished the project summary and worked on the NR1, consent form, and HIPAA form for the GOG study. I left at 4:30 PM.

August 27, 2003

I arrived at 10:00 AM. I received an email form the IRB stating pre-review was not necessary for research, which presented no more than minimal risk. Because my project is an expedited project and presents no more than minimal risk pre-review was not needed. Barbara Fitzpatrick told me to do an NR2 form to submit to the Aston center in support of my project. I waited to get appropriate signatures on my paperwork. I left at 4:30 PM.

August 28, 2003

I arrived at 10:00 AM. I did a follow-up report to an AE previously reported to the IRB. I left at 4:30 PM.

September 4, 2003

I arrived at Southwestern at 10:00 AM. I left at 4:30 PM.

September 5, 2003

I arrived at Southwestern at 10:00 AM. I did some adverse event reports. I left at 5:00 PM.

September 8, 2003

I arrived at Southwestern at 10:00 AM. I finished the AE reports I started Friday. I went over the paperwork for the GOG study I am supposed to get opened. I found out today that my project has been approved by the IRB. I left at 5:00 PM.

September 9, 2003

I arrived at 10:30 AM. I worked on opening the GOG study and prepared the file for my project. I left at 5:00 PM.

September 11, 2003

I arrived at 10:30 AM. We put the finishing touches on some paperwork for the GOG study to be sent to the IRB for pre-review. I did an AE report and tried to fill out the NR3, NR2, and radiation safety form for the GOG study. I left at 5:00 PM.

September 12, 2003

I arrived at 10:00 AM. I signed some papers. I received information back from the IRB regarding the pre-review of the GOG study. The IRB suggested some changes to be made. I spent the day making those changes and I left at 5:00 PM.

September 15, 2003

I arrived at Southwestern at 9:00 AM. I worked on the paperwork for the GOG study. I left at 1:30 PM.

September 16, 2003

I arrived at Southwestern at 10:00 AM. I checked all my emails. I took the paperwork for my project over to Parkland. The paperwork included 4 copies of the project summary, HIPAA waiver, NR3, and IRB approval letter. I helped with some filing and prepared a new spreadsheet for my project. I left at 5:10 PM.

September 17, 2003

I arrived at Southwestern at 10:15 AM. I did some filing. I made all the corrections on some paperwork. I left at 3:40 PM.

September 18, 2003

I arrived at Southwestern at 10:00 AM. I left at 1:00 PM.

September 22, 2003

I arrived at Southwestern at 10:00 AM. I checked my email. Barbara informed me that the IRB sent some more changes to be made to the GOG study papers. I made as many revisions on my own that I could. I emailed Dr. Drake concerning the charts he wanted pulled. I emailed Ortho Biotech for information pertaining to doxil. I searched the GOG web-site for the Carboplatin plus Doxil study but I did not find anything. I emailed Barbara to ask where I might find the study protocol. I went to the Bristol-Myers Squibb web-site to find information on carboplatin. I left at 5:00 PM.

September 23, 2003

Early this morning I received a phone call from Orth Biotech and was informed that they would send me some information on doxil. I arrived at Southwestern at 10:15 AM. I checked my email. I made some revisions to a consent form for a study previously approved by the IRB with stipulations. I typed the NR2, NR3, CTSU, and radiation safety forms for the GOG study I am trying to get opened. I filled in everything I could on the forms and emailed them to Barbara for her to review. I had a meeting with Dr. Miller. We discussed what was happening with the studies. I left at 5:00 PM.

September 30, 2003

I arrived at Southwestern at 11:00 AM. I made some copies. I researched endometrial and ovarian cancer again. I began writing my thesis. I emailed Bristol-Myers Squibb to send me information about carboplatin. I left at 5:00 PM.

October 1, 2003

I arrived at 11:00 AM. I worked on my thesis. I left at 5:00 PM.

October 2, 2003

I arrived at Southwestern at 11:00 AM. I worked on my thesis. I emailed Dr. Rao to send me the names of the patients that were on the carboplatin plus doxil study. I left at 5:00 PM.

October 3, 2003

I arrived at 11:00 AM. I worked on my thesis. I went to the library. I left at 5:00 PM.

October 9, 2003

I arrived at 10:00 AM. I wrote part of my abstract. I started working on my PowerPoint presentation. I did a HIPAA waiver for a laparoscopic retrospective study. I performed windows update on my computer. Barbara requested 3 of the charts I needed for my project. I left at 5:00 PM.

October 10, 2003

I had a meeting with Barbara Richardson at MedTrials at 8:30 AM. We discussed a prior meeting with Dr. Miller and my project. I arrived at Southwestern at 9:55 AM. I worked on my PowerPoint presentation. I arranged papers and typed a continuing review form. I left at 5:00 PM.

October 13, 2003

There was a new HIPAA waiver format so I did another waiver for the GOG study I am working on. There was a change in the HIPAA authorization form so I changed this form also. I left at 5:00 PM.

October 14, 2003

I arrived at 10:30 AM. I called the Pharmaceutical Management Branch that will be distributing the drug for the GOG study. I asked where I could find the FDA 1572, supplemental information, and financial disclosure form that needed to be on file for Dr. Miller. I printed them and filled in as much information as I could and I sent them to Barbara. I did a protocol outline and made copies of the CRFs to accompany the 1572. I left at 2:00 PM.

October 15, 2003

I arrived at 10:30 AM. I faxed the IRB approval letter for my project and the HIPAA waiver to Parkland so that we can receive the approval letter from them stating we could pull patient's charts. I made some changes to the spreadsheet for the GOG study. I began gathering data from the medical charts. I left at 5:00 PM.

October 16, 2003

I arrived at 10:30 AM. I found out from the research nurses how much blood is drawn and specified on the consent form. I sent the GOG study to the IRB a third time for pre-review approval. I gathered more data from the medical charts. I started entering the data into the database. I left at 4:30 PM.

October 17, 2003

I arrived at 10:15 AM. I checked my email. I met with Barbara Richardson at 11:15 AM to discuss my paper. She suggested a lot of changes. I looked through books and journals at MedTrials to gather more information for my thesis. I left MedTrials at 12:45

PM and returned to Southwestern. I filled out the CTSU forms, radiation safety form, and NR3 for the GOG study. I left at 4:30 PM.

October 20, 2003

I arrived at 10:15 AM. I revised the HIPAA waiver as specified in an email I received from the IRB today. I looked in the files to find an old NR3 to get Dr. Miller's ID number to put on the NR3 I had done for the GOG study. I printed the NR3, HIPAA waiver, and consent form. I prepared a folder with all the GOG study paperwork in it. The folder included the NR1, project summary, consent form, NR2, NR3, HIPAA authorization, HIPAA waiver, CTSU transmittal sheet, CTSU IRB certification form, protocol and supporting documents. Barbara has the IDS form I previously filled out and the FDA 1572, supplemental information, and financial disclosure form. I worked on my thesis. I left at 4:15 PM.

October 21, 2003

I arrived at 10:15 AM. I spoke with someone from the IRB about the HIPAA waiver. I revised 1 sentence in it and sent it back to the IRB. We received pre-review approval. I worked on my thesis. I got all the GOG paperwork together to get Dr. Miller's signature. I left at 4:30 PM.

October 22, 2003

I arrived at 10:15 AM. I worked on my thesis. I left at 2:00 PM.

October 23, 2003

I arrived at 10:30 AM. I worked on my thesis. I left at 4:30 PM.

October 27, 2003

I arrived at 11:00 AM. I finally was able to get in touch with someone at the Pharmaceutical Management Branch to discuss my receiving an investigator's brochure for the GOG study. I made copies of everything to submit to the IRB. I submitted the following to the IRB for full board approval: 1 copy of pre-review approval email, 2 copies of the protocol, 2 copies of the investigator's brochure, 25 copies of the NR1, 25 copies of the project summary, 25 copies of the consent form, 25 copies of the HIPAA authorization, and 25 copies of the HIPAA waiver. I left at 4:00 PM.

October 28, 2003

I arrived at 11:00 AM. I put together a folder for Barbara that has all the documents for the GOG study except those forms she has. I emailed Dr. Miller and Barbara to tell them I submitted the paperwork to the IRB and also to send them copies of everything. I worked on my thesis. I left at 4:30 PM.

October 30, 2003

I arrived at 11:00 AM. I worked on my thesis. I worked on my thesis. I left at 5:00 PM.

November 3, 2003

I arrived at 11:30 AM. I worked on my thesis. I left at 5:00 PM.

November 4, 2003

I arrived at 2:00 PM. I ran a spell/grammar check on my thesis. I shredded some papers. I added some things to the Carb/Doxil spreadsheet. I emailed the spreadsheet to Dr. Rao and Barbara Fitzpatrick. I gave Barbara the GOG study file. I left at 4:30 PM.

INTERNSHIP DISCUSSION

The internship at UT Southwestern Medical Center began in June 2003. I worked in the Division of Gynecologic Oncology for about 5 months. Clinical research involves the use of so much private patient information (PPI) that those who work in the field are required to go through special training. Training includes learning about HIPAA, ethical principles, and FDA regulations. Whenever a department or individual wishes to conduct a clinical trial, all relevant paperwork pertaining to the trial must be submitted to the IRB (Institutional Review Board) for approval. The IRB's main goal is to ensure patient safety.

My training at UT Southwestern included IRB and HIPAA training. The IRB training encompassed study of university policies as set forth in the Multiple Project Assurance. Ethical principles as discussed in the Belmont report and Federal Regulations (Title 45 Code of Federal Regulations Part 46) were also a part of IRB training. The Belmont Report spells out 3 basic principles: respect for persons, beneficence, and justice. All should be taken into consideration when conducting human research. Title 45 CFR 46 sets forth guidelines for protection of human subjects. After IRB training was successfully completed, IRB certification was given.

HIPAA is an act which covers privacy rules. It protects the privacy of individually identifiable health information. Before protected health information is used, written

authorization must be obtained. After undergoing a HIPAA test, certification was awarded.

One of my first tasks as a clinical research intern was to prepare documentation of offsite adverse events. Whenever a drug is under study and an adverse event occurs, notice of the AE is sent to various locations that may be observing the effects of the drug. These AEs have to be reported to the IRB although the AE occurred at another site and may have even occurred during a different study than that being conducted at the institution. The IRB at Southwestern has an AE report form in which a clinical researcher will take pertinent information received about the AE, type it on the AE form, and send the form to the IRB. The most important information relayed to the IRB is what drug could be responsible for the AE and a description of the incident is included. A sample AE form can be found in appendix G.

Often times a study is approved by the IRB and a sponsor may modify the protocol after that approval. When this occurs a modification form (appendix H) is filled out. Information on the approved protocol that is deleted is redlined on the old protocol. New information on the new protocol is highlighted. The modification form, old approved protocol, and new protocol are sent to the IRB.

The IRB at UT Southwestern has 3 different types of clinical study review. The first type is full board review. This is required for all studies which present more than minimal risk to a subject. Full board review is a 2 step process. Step 1 is to receive pre-review approval from a member of the IRB. The NR1, project summary, consent form, HIPAA waiver, and HIPAA authorization form must be sent via email to the IRB. After

reviewing the above documents the IRB member will send an email response either specifying changes in the documents or approving them for full board review. The documents have to continually be submitted until pre-review approval is granted then one can move to step 2. Step 2 involves submitting to the IRB the following: 1 copy of email pre-review approval; 2 copies of the protocol, investigator's brochure, grant, questionnaires, and study information sheet used for recruitment; 25 copies of the NR1, project summary, consent form, and HIPAA form(s). The study must also be approved by the clinics or hospitals where study activities will be conducted. The process involves submitting to the hospitals the IRB approval letter, NR1, project summary, consent form, NR2, NR3, and radiation safety form. There are variations in which documents are submitted to each hospital. During my time at Southwestern I only had to go through the full board review process once. The sponsor of the study was the Gynecologic Oncology Group (GOG). I sought pre-review approval 3 times, because changes needed to be made, before receiving the go ahead to submit the study for full board review (step 2). It is currently not known if the study was approved because the internship came to an end before approval was met.

The second type of review at Southwestern is exempt review. A study must be in certain categories to undergo exempt review. The categories can be found in appendix J. Exempt review can be granted to studies which present no more than minimal risk. This process involves sending a letter to the IRB describing the study and how it meets exempt review qualification. My stint at Southwestern did not involve my submitting a study for this type of review.

The third type of review is expedited. The study cannot present more than minimal risk to a subject and must fit into one of the categories found in appendix K. The NR1, project summary, study information sheet (if used), and consent form must be sent to the IRB. I submitted the carboplatin plus doxil study for this type of review. I turned in a project summary (appendix B), NR1 (appendix C), and a HIPAA waiver (appendix E). Usually a HIPAA authorization form (appendix F) must be turned in and approved, but because the carboplatin plus doxil study did not involve patient recruitment, only medical chart review, a HIPAA waiver was appropriate. IRB approval for the carboplatin plus doxil study was received September 8.

After IRB approval was granted, I sought approval from the hospital to use the medical charts. I turned in the NR3 (appendix I), project summary, HIPAA waiver, and IRB approval letter to the hospital. They approved the medical chart review within a week.

The person I worked with at Southwestern was a data manager. She had no patient contact and so neither did I. Our contribution to the research effort involved reading protocols and preparing documents for protocols. She is involved in clinical research documentation from beginning to end. I however, only experienced the beginning. It is also the data managers responsibility to meet with the monitor or sponsor representative. I did not have a part in this aspect of the job either. In short, my contribution involved reviewing protocols, summing up that protocol into a project summary, and preparing supporting documents to send to the IRB for study approval.

SUMMARY

Cancer is a devastating disease that may present in an otherwise healthy individual. It can be characterized as a group of diseases that affects the regulation of cell proliferation. The cause of cancer is unknown. It is the second leading cause of death in the United States. There are many forms of cancer. Endometrial and ovarian cancer are two forms classified as gynecologic cancers. These two forms affect thousands of women yearly. There is a lack of prevention methods and better treatments are needed. In an effort to advance treatment of the gynecologic cancers, UT Southwestern conducted a phase II study to evaluate the effectiveness of carboplatin plus doxil combination chemotherapy. There were a small number of patients, however 67% showed very promising results. It is believed that this study should be conducted on an even larger scale.

The internship did allow me the opportunity to work with the IRB. I had no patient contact, but was allowed to prepare documents for the pre-clinical phase of a study. I learned what the IRB is looking for when paperwork must be turned in to open a study. A lot of time and effort is invested in opening, running, and closing a study.

APPENDIX A

SAMPLE INFORMED CONSENT

The University of Texas Southwestern Medical Center at Dallas

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research: (if translating consent form please provide the title in English as well as the non-English language)

Sponsor:

Investigators:

	Telephone No. (regular office hours)	Telephone No. (other times)

INVITATION: You are invited to participate in this research because you have [insert medical problem].

Medical research involves offering a plan of care to a group of patients, collecting and studying information about each patient's experience, and using that information to develop the best possible care for future patients.

NUMBER OF PARTICIPANTS: The sponsor plans to include [insert total sample size across all research centers] participants in this research. (optional statement)

PURPOSE: The purpose of this research is to _____.

This research is being done because _____.

PROCEDURES

Screening: The study doctor will ask you questions about your health, medications you take for any health problems, and any surgical procedures you have had.

You will have the following evaluations: [insert, for example, any tests on samples of urine and blood, x-rays, etc. used to determine eligibility]. These procedures may be done even if you do not participate in this research.

You will have [insert standard tests done more often than usual for research purposes]. These procedures are being done more often because you are in this research.

Randomization: If the study doctor believes that you qualify to participate in this research, you will [insert "take tablets," "use creams," "have injections," etc.]. They may contain [insert the name of the medication, device, procedure, etc.] or a placebo (an inactive substance). You have [insert "an equal,""a one-in-four," etc.] chance of receiving [insert the name of the medication, device, procedure, etc.] or placebo.

The study assignment is made in advance [insert "at the sponsor's headquarters" if applicable] by a process similar to drawing straws.

Neither you, your study doctor, nor other research personnel will know what your study assignment is. However, the sponsor will release the identity of your assignment to your study doctor if that information is needed for your safety.

Treatment: For research involving the use of a placebo, select a title for this sub-heading according to what a subject will receive (for example, study tablets, ointments, injections, etc.).

For research that involves the use of a medication, device, a surgical procedure, radiation, psychotherapy, or other type of treatment, or a diagnostic procedure, explain what the procedures include, and how often they will be repeated.

For a medication, include the name, dose, route of administration, and schedule of treatments.

Evaluations during the research: Explain that evaluations (as specified in the protocol schedule of assessments) will be repeated during the study to determine the benefit and safety of study procedures.

For complex protocols, the consent form may include a table (attached to the consent form as an appendix) referenced in the consent document. For example, a table could include space for the date, week on study, blood samples to be obtained, and evaluations (such as physical examinations, chest x-rays, electrocardiograms, etc.).

Identify clearly any inconvenient procedures (such as long clinic visits, keeping a detailed diary between clinic visits, collection of multiple blood samples for pharmacokinetics, etc.).

Specify how long subjects will be involved in the study if evaluations are repeated after completion of any therapeutic or prophylactic procedures.

Specify the amount of blood drawn at any one time in teaspoons, tablespoons, or cups.

INVESTIGATIONAL PROCEDURES: For medications, clarify whether the dose, route, and schedule used in the study have been approved by the FDA or are investigational.

For devices, clarify whether the use of the device (as specified in the protocol) is approved by the FDA.

For other types of research (surgery, imaging techniques, laboratory tests, etc.), discuss the use (customary or investigational) of the procedure being studied.

POSSIBLE RISKS

[Insert a sub-heading to identify the study medication(s), device, procedure, etc.]: The [insert "medication,""medications,""device," surgical procedure," etc.] used in this research may cause problems. It is not always possible to predict whether you will have problems or not.

Most problems stop when [insert "the use of the medication," "the use of the device," etc.] stops. However, there is a possibility that some problem could remain for a long time or develop later.

Information about known problems is based upon the experiences of [insert the number] men and women [insert "children" if there have been pediatric trials] who have participated in past research using [insert the name of the study medication, device, procedure, etc.).

• In past research, 500 or more people out of 1,000 had these problems:
or
In past research, 50 % or more people had these problems:

• 200 up to 500 people out of 1,000 had these problems: **or**
20-49% had these problems:

• 10 up to 200 people out of 1,000 had these problems: **or**
1-19% had these problems:

• Fewer than 10 people in 1,000 had these problems: **or**
Fewer than 1% had these problems:

Radiation exposure from diagnostic tests: [If the amount of radiation exposure is the same in both standard care and the research, state: "There is no additional risk of harm from radiation as a result of your participation in this study expected as standard care for your medical condition."]

[If the amount of radiation exposure is more, state: "The amount of radiation exposure, in addition to standard care, that you will receive in this study is small. This risk of harm to our body from this radiation exposure is comparable to the everyday risk of driving {insert number} miles in an automobile or smoking {insert number} cigarettes." (For the comparable number, see the table at http://swnt240.swmed.edu/ehs/.)]

Radiation therapy treatments: [If the amount of radiation is the same in both standard care and the research, state: "The dose of radiation in this research is the same as the dose in the standard radiation therapy for your health problem. Therefore, the risk of harm to your body is the same. Your radiation doctor will discuss the known risks of radiation therapy with you and ask you to sign a separate consent form."]

[If the amount of radiation in the research is more than or less than the amount in standard care, state: "The dose of radiation in this research is different from the dose in the standard radiation therapy for your health

problem. Therefore, the risks to your body are different. These risks are _____."]

RISKS TO AN EMBRYO, FETUS, OR BREAST-FED INFANT: A woman who is pregnant or is breast-feeding an infant should not participate in this research.

It is not known whether [insert name of study medication, device, other procedure, etc.] may harm an embryo or fetus or an infant who is breast-feeding. It is not known whether [insert name of study medication, device, other procedure, etc.] may lead to birth defects.

If a woman is pregnant, radiation exposure to her reproductive organs may harm an embryo or fetus. Also, radioactive material used for certain types of scans may harm an embryo, fetus, or an infant who is breast-feeding.

High-dose radiation treatments to or near a man's testicles or a woman's ovaries may produce harmful changes that could be passed on to children through a sperm or an egg.

Pregnancy test: A pregnancy test will be performed for any woman who is able to have children and wishes to participate in this research. A pregnancy test [insert "may" or "will" as specified in the protocol] be repeated later. A study doctor will ask for the date when a woman's last monthly period started.

> Pregnancy tests performed during the early stages of pregnancy do not always reveal pregnancy. Therefore, radiation exposure that includes the reproductive organs will be limited to the first ten days after a woman (age 12-40 years) has begun her most recent menstrual period. This is standard policy in clinics and hospitals within UT Southwestern. This policy applies unless there is an important medical reason requiring radiation outside this time frame.

Avoiding pregnancy: Whether you are a woman or a man, you should ask your study doctor about the effective means to avoid becoming pregnant or fathering a child during participation in this research. Ask your study doctor how long you must avoid becoming pregnant or fathering a child after you complete all study procedures.

If you change your method of avoiding pregnancy or fathering a child during the research, you must notify your study doctor promptly.

[Include the following paragraph in the consent form if the sponsor specifies certain required methods of avoiding pregnancy. Omit the following paragraph for studies conducted at St. Paul Medical Center.]

The sponsor recommends that participants in this research use any one or more of the following means of avoiding pregnancy or father a child:_____.

Women: Females (ages 12-40 years) able to have children should avoid becoming pregnant until they have had three menstrual periods after the end of all radiation therapy. After three menstrual periods, there is almost no risk of harmful changes to an egg.

Men: Males must avoid fathering a child until ten weeks after the end of all radiation therapy. After that period, there is much less risk of harmful changes to sperm. Even then there is still an unknown amount of risk.

Pregnancy during participation in this research: If you are a woman who is able to have children, and you suspect pregnancy during this research, you must tell your study doctor immediately. Your participation in the research will stop. Your study doctor can discuss new care for [insert medical problem] with you. Your study doctor will report information about your pregnancy, delivery, and the baby's first two months of life to the sponsor.

Placebo: If you receive a placebo, you will not receive active medication for your health problem. If your problem becomes worse, your participation in the research will stop. If this happens, your study doctor can discuss alternative care with you.

Blood samples: [If blood samples are collected as part of standard care, state: "You will have the same amount of blood collected whether you receive standard medical care for your health problem or participate in this research. Therefore, your risk of complications from collecting the blood is the same."]

You may experience discomfort, bleeding, and/or bruising. You may feel dizzy or faint. On a rare occasion, an infection could develop at the site where the blood was collected.

Unforeseen risks: A previously unknown problem could result from your participation in this research. There could be an interaction between [insert name of study medication] and other medications you take (prescribed or over-the-counter). It is not possible to estimate the chances of such problems or how serious problems could be.

How you can help reduce some of the risks: During your participation in this research, your study doctor will watch closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep appointments.
- Follow the study doctor's instructions.
- Let your study doctor know if your telephone number changes.
- Store study materials ([insert tablets, vials of liquid, needles, etc. as apply]) in a secure place at home away from anyone who is unable to read and understand labels, especially children.
- Tell your study doctor before you take any new medication even if it is prescribed by another doctor for a different medical problem.
- Tell your regular doctor about your participation in this research.
- Talk to a family member or friend about your participation in this research.
- Carry information about the research in your purse or wallet.

What to do if you have problems: If you have problems, such as unusual symptoms or pain, at any time during your participation in the research, your study doctor can recommend treatment. Please report the problem to your study doctor promptly. Telephone numbers where he/she may be reached are listed on the first page of this consent form.

If you suddenly have a serious problem (such as difficulty breathing) or severe pain, go to the nearest hospital emergency room, or call 911 (or the appropriate emergency telephone number in your area). Tell

emergency personnel about your participation in this research. Ask them to telephone your study doctor immediately. (optional)

POSSIBLE BENEFITS

Benefit to you: (The following is only advisory language. Please edit to reflect the context of your study.) Your medical problem may get better or go away. But it could possibly get worse. Your study doctor cannot guarantee that you will benefit from participation in this research.

Benefit to other people with [insert medical problem]: In the future, other people with [insert medical problem] could benefit from the results of this research. Information gained from this research could lead to improved medical care for them. However, your study doctor will not know whether there are benefits to other people with [insert medical problem] until all of the information obtained from this research has been collected and analyzed.

Benefit to others: The sponsor of this research has a financial interest in the outcome. (optional to use in the consent form).

ALTERNATIVES TO PARTICIPATION IN THIS RESEARCH: You do not have to participate in this research to receive care for your medical problem. Alternative care includes [insert alternative procedures available to patients who do not wish to participate in research].

Please ask your study doctor as many questions as you wish. The doctor's answers to your questions could help you decide whether to participate in this research or receive the standard care that is currently available for your medical problem.

If you decide to participate in research now, and later change your mind, you may stop your participation in the research then and receive the alternative care.

THE STUDY DOCTOR'S DECISION TO STOP YOUR PARTICIPATION: Your study doctor or the sponsor may stop your participation in this research without your permission under any one of the following conditions:

- Your medical problem remains unchanged or becomes worse.
- Your study doctor believes that participation in the research is no longer

safe for you.

- Your study doctor believes that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow your study doctor's instructions.

PROCEDURES AFTER STOPPING PARTICIPATION IN THIS RESEARCH: If you, the study doctor, or the sponsor stops your participation in the research, it is your responsibility to do the following:

- Let your study doctor know immediately that you wish to withdraw from the research.
- Return to the research center for tests that may be needed for your safety.
- Return any unused study materials, including empty containers.
- Discuss your future medical care with your study doctor and/or your regular doctor.

PAYMENT TO TAKE PART IN THIS RESEARCH: You will be paid [insert the amount of money or other type of incentive] to participate in this research. If you do not complete all study procedures, you will be paid according to the number of procedures you complete.

If you are an employee of UT Southwestern, tax will be deducted from the payment given to you for your participation in the research.

UT Southwestern, as a State agency, will not be able to make any payments to you for your participation in this research if the State Comptroller has issued a "hold" on all State payments to you. Such a "hold" could result from your failure to make child support payments or pay student loans, franchise taxes, etc. Should this occur, UT Southwestern will be able to pay you for your participation in this research after you have made the outstanding payments, and the State Comptroller has issued a release of the "hold."

COSTS TO YOU: The sponsor will pay the expenses for [insert a list of the procedures] that are part of this research.

Expenses related to standard medical care for [insert medical problem] are your responsibility (or the responsibility of your insurance provider or government program).

There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

COMPENSATION FOR INJURY: Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas or [insert only Children's Medical Center of Dallas, Parkland Health & Hospital System, Texas Scottish Rite Hospital for Children, Zale Lipshy University Hospital and/or UTSW Moncrief Cancer Center].

The sponsor has expressed a willingness to help pay the medical expenses necessary to treat such injury.

You retain your legal rights during your participation in this research.

VOLUNTARY PARTICIPATION IN RESEARCH: You have the right to agree or refuse to participate in this research. If you decide to participate and later change your mind, you are free to discontinue participation in the research at any time.

Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. Refusal to participate will not affect your legal rights or the quality of health care that you receive at this center.

[If medical students, fellows, faculty, or staff throughout the medical center are included as healthy volunteers, state: "Your status as a medical student, fellow, faculty, or staff in the medical center will not be affected in any way."]

NEW INFORMATION: Any new information which becomes available during your participation in the research and may affect your health, safety, or willingness to continue in the research will be given to you.

RECORDS OF YOUR PARTICIPATION IN THIS RESEARCH

Information kept at UT Southwestern: You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law. Your study doctor and other people associated with this research at UT Southwestern will keep information about your participation in locked files. They will restrict access to the information in these files to persons directly involved with the research.

Information available to other people: The sponsor will receive written reports about your participation in this research.

Representatives of the Food and Drug Administration (FDA) and the sponsor may review your medical and research records kept at UT Southwestern to assure the quality of the information used in the research.

The FDA may photocopy your medical and research records to verify information submitted to the FDA by the sponsor.

An Institutional Review Board (IRB) is a group of people who are responsible for assuring the community that the rights of participants in research are respected. Members and staff of the IRB at this medical center may review the records of your participation in this research. A representative of the Board may contact you for information about your experience with this research. If you wish, you may refuse to answer any questions the representative of the Board may ask.

Publication of the results of the research: The results of this research may appear in scientific publications without identifying you in any way.

YOUR QUESTIONS: Your study doctor is available to answer your questions about this research. The Chairman of the IRB is available to answer questions about your rights as a participant in research or to answer your questions about an injury or other complication resulting from your participation in this research. You may telephone the Chairman of the IRB during regular office hours at 214-648-3060.

OTHER CONSIDERATIONS: (if applicable) The institution has been actively involved in the development of _____, which is included in this research. The institution has a financial interest in this product and wants to disclose this interest to you.

(insert principal investigator's name) is a paid consultant to (insert sponsor name) and wants to disclose this financial interest to you.

YOU WILL HAVE A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

Participant's Name (printed)	
Participant's Signature	Date
Legally responsible representative's name (printed)	
Legally responsible representative's Signature	Date
Witness' name (printed)	
Witness' signature	Date

Name (printed) of person obtaining Consent

Signature of person obtaining consent

Date

APPENDIX B

PROJECT SUMMARY

Project Summary: Carboplatin and Doxil for Gynecologic Cancers

Purpose: The purpose of this study is to examine one treatment for cancer. It will seek to determine the safety and efficacy of previously administered drugs carboplatin and doxil in combination chemotherapy for the treatment of gynecologic cancers, specifically endometrial and ovarian.

Background: Standard care for endometrial cancer usually involves surgeries, radiation, and hormonal therapy. At this point the effectiveness of chemotherapy for treating endometrial cancer is unclear. This cancer is very common. 35,000 new cases are reported a year while 4000-5000 women die from it a year. It has been proposed that an overabundance of estrogen without the counter effects or progesterone may lead to endometrial cancer.

Standard care for ovarian cancer is surgery along with one other form of treatment such as chemotherapy or radiation. There are usually no symptoms of ovarian cancer and it is not usually detected until it has spread beyond the ovaries. This cancer is often fatal.

Carboplatin is commonly used to treat ovarian cancer. Its exact mechanism of action is unknown, but it does undergo activation to inhibit DNA synthesis. Doxil has been used to treat metastatic ovarian cancer. It is enclosed in a liposome to allow for a greater effect of the chemotherapy. In some drug resistant patients, doxil has improved the overall survival time and response rate. It is also less toxic than another anti-cancer agent doxorubicin.

This research will be retrospective. The goal of this project will be to obtain pertinent information from appropriate sources to access the safety and effectiveness of the carboplatin and doxil chemotherapy. The trial spanned a period of 4 to 5 years.

Concise Summary of Project: This will be a retrospective study. Information will be taken from medical charts and will include tumor volume prior to treatment and after conclusion of treatment. Dates of when the tumor disappeared and when it returned will be noted. How long persons that received this treatment lived after conclusion of the trial will also be recorded. Which complications, percentage of complications, and the dosage level at which complications occurred will be noted. Other information such as height,

weight, age, race, family and patient history will also be provided by information in the charts. The data will be obtained on spreadsheets. Dr. will be responsible for storing information in a locked cabinet of a locked office. No personal identifiers (such as name or medical record #) will be maintained on the patients included in this review for data analysis or any other purpose.

Criteria for Inclusion of Subjects: The subject population will include patients who were enrolled in the carboplatin plus doxil chemotherapy trial.

Criteria for Exclusion of Subjects: Subjects who did not participate in the doxil and carboplatin combination chemotherapy study will not be included.

Sources of Research Material: Information from existing records will be used. Patient name and medical record number will be used to identify patients who were involved in the study. The data retrieved from existing records, specimens, or other medical data will be used for research purposes. The data will be collected from OACIS or medical records. No patient information will be identified as a result of the review.

Recruitment of Subjects: Informed consent will not be obtained as no information retrieved in this review of patient records will identify those included.

Potential Risks: There is no potential physical, psychological, economic, or social risk to those patients included in this chart review.

Special Precautions: All precautions will be taken to keep personal identifiers from being included as a part of this review. All records will be stored only in locked offices in the Division of Gynecologic Oncology at UT Southwestern. Computer records of patients will not record name or medical record number. No one outside the Division of Gynecologic Oncology at UT Southwestern will be given access to this information. Dr will oversee research related material. The patient's name and/or medical record will be used to access the patient record for pertinent information and then the information will be de-identified.

The IRB may review any and all research information whenever necessary; however, to maintain patient confidentiality, it is probably best that the IRB review the information after the patients have been de-identified. The IRB could review the research information to ensure that the study was protecting patient confidentiality as anticipated.

Procedures to Maintain Confidentiality: Please see above

Potential Benefits: A potential benefit could be determining whether the carboplatin plus doxil chemotherapy is effective. There may be no direct benefits to the subject population. This study may benefit others with the same condition by offering another means of treatment.

Biostatistics: The primary objective of this investigation will be fulfilled by determining the clinical outcome of this treatment. Sample size is determined by the number of women who participated in the trial. A simple spreadsheet will be used to record data.

Risk/Benefit Assessment: Retrospective analysis of this treatment may lead to better understanding of the effectiveness of carboplatin plus doxil chemotherapy. The results of this investigation may help guide future treatment practices. The benefits of this study outweigh the risks.

APPENDIX C

NR1

The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board[1]

IRB Form NR1- EXP: Application for Review of Expedited Research

(Revised November 2002)

Title of Research[2] | Carboplatin and Doxil for Gyncologic Cancers

Sponsor and Grant Number[3] | N/A

Assurances of the Principal Investigator and Sub-investigators

To safeguard human subjects involved in this research, I agree to use procedures that conform to the policies of the University of Texas Southwestern Medical Center at Dallas and the regulations of the Department of Health and Human Services and the Food and Drug Administration.
Unless it is necessary to eliminate apparent immediate hazard to a human subject, I shall seek prior approval from the Institutional Review Board (IRB) for substantive changes in the investigative procedures involving human subjects that may be called for during the research covered by this application.
I shall agree to follow the advice of the IRB.

I agree to report immediately to the IRB any unanticipated, life-threatening, or fatal complications with respect to human subjects.
My signature certifies that I assure compliance with the ethical principles and institutional policies regarding the protection of human subjects in research as stated in Title 45 Code of Federal Regulations Part 46 (revised June 18, 1991; reprinted April 2, 1996) and the Multiple Project Assurance.[4]

[1]The IRB reviews all research involving human subjects for Children's Medical Center of Dallas, Parkland Health & Hospital System, Texas Scottish Rite Hospital for Children, the University of Texas Southwestern Medical Center at Dallas, St. Paul Medical Center, Moncrief Cancer Center in Fort Worth and Zale Lipshy University Hospital. The Board also reviews all research conducted at the Presbyterian Hospital of Dallas, The Retina Foundation of the Southwest and the Veteran's Affairs Medical Center of Dallas for which a member of the faculty at UT Southwestern serves as principal investigator.

[2]Title printed on the cover of the protocol, including the sponsor's protocol number, version, and date

[3]Complete name of the organization(s) funding the research

[4]Available as an electronic file at www2.swmed.edu/irb

The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board[1]

IRB Form NR1- EXP: Application for Review of Expedited Research

(Revised November 2002)

Title of Research[2]: Carboplatin and Doxil for Gyncologic Cancers

Sponsor and Grant Number[3]: N/A

Assurances of the Principal Investigator and Sub-investigators

- To safeguard human subjects involved in this research, I agree to use procedures that conform to the policies of the University of Texas Southwestern Medical Center at Dallas and the regulations of the Department of Health and Human Services and the Food and Drug Administration.
- Unless it is necessary to eliminate apparent immediate hazard to a human subject, I shall seek prior approval from the Institutional Review Board (IRB) for substantive changes in the investigative procedures involving human subjects that may be called for during the research covered by this application.
- I shall agree to follow the advice of the IRB.
- I agree to report immediately to the IRB any unanticipated, life-threatening, or fatal complications with respect to human subjects.
- My signature certifies that I assure compliance with the ethical principles and institutional policies regarding the protection of human subjects in research as stated in Title 45 Code of Federal Regulations Part 46 (revised June 18, 1991; reprinted April 2, 1996) and the Multiple Project Assurance.[4]

[1]The IRB reviews all research involving human subjects for Children's Medical Center of Dallas, Parkland Health & Hospital System, Texas Scottish Rite Hospital for Children, the University of Texas Southwestern Medical Center at Dallas, St. Paul Medical Center, Moncrief Cancer Center in Fort Worth and Zale Lipshy University Hospital. The Board also reviews all research conducted at the Presbyterian Hospital of Dallas, The Retina Foundation of the Southwest and the Veteran's Affairs Medical Center of Dallas for which a member of the faculty at UT Southwestern serves as principal investigator.

[2]Title printed on the cover of the protocol, including the sponsor's protocol number, version, and date

[3]Complete name of the organization(s) funding the research

[4]Available as an electronic file at www2.swmed.edu/irb

Assurances of Department and Collaborating Chairmen

- I understand that responsibility for assessing the quality of research must be shared by both the department and the IRB.
- My signature certifies that I assure compliance with the ethical principles and institutional policies regarding the protection of human subjects in research as stated in Title 45 Code of Federal Regulations Part 46 (revised June 18, 1991; reprinted April 2, 1996) and the Multiple Project Assurance, and that I have reviewed the proposed research for the proper use of human subjects.
- This review encompassed experimental design, scientific merit, and accuracy of the proposed research.

Date of Application: August 22, 2003
Investigators' and Chairmen's Signatures

Name (printed)	Dept	Degree	Rank	Phone	Mail	E-mail	Signature
Investigator							
Research Coordinator							
Sub-investigator							
Sub-investigator							
Chairman							

Please note that to qualify for expedited review, the research must present no more than minimal risk to human subjects and cannot explore sensitive topics. Designate below the category that qualifies this proposal for expedited review (click on http://www2.swmed.irb/edu, "Local Guidelines", "Investigator's Manual" and then "Expedited Review" and "Approved Categories"), and justify this designation by responding to the statements below each category. The IRB will review your justification and decide if this study can be approved on an expedited basis. If it is decided that it

doesn't meet expedited criteria completely, then you will be informed and submission of an NR1 form will be necessary.

Category #: 5

Information Required for Justification (specific information in attachments):

1. **Type of materials and the purpose for which it was collected**
   Information will be collected from medical charts and OACIS. The information will include tumor volume, tumor response to chemotherapy time to progression, toxicity, and overall survival. The information will be collected to determine the safety and efficacy of carboplatin plus doxil chemotherapy.

2. **Source of material**
   Information is currently existing and will be taken from medical charts and OACIS. The study is retrospective.

1. PROBLEM UNDER INVESTIGATION:

Medical condition or scientific problem to be studied: Ovarian and Endometrial cancer response to carboplatin plus doxil chemotherapy

Describe the research in simple language **by attaching a project summary** (template available on the IRB web-site). If this is a retrospective chart review (Category 5) (health records research) all of the following must be addressed: a) describe specifically what data (variables) will be extracted from each medical record, whether or not subject identifiers (name, medical record number, social security number, etc.) will be present, and at what point in time identifiers (if used) will be destroyed. Clarify how subject confidentiality will be protected. b) State why the research could not practicably be carried out without access to and use of the protected health information.

2. SUBJECTS:

a) General Inclusion: The subject population will include patients who were enrolled in the carboplatin plus doxil chemotherapy trial.

Approximate number of subjects: 1-10

Age range (indicate whether months or years):
Gender: Male ( ) Female (x)

Explain below if either gender is excluded: Trial was conducted on gynecologic cancers only.

Will all racial/ethnic groups be included? Yes (x) No ( ) (If no, explain in project summary)
Please note that a consent document in the subject's own language will need to be provided.

Expected time to completion of enrollment or conclusion of study: The study is retrospective. No patients will need to be enrolled. Data collection should take only a few months. 6 months

b) Protocol inclusion criteria: Patients who were enrolled in the carboplatin plus doxil chemotherapy trial will be included.
c) Protocol exclusion criteria: Patients who were not enrolled in the carboplatin plus doxil chemotherapy trial will not be included.

Specify all classes of subjects included in the research: Anyone involved in the study

Healthy volunteers: Medical students ( ), Center employees ( ), Minors (<18 yrs) ( ), Men ( ), Women ( )

Patients: Outpatients (x), Inpatients (x)

Vulnerable Subjects: Pregnant women ( ), Minors (<18 yrs) ( ), Men ( ), Women (x)
Cognitively impaired ( ), Terminally ill ( ), etc.

Other: Other class ( ) please explain below

3. RECRUITMENT: Patients will not need to be recruited, the study is retrospective. Patient information will be accessed using OACIS or the medical record will be obtained to review pertinent information relating to ovarian and endometrial cancer, as well as the treatment carboplatin plus doxil chemotherapy.

Specify procedures for recruiting subjects:

4. CONSENT OF SUBJECTS:

Informed consent will not be obtained as no information retrieved in this review of patient records will identify those included.

If requesting a waiver or alteration of informed consent, justify such in accordance with the following four criteria established under 45CFR46.116(d)(1-4):
1) The research involves no more than minimal risk* to the subjects? Yes (x) No ( ) **AND**
2) The waiver or alteration will not adversely affect the rights and welfare of the subjects? Yes (x) No ( ) **AND**
3) The research could not practicably be carried out without the waiver or alteration? Yes (x) No ( ) **AND**
4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation? Yes (x) No ( )

*"***Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46).

Please note that the IRB will make the final determination if waiver of consent is appropriate.

5. RISKS AND BENEFITS:

There is no potential physical, psychological, economic, or social risk to those patients included in this chart review. Retrospective analysis of the carboplatin plus doxil chemotherapy trial may help to better understand the effectiveness of this treatment in gynecologic cancers, such as ovarian and endometrial. The results of this investigation may help to guide future treatments. The benefits of this study outweigh the risks.

6. RESEARCH PERSONNEL:

Is there a conflict of interest between any investigator and the sponsor?
Yes ( ) explain below and notify the Conflict of Interest Office
No (x)

Have all research personnel completed the required human subject protection training? (x) yes (name(s) and completion date(s) under Comments)
(enclosed with current submission)
( ) no

Is this study a clinical trial? (x) yes
( ) no **(please skip the next question)**

*A clinical trial is defined as an interventional drug or device study that falls under the FDA Phase I-IV criteria, requires a Data and Safety Monitoring Board (NIH) or needs to meet FDA standards to submit data for FDA approval regarding use or marketing of a drug or device. Also included would be those clinical trials that are designed to evaluate FDA-approved drugs prospectively using comparison treatment designs.

Have all investigators completed the required Good Clinical Practice training? (x) yes (name(s) and completion date(s) under Comments)
(enclosed with current submission)
( ) no

7. PERFORMANCE SITES:

Specify the sites where (1) study procedures will be conducted, (2) patients will be seen, and (3) resources (equipment, supplies, personnel, etc.) will be utilized. Indicate whether Form NR2 has been sent to the appropriate authority at the performance site.

Performance Site	**Recruitment**	**Resources**	**Form NR2/NR3 sent**
Aston Ambulatory Care Center			
Children's Medical Center of Dallas			
Dallas County Mental Health			
General Clinical Research Center			
Moncrief Cancer Center/Fort Worth			
Parkland Health & Hospital System	Recruitment is not necessary	Medical Charts OACIS	NR3
Presbyterian Hospital of Dallas			
Sprague Clinical Sciences Center			
St. Paul Medical Center			
Texas Scottish Rite Hospital for Children			
Veteran's Affairs Medical Center			
Zale Lipshy University Hospital			
Other (specify below)			

Other approvals needed: Environmental Health & Safety Committee

		Radiation Safety Committee
		IRB at the Veteran's Affairs Medical Center
		IRB at Presbyterian Hospital of Dallas
		Grants Management (UT Southwestern)
		General Clinical Research Center
	x	Form NR2/NR3
		Other (specify below)

Have all approvals been requested?	x	Yes
		no (explain below)

8. OTHER PAPERWORK REQUIRED:

a) Project summary including any questionnaires, surveys, telephone scripts, etc.
Also, when applicable:
b) Complete grant application, with budget (when project is federally funded). Block out confidential salary information and total dollar amount.
c) Consent form, information sheet, brochure, and/or letter, script for verbal consent.
d) Recruitment materials (e.g., posted notices, advertisements, telephone script, letters, etc.)

COMMENTS:

Names and Dates for Human Subject Protection Training and Good Clinical Practice Training

APPENDIX D

NR2

The University of Texas Southwestern Medical Center at Dallas

Form NR2: Approval of Cooperating Facility for Use of Resources in Research

It is the principal investigator's responsibility to complete one copy of Form NR2 for each institution where research subjects will be seen. If the principal investigator is not a member of the faculty, provide the information requested below for the faculty member who is responsible for the research. Utilization of radiological services in the Aston Center requires the approval of the administration at Zale Lipshy University Hospital. The phone number for St. Paul Medical Center is 214-879-3752.

Directions: Send this form bearing the principal investigator's **original signature** to the proper authority at each cooperating facility. Once signed by the hospital authority, the form is returned to the principal investigator. The research activities may then commence at that site. For all research, the principal investigator is required to consult with each hospital authority and the Investigational Drug Service at that facility prior to budget negotiations with the company/agency funding the research. In the event that additional (not previously authorized) services are provided by the cooperating facility during the research, the hospital authority reserves the right to bill the investigator for all additional services rendered.

Title of Research (abridged): Carboplatin and Doxil for Gynecologic Cancers

IRB File No. (required): _____

Principal Investigator (name printed):

Pager (with area code):

Mail Code at UT Southwestern:

Faculty Sponsor (if applicable):

Pager (with area code):

Mail Code at UT Southwestern:

Research Coordinator (name printed):

Pager (with area code):

Mail Code at UT Southwestern:

Collaborating Facility (check only one):

x Aston Ambulatory Care Center
☐ Children's Medical Center of Dallas
☐ Parkland Health & Hospital System
☐ St. Paul Medical Center
☐ Texas Scottish Rite Hospital for Children
☐ Zale Lipshy University Hospital

(1) Estimated amount of time required to complete enrollment: 6 months

(A) Inpatients (total expected at this site): 1-10

(B) Outpatients (total expected at this site): 1-10

(C) Specify particular source(s) of subjects: Obstetrics/Gynecology
(Emergency, Obstetrics, ICU, etc.)

(2) Will hospitalization be solely for research?
☐ yes (estimated number of days: _____)
x no

(3) Is an implantable device used in the study?
☐ yes (FDA approval code attached)
x no

(4) Are drugs used in the study?
☐ yes (IDS at the facility to be contacted)
x no

(5) Parties responsible for costs of the study:
☐ Sponsor/PI: study drugs/devices
☐ Sponsor/PI: study procedures (lab tests, P.E., etc.)
☐ Sponsor/PI: only an investigational drug/device
☐ Patient/insurance: study drugs/devices
☐ Patient/insurance: study procedures
☐ Patient/insurance: standard medical care
x Other arrangement (explained below)

(6) Has the principal investigator discussed this study with the hospital authority and the IDS before contract negotiations with the sponsor?
x yes
☐ no (explained below)

(A) Is funding available to the institution?
☐ yes
x no (unfunded research)
☐ no (explained below)

(B) Has an account for the study been established through the Office of Grants Management?
☐ yes
x no (explained below)

(7) Location(s) of copies of the protocol:
☐ Principal Investigator's office at the hospital
☐ Research Coordinator's office at the hospital
☐ Main hospital pharmacy
☐ Pharmacy satellite (identified below)
☐ In-patient unit (identified below)
☐ Out-patient unit (identified below)
☐ Hospital Administration
x Other (explained below)

Attach a copy of the protocol schedule of assessments. Highlight those evaluations and procedures (including frequency of repetition) that are part of the research, but not part of standard medical care for the disease or condition under investigation.

Principal Investigator's Assurance: During the research, if there are any substantive changes in the information provided above (including a change in principal investigator), they will be reported to the undersigned hospital authority **within twenty-four hours**. The hospital may receive a list of subjects in the study to facilitate cost recovery. A copy of the signed consent form will be placed in each subject's medical

record. Copies of consent forms describing any type of genetic research may not be placed in the medical record without a subject's explicit authorization.

Principal Investigator's Signature	Date
Research Coordinator's Signature	Date
Hospital Authority's Signature	Date

Comments:

This study is retrospective only. The clinical trial was previously conducted. This study involves collecting data from medical charts and OACIS to assess the effectiveness of the combined chemotherapy trial carboplatin plus doxil. No funds will need to be provided for this data collection. There is not a specific protocol to follow. The information will be collected by individuals who have gone through the protection of human subjects and good clinical pratice training. Only individuals in the Division of Gynecologic Oncolgy at UT Southwestern will be collecting information and it will be kept confidential as well as de-identified at an appropriate time.

APPENDIX E

HIPAA WAIVER

THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS
CHILDREN'S MEDICAL CENTER OF DALLAS, PARKLAND HEALTH & HOSPITAL SYSTEM
RETINA FOUNDATION OF THE SOUTHWEST, TEXAS SCOTTISH RITE HOSPITAL FOR CHILDREN
ZALE LIPSHY UNIVERSITY HOSPITAL, ST. PAUL MEDICAL CENTER
THE UNIVERSITY OF TEXAS SOUTHWESTERN MONCRIEF CANCER CENTER

REQUEST FOR WAIVER OF HIPAA PRIVACY AUTHORIZATION FOR RESEARCH

Please provide contact information for a representative who can answer any questions that the IRB might have concerning this submission:
Name:
Position:
E-mail:
Phone #:
Pager #:
2nd Contact: **name**
(e-mail/phone #):

This box is for IRB use ONLY.

IRB # _____ – _____

Principal Investigator:

Project Title: Carboplatin and Doxil for Gynecologic Cancers

1. The following protected health information will be created, collected, used or disclosed as a result of subjects' participation in this research:
Medical history and charts will be used to determine tumors response and subject response to the study drugs.

Records of physical exams will be used to determine response to study drugs.

Laboratory, x-ray, MRI, and other test results will be used to quantify the response of the tumor.

Records of study medications or drugs will be used to determine a toxicity level and determine the effectiveness.

☐

2. I certify that the use or disclosure of protected health information involves nor more than minimal risk to the privacy of individuals based on at least the following elements:

   a. An adequate plan is in place to protect the identifiers from improper use and disclosure. The plan is as follows;
   All precautions will be taken to keep personal identifiers from being included as a part of this review. All records will be stored in locked cabinets of locked offices in the Division of Gynecologic Oncology at UT Southwestern. Computer records of patients will not record name or medical record number, and these records will only be accessible by input of a password. No one outside the Division of Gynecologic Oncology will be given access to this information.

b. An adequate plan is in place to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law. The plan is described as follows;
The patient's name and/or medical record will be used to access the patient record for pertinent information and then the information will be de-identified. Any paper containing private information will be shredded at the conclusion of the study.

c. The protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by HIPAA regulations.

3. I certify that the research could not practicably be conducted without this requested waiver.

4. I certify that this research could not practicably be conducted without access to and use of the protected health information.

5. I certify that I will only access the minimum amount of PHI necessary to accomplish the purpose(s) of the research described under this waiver.

I attest that the above statements are correct and complete to the best of my knowledge

Signature of Principal Investigator		Date
Printed name of Principal Investigator		

APPENDIX F

SAMPLE HIPAA AUTHORIZATION FORM

The University of Texas Southwestern Medical Center at Dallas
Children's Medical Center of Dallas, Parkland Health & Hospital System
Retina Foundation of the Southwest, Texas Scottish Rite Hospital for Children
Zale Lipshy University Hospital, St. Paul Medical Center
The University of Texas Southwestern Moncrief Cancer Center

Authorization for Use and Disclosure of Protected Health Information for Research Purposes

1. You agree to permit *[Institution/Covered Entity]* to release your protected health information to *[Name of Principal Investigator]* and his/her staff ("Researchers") for the purpose of conducting the medical research study ***[Abbreviated** title, plus **Brief** description – e.g., comparative study of two treatments for recurrent breast cancer.]* IRB #_____

2. You agree to permit *[Name of Principal Investigator]* and his/her staff to receive health information about you, and to use and disclose that information about you, and to use and disclose that information to the sponsor of the research, *[Name of Sponsor]*, and representatives of the sponsor, *[Name(s) of Organization(s)—e.g., Contract Research Organization(s), Reference Laboratory(-ies)]*, assisting in the research ("Receiver[s]").

3. When we talk about protected health information about you to be used and disclosed, it includes all information about you collected during the research study for research purposes and the protected health information about you in medical records that is related to the research study. *[List types of medical information that will be collected, used, and disclosed – e.g., blood, urine, and bone marrow tests, x-ray examinations, etc.]*

4. Protected health information about you may also be disclosed to and reviewed by a research ethics board and representatives of government agencies, including the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) in order to ensure that the research is being conducted in accord with legal and ethical standards. If protected health information about you is required, the reviewers may need your entire medical record.

5. Protected health information about you may also be used to create information that does not identify you. The de-identified data may be used and released by Researchers, including use for other research purposes.

6. Whenever possible, only de-identified information about you is disclosed. However, if identifiable health information is disclosed, it may no longer be protected by privacy laws and may be subject to re-disclosure by the recipient. UT Southwestern cannot guarantee the confidentiality of this information after it has been disclosed.

7. In order to participate in this research study, you must sign this Authorization. However, you cannot be denied medical treatment, payment of, or eligibility for, benefits because you did not sign this Authorization.

8. This Authorization has no expiration date.

9. You have the right to revoke this Authorization at any time by a written notification to:
[Principal Investigator or Designee, address, and phone number]

10. A copy of this authorization form will be provided to you.

If you revoke this Authorization, you will no longer be allowed to participate in the research. Also, even if you revoke this Authorization, the Researchers may still use and disclose the protected health information that they have already obtained as necessary to maintain the reliability of the research.

_____ _____

Signature of Research Participant Date

_____

Printed Name of Research Participant

For Personal Representative of the Research Participant (if applicable)

Printed Name of Personal Representative: _____

Describe Personal Representative Relationship:

_____

(e.g., parent, guardian, person with power of attorney, etc.)

I certify that I have the legal authority under applicable law to make this Authorization on behalf of the Research Participant identified above.

_____ _____

Signature of Personal Representative Date

APPENDIX G

SAMPLE AE FORM

The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

IRB Form AE: Principal Investigator's Report of (1) an Unexpected Adverse Event or (2) a Serious Adverse Event

Directions: Read the attached instructions carefully before completing this form. For an unexpected or a serious adverse event that occurs at UT Southwestern or an affiliated institution, send one copy of this form to the IRB at mail code 8843 **within 48 hours** after the event becomes known to the investigator.
For other reportable adverse events, submit one copy of this form **within five workdays** of the investigator's recognition of the event.

For adverse events that occur after gene transfer, submit one copy of the NIH OBA Form instead of IRB Form AE. Additional requirements for reporting adverse events associated with gene transfer are described in a separate file ("Gene Therapy") on the IRB website at http://www2.swmed.edu/irb.

(1) IRB File Number _____

(2) Title of Research _____ Short title to include name of drug, device, or other study procedure and disease
_____

(3) Principal Investigator _____ Name printed

Mail Code _____ **Complete address** (if off campus)

Telephone Number _____

Pager _____

(4) Research Coordinator _____ Name printed

Mail Code _____ **Complete address** (if off campus)

Telephone Number _____

Pager _____

(5) Adverse Event _____ Seizure, heart attack, etc.

(6) Study Site _____ **For UT and affiliates:** (subject under local study-under local PI) specify CMC, PHHS, Retina Fdn, TSRHC, UT, ZLUH, St. Paul, Moncrief Cancer Ctr

For an external performance site (in a multi-center trial): specify EPS

(7) Study Procedure _____ Name of the specific drug(s), device(s), etc. being studied

(8) Date of the Adverse Event (local study site) _____ Indicate N/A if the event occurred at another site in A multi-center trial

(9) Date of Recognition _____ Date a local event became known to an investigator or the date when a local investigator received a sponsor's report describing an event at another site in a multi-center trial

(10) Severity of the Event _____ Mild, moderate, severe, etc.

(11) Outcome (Code[s]): circle all that apply

A: Medical or surgical intervention to prevent a serious outcome

B: Inpatient hospitalization or prolonged inpatient stay

C: Persistent or significant disability or incapacity

D: Congenital anomaly or birth defect

E: Life-threatening event

F: Death

G: Other (if "other," specify)

(12) Prior Knowledge of Event _____ **Expected:** listed in the investigator's brochure or package insert and the consent form

Unexpected: not previously described in medical literature

(13) Relationship to Study _____ Definite, probable, possible, unrelated, unknown, etc.

(14) Subject's current status _____ **Local subject:** doing well, on study, off study, etc.

Subject at another site in a multi-center trial:

N/A

(15) Is the subject's signed consent form on file with the records of the research? _____ **Local subject:** if unavailable, explain below

Subject at another site in a multi-center trial:

N/A.

(16) Discuss the medical or surgical care needed to manage the adverse event. Identify the party (parties) responsible for the costs resulting from the medical or surgical management of the adverse event.

(17) Discuss whether the sponsor and/or investigator believes that a change in the protocol or consent form is necessary to update risks to current or prospective subjects, and whether consent should be obtained again from current subjects. **Provide specific justification for making no changes at this time. This form will be returned if no justification is provided.** If changes are required, send IRB Form MOD to mail code 8843.

(18) List all other reports about this adverse event which have been submitted--to a hospital administration, professional liability, Investigational Drug Service, etc. If not applicable, indicate N/A.

(19) To protect a subject's privacy, provide an assigned code (or another anonymous tracking identifier) for a subject at UT Southwestern (or affiliated performance site) who had an unexpected or serious adverse event.

(20) Provide a sponsor's code(s) for all other documents attached to this report. If no documents are attached, indicate N/A.

Other Comments:

Principal Investigator's, Research Coordinator's, and Department Chairman's Assurance: My signature certifies the following: (1) I have reviewed this report for accuracy, (2) I agree to notify the IRB immediately if new information becomes available later and changes the information provided above, and (3) I assure compliance with the ethical principles and institutional policies regarding the protection of human subjects in research as stated in Title 45 Code of Federal Regulations Part 46 (revised June 18, 1991; reprinted April 2, 1996) and the Multiple Project Assurance (copy available at the IRB website).

_____ _____

Principal Investigator Date

_____ _____

Research Coordinator Date

_____ _____

Department Chairman (required only for a life-threatening or fatal event that occurs at a performance site affiliated with UT Southwestern and is definitely, probably, or possibly related to the study procedures) Date

---

(Space below reserved for IRB)

_____ _____

Acknowledged by the IRB Manager or Designee Date

____ referred to sub-committee

____ referred to full Board

APPENDIX H

SAMPLE MODIFICATION FORM

The University of Texas Southwestern Medical Center at Dallas

IRB Form MOD

Request for Protocol/Consent Modifications

(revised November 2003)

IRB File Number:

Title of Research: _____

Principal Investigator (name printed): _____

Department: _____

Mail Code at UT Southwestern: _____

Phone Number: _____

Research Coordinator (name printed): _____

Mail Code at UT Southwestern: _____

Phone Number: _____

Directions: Per requirements of 45 CFR 46.103(b)(4) and 21 CFR 56.108(a)(3)(4), changes in approved research cannot be initiated without IRB review and approval unless necessary to eliminate apparent immediate hazards to the subject or provide important information germane to informed consent. In this circumstance, the IRB must be notified immediately. To review your Request for Protocol/Consent Modifications, the IRB must have the following information provided according to the specific instructions in each subpart. Additional pages can be used as necessary. The information should be typed.

Section I - Changes in Protocol

____ yes
____ no

A) Description:

Describe <u>each</u> proposed change in the protocol separately in numbered sequence. If the proposed change will <u>directly</u> affect the subjects (e.g., additional tests, changes in drug dose or schedule, change in eligibility criteria, etc.), the justification/rationale for the change must be included. The investigator must advise the IRB in this section whether or not <u>each</u> proposed change that directly affects the subject requires revision of the consent document(s). Please submit (1) the previously approved protocol/project summary with **deletions red-lined**, (2) the proposed protocol/project summary with **additions highlighted**, and (3) a **fresh copy** of the new protocol/project summary. Note: Section IB must be completed and copies of the revised consent form(s) must be submitted.

B) Risk Analysis Update:
If the overall risk(s) associated with the research as originally stated in the IRB approved application are either increased or decreased, an updated assessment of the risk(s) must be provided. **If the risk profile of the research is unchanged, this should be stated.**

Section II - Changes in Consent Document(s)
____ yes
____ no

A) Description:

Describe each proposed change in the consent document(s) that is not related to changes in the protocol described under Section IA (e.g., corrections of errors, sponsor-required changes in language, addition of new side effects) and provide the justification/rationale for the change unless it is self-evident. Note: Copies of the revised consent form(s) must be submitted as follows: (1) the previously approved consent form with **deletions red-lined**, (2) the proposed consent form with **additions highlighted**, and (3) a **fresh copy** of the new consent form. The footer in the new consent form should include the IRB file number and the same date of expiration as the one printed on the previous version of the consent form. Leave the approval date blank.

B) Re-Consent:

Significant new findings (e.g., previously unknown side effects) developed during the course of the research or information concerning changes in protocol that may relate to the subject's willingness to continue participating must be provided to the subject per 45 CFR 46.116b(5) and 21 CFR 50.116b(5). Therefore, if any new information or changes could potentially affect a subject's willingness to continue participating in the study, they must be informed and consent renegotiated. **In this section, describe any plans to renegotiate consent.** If this is unnecessary, this must be stated and explained. Note: Copies of revised consent forms and/or amendments must be submitted with changes highlighted and a fresh copy provided as discussed above.

C) Change in Study Personnel:

List additions/deletions to study personnel. State the reason(s) for the change. Include copies of the revised consent documents. When adding new research personnel, please submit an NR1 Page 2 (signature page) with the new personnel's original signature. New personnel also need to submit documentation of training in policies protecting the rights and welfare of human subjects in research. The tutorial is located at http://www.2.utsouthwestern.edu/utswirb/human/.

Section III – Other Changes not related to protocol or consent

A) Description:

Describe each proposed change that is not related to changes in the protocol or consent:

My signature certifies that I assure compliance with the ethical principles and institutional policies regarding the protection of human subjects in research as stated in Title 45 Code of Federal Regulations Part 46 (revised June 18, 1991; reprinted April 2, 1996) and the Multiple Project Assurance, and that I have reviewed this report for accuracy. In addition, my signature certifies that the proposed changes are necessary for scientific, medical, administrative or disclosure reasons in order to continue the research project as originally described in the initial IRB application.

_____ _____

Principal Investigator's Signature Date

_____ _____

Research Coordinator's Signature Date

APPENDIX I

SAMPLE RADIATION SAFETY FORM

Application for Use of External Radiation in Human Research

The Institutional Review Board (IRB) requires that the Radiation Safety Committee (RSC) review all research involving the use of radioactive material in human subjects. Both IRB and RSC approval are necessary prior to beginning this procedure\research. A separate form for each procedure or radioisotope involved must be completed. Submit the application to Radiation Safety, mail code 9053. For additional information call Radiation Safety at (214) 648-2250.

Items needed for submission:		
	RSC Form RSC-022	1 original and 12 copies
	IRB Form NR1	13 copies
	Project Summary	13 copies
	Consent Form	13 copies
	Protocol/ Investigators Brochure	2 copies

Activity Title:

Principal Investigator: Phone:

Contact Person: Phone:

Department/Division: Mail Code:

Number of participants requested: Patients: Patient Controls: Non-Patient/Normals:

Duration of Project: Age Range: Sex: Female Male Both

Would the patient receive radiation if not enrolled in this study? Yes No

Radiographic Procedure	
Type of Exam:	View(s):
Number of Procedures:	Number of Films per Exam:
Effective Dose per Procedure (mrem):	Total Effective Dose (mrem):
Dosimetry Reference (must be included):	

Fluoroscopic Procedures	
Type of Exam:	Area(s) Viewed:
Total Time per Procedure:	Number of Procedures:
% of Time Medically Indicated:	% of Additional Time for Research:
Effective Dose per Procedure (mrem):	Total Effective Dose (mrem):
Dosimetry Reference (must be included):	

Computed Tomography (CT)	
Type of Exam:	Area Scanned:
Number of Exams:	Slices, Thickness, and Spacing (if known):
Effective Dose per Exam (mrem):	Total Effective Dose (mrem):
Dosimetry Reference (must be included):	

Radiation Therapy	
X-Ray	Brachytherapy
Type of Procedure:	Licensed Physician:
External Beam Energy:	Sealed Source Isotope:
Number of External Procedures:	Total Activity Used:
Area(s) Irradiated:	Number of Sealed Source Procedures:
External Dose per Procedure (rad):	Sealed Source Dose (rad):
Booster Dose (rad):	Total Dose (rad):
Dosimetry Reference (must be included):	Dosimetry Reference (must be included):

What special precautions are being taken? Is the issue of pregnancy being addressed?

SIGNATURES

Investigator Signature: _____ Date: _____

Department Chairman: _____ Date: _____

RSC Chairman: _____ Date: _____

Radiation Safety Officer: _____ RSC Approval Date: _____
(UTSWMC)

APPENDIX J

EXEMPT CATEGORIES

Title:

_____(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

_____(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

_____(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

_____(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

_____(5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

_____(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

APPENIDX K

EXPEDITED CATEGORIES

CATEGORY 1

Clinical studies of **drugs and/or devices** only when:

a) Research on drugs for which an investigational new drug (IND) application is not required (21 CFR Part 312). (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.) **or**

b) Research on medical devices for which
   i) an investigational device exemption application (IDE) is not required (21 CFR Part 812); **or**
   ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

Information Required for Justification

1. State the name of the commercially available drug to be used as described in the above requirements, **or**
   State the name of the approved device and confirm its use as described above.
2. Confirm that the research does not increase the risks or decrease the acceptability of the risks associated with the use of the product.

CATEGORY 2

Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; **or**

b) from other adults and children* considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

Information Required for Justification

1. State how the blood sample(s) will be collected.
2. Provide the health status of the research population and state whether pregnant women are eligible to participate.
   (a) For healthy, nonpregnant adults who weigh at least 110 pounds -
   Confirm that the amounts of blood to be drawn will not exceed 550 ml in an 8 week period and will not occur more frequently than 2 times per week.
   (b) For other adults (e.g., with an illness) or children*
   Confirm that the amount of blood to be collected will not exceed the lesser of 50 ml or 3 ml p/kg in an 8 week period and not occur more frequently than 2 times per week.

*Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

CATEGORY 3

Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

a) hair and nail clippings in a nondisfiguring manner;
b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
c) permanent teeth if routine patient care indicates a need for extraction;
d) excreta and external secretions (including sweat);
e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
f) placenta removed at delivery;
g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
j) Sputum collected after saline mist nebulization.

Information Required for Justification

1. State the biological specimen(s) to be collected.
2. Describe the noninvasive method by which the specimens will be collected.

CATEGORY 4

The collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples of such procedures:

a) physical sensors applied to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
b) weighing or testing sensory acuity;
c) magnetic resonance imaging (MRI);
d) electrocardiography (ECG or EEG);
e) thermography;
f) detection of naturally occurring radioactivity;
g) electroretinography;
h) ultrasound;
i) diagnostic infrared imaging;
j) doppler blood flow;
k) echocardiography;
l) moderate exercise. . . where appropriate, given age, weight, and health of the individual.

Information Required for Justification

1. State the type of data to be collected.
2 State the source of the data and the procedure that will be used to collect the data.

CATEGORY 5

Research involving materials (data, documents, records, or specimens) that have been, or will be, collected solely for non-research purposes such as medical treatment or diagnosis. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

Information Required for Justification

1. State the type of materials and the purpose for which it was, or will be, collected.
2. State the source of the material and whether it is currently existing (i.e., on the shelf at the present time) or will be collected prospectively.

CATEGORY 6

Collection of data from voice, video, digital, or image recordings made for research purposes -

Information Required for Justification

1. State the type of data and its original (clinical or research) purpose(s); how data will be stored; and who will have access.
2. State whether there will be identifiable information on the tapes and when the tapes will be destroyed.

CATEGORY 7

Research on individual or group characteristics or behavior including, but not limited to, research on:

a) perception,
b) cognition,
c) motivation,
d) identity,
e) language,
f) communication,
g) cultural beliefs or practices, and
h) social behavior,

or

Research employing -
i) survey
j) interview
k) oral history
l) focus group
m) program evaluation
n) human factors evaluation, or
o) quality assurance methodologies

(Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Information Required for Justification

1. State whether this is research on individual or group characteristics or behavior.
2. State the method to be used to gather the data.

Your research is renewed, usually annually, with an expedited review allowable if the research was originally approved under an expedited review process. At renewal time you will be required to complete an IRB Form CR to satisfy the regulatory requirements for continuing review of research.

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