NORTHERN ILLINOIS UNIVERSITY

Cisplatin-based Chemotherapy for Treatment of Head and Neck Cancers, Osteosarcomas of the Jaw Bone, and Ovarian Cancers

A Thesis Submitted to the

University Honors Program

In Partial Fulfillment of the

Requirements of the Baccalaureate Degree

With University Honors

Department of

Biological Sciences

By

Tara Ashlee Kersten

DeKalb, Illinois

May 12, 2007

University Honors Program

Capstone Approval Page

Capstone Title: **Cisplatin-based Chemotherapy for Treatment of Head and Neck Cancers, Osteosarcomas of the Jaw Bone, and Ovarian Cancers**

Student Name: **Tara Ashlee Kersten**

Faculty Supervisor: Dr. Kenneth Gasser

Faculty Approval Signature: Kent W. Gasser

Department of: Biological Sciences

Date of Approval: 4/30/07

HONORS THESIS ABSTRACT
THESIS SUBMISSION FORM

AUTHOR: **Tara Ashlee Kersten**

THESIS TITLE: **Cisplatin-based Chemotherapy for Treatment of Head and Neck Cancers, Osteosarcomas of the Jaw Bone, and Ovarian Cancers**

ADVISOR: Dr. Kenneth Gasser ADVISOR'S DEPT: Biological Sciences

DISCIPLINE: Cisplatin-based Chemotherapy YEAR: 2006-2007

PAGE LENGTH: 29 pages

BIBLIOGRAPHY: Attached

ILLUSTRATED: No

PUBLISHED: No LIST PUBLICATION: NA

COPIES AVAILABLE: Hard Copy

ABSTRACT: Attached

Cisplatin-based Chemotherapy for Treatment of Head and Neck Cancers, Osteosarcomas of the Jaw Bone, and Ovarian Cancers

Abstract

In this project, I have done extensive research on two chemotherapy regimens, cisplatin/5-fluorouracil and cisplatin/Adriamycin. My hope is to compare and contrast the effectiveness of cisplatin-based regimens in the treatment of head and neck squamous cell carcinomas, osteosarcomas of the jaw, and ovarian cancers. In addition to literature searches, I have studied the medical files of two patients who were treated with cisplatin. One patient had recurrent, unresectable head and neck cancer and one patient has a resected, metastatic osteosarcoma of the mandible. After studying the case of the patient with head and neck cancer, I found exceptional results. After only one cycle of cisplatin/5FU, CT and PET scans showed no evidence of disease. I have concluded that cisplatin was effective in this case. As for the case of the patient with an osteosarcoma of the mandible, he showed mixed responses to cisplatin/Adriamycin. However, his responses to this regimen are much improved compared with his responses to his initial chemotherapy with a furosemide regimen. While on furosemide, his disease became metastatic, spreading to his lungs. Finally, my research on cisplatin-based chemotherapy for the treatment of ovarian cancer showed that other anti-cancer drugs, like docetaxel, may be more effective.

NORTHERN ILLINOIS UNIVERSITY

Cisplatin-based Chemotherapy for Treatment of Head and Neck Cancers, Osteosarcomas of the Jaw Bone, and Ovarian Cancers

A Thesis Submitted to the

University Honors Program

In Partial Fulfillment of the

Requirements of the Baccalaureate Degree

With University Honors

Department of

Biological Sciences

By

Tara Ashlee Kersten

DeKalb, Illinois

May 12, 2007

Abstract

In this project, I have done extensive research on two chemotherapy regimens, cisplatin/5-fluorouracil and cisplatin/Adriamycin. My hope is to compare and contrast the effectiveness of cisplatin-based regimens in the treatment of head and neck squamous cell carcinomas, osteosarcomas of the jaw, and ovarian cancers. In addition to literature searches, I have studied the medical files of two patients who were treated with cisplatin. One patient had recurrent, unresectable head and neck cancer and one patient has a resected, metastatic osteosarcoma of the mandible. After studying the case of the patient with head and neck cancer, I found exceptional results. After only one cycle of cisplatin/5FU, CT and PET scans showed no evidence of disease. I have concluded that cisplatin was effective in this case. As for the case of the patient with an osteosarcoma of the mandible, he showed mixed responses to cisplatin/Adriamycin. However, his responses to this regimen are much improved compared with his responses to his initial chemotherapy with a furosemide regimen. While on furosemide, his disease became metastatic, spreading to his lungs. Finally, my research on cisplatin-based chemotherapy for the treatment of ovarian cancer showed that other anti-cancer drugs, like docetaxel, may be more effective.

Cisplatin-based Chemotherapy for Treatment of Head and Neck Cancers, Osteosarcomas of the Jaw Bone, and Ovarian Cancers

Introduction:

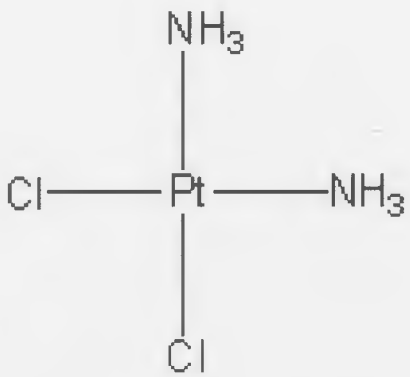
Cancer is one of the most common causes of death in developed nations. One in five people in the United States and Europe will die due to cancer (Sai Man Liu, 1999). Most people will be affected in some way by this disease at some point in their lives. Although most people know someone who has been affected by cancer, many people do not actually understand the mechanism behind cancer or the drugs used to treat it. Many people mistakenly believe that cancerous cells are those cells that divide more rapidly than normal cells. This is simply a myth. The true difference between a normal cell and a cancerous cell is that cancerous cell division is unregulated or uncontrolled. Two other characteristics of a malignant cancer cell are that it is invasive, or capable of entering other tissues, and it is metastatic, which means that it can enter the blood or lymph, causing cancer to spread to other tissues or organs (Sai Man Liu, 1999). In addition to the myth about the definition of cancer, much is unknown about cancer treatment, especially the anti-cancer drug called cisplatin.

General Discussion of Cisplatin:

My research began by studying the history, properties, and mechanism of cisplatin. Cisplatin is a widely used and effective chemotherapeutic agent. It belongs to a class called platinum-containing compounds (Sai Man Liu, 1999). Cisplatin's role as an anti-cancer drug was first discovered in 1970. Its anti-cancer capabilities were discovered purely by accident during research being done on E. coli using electric fields by Barnett Rosenberg and his colleagues. It was noticed during this research that the E. coli stopped dividing due to the electrodes, which were made of platinum (Sai Man Liu, 1999). After this, there were numerous studies done to see how effectively platinum compounds could stop cell division and how they could kill tumors. Of these platinum compounds, the cis isomer of diamminedichloroplatinum(II) (commonly called cisplatin) showed the best results as a possible anti-cancer drug in mice with leukemia. Clinical studies using cisplatin to treat cancers in humans soon followed, and it was eventually approved by the Food and Drug Administration in 1972. Early uses for cisplatin included treatments for both ovarian and testicular cancers. Its anti-cancer properties appeared to be the strongest in these two types of cancers. In one study, cisplatin, in combination with vinblastine and bleomycin, produced complete remission in 74% of testicular cancer patients (Sai Man Liu, 1999). Although its early uses were limited, cisplatin is now being prescribed to treat a wide variety of cancers. Some of these cancers include bladder cancer, gastric

cancer, head and neck cancer, lung cancer (non-small and small cell), osteosarcoma, and prostate cancer (BC Cancer Agency, 2006).

To study the effectiveness of cisplatin, one must first look at its properties. As already stated above, cisplatin is a platinum-containing compound. It is a planar compound with a central platinum atom. The platinum atom is covalently bonded to four other ligands, two ammonia groups and two chlorine atoms. The structure of cisplatin is shown below:



Structure of Diamminedichloroplatinum(II) (Cisplatin) (Miller, 2007)

To understand how cisplatin can prevent further cell division in malignant tumors and cancerous cells, one must look at its mechanism. First, cisplatin is able to gain entrance into the cell because of the concentration gradient that exists for chloride across the plasma membrane. The concentration of extracellular chloride is much higher than the internal cytoplasmic concentration of chloride. Therefore, because cisplatin is a chlorine-containing compound, cisplatin will

naturally move into the cells as a result of this concentration gradient. Once inside the cell, two water molecules will attack the cisplatin molecule and displace the two chlorine atoms. This is an important step because this activates the cisplatin molecule as it becomes positively charged (BC Cancer Agency, 2006). The cisplatin molecule is then able to react with the DNA of the cells. The DNA acts as a nucleophile and attacks the cisplatin molecule, displacing the water molecules, which are excellent leaving groups due to the fact that water is a weak base. Cisplatin specifically binds to the nitrogenous bases on the DNA creating inter and intra strand cross-links. These cross-links inhibit any further DNA replication, RNA transcription, or protein synthesis (translation), eventually resulting in programmed cell death. This cell death is called apoptosis (BC Cancer Agency, 2006).

Side Effects of Cisplatin:

Another important aspect of cisplatin to discuss before looking at its effectiveness against specific cancers is to look at why it causes side effects. Also, I will discuss what specific side effects are associated with its use. Cisplatin is typically administered through an infusion or constant drip into the vein over a certain interval (Cancer Research UK, 2007). Immediately following these treatments, many patients experience a wide range of side effects.

The biological explanation for these side effects is actually quite simple. Cisplatin, like all other anti-cancer drugs, is not cell specific. This means that

cisplatin is not specific to cancer cells, and is not capable of discriminating between normal and cancerous cells. There are a few exceptions to this rule. Sometimes anti-cancer drugs can recognize certain cell surface receptors, but for the most part, anti-cancer drugs are non-specific. In other words, cisplatin will attack and cause apoptosis in both normal and cancerous cells (Sai Man Liu, 1999). For this reason, cisplatin causes a wide range of side effects because it also attacks normal cells.

Cisplatin's effects are especially severe on types of cells that divide more often, such as the bone marrow, gastrointestinal epithelial cells, hair follicles, and the skin (Sai Man Liu, 1999). The most common side effects include thinning or brittle hair, loss of appetite, diarrhea, nausea and vomiting, taste alterations, and numbness in the hands and feet (Medline Plus, 2007).

Other serious side effects include kidney damage, hearing damage, and bone marrow effects (Cancer Research UK, 2007). Kidney damage is usually dose-dependent and is sometimes irreversible. In other words, the larger the dose of cisplatin, the more likely it is to damage the kidneys. Most of the damage is done to the cells of the proximal tubules in the nephron of the kidney (Sai Man Liu, 1999). Drinking plenty of water immediately after treatments is the main way to prevent this kidney damage. Medline Plus recommends drinking at least ten eight ounce glasses of water within the first twenty-four hours after treatment (Medline Plus, 2007). Hearing damage usually results in a ringing in the ears and

partial high-pitch hearing loss. Sometimes this damage is irreversible (Cancer Research UK, 2007).

The effects on the bone marrow can cause many symptoms. The decrease in the number of white blood cells increases the risk of infection. For this reason, patients on cisplatin should not receive immunizations while on cisplatin or be around people who have received oral immunizations. Bone marrow effects caused by cisplatin can also result in anemia and fatigue due to low red blood cell count. Finally, a drop in the function of the bone marrow can result in decreased ability to clot blood and more frequent bruising due to a decrease in the number of platelets (Cancer Research UK, 2007). Another very serious risk of taking cisplatin is developing a secondary cancer because cisplatin has been shown to be both an anti-cancer drug and a carcinogen, which means that it can also cause other types of cancers. In studies on female mice, cisplatin was shown to cause an increase in lung cancer (BC Cancer Agency, 2006). Its possible carcinogenic properties have not yet been proven in humans, however.

Although cisplatin is a powerful anti-cancer drug by itself, it is more potent in combination with other chemotherapeutic agents, especially in combination with 5-fluorouracil (5FU). The reason for this is because in combination, tumor cells are less likely to develop drug resistance to cisplatin. Also, the cisplatin/5FU combination has proven to have synergistic effects. This means that the effect of the two anti-cancer drugs in combination is much greater than would be expected if one simply added the effects that each drug has alone.

General Discussion of 5-fluorouracil (5FU):

5-fluorouracil (5FU) belongs to a group of chemotherapy medications called anti-metabolites. This group of compounds is so named because they interfere with DNA repair and stop cells from making new DNA (Cancer Research UK, 2007). It is much like a cell nutrient, so cancer cells will naturally take 5FU into the cell (Medline Plus, 2007). 5FU specifically acts by stopping the functioning of an enzyme called thymidylate synthase, which is needed for DNA replication (Wikipedia, 2007). 5FU has been used as an anti-cancer drug for forty years, which is similar to the time of discovery of cisplatin. 5FU shows its best results in patients who have pancreatic and colorectal cancers (Wikipedia, 2007). However, it also shows effectiveness as an anti-cancer drug against breast, head and neck, gastric, and some skin cancers (Cancer Research UK, 2007). In combination with cisplatin, it can also be used for a few other types of cancer. Like cisplatin and other anti-cancer drugs, 5FU's action is non-specific. Therefore, it does not discriminate between normal and cancerous cells.

Thus, there are a wide range of side effects associated with taking 5FU. They include thinning or brittle hair, headache, weakness, fatigue, diarrhea, dry skin, mouth sores, loss of appetite, numbness in the hands and feet, and bone marrow effects (Medline Plus, 2007). Another rare, but possible side effect of 5FU is GI bleeding. If especially severe, the patient can require blood transfusions. As I will discuss below, the patient I studied who had recurrent,

unresectable head and neck cancer and was treated with the cisplatin/5FU regimen, experienced severe GI bleeding that required hospitalization. In fact, it put him in intensive care, and he almost died. 5FU was most likely the cause for this severe side effect. Despite the possible side effects that can sometimes be especially severe, cisplatin-based regimens can be very effective anti-cancer drugs. However, their effectiveness varies with the type of cancer they are treating. In the remainder of this paper, I will compare and contrast the effectiveness of cisplatin-based chemotherapies using both literature and actual patient case studies. I will begin with a discussion of a patient with head and neck cancer who I researched extensively.

Case Study 1 (Cancer Center Medical Files, 2006):

Exceptional Results of Treatment of Recurrent, Unresectable Squamous Cell Carcinoma of the Head and Neck with Only One Cycle of Cisplatin and 5FU Combination:

The patient is a 66-year-old male with a history of tobacco and alcohol use. The patient discovered a bump under his tongue in 2001, and a biopsy revealed grade I squamous cell carcinoma. The staging was T2N0MX. Stage II squamous cell carcinoma is between two and four centimeters in size, and has not spread from the oropharynx (National Cancer Institute, 2005). In April 2001, he had an anterior marginal mandibulectomy and bilateral selective neck dissections to remove a squamous cell carcinoma from the anterior floor of the mouth.

However, in December 2002, the patient noticed a lump on the right side of his neck. Fine needle aspiration revealed recurrent squamous cell carcinoma of the head and neck. The carcinoma was very close to the carotid artery, so it was determined that the patient was not a surgical candidate. The plan was for the patient to undergo chemotherapy and subsequent radiation therapy. The patient was concerned about concurrent chemotherapy-radiation treatment. Chemotherapy was with cisplatin at units of 100 mg/m^2 and 5FU at units of 1000 mg/m^2 for five days of continuous infusion each week for three weeks. The patient experienced severe mucositis and dehydration with difficulty swallowing and pain in the mouth after the first round of treatment. The patient was admitted to Kishwaukee Community Hospital with GI bleeding and hypotension. The patient's condition improved after receiving four units of red blood cells. A colonoscopy revealed a cecal mass consistent with a grade 3 adenocarcinoma. The patient did not follow up for any chemotherapy or radiation as recommended. He did not finish the final two cycles of cisplatin; he completed only one cycle of chemotherapy prior to his hospitalization. Since he was so sick after the first round of chemotherapy, the patient declined any further chemotherapy or radiation.

Eight months after the patient's hospitalization, he returned for a follow-up. An MRI of the neck and a PET scan did not reveal any signs of cancer. In October 2004, another PET scan came back negative, with no glucose uptake. There was no recurrence of head and neck cancer or colorectal cancer. The

patient stated that even if the cancer recurred, he would not undergo any further treatment. By December 2005, the PET scan still showed no evidence of disease.

For more than three years there has been no evidence of recurring head and neck cancer or colon cancer. The patient completed only one cycle of chemotherapy and no radiation therapy, and yet, he has remained disease free. The first cycle of chemotherapy ended up putting the patient in the Intensive Care Unit, but it was effective, eliminating the disease.

Discussion:

The standard of care for head and neck cancer in stage II has been surgery or radiation treatment (National Cancer Institute, 2005). In this case, the patient did not undergo any adjuvant chemotherapy-radiation after he underwent the anterior marginal mandibulectomy. Studies refute any added benefit of adjuvant chemoradiation combined with surgery for a resectable squamous cell carcinoma. In a clinical trial, the effectiveness of cisplatin-based neoadjuvant chemotherapy was tested. Nine patients underwent one cycle of chemotherapy, with cisplatin, docetaxel, and 5FU before undergoing the resection. Eighteen other patients who had surgery and no adjuvant chemotherapy were used as a control group. After three years, the survival rate of the group undergoing adjuvant chemotherapy was only 29.6%, whereas, the control group had an 81.57% three-year survival rate (Umeda, Komatsubara, & Ojima, 2004). These results showed that

cisplatin-based neoadjuvant chemotherapy showed no benefits over the typical surgical treatment of resectable squamous cell carcinoma.

When the patient was diagnosed with recurrent squamous cell carcinoma in 2002, he was deemed inoperable because of the close proximity of the tumor to the carotid artery. The patient was to undergo both chemotherapy and radiation treatments, which is the standard of care for recurrent unresectable stage II head and neck cancer (National Cancer Institute, 2005). The benefits of this treatment plan have been shown in several clinical trials.

In a 1997-2002 study of 163 patients with unresectable pharyngeal carcinoma, the survival rates of patients who underwent only radiation (1.2 Gy/day) versus patients who underwent adjuvant radiation (1.2 Gy/day) and chemotherapy with cisplatin (100 mg/m^2)/5FU(750 mg/m^2/day x 5 days) were tested. After 24 months, the overall survival rate of patients receiving the chemoradiation treatment was 37.8%; whereas, it was 20.1% with radiation alone (Bensadoun, Benezery, & Dassonville, 2006). The survival rates reflect the added benefits of chemoradiation in treating unresectable squamous cell carcinoma, specifically with cisplatin and 5FU.

A 2000 study on thirty-five patients with unresectable head and neck cancer also showed the benefits of receiving both chemotherapy and radiation simultaneously. Cisplatin was given to these patients for 5 days each week at a dose of 3 mg/m^2 and 5FU was given continuously for five days each week at a dose of 150 mg/m^2. The radiation treatment was a total dosage of 60 Gy.

Seventy-nine percent of the patients in this study responded favorably to this concurrent treatment option. Nine of the patients remained completely disease free after receiving this treatment. Because of these results, it was concluded in this study that the concurrent chemoradiotherapy treatment can produce positive results for patients with unresectable head and neck cancer (Kohno, Kitahara, & Tamura, 2000).

In a 1996-2000 study with many patients who were already Stage IV for unresectable head and neck cancer, concurrent radiation and chemotherapy with cisplatin and 5FU proved effective. The dosages of cisplatin and 5FU were the same as the above study and the radiation was given at a total dosage of 68 Gy. Ninety percent of the patients in the study were stage IV for the disease. Yet, 80% of the patients in the study responded favorably to the treatment, with either a complete or partial response. The median survival was twenty-three months with this treatment. Thus, it was concluded that adjuvant chemotherapy and radiation is also an effective treatment for patients with advanced stage IV unresectable head and neck cancer (Kohno, Kitahara, & Tamura, 2002).

In a three-year trial, thirty-six patients (eighteen with locally recurrent disease) underwent chemotherapy with paclitaxel (175 mg/mq) and cisplatin (75 mg/mq) combination. The overall percentage of responders to the treatment was 41.1%. The median overall survival time was eleven months, with four patients still alive, according to statistical evaluation (Adamo, Ferraro, Pergolizzi, 2004). The results of the study led to the conclusion that the paclitaxel and cisplatin

combination is an effective and acceptably safe treatment for unresectable squamous cell carcinoma of the head and neck. This study showed that the paclitaxel and cisplatin combination has benefits similar to the cisplatin/5FU regimen; yet, it proved less toxic. The patient in this case experienced some of the toxic effects of the cisplatin/5FU regimen. He suffered severe mucositis and GI bleeding as a result of treatment with only one cycle of cisplatin and 5FU. After this response to the treatment, the patient had no further treatments, but has been disease free for over three years. This provides further evidence for the effectiveness of the cisplatin and 5FU regimen for unresectable, recurrent stage II squamous cell carcinoma of the head and neck.

In a study done in Chicago at Rush Medical College, seventy-eight patients with advanced head and neck cancer were studied over an eight year period to show how much more effective concurrent cisplatin/5FU therapy and radiation therapy was than cisplatin/5FU therapy followed by radiation therapy. The seventy-eight patients had either stage III or stage IV cancer. The five year survival rate was an incredible sixty percent with the concurrent cisplatin/5FU therapy. This is exceptional for patients with stage III and stage IV head and neck squamous cell carcinoma. In fact, of the sixteen patients with stage III cancer, none had any further progression. After eight years, 43% of the patients had survived. The best results were seen in patients with tongue and glottic cancers. The study concluded that the concurrent chemotherapy and radiation treatment

was very effective, especially since none of these patients had surgical resections (Taylor et al., 1997).

Case Study 2 (Cancer Center Medical Files, 2007):

Cisplatin-Based Chemotherapy for an Osteosarcoma of the Jaw Bone:

A cisplatin-based regimen proved very effective for the treatment of a patient with recurrent, unresectable head and neck cancer. Cisplatin is also commonly used for osteosarcomas, otherwise known as bone cancers. I did some literature searches on this topic, finding only one study. This is not surprising, as osteosarcomas of the jaw are very rare. However, this study speaks volumes for the effectiveness of cisplatin in treating this disease. I was also able to find a patient at the Cancer Center where I volunteer with this condition who was willing to let me study his medical chart. My observations of his treatment with cisplatin have been summarized.

Ongoing Treatment with Cisplatin and Adriamycin in a Patient with a Resected, Metastatic Osteosarcoma of the Mandible:

The patient is a thirty-three year old Caucasian male, with no history of tobacco use and a history of leukemia in his family. Other social and family history is unremarkable. After complaining of jaw pain in January 2006, a whole body bone scan and spot views of the mandible were done. The bone scan revealed severe isotope accumulation in the right ramus of the mandible and in

the anterior portion of the left ramus of the mandible. Tissues samples were taken two days later, and the pathologist confirmed the diagnosis of a low grade fibromyxoid sarcoma and osteosarcoma of the mandible.

After diagnosis, the patient underwent a subtotal mandibulectomy in February 2006. The entire right ramus of the mandible was removed up to the angle of the bone. The left ramus was only partially removed. It was removed anterior to the mental foramen. A bone graft was done with bone from the fibula in the leg. After the surgical resection, the patient underwent radiation therapy for two months, completing the treatment in April 2006. However, a CT scan of the neck done in April 2006 revealed asymmetric tissue in the tongue and oropharynx that indicated that the disease must have progressed.

At this point, it was recommended that the patient undergo subsequent chemotherapy. Since that time, the patient has been treated with three different chemotherapy regimens. He was started on a regimen which consisted of furosemide, Adriamycin, and methotrexate. After developing leucocytes, he stopped taking the methotrexate. However, he continued taking Adriamycin and furosemide. The patient did not respond as well as was hoped to this chemotherapy regimen. In August 2006, a CT scan of the chest showed many parenchymal and pleural nodules in the lungs. This proved that the cancer was now metastatic and had spread to the lungs. A needle biopsy of the right upper lobe of the lung confirmed that the disease was metastatic. The cells were

described as poorly differentiated, malignant, and very similar to the cells that were found in the mandible.

After discovering that the disease was metastatic, the patient discontinued his chemotherapy treatment with Adriamycin and furosemide. He was then placed on a cisplatin and Adriamycin regimen to see if there would be better results. He was placed on a dose of 45 mg of Adriamycin by infusion over a twenty-four hour period for three straight days, and he was placed on a dose of 120 mg/m^2 of cisplatin with magnesium sulfate and mannitol over an hour period on day one of treatment. He was recommended to undergo three cycles of this treatment. The patient initially had a mixed response to the new treatment. In November 2006, a Maxillofacial CT scan revealed a "moth-eaten" pattern on the anterior part of the remaining left ramus. The asymmetric tissue on the tongue and oropharynx, however, was no longer observed. The CT scan indicated that there may be recurrent disease. A chest CT scan done in November 2006 revealed that the metastatic disease in the parenchyma in the lungs had also worsened. However, in December 2006, a chest CT scan indicated that although there were some new nodules in the lungs, most of the nodules had decreased in size. Another chest CT scan done in late January 2007 also showed mixed responses to the chemotherapy treatment, with the bilateral pulmonary nodules decreasing in size, but with the pleural tissue mass in the medial part of the base of the right lung increasing in size.

In the last two months, however, the cisplatin-based regimen has produced much improvement in the metastatic disease. An April 2007 CT scan of the chest revealed a large decrease in the size of the pleural tissue mass in the right lower lobe, and there did not appear to be any new nodules in the lungs either. The patient has also been tolerating the treatments with cisplatin rather well. He has had some trouble keeping his potassium levels high enough. After developing this hypokalemia, he was prescribed potassium supplements to take three times daily. He was not very compliant at taking this medication and was hospitalized in January 2007 to get potassium supplements. At an appointment in March, he was still struggling with hypokalemia and hypomagnesia, but promised to start taking his potassium and magnesium supplements as prescribed.

The patient continues his ongoing chemotherapy treatment. Whether the osteosarcoma of the mandible or the metastatic disease in the lungs will recur is unknown; however, the last two months have shown that the cisplatin-based regimen has produced improvement in the patient's condition. His metastatic disease now appears to be under control. I will have to continue to follow this case to see the long-term results of a cisplatin-based treatment for a resected osteosarcoma of the mandible with metastatic disease. I have also done literature searches on this topic, and I was able to find a remarkable study on osteosarcomas of the jaw.

Discussion:

In a study done at the Kidwai Memorial Institute of Oncology in India, only eight cases of osteosarcomas of the jaw bone were treated over a span of seven years. Four cases were cancer of the mandible bone and four cases were cancer of the maxilla bone. Three of these patients (two with cancer of the mandible and one with cancer of the maxilla) underwent surgery and subsequent six cycles of chemotherapy with cisplatin. All survived and were disease free four and a half years after the treatment commenced. The other five patients seen at this institute either did not finish the recommended treatment or elected to undergo no treatment at all electing to have only palliative care instead. Palliative care is aimed at reducing pain and making the patient more comfortable as opposed to actually treating the disease. All five of the patients that did not complete the treatment died within two years of diagnosis. This study is incredibly important in that it shows the effectiveness of a cisplatin-based treatment for osteosarcomas of the jaw for both the mandible and maxillary bones. This treatment obviously shows that cisplatin was the key element that determined a patient's chance of survival (Doval et al., 1997).

Results of Cisplatin-based Chemotherapy for Advanced Ovarian Carcinomas and the Impact of Intraperitoneal Chemotherapy:

Over thirty years ago, cisplatin was first approved by the Food and Drug Administration. At that time, it was only approved for the treatment of testicular and ovarian cancers. Its effects against other cancers were not yet proven at that time. Thus, when I began this project, I thought cisplatin would prove most effective against ovarian cancer. After doing literature searches, I have seen that this is not necessarily the case. In one study done at Jikel University School of Medicine in Tokyo, Japan, a twenty-four year old patient with a recurrent small cell ovarian carcinoma saw much better results using a docetaxel chemotherapy regimen as opposed to cisplatin. The patient received chemotherapy with cisplatin and etoposide after an initial surgery. However, the disease later recurred. After recurrence, the patient underwent chemotherapy with docetaxel and subsequently went into remission. The patient has now been disease free for more than two years (Niimi, Kiyokawa, Takakura, Ochiai, & Tanaka, 2006). A potential reason why cisplatin is not always an effective anti-cancer drug for small cell ovarian carcinomas is due to drug resistance. There is much speculation over how the ovarian cancer cells have developed this drug resistance. Some researchers have linked the resistance to phosphorylation of ERK2 by a kinase, which leads to activation of the ERK2 and subsequently, the cell becomes

resistant to the effects of cisplatin (Lee, Yoon, & Kim, 2007). Other researchers link cisplatin-resistance in small cell ovarian carcinomas to the cancer cell's mitochondrial DNA, which does not as readily form cross-links with the cisplatin molecule. Without forming these cross-links, cisplatin can not induce apoptosis of the cell (Hirama, Isonishi, Yasuda, & Ishikawa, 2006).

While doing literature searches on the chemotherapy treatments for ovarian cancer, I found a great deal of literature concerning intraperitoneal (IP) chemotherapy. IP chemotherapy is administered directly into the abdomen rather than being administered by a drip into the vein (intravenous administration). IP chemotherapy has been shown to be much more effective at treating ovarian cancer. A review of three large Phase III trials studying the benefits of IP administration of a cisplatin-based chemotherapy regimen showed marked increases in survival with this type of treatment as opposed to the traditional intravenous treatment option. One trial showed an eight month increase in survival, another was eleven months, and the final trial was a sixteen month increase. The side effects associated with IP chemotherapy, however, were more severe than with intravenous chemotherapy, so there is a trade-off (Elit et al., 2007). Despite these side effects, more attention should be paid to this type of chemotherapy for its obvious benefits.

Cisplatin and Birth Defects:

One final issue I would like to highlight as a result of my research on cisplatin-based treatment of ovarian cancer is whether cisplatin can be safely administered during pregnancy. Although this is not typically a concern for most patients with ovarian cancer since the disease usually has a later onset, there are some patients who are diagnosed with the disease as teenagers or in their early twenties. For this reason, cisplatin has been studied for its potential to cause birth defects and to see how it would affect a developing fetus. All the articles I have read recommend that a woman not get pregnant while taking cisplatin. The larger issue, however, is what to do in the case of a woman who is diagnosed with ovarian cancer after she is already pregnant. This is a controversial topic.

However, I did find a published case study on a woman who was diagnosed with ovarian cancer during pregnancy. She elected to begin chemotherapy with cisplatin, vinblastine, and bleomycin when she was eighteen weeks into her pregnancy. A healthy baby was born at thirty-one weeks with no birth defects. The mother experienced a secondary cancer to the liver five months later. However, it was treated with chemotherapy, and she remains disease free sixty-five months later (Motegi, Takakura, Takano, Tanaka, & Ochiai, 2007). This is an isolated case, but the results give hope to expectant mothers who are faced with the difficult decision of whether to undergo chemotherapy during pregnancy.

Conclusion:

After completing my extensive research on the numerous aspects of cisplatin-based chemotherapy, I have learned a great deal about the field of Oncology. This is a specialty I am very interested in pursuing after I complete medical school at the Medical College of Wisconsin in May 2011. On a broad level, I have seen that the field of Oncology is constantly evolving and changing. For instance, in thirty years, cisplatin has gone from a little known compound to a very effective chemotherapeutic agent, capable of treating a wide variety of cancers. After completing numerous literature searches and completing two case studies on patients, I have drawn a few conclusions about cisplatin-based treatments. The Cisplatin/5FU combination is very effective at treating recurrent head and neck cancer. Despite the severity of this type of cancer, remission becomes more likely with this type of chemotherapy, especially in combination with surgery, radiation therapy, or both. In the patient I studied with head and neck cancer, he showed remarkable and often rare results. One cycle of chemotherapy hit him so hard that he was placed in intensive care; yet, it proved effective. All subsequent PET and CT scans showed absolutely no evidence of disease. This is truly a remarkable case.

Osteosarcomas of the jaw bone are also very rare types of cancers. Yet, chemotherapy with a cisplatin-based treatment was shown to be the crucial element for survival in patients in one study. This study further illustrates the wide variety of effective uses for this platinum-containing anti-cancer drug.

Although the patient who I studied showed mixed responses to the initial treatment, his metastatic disease has been under control recently. His long-term response remains to be seen; however, it is clear that he has responded much better to the cisplatin regimen than to the furosemide regimen.

Studies on ovarian cancer, one of the first types of cancers treated with cisplatin chemotherapy regimens, have shown uncertain results for the effectiveness of a cisplatin-based treatment. Drug resistance appears to be the major source of concern. I wish I had been able to gain access to the medical file of a patient with ovarian cancer treated with cisplatin to further look at this. Possibly, I will be able to do this in the future. I am still very interested in this topic, and I believe more research can be done. My hope is to further study Oncology and Hematology in medical school because the future of cancer research and treatment seems to be filled with many possibilities and will likely result in many monumental discoveries. And hopefully, future discovery will lead researchers to the light at the end of the tunnel: a cure!

References

Adamo V, Ferraro G, Pergolizzi S, et al. (2004). Paclitaxel and cisplatin in patients with recurrent and metastatic head and neck squamous cell carcinoma. Oral Oncology, 40(5), 525-31.

BC Cancer Agency Cancer Drug Manual. (2006, March). Cisplatin CAS No. 15663-27-1. Report on Carcinogens, 11th ed. Vancouver: BC Cancer Agency.

Bensadoun RJ, Benezery K, Dassonville O, et al. (2006). French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: Results at 2 years (FNCLCC-GORTEC). International Journal of Radiation Oncology*Biology*Physics, 64(4), 983-94.

Cancer Center Patient #1 Medical Files. (2006). [HIPAA Laws prevent revealing further information.]

Cancer Center Patient #2 Medical Files. (2007). [HIPAA Laws prevent revealing further information.]

Cancer Research UK. (2007). Cisplatin/Fluorouracil (5FU). Retrieved April 20, 2007 from: http://www.cancerhelp.org.uk/help/default.asp?page=4007

Cancerbackup. (2007). Cisplatin/Fluorouracil (5FU). Retrived April 20, 2007 from: http://www.cancerbackup.org.uk/Treatments/Chemotherapy/Individualdrugs/Fluorouracil

Doval, DC, et al. (1997, October). Osteosarcoma of the jaw bones. British Journal of Oral Maxillofacial Surgery, 35(5), 357-62. Retrieved April 19, 2007 from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pubmed

Elit, L. et al. (2007, February). Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses. Cancer, 109(4), 692-702. Retrieved April 23, 2007 from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed

Hirama, M., Isonishi, S., Yasuda, M., & Ishikawa H. (2006, November). Characterization of mitochondria in cisplatin-resistant human ovarian carcinoma cells. Oncology Report, 16(5), 997-1002.

Kohno N, Kitahara S, Tamura E, et al. (2000). Concurrent chemoradiotherapy for locally unresectable head and neck cancer. Nippon Jibiinkoka Gakkai Kaiho, 103(8), 894-99.

Kohno N, Kitahara S, Tamura E, et al. (2002). Concurrent chemoradiotherapy with low-dose cisplatin plus 5-fluorouracil for the treatment of patients with unresectable head and neck cancer. Oncology, 63(3), 226-31.

Lee, S., Yoon, S., & Kim, D.H. (2007, February). A high nuclear basal level of ERK2 phosphorylation contributes to the resistance of cisplatin-resistant human ovarian cancer cells. Gynecological Oncology, 104(2), 338-44. Retrieved April 23, 2007 from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed

Medline Plus. ((2007). Cisplatin/Fluorouracil. Retrieved April 20, 2007 from: http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682708.html

Miller, Mitch. (2007). Cisplatin. Retrieved April 20, 2007 from: http://www.chm.bris.ac.uk/motm/cisplatin/htmlonly/cptitleframe.htm

Motegi, M., Takakura, S., Takano, H., Tanaka, T., & Ochiai, K. (2007, February). Adjuvant chemotherapy in a pregnant woman with endodermal sinus tumor of the ovary. Obstetrics & Gynecology, 109(2 Pt2), 537-40. Retrieved April 23, 2007 from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd

National Cancer Institute. U.S. National Institutes of Health. (2005, June 8). Oropharyngeal Cancer (PDQ®): Treatment. Bethesda, MD: National Institutes of Health. Retrieved June 26, 2006 from: http://www.cancer.gov/cancertopics/pdq/treatment/oropharyngeal/Patient/page 2

Niimi, S., Kiyokawa, T., Takakura, S., Ochiai, K., & Tanaka, T. (2006, September-October). Recurrent small cell carcinoma of the ovary treated with docetaxel: A case report. International Journal of Gynecological Cancer, 16(5), 1944-6. Retrieved April 23, 2007 from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd

Sai Man Liu. (1999). Preface: Why Cisplatin? Retrieved April 19, 2007 from: http://www2.mrc-lmb.cam.ac.uk/personal/sl/Html/Preface.html

Taylor, SG 4th, et al. (1997, December). Concomitant cisplatin/5FU infusion and radiotherapy in advanced head and neck cancer; 8-year analysis of results. Head Neck, 19(8), 684-91. Retrieved April 20, 2007 from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed

Umeda M, Komatsubara H, Ojima Y, et al. (2004). Lack of survival advantage in patients with advanced, resectable squamous cell carcinoma of the oral cavity receiving induction chemotherapy with cisplatin (CDDP), docetaxel (TXT) and 5-fluorouracil (5FU). Kobe Journal of Medical Sciences, 50(5-6), 189-96.

Wikipedia, the free encyclopedia. (2007, April 17). Fluorouracil. Retrieved April 20, 2007 from: http://en.wikipedia.org/wiki/5-fluorouracil