Is Less Really More?: Determining the Efficacy and Advantages of Low Dose Chemotherapy

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Abstract

Chemotherapy is the preferred treatment for patients with breast cancer nationwide; however, the dosage and duration of this treatment have come under recent scrutiny. The efficacy of high dose chemotherapy is many times inadequate, and the adverse physical effects resulting from this regimen have a negative holistic impact on the patients. Studies suggest that low dose chemotherapy, through antiangiogenesis, affects the spread of breast cancer carcinomas and may produce less harmful side effects in relation to the heart, brain, and eyes. Thus, oncological research proposes that a low dose regimen improves the patient's quality of life and may be an effective regimen to treat breast cancer, simultaneously. Chemotherapy administered in low doses, coupled with innovative treatments such as insulin potentiation, may prove to be a regimen able to weaken breast malignancies without debilitating the patient's daily functioning.

Is Less Really More?: Determining the Efficacy and Advantages of Low Dose Chemotherapy

As Breast Cancer percentages continue to escalate, the search for a cure continues to gain ground. Breast cancer is the most common cancer among women worldwide, and comprises 16% of female cancers (Pinto & Azambuja, 2011). Although scientists around the world strive to cure breast cancer, and cancer in general, it is important that research developments in alternative oncological treatments are given consideration. The search for a cure is important, and the vital nature surrounding a cure for cancer should not be discouraged. However, current treatment for breast cancer, chemotherapy more specifically, should perhaps draw some of the intention solely focused on a cure and be viewed with a scrutinizing eye concerning the duration, the liberality of use, and the negative effects of the treatment.

Chemotherapy has played the lead role in treating breast cancer since its induction. Physicians have advised women struggling against this illness to undergo the extensive, and often detrimental, effects of high dose chemotherapy. This regimen has somewhat been deemed the "holy grail" of breast cancer treatment, as well as the first line of defense. However, the physical implications and efficacy of the dosage should be considered before undergoing a traumatic treatment. The benefits of chemotherapy should not be overlooked; however, the extent to which chemotherapy treatments are performed should be closely examined by both the physician and the patient. A serious regard for the symptoms, melded with a passion and heart for treatment and the best possible outcome for a patient, should take precedence over a "the more the better" medical outlook. Although modern scientists unswervingly digress to high dose

chemotherapy for breast cancer patients, a conservative mindset regarding the duration of treatment in support of low dose therapy, and a realistic perspective of chemotherapy's efficacy, may warrant further study.

Background

Breast Cancer Pathophysiology

Breast Cancer is the most common malignancy in women worldwide except for skin cancer and is second only to lung cancer as the leading cause of cancer related death in women. Patients diagnosed with breast cancer that showing no axillary node involvement have a 98% five-year-survival rate. In contrast, there is only a 6% 5-year-survival rate for those with advanced stage breast cancer that has metastasized to distant sites (Buchner, Dirksen, Heitkemper, Lewis, & O'Brien; 2009). As this disease continues to impact more lives each day, the quest for an effective treatment has impelled scientists worldwide to optimize treatment.

Etiology. Cancer encompasses a variety of diseases of multiple causes that can arise in any cell of the body capable of evading regulatory controls over proliferation and differentiation. Normally the processes of cell division and proliferation are activated only when the body has a need for more cells, such as increased white blood cell count to fight an infection. Normal cells also respect the boundaries and territory of the surrounding cells in a phenomenon called contact inhibition. Cancer cells are characterized by a loss of contact inhibition; they "have no regard for cellular boundaries and will grow on top of one another and also on top of or between normal cells" (Buchner et al., 2009, p. 273). This lack of boundaries results in the proliferation of cancer that far exceeds healthy cell production.

Cancer progresses through three stages in an orderly and maliciously efficient manner: initiation, promotion, and progression. In initiation there is a mutation in the cell's genetic structure resulting from an inherited mutation or an environmental exposure to radiation, chemicals, or a viral agent. This altered cell has the ability to develop into a group of mutated neoplastic cells. These cells may continue to multiply and form a tumor, or they undergo apoptosis and are destroyed. Promotion, the next stage of cancer, is characterized by the "reversible proliferation of the altered cells" (Buchner et al., 2009, p. 276). Promoting agents, such as cigarette smoking, obesity, dietary fat, and alcohol consumption, are modifiable factors that increase the chances for the development of cancer by providing an environment in the body that potentiates cancer growth. The progression stage marks the final phase of cancer development. During progression, there is increasing growth of the tumor, increased invasiveness, and the metastasis of the cancer (Buchner et al.).

Epidemiology. Although the exact cause for cancer is unknown, it has been linked with many chemical, environmental, genetic, immunologic and viral origins. Most cancer cells exhibit a characteristic called genetic instability, considered the hallmark of cancer. Uncontained mutations in normal cells are rare because of the multiple built in mechanisms that prevent unwanted changes. Scientists characterize genetic instability as mutations stemming from aneuploidy (the loss or gain of chromosomes), intrachromosomal instability, repetitive sequences of short DNA, and point mutations (Buchner et al., 2009).

Genetic alterations in tumor suppressor genes, such as the BRCA-1 gene, have been linked with an increased risk of developing breast cancer due to heredity. Slight

changes in BRCA-1 inhibit its ability to stop tumor proliferation, and those with these mutations have a 40% to 80% lifetime chance of developing cancer (Buchner et al., 2009). Changes in the BRCA-2 gene, located on chromosome 11, evidently increase the risk of breast cancer as well. As many as 1 in 200 to 400 women in the United States may carry the BRCA-1 or BRCA-2 abnormalities (Buchner et al., 2009). These genetic modifications show that, despite a conscious avoidance of all modifiable risk factors, many women who develop this disease were already endangered since birth simply because of their genetic makeup. Thus, the maintenance of their quality of life through administration of low dose chemotherapy could significantly influence the treatment of the cancer and the self-efficacy of the patient.

The natural history of breast cancer fluctuates considerably from patient to patient, and the rate of the growth can range from slow to rapid. Tumor differentiation, estrogen and progesterone sensitivity, and the overexpression of human epidermal growth factor receptor 2 all affect cancer prognosis. Recurrence, or the advancement of the cancer, is considered the primary complication of breast cancer. Metastasis may be local or regional (confined to the soft tissue, mastectomy site, and axillary nodes surrounding the primary tumor), or they may be distant (involving the lung, brain, bone, and liver). Patients with a higher percentage of proliferative cells in the S phase of the cell cycle have a greater risk for recurrence and cancer deaths (Buchner et al., 2009). Low dose chemotherapy may take precedence as the vital treatment for breast cancer patients because it diminishes recurrence and halts the progression of cancer cell transportation from local regions to distant sites.

Chemotherapy

Breast cancer tumors respond to chemotherapy more than most malignancies. Physicians administer chemotherapeutic agents in combination treatments that allow the individual effects of select cytotoxic drugs to treat the cancer simultaneously. Cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, and epirubicin are the most prominent chemotherapy drugs used in breast cancer management, and are the deliberated prototypes in most major studies concerning chemotherapy usefulness (Matfin & Port, 2009).

Cancer chemotherapeutic drugs exert their effects through multiple means primarily on the cellular level. Their lethal capabilities rely on their ability to target the growth and replication of cancer cells by "disrupting the production of essential enzymes; inhibiting DNA, RNA, and protein synthesis; and preventing cell mitosis" (Matfin & Port, 2009, p. 183). Cytotoxic drugs treat tumors most effectively because they kill rapidly dividing cells. Chemotherapy efficiency is measured by the percentage of tumor cells killed, rather than the absolute number of cells destroyed, in a process termed "exponential killing" (Matfin & Port, p. 183).

Cellular resistance to cancer chemotherapy poses a major problem in breast cancer treatment. Acquired resistance to cytotoxic agents can be highly specific. This results from genetic changes in the tumor. Experimentally, a multi-drug resistant phenomenon has been observed. Scientists believe the presence of drug resistance results from an increase in the number of transporter genes involved in the intracellular influx of chemotherapeutic agents (Matfin & Port, 2009).

Chemotherapy drugs are divided into varying subgroups depending on their mechanism of action. Cell specific drugs exert their lethal action during particular phases of the cell cycle. Methotrexate, an antimetabolite, interferes with the DNA synthesis that takes place during the S phase of the cell cycle. It disrupts DNA synthesis progression, causing misincorporation into DNA, and alters the function of biosynthetic enzymes. Alkylating agents, such as cyclophosphamide and ifosphamide, are not specific to a certain cycle, and are therefore capable of impeding DNA synthesis when cells are dividing and when they are at rest. The disadvantage of these agents results from their dose related toxicity that occurs in rapidly proliferating cells of the bone marrow, reproductive tissues, and gastrointestinal tract (Matfin & Port, 2009).

The Efficacy of Low Dose Chemotherapy

In a nation that holds a "the more the better" outlook on medicine, it can be difficult to persuade a patient that in some instances, less is more. Patients receiving high dose regimens of chemotherapy find that they succumb to the destructive symptoms of their chemotherapy in order to observe the benefits of their treatment. When given in low doses over extended periods of time, chemotherapeutic agents effectively combat cancerous tumors. Further knowledge of antiangiogenic mechanisms, as well as its efficacy concerning vascular endothelial growth factors, may make low dose chemotherapy an attractive alternative to high dose chemotherapeutic regimens (Albertsson, Lennernas & Norrby, 2009; Andre, Kavallaris & Pasquier, 2010).

Antiangiogenic Effects

According to an analysis published in *Cancer Biology & Therapy*, metronomic chemotherapy is defined as, "the chronic administration of chemotherapy at low doses

without toxicity or with only minimal toxicity -- a frequent schedule of administration at close regular intervals and without prolonged drug-free breaks" (Giuseppe, Schiavon, Silletta, Vincenzi & Santini, 2007, p. 183). Angiogenesis refers to the process of new blood vessels branching from existing vessels in order to increase the vasculature and promote growth in the cancerous tumor. Conventional MTD therapy primarily disturbs the production of rapidly proliferating cancer cells in contrast to metronomic drug administration, which targets stable microvessel cells involved in angiogenesis. The normal endothelial cells produce at a much slower rate, which reduces the risk of drug resistance, in turn making the drug regimen more affective. Scientific support of metronomic administration reasons that low dose chemotherapy proactively affects the spread of cancer by focusing on the cells of the microvasculature that have greater sensitivity compared to the neoplastic cells of a proliferative tumor (Albertsson, et al., 2009; Andre et al., 2010).

A breast cancer tumor becomes increasingly dangerous as angiogenesis causes microvasculature stemming from the malignancy to proliferate throughout the body. Breast malignancies are fortified through glucose stores in the blood (Albertsson, et al., 2009). In fact, many tumors create their own insulin in order to draw the glucose into the cancer cells. An increase in angiogenesis causes a surge in the circulation of blood that feeds the tumor, leading to the exponential growth of the cancerous mass (Kerbel, 2007).

The vasculature also acts as a prime pathway for the transportation of seeding cancer cells to other areas of the body, leading to metastasis of the cancer. The migration of the cancer cells to the lymph nodes, and from thence to the lymph and other vital organs and tissues, depends on the angiogenesis of the prime and successive tumors

(Cronin, 2010). Thus, the fight against cancer must often start at the tumor's vasculature instead of the tumor itself. In order to destruct the malignancy at its foundation, its nutrient supply and means of metastasis must be obliterated. The philosophy motivating research regarding the administration of metronomic chemotherapy stems from its ability to halt the mobilization of endothelial cells from the bone marrow in order to arrest angiogenesis (Cronin, 2010; Albertsson, et al., 2009). In order to combat cancer expansion, studies suggest that low dose chemotherapeutic agents have an antiangiogenic capacity that

Browder et al. played a pivotal role in the development of breast cancer treatment when they first examined the effectiveness of low dose chemotherapy and its antiangiogenic capabilities. Tumor-bearing mice that were given cyclophosphamide, a standard chemotherapeutic drug for breast cancer, at their maximum tolerated dose required 3 weeks to allow for bone marrow recovery before their next dose (Browder, Butterfield & Kraling, 2000). The prolonged rest period over several weeks allowed the apoptosis, or cell death, that had taken to place in the tumor to be repaired. Hence, the tumor was only superficially affected and the high dose of cyclophosphamide minimally combated the cancer malignancy. When the same drug was administered to the mice at a rate of once a week, the antiangiogenic effects remained. The tumor cells did not have the chance to repair because of the continuous influx of cytotoxic therapy, and the mice withstood the toxic effects of the drug because they were only given one third of the maximum tolerated dose (MTD). This provocative study concluded that the focus of cancer treatment may need to shift from a purely transient cytotoxic regimen, to a more conservative antiangiogenic regimen that limits chemotherapy resistance (Browder et al.).

This research resurfaced in the sphere on oncological research, and has been cited in current studies that support a metronomic dosage of drugs in order to combat tumor angiogenesis (Kerbel, 2007; Zelnak & ORegan, 2007; Albertsson, et al., 2009; Andre et al., 2010)

Research continues to delve into the low dose chemotherapy regimen stipulated by Browder et al. more than ten years ago. Since the introduction of cytotoxic chemotherapeutic agents, high dose chemotherapy has remained the mainstay of cancer treatment; however, an antiangiogenic, low-toxicity preference may breathe new life into breast cancer research. The existence of fibrocystic lesions with a higher vascular density has been linked with increased risk of breast cancer and a microvessel density that is much more sensitive to antiangiogenic treatment. A study of 49 primary breast carcinomas, as well as a blind study of 165 patients with invasive breast cancer, showed that "an elevated tumor microvessel density was associated with poorer overall and relapse-free survival in all patients" (Zelnak & ORegan, 2007, p. 210). The evidence linking microvasculature to angiogenic chemotherapy treatment sparked further research into low dose chemotherapy efficacy by Zelnak and ORegan. Metronomic therapy using low doses of oral methotrexate and cyclophosphamide in patients with metastatic breast cancer demonstrated an overall response rate of 19%; the overall clinical benefit, which took into account complete response, partial response, and those with stable disease, indicated that 32% or patients given low doses of the same chemotherapy agents had a statistically significant improvement in disease treatment (Zelnak & ORegan).

In an article published in *Nature Reviews Clinical Oncology* it was noted that the administration of minimally toxic doses of chemotherapeutic agents "inhibits tumor

growth primarily through anti-angiogenic mechanisms while significantly reducing undesirable toxic side effects" (Andre et al., 2010, p. 456). A breast malignancy that is treated with a continual low dose regimen is not given time to recuperate between doses. The chemotherapeutic agents act as a consistent force against the proliferation and metastasis of the tumor, and the cancer is unable to combat the opposition (Andre et al.; Munoz, 2006).

High dose chemotherapy, as opposed to metronomic treatment, often elicits future resistance to the cytotoxic drugs that were administered. Andre et al. (2010) proposed that patients who had undergone this regimen were minimally affected by their chemotherapy at a later time because their bodies were able to produce antibodies against their chemotherapy during the weeks set apart for their recovery between doses. Unfortunately, the patients required a rest in between doses in order to physically recuperate, but the time period was found to be detrimental to the response of their breast malignancy to their chemotherapy. Each dose patients were given using a transient, high-dose approach contributed progressively more to their chemotherapy resistance, and progressively less to their fight against cancer (Andre et al., 2010).

Vascular Endothelial Growth Factor

The case for metronomic therapy is taken a step further when one examines an angiogenic polypeptide called vascular endothelial growth factor (VEGF). A variety of human malignancies, including breast, lung, gastrointestinal tract and brain tumors, exhibit this factor (Buchner et al., 2009). The "increased expression of VEGF has been shown to be of prognostic significance in both node-negative and node-positive breast

carcinoma, with higher VEGF expression associated with worse overall survival," and is an indicator of tumor vasculature growth potential (Donovan & Kummar, 2006, p. 9).

The production of VEGF is directly correlated to the angiogenesis and metastasis of breast cancer, while anti-VEGF substances are equally indicative of tumor inhibition. The importance of this polypeptide lies in the fact that the ability of a chemotherapeutic agent to oppose its effects has become a marked indicator of cancer remission. Patients with disseminated breast cancer have been noted to show higher serum VEGF concentrations in comparison to those with localized cancer. The presence of VGEF and its relationship with breast cancer may indicate the growth factor's specific role in angiogenesis and breast cancer development (Salter & Miller, 2007). Normal physiologic conditions exhibit a clear balance between angiogenic mediators and antiangiogenic substances. When the body is faced with a hypoxic or inflammatory stimulus, such as a malignant mass, "the balance is 'tipped' in favor of angiogenesis, and the switch promoting new vessel growth and recruitment is activated" (Salter & Miller, 2007, p. 518).

VEGF is responsible for endothelial cell activation that is necessary for the formation of microvasculature. The inhibition of this polypeptide is vital to decreasing angiogenesis and its role in breast cancer metastasis. VEGF causes "upregulation of integrin expression and changes in the cell cytoskeleton" (Donovan & Kummar, 2006, p. 10). The intricate, cellular process facilitates the movement and development of endothelial cells and the formation of new blood vessels. If chemotherapeutic drugs can act as a barrier to the production of VEGF, and thus stop angiogenesis at its roots, then their efficacy is greatly increased (Scharovsky, Mainetti & Rozados, 2009).

Research regarding the ability of low dose chemotherapy to restrict the formation of endothelial growth via VEGF was first performed, and published in the *Annals of Oncology.* Colleoni et al. studied 63 patients with metastatic breast cancer that had been previously treated with various chemotherapeutic agents. These patients had been given chemotherapeutic drugs previously, but had developed resistance to the cytotoxicity of their prescribed treatments because their chemotherapy was apportioned to them in high doses. The median serum VGEF level baseline at the initiation of the study was calculated at 315 pg/ml, and after 6 months the VGEF levels had decreased to a significantly lower level of 195 pg/ml. Colleoni et al. concluded that low doses of cyclophosphamide and methotrexate "demonstrated significant efficacy in pre-treated metastatic breast cancer" (Colleoni et al., 2002, p. 78). The study also indicated that a low dose chemotherapeutic regimen counteracts malignancy over time by inhibiting tumor proliferation by decreasing serum levels of VGEF (Scharovsky, Mainetti & Rozados, 2009). The groundbreaking research performed by Colleoni et al. has sparked research that further supports the VEGF role in therapeutic philosophy, and may lead to the implementation of this therapy in future oncological treatment.

Quality of Life

Patients with breast cancer are often seen as a physical diagnosis, a metastasizing tumor, or a medical challenge to many physicians. In reality, oncologists must recognize their humanity primarily, and then their disease, and all facets of their personhood should be of upmost importance. In order to accomplish holistic care, the quality of life of the patient must take precedence along with their physical healing. Fedele et al. stated this concept perfectly in their study found in the *European Journal of Cancer*:

> Metastatic breast cancer (MBC) is a highly heterogeneous disease, and decisions regarding its treatment must be driven by multiple considerations, including not only the clinical and biological parameters of the case but also patient preferences. Despite recent advances in our understanding of the biology of MBC and in the development of new types of therapy, the disease remains incurable. The goals of treatment are, therefore, palliative – prolonged survival, control of symptoms, improvement or maintenance of quality of life – all of which require a careful balance between treatment efficacy and toxicity (Fedele, Marino, Orlando, Schiavone, Nacci, Sponziello, Rizzo et al., 2011).

It has long been thought that in order to reap the benefits of chemotherapy one's quality of life must also suffer. The origins of chemotherapy were derived out of a mentality that the greatest amount of cytotoxic drugs tolerated by the patient would produce the greatest antitumor result. Chemotherapy has been pumped liberally into women fighting breast cancer for decades and has left society with the standard mental image of a woman in the midst of her battle: suffering from significant alopecia, ever-present fatigue, unable to participate in life's routines, and frail. In essence, the public has come to define chemotherapy as a drug that sustains the duration of life but saps the patient's ability to thrive. If low dose chemotherapy is to take its place amongst the mainstream treatments for breast cancer, patients may question its effectiveness: Is it really possible that cancer can be fought without completely dismantling the activities of daily life?

Levels of toxicity may measure chemotherapy benefits on the cellular level, but surveys concerning the health related quality of life take into account the effects of the

breast cancer on a woman's well-being (Richardson, Wang, Hartzema, & Wagner, 2007). In fact, if the quality of life drops significantly, the affected breast cancer patient may choose to discontinue treatment. When given the chance to live longer while suffering the repercussions of cytotoxic treatment or decrease one's lifespan but live free of the side effects, the patient will often choose the latter. If the side effects of chemotherapeutic drugs become so severe that the patient drops out of treatment, then the utility of chemotherapy is greatly compromised (Richardson et al.).

If further research illuminates anti-cancer success with a low dose chemotherapy regimen, a solution to women who will to experience the anticancer benefits of chemotherapy, without losing their quality of life in the process, may be on the horizon. Decreased doses of chemotherapeutic agents produce less harmful side effects without losing efficacy, making them an advantageous choice for oncologists nationwide.

Physical and Symptomatic Advantages of Low Dose Chemotherapy

Women battling breast cancer may believe that the extent of their trials resulting from their therapy is the loss of their hair and nausea. However, the potential for a more severe illness or symptoms to arise from the effects of chemotherapeutic agents is a grave reality that must be considered before entering into a chemotherapy regimen. The quality of life for breast cancer patients is already compromised due to neutropenic tendencies and a lingering muscle weakness. When high dosages chemotherapy are added to the quality of life equation, severe cardiac, cognitive, and ocular effects have been noted (Azim, Azambuja, Colozza, Bines & Piccart, 2011; Dutta, 2011; Schmid, Kornek, Scheithauer & Binder, 2006).

Cardiotoxicity

The effects of aggressive chemotherapy using the breast cancer patient's maximum tolerated dose suggest a trend between increased dosage and damage to cardiac health. For many breast cancer patients, the diagnosis of cancer is not their first medical complication. In today's modern society, where heart disease has grown to play the major role in mortality amongst the American public, it is vital that oncologists subject their patients to as little cardiac toxicity as possible. Low dose chemotherapy is able to target the patient's carcinoma without leading to proliferative cardiac cell death.

Anthracycline-based regimens using doxorubicin or epirubicin have become widely used cytotoxic drugs in the past thirty years. These agents carry a significant risk for cardiac toxicity, which increases directly with the administration of transitory high dose of chemotherapy using a MTD regimen (Azim et al., 2011; Matfin & Port, 2009). The elevated dose of cytotoxic drugs, more specifically those included from the arthracycline spectrum, correlated with an increase in cardiac injury. Free radicals derived from these toxic medications are believed to damage myocardial cells, but the symptoms of the damage often lie dormant for years following the immediate injury (Bird & Swain, 2008). Even though the effects of the aggressive chemotherapy are not always immediately diagnosed, the impact of the cardiac impairment can express itself years later as congestive heart failure. Azim et al. studied the likelihood of breast cancer patients acquiring congestive heart failure (CHF) in relation to chemotherapy dosages. They documented that patients who received cumulative doses not exceeding those used in standard regimens had an 8-year probability of acquiring CHF calculated at 0.37% compared with 4.97% probability for those who received higher doses (Azim et al.).

In 2008, *Clinical Cancer Research* published a study that delved further into CHF and the prevalence of chemotherapeutic regimens that promoted the disease. For eight years, 85 breast cancer patients were given a cumulative dose of 600mg/m2 of epirubicin and were tracked alongside 65 patients who were administered a cumulative dose of 300mg/m2 of epirubicin. The end results revealed that not one of the sixty-five patients given the lower dose acquired CHF, but 2% of those given the larger 600mg/m2 dose were diagnosed with the cardiac disease. Although 2% may seem like a small margin, in the scheme of the big picture that small percentage amounts to thousands of breast cancer patients diagnosed with heart failure. Epirubicin is neither an obscure chemotherapeutic drug, nor is it considered to be more harmful or toxic compared to other cytotoxic drugs (Bird & Swain, 2008). The effects of this study gave scientists heightened insight into cytotoxic regimens as a whole, and the significance the amount and duration of a drug given has on the heart compared to the drug itself.

In those patients who had risk factors for cardiac complications in addition to their malignancy, such as old age, smoking, hypertension, mediastinal radiotherapy, and preexisting coronary artery disease; the harm that ensued high dose chemotherapy was even greater. Acute cardiac side effects of the high dose cytotoxic medications included left ventricular dysfunction, arrhythmias, pericarditis, and myocarditis (Bird & Swain, 2008).

In addition to congestive heart failure, cardiomyopathy in general has also been linked with the ingestion of high doses of chemotherapeutic drugs. The connection between increased dosages of doxorubicin and damage to cardiac musculature is often apparent 2 to 3 days after the initiation of high dose therapy. A patient may also present

with arrhythmias, conduction disorders, and acute pericarditis and myocarditis after undergoing an anthracycline-based regimen. Instances of dose-dependent cardiomyopathy, secondary to cytotoxic medication ingestion, often lead to chronic debilitation of the patient's cardiac health (Matfin & Port, 2009).

The rise in dosage correlated diametrically to the percentages of those who developed CHF and/or suffered from a cardiac event. After supporting the existence of the aforementioned relationship, *Expert Reviews* (Yusuf, Ilias-Khan, & Durand, 2011) expanded on the specific ways the chemotherapeutic anthracycline-based regimen negatively affects the heart. Cytotoxic drugs lead to cardiomyopathy by disrupting myofilament protein synthesis, resulting in the necrosis of the cardiac cells inhibited by the resulting lack of cardiac proteins. These mechanisms have been linked with the swelling of the mitochondria and chromatin loss hours after the initial maximum tolerated dose. These microscopic changes present as cardiac remodeling and eventually lead to left ventricular systolic failure, diastolic dysfunction, and even mortality (Yusuf et al.).

Chemotherapy Induced Cognitive Impairment

As breast cancer awareness has increased, so has the demand for research concerning the specifics of the illness. In an article found in the *Journal of Cancer Research and Therapeutics*, clinical neuropsychologist Varsha Dutta discussed the decrease in cognitive capabilities reported by women following chemotherapy called CICI, or chemotherapy-induced cognitive impairment. Terms such as "chemobrain" and "chemofog" have been coined to describe women who have reported experiencing increased difficulties with concentration or planning and loss of short-term memory. Chemotherapeutic drugs that induce an inflammatory cellular environment raise TNF

Alpha levels that have been shown to produce neuronal injury and disrupt brain metabolism because they target the nerve fibers that act as transmitters for electric signals in the brain (Dutta, 2011).

The *Journal of Pain and Symptom Management* reported: "The incidence of long term CICI can affect a significant portion of cancer survivors, with an incident rate ranging from 16 to 75%," and has been shown to progress for 2 to 10 years after its manifestation in some patients (Argyriou, Assimakopoulos, Iconomou, Giannakopoulou & Kalofonos, 2011, p. 127). This sheds light on the concept that the cognitive effects of high dose chemotherapy, be they serious or simply inconvenient, may endure for years, and the cessation of symptoms is not contingent on chemotherapy termination.

The *Journal of the National Cancer Institute* found that those who received high dose chemotherapy had a statistically significant increased risk of cognitive impairment compared with those who did not undergo chemotherapy. However, low dose chemotherapy treatment was also included in the equation, and the same study showed a decreased risk for CICI in patients taking metronomic doses. In fact, that same selection of patients did not show a statistically significantly elevated risk compared with the control group comprised of healthy individuals who did not have breast cancer, and had no previous exposure to chemotherapeutic agents (Schagen, Muller, Boogerd, Mellenbergh & Van Dam, 2006, p.1743). It was concluded that the probability of a patient developing debilitated cognitive capabilities decreased when cytotoxic drugs were received in smaller increments on a more continual basis.

In addition to brain matter as a whole, the hippocampus is also a target, due to its glucocorticoid receptors. Chemotherapeutic agents elevate glucocorticoids, which can

have “a detrimental effect in the form of heightened susceptibility to neurotoxic stress, obstructed neuronal growth, and increased cell death within the hippocampus” (Dutta, 2011, p. 267). Simply stated, Dutta contends that increased doses of cytotoxic drugs induce a heightened stress response, causing the release of glucocorticoids, which in turn damages the hippocampus. The end result of this process is a decrease in functioning of the brain, and a symptomatic response shown as an inability to focus, or as a patient in the study stated, “vague forms of cloudiness that often comes in the way of daily planning of even routine chores” (Dutta, 2011, p.266).

Optic Side Effects

(sentence erased) Vision is an imperative component in evaluating a breast cancer patient’s quality of life, and risk to one’s visual acuity can essentially dissuade a decision to undergo chemotherapy. The recommendation of cytotoxic drugs for treatment of cancer requires an attention to detail and a holistic approach that encompasses all the potential physical harm of the treatment before the first dose is administered. If a breast cancer patient realizes she is consuming drugs that have a risk for a loss in vision, she may reconsider the end result of her chemotherapy prescription and opt for an alternative approach (Schmid, Kornek, Scheithauer & Binder, 2006).

In an ideal medical environment, oncologists would work closely with each medical profession, including the ophthalmologist, and cover the entire spectrum of potential obstacles when treating a breast cancer patient. However, physicians do not have the time, or the capabilities, to converse with every single player on a patient’s healthcare team. In view of this reality, it is thus even more critical that oncologists develop a wide scope of knowledge of the visual symptoms of the chemotherapeutic

drugs they prescribe, and work closely with the patient recipient of the cytotoxic treatment to ensure that their needs are the number on priority.

Visual deformities, as a result of cytotoxic medication, will often progress slowly and subtlety. Patients will report ocular disturbances when they have grown to be a nuisance, but by that time the chemotherapy has usually caused serious damage. At first, the clinician and breast cancer patient may find it difficult to detect many of these ocular toxicities. However, if the symptoms are not recognized early, the optic damage may have progressed to the point of becoming irreversible (Schmid et al., 2006).

Further research has been performed to evaluate optic nerve and retinal changes in patients exposed to high dose chemotherapy. *The American Journal of Medical Sciences* published the research of Dr. Preston Blomquist, who observed that ocular toxicity is seen in up to 25% of patients who have undergone a high-dose intravenous therapy using the chemotherapeutic agent methotrexate (Blomquist, 2011). Periorbital edema, orbital pain, blurred vision, photophobia, and conjunctivitis were all taken into account under the definition of ocular toxicity. Blomquist's metanalysis found that at the culmination of chemotherapy varying degrees of vision loss and microvascular lesions on the optic disc and retina indicated widespread ocular toxicity potentiated by a high dose regimen. Noted side effects included flashes of light across the visual field caused by paclitaxel and docetaxel, retinal hemorrhages due to interferon therapy, and keratopathy as a result of an aggressive tamoxifen regimen. In light of his research he concluded, "Ocular toxicity is common at high dosages," and "the risk of toxicity is much lower with low-dose treatment" (Blomquist, 2011, p. 65).

For patients receiving combination or single-agent chemotherapy it is felt that ocular toxicity may occur with more intensive regimens, otherwise noted as high dose chemotherapy. Chemotherapeutic drugs from all classifications induced ocular toxicities. Noted opthalmic symptoms of cyclophosphamide included blurred vision, keratoconjunctivitis sicca, pinpoint pupils, and blepharcoconjunctivitis. Cisplatin was connected to papilledema, optic neuritis, color blindness, and cortical blindness. Injections of 5-fluorouracil produced a host of negative symptoms: blurred vision, ocular pain, circumorbital edema, and irritative conjunctivitis comprised only part of the list. In review, the presence of optic effects subsequent to high dose chemotherapy may play a role in the development of an oncological preference geared toward metronomic chemotherapeutic administration (Wickremasinghe, Dansingani, Tranos, Davey, Liyanage & Jones, 2007).

The Adjuvant Potential of Low Dose Chemotherapy

The compatibility of low dose chemotherapy, in relation to adjunctive agents, must be established if it is to act as a contributing factor in the realm of oncological treatment. Scientific dialogue surrounding the use of insulin in potentiating the effects of chemotherapy foresees that lower doses of cytotoxic drugs, when coupled with insulin administration, may be effective in fighting breast cancer. This hypothesis, though still fresh in the research field, may prove to establish itself as more than optimism if fostered through further scientific understanding.

Insulin Potentiated Chemotherapy

Surprisingly, the role of insulin in the transportation of chemotherapeutic agents intracellularly may be a contributing factor in treating breast cancer malignancies. Those

in support of Insulin Potentiation Therapy maintain that administering insulin along with low doses of chemotherapy helps to promote the uptake of the cytotoxic drugs by tumors. Their research suggests that because a greater percentage of the chemotherapeutic drugs are engulfed by the tumor, less of the anti-cancer drugs are needed to ensure malignancy destruction (Damyanov, Radoslavova, Gavrilov & Stoeva, 2009).

It is important to note the effects insulin has on healthy cells that led scientists to research its value in fighting cancer. Advocates of Insulin Potentiated Therapy believe that cancer cells are more sensitive to insulin because they consume more glucose than normal cells (Memorial Sloan-Kettering Cancer Center, 2011). Insulin increases cell membrane permeability and facilitates the movement of particles and toxins across the semipermeable membrane. It also, "Influences the metabolic processes with a number of physicochemical changes which help the recuperating processes" (Damyanov et al., 2009, p. 712). Simply stated, insulin has the ability to carry multiple biological factors into the cell, as well as the ability to alter cellular function in order to ignite the healing process.

The first in-depth study to elaborate in insulin potentiated therapy was cited in *Clinical Cancer Pharmacology.* This research examined the effects of insulin in a randomized clinical trial comprised of 30 women with metastatic breast cancer (Lasalvia-Prisco, Cucchi, Vazquez, Golomar, Lasalvia-Galante & Gordon, 2004). All of the patients had measurable lesions that were resistant to flourouracil, adriamycin, cyclophosphamide, and hormone therapy. They found that the hypothesized antitumoral effect of methotrexate was supported by their data, and that methotrexate administered with insulin produced the greatest benefit in their patients. Those who were given the

combination of the two, instead of solely insulin or solely methotrexate, had the lowest increase in tumor size and greatest antitumoral influence (Lasalvia-Prisco et al., 2004).

Lasalvia-Prisco et al. played a pivotal role in placing insulin potentiated therapy on the radar for other oncology researchers (Damyanov et al., 2009). In an article published in the *Journal of BUON*, it was projected that insulin stayed true to its role in normal functioning as a carrier of particles when given with chemotherapy. This study theorized that the increased permeability of the cancer cell due to insulin administration allows for an increase in the levels of the intracellular chemotherapeutic agents (Damyanov et al., 2009; Memorial Sloan-Kettering Cancer Center, 2011). Insulin also affected the metabolism in the tumor cells, thereby increasing the amount of cells that stayed in the S phase- a phase during which they are more sensitive to cytotoxic agents. Tumor cells also have an increased number of insulin receptors, which make them more susceptible to both of these processes and significantly more vulnerable to low doses of chemotherapy (Damyanov et al., 2009).

The patients who comprised this study were all diagnosed with metastatic malignancies that had been unsuccessfully treated with previous regimens. Their chemotherapy was well tolerated and the only side effects they identified were weakness and sleepiness following their first injections. Their labs showed no toxicity and there were minor elevations in their liver enzymes in the first six weeks but they normalized "without any addition measures during treatment" (Damyanov et al., 2009, p. 714).

Damyanov et al. and Lasalvio-Prisco et al. performed small studies, but the evidence formed may prove to have a large impact on the future of chemotherapy. These studies advocate for the benefits of a low dose regimen in preference to high doses of

chemotherapy, and offer hope of developing alternative approaches in the fight against breast malignancy. Further research is required to construct a holistic view of this therapy; however, the flexibility of low dose chemotherapy considering its minimal toxicity, makes it a prime candidate for adjunctive chemotherapy research.

Conclusion

Women around the world diagnosed with breast cancer are battling every day for survival. The effects of high dose chemotherapy have formed a distorted picture of the necessity for a decreased quality of life in order to insure cancer remission. The evidence supporting low dose chemotherapy and its efficacy may potentially act as an answer for women who desire to hold the upper hand in their fight against cancer, while continuing to perform activities of their daily life.

The allure of low dose chemotherapy is in large part due to its antiangiogenic basis. Those in favor of metronomic chemotherapy administration propose this regimen combats breast malignancies at their foundation by impeding the tumor microvasculature. The inability of a tumor to create vessels cuts off its nutrition supply and restricts further metastasis. Vascular endothelial growth factor has also been targeted as a key factor in tumor angiogenesis. Low doses of chemotherapeutic agents decrease the release of this polypeptide and halt the endothelial growth that forms the tumor blood vessels. This physiologic finding, if nurtured through future scientific research, may establish low dose chemotherapy as an effective, yet conservative, breast cancer therapy.

Reduced dosages of chemotherapy may improve the breast cancer patient's quality of life by limiting the probability of serious side effects. Studies propose that a low dose regimen has been linked with decreased cardiotoxicity, maintenance of cognitive

functioning, and lesser optic destruction. A diminished symptomatic reaction to chemotherapy increases the affected breast cancer patient's ability to thrive.

Low doses of chemotherapy demonstrate increased compatibility and the ability to combine with other therapies in order to potentiate the effects of the cytotoxic drugs. With additional research, insulin may be proven to maximize the therapeutic benefit of chemotherapy and limit the destruction of cytotoxic drugs on healthy cells. The perceived benefits of insulin potentiated therapy inspire inquisition regarding advances in adjuvant treatments that use low dose chemotherapy, and may indicate the future of conservative chemotherapy dosing.

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