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The Effect of Fasting on Toxicity Profiles of Patients Undergoing Chemotherapy

Sarah Pope

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The Effect of Fasting on Toxicity Profiles of Patients Undergoing Chemotherapy

Abstract
Cancer is the second leading cause of death overall in the United States yet accounts for most cases of premature mortality in those younger than 85 years of age. Chemotherapy acts as one of the major treatment options. Unfortunately, the toxic properties of chemotherapy are not limited solely to neoplastic tissue and the quest for cancer reduction or elimination often leads to serious side effects. However, preliminary research has demonstrated that cycles of short-term fasting (STF) promote selective toxicity of cancer cells while protecting normal, healthy cells from chemotoxic damage, suggesting the practice may be a promising adjunct to human chemotherapy. Yet, is fasting safe, efficacious and tolerable? In order to explore the potential of fasting as an adjunct to cancer treatment, we must first ask: can periodic fasting alter toxicity profiles in cancer patients undergoing chemotherapy?

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Keywords
Breast cancer, fasting, chemotherapy, short-term calorie restriction, side-effect profile

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The Effect of Fasting on Toxicity Profiles of Patients Undergoing Chemotherapy

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 2017
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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Abstract

Background:

Cancer is the second leading cause of death overall in the United States yet accounts for most cases of pre-mature mortality in those younger than 85 years of age. Chemotherapy acts as one of the major treatment options. Unfortunately, the toxic properties of chemotherapy are not limited solely to neoplastic tissue and the quest for cancer reduction or elimination often leads to serious side effects. However, preliminary research has demonstrated that cycles of short-term fasting (STF) promote selective toxicity of cancer cells while protecting normal, healthy cells from chemotoxic damage, suggesting the practice may be a promising adjunct to human chemotherapy. Yet, is fasting safe, efficacious and tolerable? In order to explore the potential of fasting as an adjunct to cancer treatment, we must first ask: can periodic fasting alter toxicity profiles in cancer patients undergoing chemotherapy?

Methods:

A thorough and time-consuming search of MEDLINE-Pubmed, CINAHL, Clinical key, Web of Science and Google scholar using the terms fasting, cancer and chemotherapy. The studies were assessed using GRADE criteria.

Results:

The search revealed 386 articles of which 2 studies met exclusion criteria and addressed the clinical question. Fasting prior to chemotherapy significantly reduced both signs (hematologic) and symptoms (fatigue, nausea, vomiting, abdominal cramps, and weakness) of toxicity associated with chemical cancer treatment.

Conclusion:

Current research suggests that fasting during cancer therapy is safe and may help protect against chemotoxicity, implying the practice could conceivably be employed as an adjunct to chemotherapy. The major limitation of this review lies in the sparseness of human trials that focus on fasting and chemotherapy. Of these studies only one is a randomized controlled trial (pilot), the sample size for each
study is small with a relatively homogenous participant population (women >60yo with breast cancer). Also, the number of hours spent fasting was different between the trials. More research is necessary with larger, more diverse sample sizes.

Keywords: Short-term fasting, chemotherapy, neoplasm
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To The PA class of 2017: To The PA class of 2017: You continuously offered an example of impressive skill and impeccable grace. Thank you for allowing me the opportunity to share in this process.
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Figure 1: Self-reported side-effects after chemotherapy with or without fasting

List of Abbreviations

DSR Differential Stress Resistance
STF Short-Term Fasting
ROS Reactive Oxygen Species
TAC Docetaxel (Taxotere), Doxorubicin (Adriamycin) and Cyclophosphamide
PBMC Peripheral Blood Mononucleated Cells
The Effect of Fasting on Toxicity Profiles of Patients Undergoing Chemotherapy

Background

Cancer is the second leading cause of death overall in the United States and accounts for most cases of pre-mature mortality in those younger than 85 years of age.\textsuperscript{1} According to the US National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) Database, the individual lifetime risk of developing some form of cancer is 1 in 2 for men and 1 in 3 for women.\textsuperscript{2} Although heart disease is a more prolific arbiter of death, cardiovascular treatment has advanced to such a degree that North America has seen a 45% reduction in cardiovascular mortality within the past 66 years.\textsuperscript{1} By contrast, cancer mortality rates increased between 1950-1990 and although cancer related death has decreased from 1990-2010, this has been marginal in comparison to cardiovascular statistics (a reduction of 21% for men and 12.6% for women).\textsuperscript{1,3}

Traditional oncological care relies on one of three modalities, alone or in conjunction: surgery, radiation and/or chemotherapy.\textsuperscript{4} Chemotherapy acts as one of the major treatment options and has enhanced the efficacy of medical management since 1950.\textsuperscript{5} The standard for chemotherapeutic treatment utilizes medication designed
with direct toxic effect on neoplastic cells. Unfortunately, the toxic properties of chemotherapy are not limited solely to neoplastic tissue and the quest for cancer reduction or elimination often leads to serious consequences such as alteration of the normal hematologic profile, nausea & vomiting, fatigue, weakness, hair loss, headaches, gastrointestinal discomfort, peripheral neuropathy and even death.\textsuperscript{6}

The ability to develop and employ pharmacological agents that differentially target cancerous tissue has long vexed the research and medical community. However, recent research\textsuperscript{5} has demonstrated that cycles of short-term fasting (STF) promote selective toxicity of cancer cells while protecting normal, healthy cells from chemotoxic damage.

The ability of STF to render cancer cells vulnerable to pharmacological agents is known as differential stress resistance (DSR).\textsuperscript{7,8} Research utilizing in-vitro and mouse models have demonstrated that under conditions of nutrient deprivation, normal cells are capable of reorganizing molecular function to support maintenance and repair activities—a relative quiescence. By nature of oncogenic alteration, cancer cells do not respond to anti-growth signals and it is believed that unchecked division in absence of nutritional support leads to an accumulation of reactive oxygen species (ROS) with subsequent apoptosis and vulnerability to chemotherapy.\textsuperscript{5–8} Since damage to healthy cells (with subsequent side-effects) limits the
length and dose of medication used in cancer therapy, STF’s potential to protect against chemotherapy’s harmful effects may act as a promising adjunct to standard treatment.

Indeed, animal studies that have operated under this premise have demonstrated enhanced medical efficacy of a number of chemotherapy drugs, allowing for cancer cell sensitization as well as the ability to increase medication dose while limiting detrimental biological consequences. Could these promising results from non-human studies be translated into applicable clinical practice? That is, could STF be integrated within cancer therapy in a safe and tolerable manner? The need for better cancer treatment, specifically where chemotherapy has become a main course of therapy for cancer treatment, brings this question into review.

**Methods**

A thorough search of MEDLINE-Pubmed, CINAHL, Clinical key, Web of Science and Google scholar using the terms fasting, cancer and chemotherapy. Studies were included if they were conduct on humans and published in English in the last 5 years. Articles were then appraised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines. (cite the working group website, can be copied directly from an example
Results

A systematic search for relevant literature revealed 386 results. Screening of these titles and abstracts led to an exclusion of 380 studies due to duplication and/or irrelevance. Of the 6 remaining articles, 4 were rejected for their inability to meet eligibility criteria. The two articles kept for review include a case series report\(^9\) and a randomized pilot study.\(^{10}\) A quality summary of these articles can be found in Table 1: Quality Assessment of Reviewed Studies.

**Safdie et al (2009)**

In this case series report,\(^9\) 10 patients with heterogeneous cancer diagnoses were given the option of fasting prior to and/or after receiving chemotherapeutic agents during the period of April 2008 to August 2009. The 10 patients who volunteered for this investigation chose to fast for at least 1 cycle of chemotherapy with a minimum of 48 hours (and up to 140 hours) prior to treatment and/or 5-56 hours after medication administration. The main intent of this study was to collect information regarding chemo-toxicity both with and without fasting; information from this was provided to help determine feasibility of randomized controlled trials utilizing STF.\(^9\)

Patients were recruited for observation from a variety of
oncology clinics across the United States. The only eligibility criterion required to participate was the willingness to include STF within their standard chemotherapy treatment(s) at least 48 hours prior to medication administration. Ten patients volunteered to employ STF—7 women and 3 men with varying diagnoses, including 4 patients with breast cancer, 2 with prostate cancer and 1 patient each with, uterine, esophageal, ovary, or lung (non-small cell carcinoma) cancer. Some patients chose to fast beyond 48 hours before chemotherapy (up to 140 hours) and all 10 participants fasted after receiving medication for at least 1 cycle of chemo. As this was a case series report rather than a randomized control trial, blinding was not possible; patients volunteered to fast and were fully cognizant of this choice. Eight of the 10 patients fasted during some but not all cycles of chemotherapy, and were thus able to act as their own controls.⁹

To assess the potential impact of fasting on side-effect profiles, patients were provided a self-assessment survey that contained 16 common side effects associated with chemotherapy. This survey was developed as a guide by Safdie and colleagues using the Common Terminology Criteria for Adverse Events of the National Cancer Institute version 3.0. Self-reported side effects were graded from 0-4, 0 being no side effect and 4 representing “severe.” These adverse experiences were further subdivided into “gastrointestinal, nervous
system and general” categories. It is known that chemotherapy exerts cumulative effects. That is, as the number of chemotherapy cycles increases, so too does the potential for associated adverse effects; to account for this phenomenon, researchers within this study assessed data serially (see Figure 1). All patients reported a decrease in severity of chemotherapy side effects when undergoing STF during treatment. Although only reduction of fatigue and weakness were statistically significant, it should be noted that vomiting, abdominal cramps, diarrhea and mucositis were nearly nonexistent during the STF cycles.\textsuperscript{9}

**De Groot et al (2015)**

This randomized pilot study\textsuperscript{10} aimed to determine if STF could be safe, tolerable and efficacious when undertaken during chemotherapy for HER-2 negative breast cancer. In particular, de Groot and colleagues were interested in what effect STF may have on toxicity profiles in the form of undesirable side effects and hematologic function. To determine this, 13 women with stage II or III HER-2 negative breast cancer were recruited for observation. Inclusion criteria required that these women were to undergo TAC (docetaxel, doxorubicin and cyclophosphamide) treatment, were above the age of 18, had a life expectancy > 3 months, had no prior diagnosis of diabetes mellitus, were not pregnant or nursing and began with
adequate cardiac, liver, kidney and bone marrow function.\textsuperscript{10} Subjects were randomly assigned into 1 of 2 groups. After blind allocation 7 patients were designated to fast for 24 hours before and after chemotherapy while 6 were to maintain a “healthy” diet. The content of the \textit{ad libitum} diet was not given in detail but it was mentioned that patients were encouraged to eat at least 2 pieces of fruit per day. As one would expect, it was not feasible to conceal which of the 2 groups each patient belonged. Thus, subject blinding was not possible for this study.\textsuperscript{10}

In order to assess the effect of STF during chemotherapy, serial blood samples were collected prior to and after TAC administration and analyzed for metabolic, endocrine, hematologic and inflammatory parameters. Damage to peripheral lymphocytes and monocytes was inferred via accumulation of phosphorylated serum H2AX, the presence of which has been implicated in the damage of healthy cellular material.\textsuperscript{11,12} After each cycle of chemotherapy, patients in both study and control groups provided a self-report of TAC associated side effects ranging from mild to severe via the Common Terminology Criteria for Adverse Events version 4.03.\textsuperscript{10}

Statistical analysis of patient data determined no significant difference in self-reported side effects such as fatigue, diarrhea, dizziness, nausea, mucositis and etc.\textsuperscript{10} However, there was a
significant decrease in levels of phosphorylated H2AX in peripheral myeloid cells seen in the STF compared to the non-STF group 30 minutes and up to 7 days after chemotherapy. This observation may suggest attenuation of DNA damage to peripheral blood mononucleated cells as a result of fasting during pharmacological management of breast cancer. Serum analysis also demonstrated a significant increase in erythrocyte and thrombocyte levels within the STF group.10

Discussion

Non-human preliminary studies5-8,13 have suggested a benefit of STF via molecular signaling pathways that involve insulin-like growth factor-I (IGF-I) and glucose. This research has demonstrated that fasting decreases circulating levels of IGF-I. This decrease in IGF-I leads to a shift of energetic resources in healthy, normally functioning cells to a state of relative quiescence while cancerous cells continue the processes of translation and division despite a condition which would normally temper growth.5,7,13 As such, it has been postulated that this unchecked cellular division in absence of sufficient fuel for aerobic respiration (glucose) leads to an accumulation of reactive oxygen species (ROS) and DNA damage which renders cancerous cells more susceptible to chemotherapeutic agents while selectively
protecting healthy tissue.\textsuperscript{5-8} This phenomena is known as differential stress resistance (DSR).\textsuperscript{5-8} Both in-vitro and animal models\textsuperscript{5,7,8} have supported this proposed mechanism of fasting’s benefit. If found to be safe and feasible to use in human patients, DSR could potentially be applied in oncological management regardless of cancer type.

The studies\textsuperscript{9,10} reviewed here directly address both safety and viability of STF during chemotherapy while also offering a nod to potential clinical benefit. Safdie and colleagues\textsuperscript{9} gathered self-reported side effects from 10 patients with a variety of different cancer diagnoses and varying chemotherapeutic treatments. This was not a clinical trial, as such, patients were not placed into a control group. However, patients did often act as their own control by utilizing STF during some (but not all) of their fasting cycles.\textsuperscript{9} All 10 patients who undertook STF reported a decrease in chemotherapy associated side effects (see Figure 1). Not only were side effects diminished, STF did not appear to hinder the benefit of chemotherapy as demonstrated by a reduction of cancer burden and/or endocrine markers such as CA-125 and PSA.\textsuperscript{9}

However, it should be acknowledged that by nature of being a case report study, major limitations exist within this piece of research. Of particular note is the very small sample size, inability to blind patients to treatment type and lack of an established control group.
Yet, despite these limitations, the self-reported improvement in adverse symptoms associated with chemotherapy and apparent lack of detrimental consequence during STF bodes well for future clinical trials employing STF during chemotherapy.

More recently, de Groot et al\textsuperscript{10} were able to demonstrate a potential benefit of STF on hematologic parameters typically deranged through chemotherapeutic toxicity. As mentioned in the results section for this paper, the de Groot et al study\textsuperscript{10} was unable to glean a significant difference between the control and STF groups in regard to side effect profiles, absolute neutrophil and leukocyte counts or levels of IGF-I. In light of this, future research employing STF and chemotherapy may see an enhanced benefit of STF if dexamethasone is not given prophylactically and/or with an extension of STF beyond the 24 hours prior to and after chemotherapeutic treatment.

Although the self-reported side effect profile did not appear to be altered by STF, a significant improvement in certain hematologic parameters (ie, erythrocyte and thrombocyte count) as well as a decrease in a by-product of PBMC genetic damage was noted. Not only was this improvement discerned, it can also be stated that fasting for these patients (7 total with HER-2 negative breast cancer) was both safe and tolerable.\textsuperscript{10}

The most obvious limitations of this study are its small sample
size and attrition of 2 subjects from the STF group. Aside from its limited power, this trial has a number of other subtle yet potentially dramatic confounders. For example, both dexamethasone and pegfilgrastim (a granulocyte colony stimulating factor) were given to all patients while undergoing cycles of TAC.\textsuperscript{10} The use of these drugs may have led to alterations in metabolic and hematologic profiles, which could have obscured the potential benefit of STF. Finally, patients in the STF group undertook only 48 total hours of fasting whereas prior research\textsuperscript{9,13} has suggested that longer periods of fasting may be required for the metabolic benefit fasting may imbue.

Conclusion

The current studies that have employed STF as an adjunct to chemotherapy do not provide adequate evidence to suggest the judicious application of this method currently. Only randomized controlled trials with a sample size sufficient to offer substantial power could establish STF as a beneficial compliment to traditional cancer treatment modalities. However, the two studies reviewed here do imply that STF may be safe, feasible and perhaps even beneficial to study in future randomized controlled trials.
References


5. Lee C, Longo VD. Fasting vs. dietary restriction in cellular protection and cancer treatment from model organisms to patients,


11. Olive PL, Banath JP. Phosphorylation of histone H2AX as a


Table I: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Study Designs</th>
<th>Downgrade Criteria</th>
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<td></td>
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<td></td>
<td>Limitations</td>
<td>Indirectness</td>
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<td>chemotoxic symptoms</td>
<td>1</td>
<td>Case Series Report</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td>hematologic profile</td>
<td>1</td>
<td>Randomized pilot study</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not Serious</td>
</tr>
</tbody>
</table>

<sup>a</sup> Small sample size
<sup>b</sup> Attrition of 2 original participants
Figure 1. Self-reported side-effects after chemotherapy with or without fasting. Data represent average of CTCAE grade from matching fasting and non-fasting cycles (Ad Lib). 6 patients received either chemotherapy-alone or chemo-fasting treatments. Self-reported side effects from the closest two cycles were compared one another. Statistic analysis was performed only from matching cycles. Data presented as standard error of the mean (SEM). P value was calculated with unpaired, two tail t test. (*, P<0.05).