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Fasting Reduces the Incidence of Delayed-Type Vomiting Associated with Doxorubicin Treatment in Dogs with Lymphoma[1]

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Abstract

Fasting reduces gastrointestinal cellular proliferation rates through G_1 cycle blockade and can promote cellular protection of normal but not cancer cells through altered cell signaling including down-regulation of insulin-like growth factor 1 (IGF-1). Consequently, the purpose of this study was to determine the effects of fasting on delayed-type chemotherapy-induced nausea and vomiting in dogs receiving doxorubicin. This prospective randomized crossover study involved intended administration of two doses of doxorubicin. Cancer-bearing dogs were randomized to be fasted for 24 hours beginning at 6 P.M. the night before the first or second doxorubicin administration, and all treatments were administered within an hour before or after 12 P.M. Dogs were fed normally before the alternate dose. Circulating IGF-1 concentrations were determined from serum samples obtained immediately before each doxorubicin treatment. Data from 35 doses were available from 20 dogs enrolled. Dogs that were fasted exhibited a significantly lower incidence of vomiting, when compared to fed dogs (10% compared to 67%, $P = .020$). Furthermore, among the 15 dogs that completed crossover dosing, vomiting was abrogated in four of five dogs that experienced doxorubicin-induced vomiting when fed normally ($P = .050$). No differences in other gastrointestinal, constitutional, or bone marrow toxicities or serum IGF-1 levels were observed.

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Introduction

Despite significant advances in anti-emetic drug therapy, chemotherapy-induced nausea and vomiting (CINV) remains a significant problem in the practice of clinical oncology [1]. CINV ranks among the most distressing side effects of chemotherapy and therefore contributes to patient non-compliance, treatment curtailment, and poor nutritional status. CINV is commonly classified into one of three categories: acute-onset CINV that occurs within 24 hours of initial administration of chemotherapy, delayed-type CINV occurring 1 to 5 days after initial treatment, and anticipatory CINV in patients whose emetic episodes are triggered by senses, thoughts, or anxiety associated with prior chemotherapy.

Various mechanisms for delayed-type CINV have been proposed, including disruption of the blood-brain barrier, disruption of

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gastrointestinal motility and/or changes in its permeability, influence of endogenous adrenal hormones, and accumulation of emetogenic chemotherapy metabolites [2]. Damage to intestinal crypt cells after exposure to cytotoxic drugs can result in delayed-type CINV through release of 5-hydroxytryptamine 3, substance P, and cholecystokinin. When bound to 5-hydroxytryptamine 3 and neurokinin-1 receptors, these mediators stimulate the terminal ends of vagal afferents that transmit signals to the vomiting center [3]. The considerable morbidity associated with CINV has prompted prophylactic treatment with serotonin antagonists, corticosteroids, dopamine antagonists, and neurokinin-1 inhibitors to become commonplace in clinical practice. Unfortunately, approximately 75% of human breast cancer patients still report some symptoms of delayed-type CINV when treated with doxorubicin-containing chemotherapy protocols [4,5]. Acute CINV due to doxorubicin administration is also common in human patients but is less frequent than the delayed type [5]. CINV has been reported in 30% to 40% of dogs receiving doxorubicin but is almost exclusively comprised of the delayed type, with one study reporting 91% of all vomiting occurring after 48 hours [6].

Although doxorubicin is classified as a non–cell cycle–specific agent, experimental studies have determined that selective lethal cellular toxicity occurs when cells are in S-phase, whereas cells in G_1 appear to be least sensitive [7–9]. Interestingly, animal studies have determined that proliferative activity of gastrointestinal cells is subject to circadian fluctuation that is largely driven by patterns of food consumption [10]. Furthermore, studies have demonstrated that fasting can dramatically reduce gastrointestinal cellular proliferation rates through G_1 cycle blockade, and refeeding of mice after a period of fasting results in peak levels of S cellularity that can exceed four times those of fasted mice [11].

Proliferative activity begins to decrease within 24 hours of initiating fasting, and after refeeding, maximum proliferation usually exceeds baseline in most tissues of the gastrointestinal tract within 24 hours [10,11]. Taken together, these data provide evidence that patterns of food consumption around the time of chemotherapy administration could contribute to delayed-type CINV in clinical cancer patients.

Fasting has also been shown to increase cellular resistance to stress, inducing a protective effect on normal cells [12,13]. This protection is believed to be mediated by reduced insulin-like growth factor 1 (IGF-1) signaling and decreased activity of downstream effectors such as Akt, Ras, and the mammalian target of rapamycin (mTOR) [12]. In normal cells, this results in changes in gene expression and promotes resistance to oxidative stress, thought to be one of the major mechanisms of cytotoxicity caused by doxorubicin [14–16]. In contrast, it appears that the cancer cell's inability to adapt to reduced nutrients results in increased oxidative stress and cell death [17]. Therefore, fasting-induced reduction in IGF-1 not only mediates the protective effects on normal cells *in vivo* but is also implicated in the chemotherapy sensitization of cancer cells [17,18]. Thus, fasting may have the potential to modulate the therapeutic index of some chemotherapy drugs.

A feasibility study recently reported 10 people voluntarily fasting for 48 to 140 hours before treatment and for 5 to 56 hours after receiving various different chemotherapeutic agents [19]. Minimal adverse effects were described during fasting, and most subjects maintained that fewer chemotherapy-related toxicities were experienced after cycles for which they fasted at the time of treatment. However, to the authors' knowledge, a formal prospective study has not evaluated the effects of fasting on delayed-type CINV. A reduced incidence of anticipatory and acute CINV in dogs, both of which can contribute to the delayed-type in people, makes the canine species ideal for the study of delayed-type CINV. Herein, we report the findings of a prospective, randomized study using a crossover design to primarily evaluate the effects of fasting on delayed-type CINV in cancer-bearing dogs. Because IGF-1 levels have been implicated as playing an important role in selective chemosensitization in mouse models and could have been affected by fasting, serum IGF-1 concentrations in both fasted and fed dogs were determined from samples collected immediately before doxorubicin administration. The effects of fasting on the incidence and severity of other commonly observed doxorubicin-induced toxicities including diarrhea, decreased activity, and bone marrow suppression were also evaluated.

Materials and Methods

Ethics Statement

The protocol and owner consent form were approved by the University of California, Davis (UC Davis) Veterinary Medical Teaching Hospital Clinical Trials Review Board (No. 11-11-10) in accordance with campus policy regarding trials involving client-owned dogs. Informed owner consent was obtained before enrollment of all patients.

Patient Selection

Cancer-bearing dogs presenting to the UC Davis William R. Pritchard Veterinary Medical Teaching Hospital (VMTH) between February 2012 and June 2013, with the intention of pursuing at least two doses of doxorubicin during the course of their chemotherapy protocol were considered candidates for enrollment. All dogs received an examination by a VMTH oncology clinician before enrollment. To be included, dogs were required to have a physical examination and weight recorded, in addition to a complete blood count (CBC) and chemistry panel (performed within 2 weeks before enrollment). Clinical chemistry panels and CBCs from veterinary clinics other than the VMTH were considered acceptable.

Both therapy-naïve and patients in relapse after standard of care were eligible for entry into this study. In addition, a favorable performance status indicating a high likelihood of receiving two doses of doxorubicin was necessary for inclusion. Dogs were required to be fed twice daily (A.M. and P.M.), or be fed *ad lib*, as part of the normal husbandry practices in the home. For entry into the study, owners consented to feed a consistent diet throughout the duration of the study.

Dogs were excluded if they had previously received doxorubicin therapy, were believed to be at risk of the multidrug resistance gene-1 (MDR-1) mutation, were normally fed only once daily, experienced a diet change within 1 week of treatment or showed signs of nausea, vomiting, inappetence, or diarrhea within 2 days before receiving a dose of doxorubicin. Dogs receiving concurrent medications with the potential to alter gastrointestinal toxicosis, such as prednisone or nonsteroidal anti-inflammatory drugs, were excluded unless they had received this medication for a minimum of 2 weeks (1 week for prednisone) before scheduled doxorubicin administration with no reported gastrointestinal adverse effects, and they were anticipated to stay on these medications for the duration of the study period. Dogs with gastrointestinal tract involvement, suspicion of gastrointestinal ulceration or brain metastasis, or pre-existing chronic gastrointestinal