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Not so fast: dietary restriction improves chemotherapy-related toxicity

Comment on: Huisman SA, et al. Fasting protects against the side effects of irinotecan but preserves its anti-tumor effect in Apc15lox mutant mice. Cell Cycle 2015; 14(14):2333-9; PMID: 25955194; http://dx.doi.org/10.1080/15384101.2015.1044170

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Chemotherapy related-side effects remain a leading cause of patient morbidity and treatment interruption. Irinotecan is a derivative of camptothecin, an alkaloid extract from *Camptotheca acuminate*, and is often used in the treatment of advanced gastrointestinal malignancies. Irinotecan and its potent metabolite SN-38, exert their anti-tumor effects by binding to the topoisomerase I-DNA complex, preventing repair of single-strand breaks. Unfortunately, the use of irinotecan is often associated with severe toxicities, particularly diarrhea. Irinotecan can induce both early and late forms of diarrhea, each of which appears to be mediated by separate mechanisms.[1] Acute diarrhea is thought to be caused by a cholinergic response and is often treated with atropine. The later form of diarrhea may be related to SN-38 toxicity, is typically more severe, and can be life-threatening if untreated. Other significant side effects of irinotecan include neutropenia, asthenia, and alopecia. SN-38 is metabolized by glucuronidation, and biliary excretion is an important mechanism in its elimination.[2] A number of agents targeting these pathways to reduce the incidence of side effects have been proposed, but none have achieved clinically meaningful success.

Caloric or dietary restriction (DR) is an emerging therapeutic adjunct to standard cytotoxic treatments. Restricted food intake is thought to lessen the incidence of age-related changes, decrease oxidative stress, and extend lifespan in mammals.[3] At the molecular level, DR is thought to exert its effects by targeting both inflammation and growth factor-regulated cellular proliferation pathways.[4] More recently, a growing body of evidence suggests DR may increase detoxification through glucuronide and glycine conjugation pathways.[5] Increasing research has not only focused on the use of DR to increase the efficacy of treatment,[6] but also to improve therapeutic ratio by mitigating the side effects of toxic therapeutics.

In a recent issue of Cell Cycle,[7] Huisman and colleagues utilize DR to ameliorate several of the well-known side effects of irinotecan, including diarrhea and leukopenia. This group has previously published studies demonstrating up-regulation of a number of cytoprotective processes in response to dietary restriction, resulting in protection from oxidative stress from a variety of sources. In the current study, the authors used a conditional Apc15lox mutant mouse model in which spontaneous colonic tumor growth occurs to investigate the effect of dietary restriction on a number of toxicity metrics. Using this model, mice were randomized in a 2×2 design to either a standard *ad libitum* diet or a 3-day dietary restricted fast, in which mice only had access to water. Each group was then randomized to receive irinotecan or control.

Following exposure to irinotecan, tumor growth was noted to be decreased in mice with *ad libitum* and restricted diets, as expected. However, mice fed a standard *ad libitum* diet developed visible signs of chemotherapy-related distress, including weight loss, decreased activity, ruffled coat, poor posture, leukopenia, and diarrhea. Fasted mice seemed to be protected from chemotherapy-related toxicity, and exhibited statistically far fewer side effects. Importantly, late onset diarrhea was significantly reduced and appeared to be no higher than mice receiving control sodium chloride. Mice in the DR group even appeared to demonstrate weight gain after resuming a normal diet.

The authors also investigated a number of molecular end points. Importantly, the authors demonstrated that DR did not compromise the anti-tumor activity of irinotecan, showing suppression of mitosis and proliferation in both DR and *ad libitum* fed mice. In addition, there was a trend for decreased proliferation in mice receiving both irinotecan and dietary restriction vs. irinotecan alone, suggesting interaction between the 2 treatments, however this did not reach statistical significance.

In summary, this is a well-designed study demonstrating that dietary restriction can be an effective adjunct in reducing the toxicity of irinotecan-based chemotherapy in a murine model. This study adds to the growing body of literature demonstrating that dietary restriction can ameliorate treatment-related toxicity. Intriguingly, the benefits of dietary restriction were shown to be effective with as little as 3 days of fasting in this study. The authors hypothesize that the effectiveness of this regimen may be due to differential stress sensitization, in which cancer cells are unable to achieve a protected state induced by dietary restriction. By combining with other cytotoxic therapies, this phenomenon may be further exploited by both increasing the therapeutic effectiveness of treatment while lessening the burden of toxicity. This innovative approach may be a promising adjunct to existing treatments and warrants further investigation in the clinical trial arena.

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