Cell Cycle 9:22, 4474-4476; November 15, 2010; © 2010 Landes Bioscience

Fasting and differential chemotherapy protection in patients

Lizzia Raffaghello,[2,†] Fernando Safdie,[1,†] Giovanna Bianchi,[2] Tanya Dorff,[5] Luigi Fontana[3,4] and Valter D. Longo[1,*]

[1]Andrus Gerontology Center; Dept. of Biological Sciences; and [5]Norris Cancer Center; University of Southern California; Los Angeles, CA USA;

[2]Laboratory of Oncology; Giannina Gaslini Institute; Genova, Italy; [3]Division of Geriatrics and Nutritional Science; Washington University in St. Louis; St. Louis, MO USA; [4]Division of Nutrition and Aging; Istituto Superiore di Sanità; Rome, Italy

[†]These authors have contributed equally to this work.

Chronic calorie restriction has been known for decades to prevent or retard cancer growth, but its weight-loss effect and the potential problems associated with combining it with chemotherapy have prevented its clinical application. Based on the discovery in model organisms that short term starvation (STS or fasting) causes a rapid switch of cells to a protected mode, we described a fasting-based intervention that causes remarkable changes in the levels of glucose, IGF-I and many other proteins and molecules and is capable of protecting mammalian cells and mice from various toxins, including chemotherapy. Because oncogenes prevent the cellular switch to this stress resistance mode, starvation for 48 hours or longer protects normal yeast and mammalian cells and mice but not cancer cells from chemotherapy, an effect we termed Differential Stress Resistance (DSR). In a recent article, 10 patients who fasted in combination with chemotherapy, reported that fasting was not only feasible and safe but caused a reduction in a wide range of side effects accompanied by an apparently normal and possibly augmented chemotherapy efficacy. Together with the remarkable results observed in animals, these data provide preliminary evidence in support of the human application of this fundamental biogerontology finding, particularly for terminal patients receiving chemotherapy. Here we briefly discuss the basic, pre-clinical and clinical studies on fasting and cancer therapy.

Key words: fasting, cancer, chemotherapy, calorie restriction stress resistance

Submitted: 10/06/10

Accepted: 10/13/10

Previously published online: www.landesbioscience.com/journals/cc/article/13954

DOI: 10.4161/cc.9.22.13954

*Correspondence to: Valter Longo; Email: vlongo@usc.edu

After decades of slow progress in the identification of treatments effective on a wide range of malignancies, cancer treatment is now turning to personalized therapies based in part on pharmacogenomics. By contrast, aging research is moving in the opposite direction by searching for common ways to prevent, postpone and treat a wide range of age-related diseases, based on the modulation of genetic pathways that are conserved from yeast to mammals.[1] In fact, it may be a solid evolutionary and comparative biology-foundation, which makes this ambitious goal of biogerontologists a realistic or at least a promising one. On the other hand, the progress of biogerontology is viewed by many clinicians as too fundamental and far from translational applications. In most cases, it is not clear how aging research will be translated into FDA approved drugs or treatments that have effects that are superior to those already available or being developed. For example, it is not clear how the long-term 20–30% reduction in calorie intake (dietary restriction, DR) that we and many others before us have shown to be effective in extending the life span of model organisms will make humans live longer or healthier.[1-3] Furthermore, despite the fact that long-term DR was confirmed to reduce cancer and cardiovascular disease in monkeys[4] and to be effective in preventing obesity, type 2 diabetes, inflammation, hypertension and atherosclerosis, as indicated by the early results in humans studies,[5] it is highly unlikely to be adopted in its more extreme and effective version by even a small portion of the population. For example, the 20 to 40% chronic reduction in daily calorie intake shown to be effective in retarding cancer

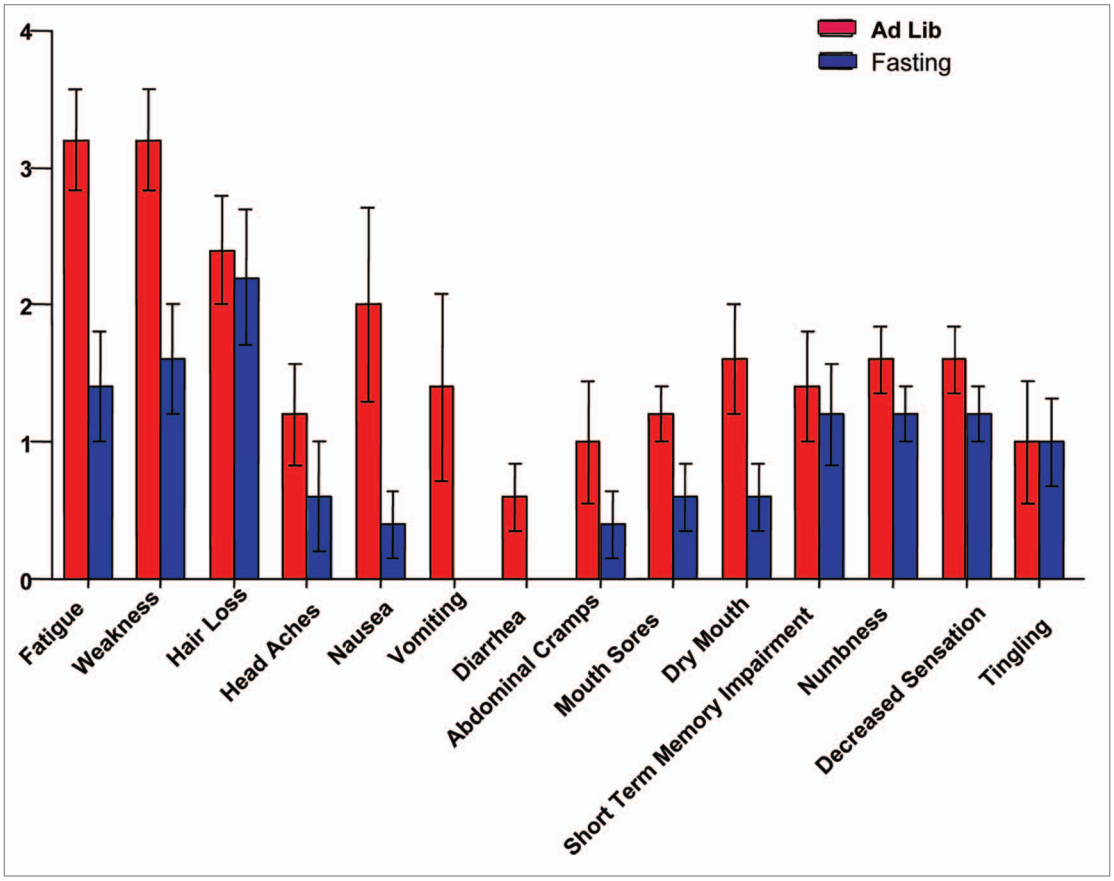

Figure 1. Average self-reported severity of symptoms in patients that have received chemotherapy with or without fasting.

growth in mice would not be feasible for cancer therapy for multiple reasons: (1) the effects of chronic DR in patients with a clinically evident tumor is expected to delay but not stop the progression of the disease[6-8] and this delay may only occur for a portion of the malignancies,[9] (2) although weight loss and cachexia in the early stages of treatment are less prevalent than commonly thought,[10-12] the ~15% loss of BMI and ~30% long-term loss of body fat caused by a moderate (20%) calorie restriction[13] may be tolerated by only a very small portion of cancer patients receiving treatment, (3) Because this long-term restriction is accompanied by delayed wound healing and immunologic impairment in rodents,[1,14,15] it is not clear what risks it may impose on cancer patients receiving treatment.[16] Our studies of DSR, which were triggered by our fundamental findings that switching yeast cells to water protected them against a wide range of toxins, started as a way to address these concerns but also as an attempt to achieve a much more potent therapeutic effect than that achieved by DR.[17,18] Because starvation-induced protection can increase many fold when combined with modulation of pro-aging pathways and since it is in principle blocked by the expression of any oncogene, it has the potential to provide a method to allow common chemotherapy to selectively kill cancer cells, independently of the type of cancer.[19-21] The DSR experiments in mammals were also based on our hypothesis that stress resistance and aging regulatory pathways were conserved from yeast to mammals.

We found that fasting for 48 or more hours or in vitro starvation conditions that mimic fasting protected mice and/or normal cells but not cancer cells from various chemotherapy drugs and other deleterious agents.[21] This effect was shown to depend in part on the reduction of circulating IGF-I and glucose levels.[21,22] Although a differential regulation of cell division in normal and cancer cells[23,24] is likely to contribute to DSR, much of it appears to be dependent on protective systems which are normally maintained in an inactive or low activity state even in non-dividing cells.[1,25] In fact, in non-dividing yeast and mice, deficiencies in glucose or IGF-I signaling that match those observed after starvation promote resistance to doxorubicin, a chemotherapy drug that specifically targets muscle cells in the heart.[21,22]

As expected, many clinicians were skeptical of our hypothesis that cancer treatment could be improved not by a "magic bullet" but by a "not so magic DSR shield" as underlined by Leonard Saltz, an oncologist at Memorial Sloan-Kettering Cancer Center: "Would I be enthusiastic about enrolling my patients in a trial where they're asked not to eat for 2.5 days? No".[26] However, ten oncologists did allow their patients, suffering from malignancies ranging from stage II breast cancer to stage IV esophageal, prostate and lung malignancies to undergo a 48–140 hours pre-chemotherapy and a 5–56 hours post

chemotherapy water-only fast. The six patients who received chemotherapy with or without fasting reported a reduction in fatigue, weakness and gastrointestinal side effects while fasting[27] (**Fig. 1**). A trend for a reduction of many additional side effects was also reported by the group of patients who always fasted before chemotherapy.[27] In those patients whose cancer progression was assessed, chemotherapy was effective and in some cases it was highly effective.[27] A clinical trial sponsored by the V-Foundation for Cancer Research, aimed at testing the safety and efficacy of a 24 hour fast in combination with chemotherapy, is in its safety stage. Because it was originally limited to patients diagnosed with bladder cancer the clinical trial progressed slowly. However, its recent expansion to include patients receiving platinum-based chemotherapy (breast, ovarian, lung cancer), is expected to expedite it. Conclusive results for the effect of a 3–4 day fast on chemotherapy-dependent side effects and possibly therapeutic index are not expected to become available for several years. Even if a more modest effect than the 1,000-fold differential protection against oxidative stress and chemotherapy observed in normal and cancer-like yeast cells was achieved in humans, this method could result in long-term survival for many patients with metastatic cancers, particularly those in which malignant cells have not acquired multidrug resistance.

Acknowledgements

Lizzia Raffaghello is a recipient of a My First AIRC Grant (MFAG) and Giovanna Bianchi is a recipient of a FIRC (Italian Foundation for Cancer Research) fellowship. This study was also funded in part by NIH/NIA grants AG20642 and AG025135, Ted Bakewell (The Bakewell Foundation), the V Foundation for Cancer Research and a USC Norris Cancer Center pilot grant to V.D. Longo.

References

1. Fontana L, Partridge L, Longo VD. Extending healthy life span: From yeast to humans. Science 2010; 328:321-6.
2. Weindruch RWR. The retardation of aging and disease by dietary restriction. (Springfield, Ed.) (Charles C Thomas Publisher, IL 1988).
3. Masoro EJ. Overview of caloric restriction and ageing. Mech Ageing Dev 2005; 126:913-22.
4. Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 2009; 325:201-4.
5. Fontana L, Klein S. Aging, adiposity and calorie restriction. Jama 2007; 297:986-94.
6. Bonorden MJ, Rogozina OP, Kluczny CM, Grossmann ME, Grambsch PL, Grande JP, et al. Intermittent calorie restriction delays prostate tumor detection and increases survival time in TRAMP mice. Nutr Cancer 2009; 61:265-75.
7. Mukherjee P, Abate LE, Seyfried TN. Antiangiogenic and proapoptotic effects of dietary restriction on experimental mouse and human brain tumors. Clin Cancer Res 2004; 10:5622-9.
8. Shelton LM, Huysentruyt LC, Mukherjee P, Seyfried TN. Calorie restriction as an anti-invasive therapy for malignant brain cancer in the VM mouse. ASN Neuro 2010; 2:171-6.
9. Kalaany NY, Sabatini DM. Tumours with PI3K activation are resistant to dietary restriction. Nature 2009; 458:725-31.
10. Tisdale MJ. Cachexia in cancer patients. Nat Rev Cancer 2002; 2:862-71.
11. Fox KM, Brooks JM, Gandra SR, Markus R, Chiou CF. Estimation of Cachexia among Cancer Patients Based on Four Definitions. J Oncol 2009; 2009:693458.
12. Fearon KC, Von Meyenfeldt MF, Moses AG, Van Geenen R, Roy A, Gouma DJ, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. Gut 2003; 52:1479-86.
13. Racette SB, Weiss EP, Villareal DT, Arif H, Steger-May K, Schechtman KB, et al. One year of caloric restriction in humans: feasibility and effects on body composition and abdominal adipose tissue. J Gerontol A Biol Sci Med Sci 2006; 61:943-50.
14. Kristan DM. Calorie restriction and susceptibility to intact pathogens. Age (Dordr) 2008; 30:147-56.
15. Reed MJ, Penn PE, Li Y, Birnbaum R, Vernon RB, Johnson TS, et al. Enhanced cell proliferation and biosynthesis mediate improved wound repair in refed, caloric-restricted mice. Mech Ageing Dev 1996; 89:21-43.
16. Kim SK, Demetri GD. Chemotherapy and neutropenia. Hematol Oncol Clin North Am 1996; 10:377-95.
17. Longo VD, Ellerby LM, Bredesen DE, Valentine JS, Gralla EB. Human Bcl-2 reverses survival defects in yeast lacking superoxide dismutase and delays death of wild-type yeast. J Cell Biol 1997; 137:1581-8.
18. Wei M, Fabrizio P, Madia F, Hu J, Ge H, Li LM, et al. Tor1/Sch9-regulated carbon source substitution is as effective as calorie restriction in life span extension. PLoS Genet 2009; 5:1-15.
19. Longo VD. Mutations in signal transduction proteins increase stress resistance and longevity in yeast, nematodes, fruit flies and mammalian neuronal cells. Neurobiol Aging 1999; 20:479-86.
20. Fabrizio P, Pozza F, Pletcher SD, Gendron CM, Longo VD. Regulation of longevity and stress resistance by Sch9 in yeast. Science 2001; 292:288-90.
21. Raffaghello L, Lee C, Safdie FM, Wei M, Madia F, Bianchi G, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. Proc Natl Acad Sci USA 2008; 105:8215-20.
22. Lee C, Safdie FM, Raffaghello L, Wei M, Madia F, Parrella E, et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. Cancer Res 2010; 70:1564-72.
23. Blagosklonny MV, Darzynkiewicz Z. Cyclotherapy: Protection of normal cells and unshielding of cancer cells. Cell Cycle 2002; 1:375-82.
24. Blagosklonny MV, Pardee AB. Exploiting cancer cell cycling for selective protection of normal cells. Cancer Res 2001; 61:4301-5.
25. Longo VD, Lieber MR, Vijg J. Turning anti-ageing genes against cancer. Nat Rev Mol Cell Biol 2008; 9:903-10.
26. Couzin J. Cancer research. Can fasting blunt chemotherapy's debilitating side effects? Science 2008; 321:1146-7.
27. Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, et al. Fasting and cancer treatment in humans: A case series report. Aging (Albany NY) 2009; 1:988-1007.