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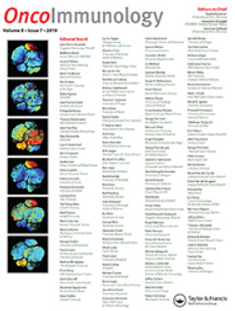

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REVIEW

Trial watch: dietary interventions for cancer therapy

Sarah Lévesque[a,b,c,d,e], Jonathan G. Pol[a,b,c,f,g], Gladys Ferrere[h,i], Lorenzo Galluzzi[f,j,k,l], Laurence Zitvogel[d,h,i], and Guido Kroemer[a,b,c,d,f,g,m,n]

[a]Equipe 11 labellisée par la Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers, Paris, France; [b]INSERM, U1138, Paris, France; [c]Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France; [d]Université Paris-Saclay, Orsay, France; [e]Fondation pour la Recherche Médicale, Paris, France; [f]Université Paris Descartes/Paris V, Sorbonne Paris Cité, Paris, France; [g]Université Pierre et Marie Curie/Paris VI, Paris, France; [h]INSERM U1015, Villejuif, France; [i]CICBT507, Villejuif, France; [j]Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, USA; [k]Sandra and Edward Meyer Cancer Center, New York, NY, USA; [l]Department of Dermatology, Yale School of Medicine, New Haven, CT, USA; [m]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France; [n]Department of Women's and Children's Health, Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

Dietary interventions have a profound impact on whole body metabolism, including oncometabolism (the metabolic features allowing cancer cells to proliferate) and immunometabolism (the catabolic and anabolic reactions that regulate immune responses). Recent preclinical studies demonstrated that multiple dietary changes can improve anticancer immunosurveillance of chemo-, radio- and immunotherapy. These findings have fostered the design of clinical trials evaluating the capacity of dietary interventions to synergize with treatment and hence limit tumor progression. Here, we discuss the scientific rationale for harnessing dietary interventions to improve the efficacy of anticancer therapy and present up-to-date information on clinical trials currently investigating this possibility.

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Alternate-day fasting; caloric restriction mimetics; chemotherapy; fasting-mimicking diet; immune checkpoint blockers; ketone bodies

Introduction

In the Western world, overnutrition has overcome undernutrition as a medical and societal problem.[1–3] Beyond quantitative considerations, it appears that the consumption of ultra-processed food (rich in carbohydrates, sugars, salt, and fat) and soft drinks coupled to a relative scarcity of fruit and vegetables affects the majority of individuals even in high-income countries.[4–9] Against this background, it is clear that the "normal diet" cannot be appreciated as a statistical norm (i.e., the diet of the average individual), but must be defined by public guidelines. Such guidelines, however, are overshadowed by political decisions and arguable observational epidemiology, meaning that they tend to differ among distinct countries.[10] Moreover, much of the preclinical research done with laboratory animals (mostly mice) is based on the comparison of different types of chemically non-defined regimens, meaning that the conclusions of such studies are often based on methodologically suboptimal approaches.[11,12] Indeed, in pharmacology, it is common practice to compare different experimental conditions that only differ with respect to the absence and the presence of a drug administered at different concentrations. This kind of rigor is absent from most nutritional studies, which ideally should be designed to test the effects of just one single macro- or micronutrient admixed as a chemically defined entity (*e.g.*, sucrose, sodium chloride, cholesterol or specific vitamins).[13] Notwithstanding these limitations, it has become clear that the quantity and quality of nutrition plays a major role in determining the risk of cancer.[14–16] Obesity is nowadays on the verge of beating tobacco as the principal avoidable risk factor for cancer.[17–19] Along similar lines, a high variety of food that supplies all necessary micronutrients appears to be one of the principal factors that link high socioeconomic status with low disease risk.[20] Finally, multiple animal studies favor the idea that nutritional interventions may curb the progression of established cancers and improve the efficacy of anticancer treatments.[21–27] These effects rely on the alteration of both oncometabolism (the anabolic and catabolic reactions that support oncogenesis, disease progression and resistance to treatment)[28,29] and immunometabolism (the metabolic features that regulate immune responses).[30–34]

Along the lines of our Trial Watch series,[35,36] we discuss the rationale for harnessing nutritional interventions in support of cancer therapy and the progress of recent clinical trials testing this therapeutic paradigm in cancer patients.

Anticancer effects of dietary interventions – a cell-autonomous rationale

Cancer cells, especially those studied in the laboratory, are characterized by an increase in anabolic reactions that give rise to the so-called Warburg effect, the fact that such cells tend to take up large amounts of glucose even in conditions in which oxidative phosphorylation can proceed in an unlimited fashion.[37–40] This so-called 'aerobic glycolysis' allows glucose-derived carbon atoms to be used for biosynthetic reactions.

CONTACT Guido Kroemer kroemer@orange.fr; Laurence Zitvogel laurence.zitvogel@orange.fr Equipe 11 labellisée par la Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers, Paris, France

Cancer cells also take up large amounts of amino acids through specific transporters in the plasma membrane, acquire increased amounts of proteins by pinocytosis, and even engulf their neighbors to cannibalize them.[41–43] In an analogous fashion, cancer cells are avid consumers of lipids.[44] Given their anabolic appetite, it is not surprising that nutritional interventions designed to reduce tumor growth involve a reduction in macronutrient uptake. Thus, it has been shown in mice that short-term starvation (STS, meaning no food supply for 1–2 days with access to drinking water *ad libitum*) and alternate-day fasting (ADF, meaning the alternation of 1-day intervals with and without access to food) can reduce tumor progression.[25,27] Moreover, the specific depletion of proteins (as well as selected aminoacids) from nutrients can be harnessed to limit cancer growth.[45,46] One particular dietary intervention consists in a close-to-zero carbohydrate, low-protein, high-fat regimen that causes ketosis (*i.e.*, the accumulation of 3-hydroxybutyrate, acetoacetate, and acetone, commonly known as ketone bodies).[47] Ketone bodies can be used by multiple tissues in replacement of glucose for energy metabolism.[48] In mice, multiple variants of ketogenic diet slowdown the progression of some cancer types and boost the efficacy of targeted therapeutic agents,[49,50] an effect that (at least in some setting) is linked to reduced insulin signaling.[50,51]

One particular facet of these dietary interventions is their capacity to reduce the unwarranted side effect of genotoxic chemotherapy. For example, periodic fasting as well as the administration of a hypocaloric 'fasting-mimicking diet' (FMD) can enhance the efficacy of chemotherapy and, at the same time, limit chemotherapy-related weight loss and cardiotoxicity.[27,52] It has been theorized that transient calorie deprivation enhances the 'differential stress resistance' between chemotherapy-treated cancer cells (that would become more susceptible to the treatment) and normal, non-neoplastic cells (that would become more resistant to the toxic side effects to chemotherapy).[53–56]

Anticancer effects of dietary interventions – an immunological rationale

Over the past years, an ever-expanding body of evidence pleads in favor of the notion that the long-term success of chemotherapy, targeted therapy and radiotherapy requires the reestablishment of immunosurveillance.[57] In other words, the efficacy of antineoplastic treatments, which has long been thought to exclusively rely on cancer cell-autonomous effects, now turns out to require the induction of a protracted anticancer immune response to be efficient.[58–61] Logically, the impact of dietary intervention on such immune-dependent antitumor effects has been studied in preclinical models.

In immunocompetent mice bearing transplantable tumors or carcinogen-induced breast cancer, chemotherapy with anthracyclines or oxaliplatin becomes more efficient if combined with shorts periods of starvation.[22,24] These combinatorial effects of chemotherapy and dietary intervention fully rely on a T lymphocyte-mediated anticancer immune response, meaning that they are lost upon T cell depletion.[22,24] Mechanistically, they have been linked to the induction of heme oxygenase-1 (HO-1) in cancer cells, the stimulation of autophagy in cancer cells (which would enhance their immunogenicity),[62–64] a decrease in circulating insulin-like growth factor-1 (IGF1), as well as an increase in the frequency of common lymphocyte precursors (which would be immunostimulatory).[22,24,65] Whether such effects might involve major shifts in the gut microbiota has not been investigated thus far.[66,67] Moreover, the impact of dietary interventions on immunotherapies has been poorly explored, at least to our knowledge.[68,69] Available clinical evidence suggests that anti-melanoma immunotherapy with PD-1/PD-L1 blocking antibodies[70,71] is more efficient in obese than lean males,[72] casting doubts on the possibility to improve such therapies by brutal interventions designed to reduce overweight.

Published and ongoing clinical trials

Very few trials testing the ability of nutritional interventions to boost the efficacy of cancer therapy have been reported in the peer-reviewed literature so far. A series of anecdotal cases of self-imposed starvation during chemotherapy suggested an improvement of subjective well-being suggestive of a reduction of side-effects.[73] In the same line, fasting for 48 h prior and 24 h after platinum-based chemotherapy proved its safety and feasibility in patients treated for diverse cancer types.[74] A Phase I trial confirmed that STS for 60 h (from 36 h prior to chemotherapy to 24 h post-chemotherapy) improves quality of life and fatigue in patients with gynecological cancer.[75] In breast cancer patients treated with neoadjuvant multimodal chemotherapy,[76] a 48-h starvation period (from 24 h before to 24 h after chemotherapy) reduced hematological toxicity and accelerated recovery from DNA damage in circulating leukocytes.[77] Women with ovarian and endometrial cancer following a ketogenic diet for 12 weeks reported higher physical and energy status compared to the control group, highlighting the feasibility of this regimen.[78] A special ketogenic diet, the so-called 'modified Atkins diet', reportedly reduces the progression of some advanced cancer patients, especially individuals experience robust weight reduction.[79] Similarly, a ketogenic regimen has been reported to induce objective responses in 6 out of 7 patients with recurrent glioblastoma that simultaneously were treated with the antiangiogenic drug bevacizumab.[80–82] This effect appeared particularly strong in patients with stable ketosis.[80]

The website ClinicalTrials.gov informs on multiple clinical trials that are either ongoing or completed, yet generally lack published information on the outcome (Table 1). Many of these trials evaluate dietary interventions without further treatment (NCT01092247, NCT01865162, NCT02092753, NCT02286167, NCT03160599, NCT03194516, NCT03328858, NCT03785808, NCT00003367, NCT00020995, NCT00082732, NCT00444054, NCT01692587, NCT02129218, NCT02176902, NCT03221920, and NCT03679260). Such interventions include STS, intermediate fasting, FMD, multiple ketogenic and low-carbohydrate diets, low-fat/high-fiber regimens, protein-restrictive diets, low-calorie and low-glycemic regimens and a vegan diet in patients with a variety of advanced solid malignancies including glioblastoma (the most frequent indication),

Table 1. Clinical trials employing diet for cancer therapy.

Dietary intervention	Additional details (when available)	NCT	Therapeutic intervention	Cancer type	Phase	Status
Short-term starvation	24, 48, or 72 h of fasting or 48 h of FMD	NCT00936364	Platinum chemotherapy	Advanced solid tumors		Recruiting
	24, 36, or 48 h of fasting before chemotheray	NCT01175837	Chemotherapy		Pilot study	Completed
	STS 24 h before and 24 h after chemotherapy	NCT01304251	Docetaxel, Doxorubicin, Cyclophosphamide	Breast cancer	Pilot study	Completed
	STS 24 h before and 24 h after chemotherapy	NCT02379585	Doxorubicin, cyclophosphamide, paclitaxel, docetaxel, trastuzumab, pertuzumab	Breast cancer	Phase 1/2	Terminated, has results
Fasting-mimicking diet	FMD 36 to 48 h before and 24 h after chemotherapy	NCT01954836	Chemotherapy	Gynecological	Pilot study	Completed
	FMD	NCT02126449	Neoadjuvant chemotherapy	HER2-negative breast cancer	Phase 2/3	Terminated
	FMD 36 h before and 24 h after chemotherapy	NCT02710721	Chemotherapy	Prostate		Recruiting
	FMD or vegan diet 36 to 48 h before and 24 h after chemotherapy	NCT03162289	Chemotherapy	Breast and ovarian		Recruiting
	FMD (low calorie, low protein, and low carboydrates) for 5 days	NCT03340935	Standard therapies	Any malignancy except small-cell neuroendocrine tumors		Recruiting
	5 days of FMD 13 to 15 days before or 1 month after surgery	NCT03454282	Surgery	Breast and melanoma tumors		Recruiting
	FMD for 5 days	NCT03595540	Chemo-, hormono-, targeted or immuno-therapies			Recruiting
	FMD 72 h before and 24 h after chemo-immunotherapy	NCT03700437	Carboplatin/pemetrexed and pembrolizumab	NSCLC		Not yet recruiting
	FMD for 5 days	NCT03709147	Metformin	Advanced LKB1-inactive lung adenocarcinoma	Phase	Not yet recruiting
Ketogenic diet	KD	NCT00575146	Bevacizumab	Recurrent glioblastoma	Phase 1	Completed, has results
	KD for up to one year	NCT01092247	No	High-grade glial tumors		Unknown
	KD starts 2 days before chemoradiation and last at least during 5 weeks throughout the treatment	NCT01419483	Chemoradiation	Pancreatic		Terminated
	KD starts 2 days before chemoradiation and last at least during 5 weeks throughout the treatment	NCT01419587	Chemoradiation	Carcinoma, non-small cell lung cancer		Terminated
	Energy-restricted KD starts after surgery and continues through radio and chemotherapy, ending 6 weeks after treatments completion	NCT01535911	Surgery followed by chemo- and radiotherapy	Brain tumors		Active, not recruiting
	KD	NCT01716468	No	Metastatic cancer		Completed
	2 cycles of 3 days calorie-restricted KD separated by 3 days fasting	NCT01754350	Reirradiation	Recurrent glioblastoma		Active, not recruiting
	KD with calorie restriction for 6 months	NCT01865162	No	Refractory/end-stage glioblastoma	Phase 1	Recruiting
	KD starts 2 days before chemoradiation and last at least during 5 weeks throughout the treatment	NCT01975766	Chemoradiation	Head and neck cancer	Phase 1	Terminated (poor accrual)
	KD starts after surgery and continues through radio and chemotherapy. A modified Atkins diet is implemented during the following month of chemotherapy.	NCT02046187	Chemoradiation	Glioblastoma	Phase 1/2	Terminated
	KD or low glycemic and insulinemic diet for 20 weeks	NCT02092753	No	Breast cancer		Completed
	Modified Atkins-based with intermittent fasting diet	NCT02286167	No	Glioblastoma		Recruiting
	KD starts at the radiation initiation and continues 6 months	NCT02302235	Radiation and temozolomide	Glioblastoma multiforme	Phase 2	Recruiting
	Ketogenic breakfast after overnight fasting and before chemoradiation or KD throughout the entire period of chemoradiation	NCT02516501	Chemoradiation			Recruiting
	Low-carbohydrate vs low-fat diet before surgery	NCT02744079	Surgery	Breast ER+ cancer	Pilot presurgical study	Recruiting
	Modified Atkins diet	NCT02768389	Bevacizumab	Glioblastoma	Early Phase 1	Active, not recruiting
	KD	NCT02939378	Salvage chemotherapy	Recurrent glioblastoma	Phase 1/2	Unknown

(*Continued*)

Table 1. (Continued).

Dietary intervention	Additional details (when available)	NCT	Therapeutic intervention	Cancer type	Phase	Status
	KD	NCT02983942	Methotrexate	Primary central nervous system lymphoma	Phase 1/2	Not yet recruiting
	Modified KD or medium-chain triglyceride KD for 12 weeks	NCT03075514	Chemo- and/or radiotherapy	Glioblastoma	Pilot study	Active, not recruiting
	Restricted calorie KD	NCT03160599	No	Glioblastoma multiforme		Recruiting
	KD for 12 weeks	NCT03171506	No	Ovarian and endometrial cancer		Completed
	KD for 8 weeks	NCT03194516	No	Prostate cancer		Enrolling by invitation
	Modified Atkins KD	NCT03278249	Temozolomide and radiation	Malignant glioma		Recruiting
	KD for 7 days before surgery	NCT03285152	Surgery	Endometrial cancer		Recruiting
	KD for at least 1 year	NCT03328858	No	Brain tumors		Recruiting
	KD for 16 weeks througout chemoradiation treatment	NCT03451799	Radiation and temozolomide	Glioblastoma	Phase 1	Recruiting
	KD for 3 months	NCT03535701	Paclitaxel	Stage IV breast cancer		Recruiting
	Low-carbohydrate high-fat ketogenic-type diet vs low-fat high low-glycemic carbohydrates diet	NCT03785808	No	Lung cancer		Recruiting
Specific low-nutrient	Low-fat high-fiber diet	NCT00003367	No	Prostate cancer	Phase 3	Completed
	Low-fat high-fiber diet for 3 weeks	NCT00020995	No	Prostate cancer	Phase 2	Completed
	Low-fat high-fiber diet	NCT00082732	No	Hormone-refractory prostate cancer	Phase 1	
	Very low-carbohydrate diet for 28 days	NCT00444054	No	Advanced cancer	Pilot study	Completed
	Low-fiber vs high-fiber diet	NCT01170299	Radiation	Gynecological, bladder, colorectal, or anal cancer		Completed
	Protein-restrictive diet	NCT01692587	No	Prostate cancer		Completed
	Low-calorie diet from 3 days before to 2 days after the 12 weeks of chemotherapy	NCT01802346	Chemotherapy	Breast, hormone-resistant, and recurrent prostate cancer	Phase 2	Recruiting
	Carbohydrate-restricted diet	NCT02019979	Metformin with platinum-based chemotherapy	Non-squamous non-small cell lung cancer	Phase 2	Terminated, has results
	Low- or medium-glycemic diet for 12 weeks	NCT02129218	No	Colon cancer	Pilot study	Completed
	Low-fat omega-3 supplement diet for one year	NCT02176902	No	Prostate cancer	Phase 2	Recruiting
	Vegetarian vs vegan diets for 6 months	NCT02437474	Prescribed therapy	Any cancer type	Pilot study	Completed
	Very low-carbohydrate and high-fat diet	NCT03221920	No	Colorectal adenocarcinoma		Not yet recruiting
	Low protein diet from 1 week before to 10 days after treatment	NCT03329742	Sipuleucel-T	Metastatic castrate-resistant pancreatic cancer		Recruiting
	Carbohydrate restricted diet for 6 months	NCT03679260	No	Prostate cancer	Phase 2	Recruiting

breast and gynecological cancer, melanoma, head and neck cancer, non-small cell lung carcinoma, ovarian cancer, pancreatic adenocarcinoma, and prostate cancer. Several trials also aim at investigating the combination of dietary interventions with (1) chemotherapy (NCT01175837, NCT02379585, NCT02126449, NCT02710721, NCT03162289, NCT03340935, NCT03595540, NCT03700437, NCT01419483, NCT01419587, NCT01975766, NCT02046187, NCT02302235, NCT02516501, NCT02939378, NCT02983942, NCT03075514, NCT03278249, NCT03451799, NCT03535701, NCT01802346, NCT02019979, and NCT02437474), (2) radiotherapy (NCT 03340935, NCT01419483, NCT01419587, NCT01754350, NCT01975766, NCT02046187, NCT02302235, NCT0251 6501, NCT03075514, NCT03278249, NCT03451799, NCT01 170299, and NCT02437474), (3) metformin, a medication for type II diabetes with pleiotropic effects on cancer cells[83–85] (NCT03709147 and NCT02019979), (4) targeted-therapies (NCT02379585, NCT03595540 and NCT02768389), and (5) immunotherapies such as immune checkpoint blockers targeting PD-1[86,87] (NCT03595540 and NCT03700437) or the dendritic cells based-vaccine Sipuleucel-T[88,89] (NCT03329742). Interestingly, one study also sets to monitor anticancer immune responses induced by an FMD (NCT03454282).

It will be interesting to see whether any of these studies will document a clinical benefit linked to a specific nutritional intervention.

Concluding remarks

Knowing the importance of nutrition and metabolism for human physiology, including the crosstalk between malignant and immune cells, it is not surprising that dietary interventions are attracting attention as safe means to limit tumor progression or restore disease control by the host immune system.[90–92] While evidence from preclinical studies suggests that reducing total calorie intake (and perhaps specific macronutrients) may stimulate anticancer immunity, such evidence has not yet been obtained in clinical trials. Multiple trials testing these possibilities in patients with multiple types of cancer are on the way (Table 1). Unfortunately, it will be difficult to compare results from different studies for at least two reasons that add upon the usual heterogeneity of clinical trials. First, dietary interventions are quite heterogeneous in nature.[13] Thus, the term 'ketogenic diet' may refer to distinct regimens differing in quantity, composition and even in the gross protein:fat ratio.[93] Second, the control arms of the studies, when exist, usually receive consulting on 'healthy dietary habits', which (1) is a non-standardized notion (with major cross-continental and cross-cultural divergences), (2) is usually not enforced, and (3) is extremely complex to monitor.

Thus, the studies listed in Table 1 might examine the differences between salutary (interventional) and poor (control) regimens, meaning that control regimens can be expected to have a negative impact on health status. For this reason, it will be important to standardize control diets, ensure compliance, and to define interventional regimens in an accurate fashion. This implies strict guidelines, their enforcement by connected objects and phone app-mediated control, as well as monitoring of multiple metabolic parameters (such as plasma metabolome, cytokine and hormone status, stool microbiota). Moreover, it will be important to monitor immune parameters in the tumor and the peripheral blood to gain insights into therapeutically relevant anticancer immune responses. Without this information, it will be difficult to obtain any useful knowledge on the impact of nutritional interventions on cancer therapy.

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Disclosure of Potential Conflicts of Interest

LG provides remunerated consulting to OmniSEQ (Buffalo, NY, USA), Astra Zeneca (Gaithersburg, MD, USA), VL47 (New York, NY, USA) and the Luke Heller TECPR2 Foundation (Boston, MA, USA), and he is member of the Scientific Advisory Committee of OmniSEQ (Buffalo, NY, USA). GK and LZ receive a research grant by Elior.

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ORCID

Laurence Zitvogel http://orcid.org/0000-0003-1596-0998
Guido Kroemer http://orcid.org/0000-0002-9334-4405

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