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Modulation of response to cancer chemotherapeutic agents by diet constituents – is the available evidence sufficiently robust for rational advice for patients?

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Abstract

Background: Patients who are diagnosed with cancer want advice on how they may alter their diet or which diet supplements they should take to augment chemotherapy.

Methods: We conducted a review of the literature mostly from the last 15 years on the interaction between dietary constituents and antineoplastic therapy in preclinical rodent models and in clinical trials.

Results: Studies have explored the effect of predominantly antioxidant vitamins and folate on efficacy or toxicity mediated by cisplatin and anthracyclins. Cisplatin toxicity in rodents was ameliorated by vitamin E. The design of clinical studies of dietary agents in combination with cytotoxic agents has been very heterogeneous and results have been inconclusive.

Conclusions: Whilst preclinical experiments hint at a potential benefit of certain dietary agents, the evidence emanating from clinical studies does not allow firm conclusions to be made. Future studies should explore physiological doses of dietary agent and include pharmacokinetic and pharmacodynamic measurements.

Keywords: Diet, cytotoxic therapy, drug interaction

Introduction

After a diagnosis of cancer, patients are highly motivated to seek information about diet and dietary supplement use. Studies of women with breast cancer indicate that a majority of them are interested in altering their diet to aid therapy [1]. Whilst oncologists often face patients' questions as to which dietary measure, if indeed any, might support their therapeutic strategies, evidence-based information, which may help formulate such dietary advice, is scarce. In the absence of robust scientific information patients easily fall victim to unscientific propaganda. In principle there might be dietary agents the use of which might be encouraged, because they, in concert with drugs, may help to reduce tumour growth, and agents which should best be avoided, because they may counteract antineoplastic drug activity. Here we review preclinical and clinical information published within the past two decades describing the impact of diet constituents on antineoplastic therapy. The aim of the commentary is to pinpoint strategies designed to identify diet constituents worthy of further clinical evaluation to augment chemotherapy. The commentary focuses on discreet diet-derived chemical entities rather than intact food matrices, which, as variable mixtures of numerous bioactive components, confound robust and reproducible pharmacological characterization. Literature describing potential intrinsic antineoplastic activity of dietary compounds [2] is excluded, and the commentary is not a comprehensive review the literature. Most of the published information available deals with vitamins, antioxidants and folic acid, which are arguably among nutritional supplements used most frequently by the general public.

Nutritional status of cancer patients

The nutritional status in cancer patients can be compromised by the disease itself, e.g. by cancer-related cachexia. Poor nutritional status in such patients has been linked with poor prognosis [3]. It is conceivable that poor prognosis may be related to the detrimental impact of malnutrition on the efficacy, toxicity or pharmacokinetics of antineoplastic drugs. Nutritional imbalance in cancer patients has been well documented. The effect of selenium and zinc supplementation was evaluated in malnourished patients with gastro-intestinal or oesophageal cancer, who received chemotherapy [4]. Prior to commencement of therapy, serum concentrations of selenium and zinc were significantly lower than those in control (non-cancer) patients. In contrast, serum copper concentrations were elevated over those in controls. In this study the nutritional status of 70% of the patients on supplements did not deteriorate, whilst it worsened in 80% of patients on un-supplemented diet. In a case study involving lung cancer patients, 64% displayed serum vitamin C levels below the threshold associated with development of scurvy [5]. In contrast, surgically resected lung cancer tissues contained higher levels of vitamin C compared with normal adjacent tissue [6]. Several studies reported that patients with advanced cancer have low folic acid levels [7-12]. All these imbalances may conceivably impact detrimentally on chemotherapy (*vide infra*). *Vice versa* nutritional intervention can probably improve prognosis. Consistent with this notion, a cross sectional study in patients with non-small cell lung cancer suggested that supplemental vitamin intake was associated with an increase in long-term survival from a median of 11 months in non-users of supplements to 41 months in supplement users [13].

Effect of diet constituents on chemotherapy: preclinical evidence

The influence of diet constituents on the response to antineoplastic drugs can occur on different levels, affecting either drug efficacy, toxicity and/or pharmacokinetics. Table 1 provides examples of interventions, which have been shown to augment efficacy or reduce toxicity of cytotoxic chemotherapy in rodents.

Modulators of drug metabolism

An instructive example of a diet constituent which alters the pharmacokinetics of a cytotoxic agent is provided by dimethyl fumarate, a dietary metabolite of fumaric acid found in fruits and vegetables [14]. Dimethyl fumarate induces NADPH:quinone oxidoreductase I (NQO-1). When added to the diet at 0.3%, it increased NQO-1 activity in tumor tissue of nude mice bearing the HCT116 cell tumour. Mitomycin C is activated to a cytotoxic species *via* catalysis by reducing enzymes such as NQO-1. In mice, which received mitomycin C together with dimethyl fumarate, tumors were significantly smaller than those in mice on mitomycin C only, yet dimethyl fumarate did not increase host toxicity.

Antioxidants

Examples of dietary antioxidants are vitamins A, C and E, selenium and flavonoids such as quercetin and genistein. In several *in vitro* and animal studies the hypothesis has been tested that antioxidants benefit patients receiving chemotherapy. In principle two opposing mechanistic arguments could be advanced supporting or refuting this notion. On the one hand, antioxidants might protect cancer cells against the oxidative damage induced by chemotherapy, which would mitigate against their use. On the other hand they may enhance drug-induced cytotoxicity by blocking reactive oxidant

species. Reactive oxidant species generated by cancer cells or by cytotoxic agents [15] are thought to decrease cell proliferation rate, prolonging the G1 phase of the cell cycle and consequently rendering cells less susceptible to cytotoxic drug attack. Antioxidants might counteract this unwanted inhibitory effect of oxidative stress on cell proliferation. Evidence supporting the former notion is provided by the finding that α -tocopherol (vitamin E) inhibited reactive oxygen generation and blocked cisplatin-induced apoptosis in human-derived breast cancer cells [16]. In contrast, Prasad et al [17] showed that 5-FU, bleomycin, adriamycin, cis-platin or sodium butyrate combined with the dietary antioxidants vitamin C and E, A or beta-carotene inhibited the growth of murine neuroblastoma cells more potently than the antineoplastic agents alone. In another study dietary supplementation with vitamin C in rats, which received cisplatin, failed to significantly reduce cisplatin-induced kidney toxicity or oxidative DNA damage as reflected by urinary levels of 8-OHdG, even though a trend towards protection was observed [18]. The whole-body toxicity of high-dose cis-platin in mice bearing human melanoma was reduced by coadministration of vitamin E without compromising antitumour activity [19]. This protection was accompanied by an antioxidant effect as reflected by polyunsaturated fatty acids and thiobarbituric acid-reactive substances in kidneys and liver. In a review evidence emanating from rodent studies was presented suggesting that antioxidant vitamins A and C, coenzyme Q, flavonoids from herbs, olive oil or selenium can ameliorate the cardiac toxicity associated with adriamycin [20]. The pharmacodynamic parameters studied were cardiomyopathy and oxidative stress. Whilst tentative evidence for protection against adriamycin-induced cardiotoxicity was observed in some studies, results were negative in most.

Folate

The interaction between nutritional folate and anticancer drug response has received considerable attention. In an early investigation, mice bearing the P388 lymphocytic leukaemia were significantly more sensitive to 5-FU, cytosine arabinoside, 6-mercaptopurine or methotrexate, when these drugs were administered together with, or subsequent to, a large dose of folate [21]. More recently mice bearing the C3H mammary carcinoma on a low folate diet were shown to suffer 3000-fold more toxicity, as measured by lethality, after treatment with lometrexol, an antipurine antifolate, than control animals on normal folate [22]. In this study lometrexol caused hardly any efficacy in terms of tumor growth inhibition in the low-folate mice. In contrast, supplementation of the diet with folate improved efficacy and ameliorated toxicity. The effect of folate supplementation on toxicity exerted by cyclophosphamide or 5-FU was studied in rats [23]. Protocols included a folate-free diet, or a diet with folate-containing cereal, or a low folate diet (2mg folate/kg diet) or high folate treatment (dietary folate plus 50 mg/kg ip daily). Whole body toxicity exerted by cyclophosphamide as reflected by the LD₅₀ was lower for the cereal diet group than the other groups. With respect to 5-FU toxicity, there was no significant effect of the low folate diet in comparison to the folate-free diet. However 5-FU caused more severe anaemia, azotemia and leukopaenia in the high-folate group than in the other groups, suggesting that excessive amounts of folic acid may be deleterious. In a study using *Apc^{Min}* mice, a model of familial adenomatous polyposis, which develop adenomas in the small intestine, folate depletion enhanced the efficacy of 5-FU in reducing polyp numbers [24].

Other micronutrients, fatty acids and sugars

Amelioration of toxicity caused by methotrexate in rats was achieved with zinc (1g/kg diet) or growth factors derived from bovine cheese, or a combination of the two [25]. Animals received these agents for 7 days before and during treatment with methotrexate at 2.5 mg/kg daily for 3 days. Intervention with the dietary agents significantly reduced intestinal damage consequent to methotrexate therapy.

Docosahexanoic acid is a n-3 fatty acids, for which several beneficial health claims have been advanced. The hypothesis was tested that it can increase the activity of arabinosylcytosine in mice bearing the L1210 leukaemia [26]. Mice, which received arabinosylcytosine together with modest amounts of docosahexanoic acid (1.5% in the diet, average intake 1.8 g/kg/day), displayed a significantly longer life span than mice on arabinosylcytosine only. However a higher intake of fatty acid (4.5g/kg/day) resulted in a detrimental effect, as borne out by shorter survival time and increased tumor burden compared to mice on arabinosylcytosine alone. This finding indicates the existence of defined concentration windows, which determine the efficacy of dietary compounds, whilst higher concentrations can lead to detrimental effects.

There is also information on the effect on cancer chemotherapy of modification of the diet with sugars. The effect of oligofructose or inulin was studied in mice bearing a murine liver tumour [27]. Consumption of these sugars with the diet at 15% until the end of the study potentiated the therapeutic efficacy of a range of cytotoxic drugs given as a single dose.

Effect of diet constituents on chemotherapy: clinical evidence

Retrospective studies

In several recent studies of the influence of dietary supplements on outcomes from cancer chemotherapy, consumption of supplements was probed for by food frequency questionnaires. In one such study a total of 178 patients with small cell lung cancer were enrolled, of whom 60% reported the use of vitamin and mineral supplements [28]. The relative risk of death in the supplement cohort was 0.63, thus more favourable than in patients who did not take the supplements. A second survival analysis of the same patients, in which an alternative definition of vitamin/mineral consumption was used, showed only a non-significant trend towards improvement of survival by vitamin/mineral use. The supplements did not affect quality of life in this study.

In a historical cohort study 90 patients with early stage breast cancer who had consumed high doses of combinations of vitamins, minerals and other antioxidants concurrent with standard chemotherapy, were compared with 180 matched controls, who received chemotherapy only [29]. Patients on supplements displayed worse breast cancer-specific survival and disease-free survival than the control group.

In breast cancer patients, who recorded consumption of multivitamin preparations by questionnaire, blood levels of folate and vitamin B12 levels were measured [30]. The decrease in neutrophil count caused by cytotoxic chemotherapy seemed to be ameliorated by ingestion of dietary supplements. But women with serum folate levels >20ng/mL exhibited a greater decrease in neutrophil count after chemotherapy than women with lower folate levels. This result is consistent with the preclinical data, which suggests potential detrimental modulation by excessive folate of cytotoxic chemotherapy (*vide supra*).

In another study the hypothesis was tested that high folate intake can diminish the effectiveness of breast cancer chemotherapy [31]. Women who participated in the Iowa Women's Health Study, estimated their folate intake by questionnaire during a 14 year patient follow-up. High folate intake was not associated with poor survival, supporting the notion that folate supplementation does not detrimentally affect breast cancer chemotherapy.

The potential usefulness of dietary questionnaire to assess dietary intake of carotenoids, tocopherols and fatty acids has been validated in cancer patients receiving chemotherapy [32]. Data obtained by questionnaire correlated satisfactorily with biomarkers measured in plasma samples.

Prospective studies

Among the dietary agents which have been explored in prospective clinical trials to modulate cancer chemotherapy vitamins and antioxidants predominate (Table 2). The spectrum of results obtained in these studies encompasses detrimental outcome, lack of effect as well as hint of benefit, as is illustrated in the following by examples:

Cancer patients on cisplatin received supplementation with vitamin C (1g), vitamin E (400g) and selenium (100 µg) contained in a beverage twice daily beginning 7 days prior to the onset of chemotherapy until 3 weeks after cessation of therapy [33]. Supplementation failed to affect the incidence of cis-platin-mediated nephrotoxicity and ototoxicity significantly. A slight benefit of supplementation was intimated in patients with the highest plasma levels of antioxidants, who experienced significantly less loss of high-tone hearing. In a clinical antioxidant study involving patients with mainly lung cancer, all of whom received cisplatin chemotherapy [34], 14 patients ingested vitamin E (330mg/day) prior to cisplatin, and supplement intake was continued for 3

months after termination of cytotoxic therapy. The control group (14 patients) received chemotherapy only. Vitamin E decreased the incidence of peripheral neurotoxicity, and the neurotoxicity score based on clinical and neuro-physiological parameters was significantly lower in patients on vitamin E than in the control group. In an accompanying preclinical experiment, vitamin E failed to adversely affect the antitumour efficacy of cisplatin in nude mice bearing the human M14 melanoma. Selenium administration reduced cisplatin-induced nephrotoxicity in the acute stages but not over the long term [35]. A phase I trial of 5-FU and leucovorin with high-dose vitamin E in patients with advanced disease failed to show therapeutic benefit or reduced toxicity [36]. In five studies, in which the ability of vitamin E containing supplements to protect patients receiving anthracyclin-based therapy against cardiac toxicity or alopecia was studied, the supplement did not confer any benefit [37-41].

Supplementation of the diet with amino acids is common. Glutamine, an amino acid that acts as a substrate for nucleotide synthesis in dividing cells, is the most abundant amino acid in blood and constitutes 60% of the free amino acid pool in skeletal muscle. As cancer patients often suffer from glutamine depletion, attempts have been made to supplement their diet with the aim to ameliorate the incidence or severity of mucositis caused by chemotherapy, diarrhea associated with irinotecan, neurotoxicity elicited by paclitaxel and anthracycline cardiotoxicity. A review of this work [42] suggests that glutamine at doses of up to 30 g daily given for several days can indeed decrease drug toxicity.

A well-known example of a group of dietary constituents capable of interfering with the metabolism of drugs, are grapefruit flavonoids. They block the activity of cytochrome P450 3A4 isoenzyme in the intestinal wall thereby preventing the presystemic first-pass metabolism of a wide variety of drugs [43]. An influence of

grapefruit on the disposition of anticancer drugs such as taxol has to our knowledge not yet been published.

What advice for cancer patients?

Reviewing the pertinent literature certainly supports the notion that, in spite of the interest which diet and dietary supplements continue to elicit among the general public, evidence permitting rational advice to patients remains weak. The studies described above suggest that supplementation with low dose selenium or folate may be worthy of further clinical investigation in patients who are deficient of these nutrients. A recent systematic review of antioxidant use and cancer therapy [44] deduced that inconsistencies in study design, timing of observation/ intervention, intervention protocol, malignancy and anticancer regimens preclude definitive conclusions to be drawn as to the effect of therapy on patients' antioxidant status or of antioxidant intervention on therapy. D'Andrea [45] came to a similar conclusion after summarizing the evidence supporting the usefulness of antioxidant supplements in the reduction of host toxicity of cytotoxic chemotherapy or radiotherapy. A recent analysis of potential benefit of nutritional intervention for outcome of patients with cancer or preinvasive lesion [46] concludes that robust evidence is lacking for improvement of patient survival or disease prognosis by dietary modification. This report emphasizes the paucity of the scientific basis for nutritional advice to cancer patients, and the pharmacological analysis with respect to dietary supplements presented here is consistent with that notion. Carefully conducted studies exemplified by Pace *et al* [42], who investigated cisplatin in combination with vitamin E, will permit a better assessment of the role specific dietary supplements may be able to play. The situation is tantalizing with respect to therapy with novel molecularly

targeted agents. Relevant information of the effect of dietary supplements on the efficacy or unwanted effects of such therapies is virtually non-existent. In the light of the emerging multi-faceted effects of diet constituents on cellular signalling cascades it is conceivable that they counteract or synergize with agents such as kinase inhibitors. Consistent with this hypothesis, supplementation with selenium has recently been hypothesized to increase the efficacy of cetuximab in metastatic colorectal cancer *via* decreasing COX-2 and PGE-2 in malignant tissues [47].

Studying potential interactions

How should we design investigations of interactions between antineoplastic drugs and diet constituents? Firstly we need more information on mechanisms of dietary constituents which may be pertinent to drug toxicity or efficacy. Nutritional pharmacology is a subject in its infancy, but the interest of health providers and biomedical researchers has recently grown considerably, as illustrated by the fact that there is now a journal specifically devoted to this topic (“Molecular Nutrition and Food Research”). More and more diet constituents are being scrutinized in terms of their ability to interfere with oncogenic pathways [48]. It might be appropriate to complement studies of anticarcinogenic properties of dietary agents in cells *in vitro* with those of mechanisms pertinent to antineoplastic drug response/toxicity. The emerging disciplines of nutritional genomics and proteomics will improve the methodologies required to optimise the acquisition and rationalization of pertinent mechanistic insights. Testing of combinations in rodent models should be governed by a mechanism-led rationale based on results of *in vitro* experiments. Studies in rodents *in vivo* should be conducted in those models, which in the past have convincingly predicted efficacy or toxicity in humans of the antineoplastic agent under study. A recent paper on the role of 5-methylselenocysteine and seleno-L-methionine in the response of nude mice bearing human colorectal tumour xenografts to irinotecan, 5-FU, oxaliplatin, cisplatin and doxorubicin [49] constitutes a suitable example of a thorough preclinical investigation of the modulation of cytotoxic therapeutic efficacy by dietary constituents, even though the authors refrained from investigation of mechanisms or pharmacodynamics. Ultimately clinical studies of dietary agents should be designed based on relevant preclinical data, and they should preferably employ doses which resemble dietary doses of these agents, to minimize

the chance of unwanted effects mediated by “mega” doses, as exemplified above at the preclinical level for folate [29] and fatty acids [26]. Clinical studies should also include, if possible, measurement of pharmacokinetics and pharmacodynamics of the diet constituent, in order to enable rational interpretation of pharmacological and/or toxicological effects or their absence. In contemporary cancer chemotherapy, pharmacogenetics plays an increasingly important role. Irinotecan provides an instructive example. A recent comprehensive analysis explored polymorphisms in uridine diphosphate-glucuronyl transferase (UGT) enzymes in patients with non-small-cell lung cancer treated with irinotecan [50]. The authors suggest that certain UGT genotypes may be associated with irinotecan efficacy and/or toxicity, as they regulate the rate of glucuronidation of SN-38, the active metabolite of irinotecan. Dietary cruciferae such as broccoli, citrus fruits or onions contain agents which can increase the activity of UGT isoenzymes [51]. These two findings, when juxtaposed, should alert oncologists to the possibility of pharmacokinetic interactions between dietary cruciferae and irinotecan, which seem worthy of clinical evaluation.

Recently a carefully formulated nutraceutical supplement programme with antiangiogenic properties has been described and suggested to potentially improve the efficacy of cytotoxic therapy [52]. Components of this diet are eicosapentanoic acid-rich fish oil, epigallocatechin-3-gallate (from green tea), selenium, glycine, and silymarin (milk thistle extract). Ultimately this type of approach involving standardized food components, if based on robust science, seems logical and desirable. However at present nutraceutical supplement combinations are likely to meet scientific scepticism, as the current level of knowledge of the multiple pharmacological properties of complicated mixtures is insufficient to allow a rational judgement to be made as to the therapeutic situation, in which they may be beneficial.

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Table 1. Beneficial effects of dietary agents administered with anticancer drugs in rodents

Dietary agent	Cytotoxic drug	Effect ^a	Reference
Dimethylfumarate	Mitomycin	e, colorectal	[14]
Vit C, E, A	5-FU, bleo, adria	e, neuroblastoma	[17]
Vit E	cisplatin	t, mice	[18]
Vit A, C coenzyme Q, selenium	Adria	t, cardiac	[20]
Dietary folate	5-FU Cyclophosphamide	t, whole body	[23]
Zinc	Methotrex	t, intestinal	[25]
Docohexanoic acid	Arabinosyl-cytosin	e, murine leukaemia	[26]

^a e = increased efficacy, t = decreased toxicity

Table 2. Dietary agents used in prospective clinical trials to aid cytotoxic therapy

Dietary agent	Cytotoxic drug	Reference
Vit E	5-FU	[36]
Vit E	Adria, vincr, bleo, 5-FU, mitomycin, procarb, methotrex	[37]
Vit E	5-FU, adria, cyclophos	[38]
Vit E	Doxorub, vincr, 5-FU, cyclophos, cisplatin	[39]
Vit E	Cisplatin	[34]
Vit C,E, selenium	Cisplatin	[33]
Selenium	Cisplatin	[35]
Selenium, vit C, E; β -carotene	Cisplatin, cyclophos	[41]
Vit C, E	Adria, cyclophos, bleo, vincr, procarb, prednis, dacarb, vinblast, VP16	[40]
Glutamin	Paclitaxel, anthracyclins	[42]