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ANTI-TUMOUR TREATMENT

Ingestion of selenium and other antioxidants during prostate cancer radiotherapy: A good thing?

A. Tabassum [a,e], R.G. Bristow [b,c,f], V. Venkateswaran [d,*]

[a] Molecular and Cellular Biology, Sunnybrook Health Science Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5
[b] Departments of Radiation Oncology and
[c] Medical Biophysics, University of Toronto, and Princess Margaret Hospital (University Health Network), 610 University Avenue, Toronto, Ontario, Canada M5G 2M9
[d] Department of Surgery, University of Toronto, Division of Urology, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5

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SUMMARY

Radiation and many chemotherapy agents work to kill cells by inducing free radicals that damage DNA and proteins. Antioxidants such as vitamin E, β carotene, lycopene, and selenium have been associated with a reduction in cancer risk when ingested by prostate cancer patients. Selenium is a promising agent currently being evaluated as a prostate cancer prevention agent. Selenium is an essential trace element and is involved in antioxidant protection and the redox-regulation in humans. Several adverse effects of radiotherapy and chemotherapy in cancer patients have been linked to oxidative cell processes in the human body. Selenium supplementation may protect healthy tissues and reduce the side effects of treatment. Despite two decades of research into this question, no clear answer has appeared. Therefore, understanding the mechanism(s) by which dietary nutrients exert their effects in prostate carcinogenesis, may lead to the exploitation of new chemoprevention agents. A large body of epidemiological evidence, including observational, trials, and randomized controlled clinical trials, support the proposition that selenium may prevent prostate cancer in humans. These clinical studies are supported by *in vitro* and *in vivo* data using prostate cancer models. This systematic review provides the first evidence that antioxidant supplementation during chemotherapy holds potential for reducing dose-limiting toxicities. The pre-clinical and clinical evidence as to whether ingestion of supplemental selenium, in addition to radiotherapy/chemotherapy is beneficial, detrimental or neutral towards patient outcome is also discussed.

Introduction

Radiation therapy is an important curative treatment modality in the management of prostate cancer. Impressive progress has been made by improving the physical targeting of radiation to tumor tissue relative to increased sparing of normal tissue. This has led to enhanced PSA-free relapse rates accurately associated with decreased rectal and bladder toxicity.[1] Chemotherapy (e.g. mitoxantrone or taxane) has traditionally been used for the treatment of metastatic disease, but is currently being used in neo-adjuvant protocols, either alone or in addition to hormone therapy, prior to surgery or radiotherapy.[2,3]

Both chemotherapy/radiotherapy lead to genotoxic stress that in turn leads to cancer cell killing through apoptosis, mitotic catastrophy, atrophy or terminal growth arrest. Therefore the relative efficacy of these treatments may be affected by the antioxidation that occurs in tumor tissues. A recent study suggested that 40–80% of patients who were at a high-risk percentile of developing prostate cancer or who were diagnosed with prostate cancer, were taking complementary/alternative therapies, including the use of antioxidants.[4]

Based on pre-clinical and clinical evidences vitamin D, C, A, E and selenium may have a protective effect against prostate cancer. Hence it is possible for these agents to be part of chemopreventive strategies.[5] However, these agents could alter the DNA damage produced in cancer cells during radiotherapy or chemotherapy.[6] The potential interaction of antioxidants with radiotherapy, chemotherapy or hormonal therapy for prostate cancer is currently unclear and it is difficult to advise patients as to whether to consider antioxidant use during cancer treatment. This systematic review provides the first evidence that antioxi-

* Corresponding author. Tel.: +1 416 4806 6100x3127; fax: +1 416 480 5737.
E-mail addresses: atabassum@sri.utoronto.ca (A. Tabassum), rob.bristow@rmp.uhn.on.ca (R.G. Bristow), vasundara.venkateswaran@sunnybrook.ca (V. Venkateswaran).
[e] Tel.: +1 416 4800 6100x7430.
[f] Tel.: +1 416 946 4501x2936; fax: +1 416 946 4586.

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dant supplementation during chemotherapy holds potential for reducing dose-limiting toxicities. The pre-clinical and clinical evidence as to whether ingestion of supplemental selenium, in addition to radiotherapy/chemotherapy is beneficial, detrimental or neutral towards patient outcome is discussed. However, large scale trials, better designed to evaluate patients administered antioxidants relative to chemotherapy are warranted.[7]

Antioxidants as chemopreventive agents

Antioxidants, such as vitamin E, β carotene, lycopene, and selenium have been associated with a reduction in cancer risk when ingested by prostate cancer patients.[8] Selenium is a promising agent currently being evaluated as a prostate cancer prevention agent. It is an important trace element essential to human health.[9] The typical dietary intake of selenium in the United States is 80–165 μg/day, and the recommended dietary allowance is 55 μg/day.[10–12] Selenium is present in both organic (e.g. selenocysteine and selenomethionine) and inorganic forms (e.g. selenite and selenate). The metabolism and bioavailability of selenium is influenced by absorption in the gastrointestinal tract, transport in the blood, metabolism in the tissue and excretion in the urine and feces.[13] Selenium is an essential constituent of extracellular and cellular metalloenzymes, glutathione peroxidase, thioredoxin reductase and other selenoproteins.[14] A large body of epidemiological evidence, including observational, trials, and randomized controlled clinical trials, support the proposition that selenium may prevent prostate cancer in humans.[15–18] These clinical studies are supported by *in vitro* and *in vivo* data using prostate cancer models[19] as discussed below.

Double blind, placebo-controlled cancer prevention trial by Clark et al[20] showed a 63% reduction in prostate cancer incidence among men supplemented with selenized-yeast. A follow up of this study continued to show a marked reduction in the incidence of prostate cancer following selenium supplementation.[21] Although the anticancer mechanism(s) of selenium-enriched diets have not been clearly defined, the positive outcome of this initial trial has prompted additional clinical trials: (1) Prevention of cancer by Intervention with selenium (PRECISE), in three European countries and (2) selenium and vitamin E cancer prevention trial (SELECT) in the United States, and the Australian Prostate Cancer Prevention Trial Using Selenium (APPOSE) trial.[22–24] The large randomized SELECT study will further define the role of the antioxidants selenium and vitamin E in the prevention of prostate cancer: It is anticipated that complete outcome data from the study will be available in the year 2012 years.[23,25,26] Taken together, these studies provide incentives for mechanistic evaluation of the potential effects of organo-selenium compounds in the control of initiation and progression of prostate cancer as well as decreasing risk of men with a family history or first-degree relative with prostate cancer. Recently, published interim futility analysis lead to the cessation of the SELECT.[26] Secondary analysis of this trial reported that selenium and vitamin E alone or in combination at the doses and formulations used did not prevent cancer in the relatively healthy population of men. These findings are timely as we have analogous findings using our *in vivo* transgenic model system that a combination of vitamin E and selenium was not effective in reducing the incidence of Pca.[27]

There are several criteria's for chemoprevention. Antioxidants in particular, are considered in terms of scavenging reactive oxygen species which would otherwise lead to DNA damage and mutation, resulting cellular carcinogenesis.[26,28] Therefore, understanding the mechanism(s) by which dietary nutrients exert their effects in prostate carcinogenesis, may lead to the exploitation of new chemoprevention agents. Based on lay information, related to chemotherapy many men consumed selenium, and continued the use of selenium supplementation when diagnosed with prostate cancer.

Mechanism of selenium action: Potential interaction with radiotherapy/chemotherapy

Growth arrest and alterations in gene expression following selenium exposure

Radiotherapy induces G1, S and G2 arrest in a p53-dependent manner in response to the DNA damage induced by ionizing radiation and the production of free radicals which attack the DNA backbone.[29] Similar effects have been reported for mitoxantrone and taxane that lead to mitotic arrest based on inhibition of the cell cytoskeleton apparatus.[30] However, the biological effects of selenium on prostate cancer cells *in vitro* may vary depending on the form of selenium under study.

High doses of selenite can cause DNA breaks resulting in decrease DNA synthesis and cell death.[31] Selenite exposure can also causes caspase-independent apoptotic DNA fragmentation, associated with a decreased expression of the G1 cyclin-dependent inhibitors, $p27^{Kip1}$ and $p21^{WAF1}$. Increased phosphorylation of the signaling with increases AKT, JNK1/2, and p38MAPK have also been observed.[32]

Other commercially available supplemental antioxidants consumed by cancer patients include selenomethionine (SeMet) and methylseleninic acid (MSA). These, have been shown to inhibit the growth of prostate cancer cells (e.g. LNCaP, PC-3, and DU-145 cells) *in vitro* and arrest cells at G1-S and G2/M transitions in a p53-dependent manner.[32,33] This was accompanied by increased expression of CDK inhibitors such as $p27^{Kip1}$ and $p21^{WAF1}$.[34] Selenomethionine treatment on the other hand was associated with the phosphorylation of cdc2 and decreased expression of cyclins D1 and D3.[35] These data on growth inhibition are supported by cDNA microarray analyses in which a number of cell cycle regulatory genes (e.g. *GADD153, CHK2, p21 (WAF), cyclin A, CDK1,* and *DHFR*) are differentially expressed in cells exposed to selenomethionine.[36,37] Therefore, multiple molecular pathways are likely to be targeted by the selenium metabolite pools to mediate tumor cell arrest and/or death during cancer chemoprevention[32] and these pathways overlap with the effect of radiotherapy/chemotherapy on cell cycle and cell death (Fig. 1).

Selenium, DNA repair and cytotoxic therapy

The relative induction and repair of DNA breaks following radiotherapy/chemotherapy could theoretically be altered in patients ingesting selenium. A decrease in the DNA damage imparted within tumor cells using antioxidant therapy could hypothetically lead to decreased cell destruction with a concomitant decrease in local or systemic tumor control following radiotherapy of chemotherapy. Redman et al.,[36] demonstrated *in vitro* that inhibition of growth and induction of DNA damage in DU-145 cells after Selenomethionine treatment produced lesser such effects in normal diploid fibroblasts. It is not however known whether selenium affects the DNA response during radiotherapy-induced breaks caused by ionizing radiation or specific lesions resulting from chemotherapy. There are interacting proteins and specific pathway to repair the lesions that are definite for each type of DNA lesion that has incurred. DNA-double strand breaks (DNA-dsbs) are repaired by homologous or non-homologous recombination, DNA base damage or mismatches are repaired by base excision repair (BER) or mismatch repair

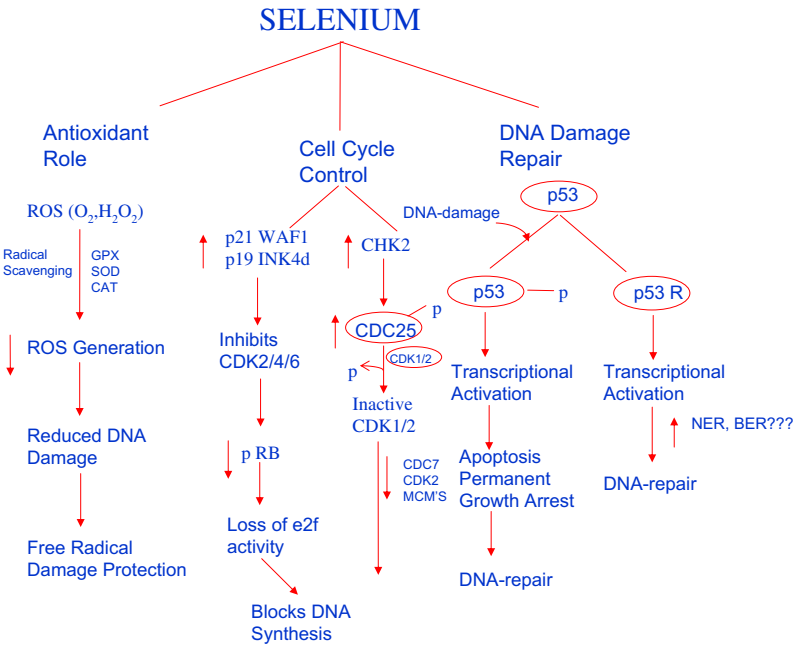

Fig. 1. Relationship between selenium and DNA damage in cancer prevention.

(MMR) proteins, whereas DNA intra-strand cross-links may be repaired by nucleotide excision repair (NER).[37,38]

The DNA damage and signaling during radiotherapy involves the p53 tumor suppressor protein.[39,40] Depending on the cell type and condition, p53 can activate up to 100 genes involved in DNA repair, cell death or cell cycle checkpoints. Smith and his co-workers (1996) have defined the relationship between selenomethionine exposure and nucleotide excision repair (NER) following ultraviolet irradiation (UV) in relation to p53 genotype. Selenomethionine radio-protected normal fibroblasts from UV-induced DNA damage in the presence of functional p53.[41,42] More recently, studies have suggested that p53 may be an important genetic determinant that distinguishes normal cells from cancer cells. Combinatorial chemotherapeutics that act by p53-dependent mechanisms may enhance chemotherapeutic efficacy by increasing the chemotherapeutic window distinguishing cancer cells from normal cells.[43] This protective effect was however lost in tumor cells that lack p53 protein and/or function. In addition, selenomethionine was incapable of enhancing survival in defective cells, suggesting that the protective effect required the presence of DNA repair proteins specific for this pathway. If true, this might suggest that selenomethionine would protect normal cells from radiotherapy or chemotherapy but in tumor cells (many of which lack p53 function) there would be no protective effect giving rise to increased tumor cell toxicity. To date, no such experiments have been carried out utilizing this approach. However, unpublished data from our laboratory has shown that combination of selenium (Seleno-DL-methionine) with radiotherapy (Radiation dose: 4 Gy) increases prostate cancer cell killing.

Although limited by *in vitro* systems, the data suggests that selenomethionine could radio- or chemoprotect normal tissues by arresting these cells during therapy and augmenting the DNA repair process. If proven through human clinical trials, this would lead to the use of selenium during chemotherapy or radiotherapy to improve the therapeutic ratio. However, further *in vitro* and *in vivo* work is required within DNA repair pathways (DNA-dsb repair, BER, MMR, etc.), pertinent to the DNA damage imparted by each cytotoxic agent, to authenticate that this effect can be generalized to all prostate cancer patient.

Selenium and tumor progression

Is there a danger that the use of selenium could give tumor cells a growth advantage during radiotherapy? *In vivo* experimental studies have shown that selenium (200ugms, Seleno-DL-methionine) supplementation inhibits the progression of hormone-refractory prostate cancer in an experimental xenograft model.[44] Orthotopic PC-3 tumors were established in the prostates of 6 week-old male nude mice and fed a baseline selenium replete diet (0.07 ppm), supplementing intake with different forms of selenium (sodium selenate, selenomethionine, methylselenocysteine and selenized-yeast) at 2 different concentrations (0.3 and 3 ppm) in drinking water. Results showed that inorganic selenium (sodium selenate) significantly retarded the growth of primary prostatic tumors and prevented the development of retroperitoneal lymph node metastases.[45] Whether this is factual for remains to be tested.

Interaction with other antioxidants

Although this review has focused on the use of selenium, other compounds such as vitamin E, have been tested in combination with selenium in clinical trials relating to chemoprevention.[44] Previous studies reported, have shown that vitamin E and selenium in combination produced a synergistic effect on cell growth suppression.[46,47] Cell lines from a wide variety of human cancers have shown G1 phase growth arrest when incubated with vitamin E, possibly by activation of the G1cyclin-cdk inhibitor, p27 *KIP*.[34] Treatment of LNCaP cells with 20 μM vitamin E succinate (VES) inhibited their growth *in vitro* by inducing a G1 phase arrest. This effect was associated with decreased expression of the cell cycle regulatory proteins cyclin D1, D3, Rb phosphatases and E and cdk2 and 4. Indeed, Fleshner and colleagues[43] have shown that supplementation of vitamin E can inhibit tumor progression in human prostate cancer xenografts *in vivo* beyond that

obtained with selenium alone. These studies have not been conducted in patients with the view of determining gene expression relating to the cell cycle within tissue biopsies pre- and post-treatment.

Clinical studies needed by the field

In summary, there are very few *in vitro* studies and practically no *in vivo* studies, which can direct clinical staff and patients as to the use of antioxidants during cytotoxic therapeutic procedure. Although, *in vitro* data are provocative, there is a complete lack of *in vivo* studies using selenium in combination with either radiotherapy or chemotherapy. Furthermore, there are no randomized clinical documenting patient outcome, and or acute and late effects using similar regimens. The few anecdotal reports are inconclusive and suffer from lack of, poor recording of agent concentration ingested and varied endpoints for patient outcome.

At present, further studies are required in both the pre-clinical and clinical setting to determine the precise effects of antioxidants *in vivo*, in relation to their reported effects i*n vitro*. This will require immunohistochemical analysis for cell cycle or DNA repair complexes and altered phosphoforms of DNA damage proteins. However, a randomized clinical trial to support the advantage of antioxidant supplementation during radiotherapy or chemotherapy will be required. At present, our institutional policy is conservative and states that patients should stop antioxidant use 1 week prior to radiotherapy and to resume use (at the patient discretion), a week following radiotherapy. As clear guidelines to patients will require definitive clinical studies, the onus is on the urologic community to prove benefit if patients are counseled to continue antioxidants during non-surgical therapies.

Conflict of interest

None declared.

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