

Minireview

Selenium in Oncological Intervention

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Abstract

Nutritional supplements are widely used among patients with cancer. Recent studies have provided increasing evidence that treatment is tolerated better with an increase in patient compliance and a lower rate of treatment discontinuations when the trace element selenium, is added as appropriate to the patient's medication. Clinicians should have an open dialogue with patients about nutritional supplements such as selenium. Supplementation of selenium needs to be individualized and come from a credible source, and it is best communicated by the physician.

Keywords: selenium; cancer, treatment related side effects, chemotherapy, radiotherapy

Introduction

Selenium is an essential micronutrient for human health whose biological activities and anti-carcinogenic properties likely result from its incorporation as the 21st proteinogenic amino acid selenocysteine in selenoproteins encoded by 25 separate human genes with roles in cell protection from oxidative stress, redox control, and the inflammatory response. Selenium-dependent glutathione peroxidases and thioredoxin reductases are necessary for optimal function of immune cells by controlling oxidative stress and redox regulation. Specific selenoproteins also have ROS-independent roles in modulating inflammatory responses [1]. Pharmacodynamics data suggest that selenite targets several key cancer-associated signaling pathways and induces multimodal regulated cell death pathways [2,3]. Deficiencies of micronutrients, including essential trace elements such as selenium, affect up to 3 billion people worldwide. The dietary availability of the trace element selenium is determined largely by their soil concentrations. Thus the change in climate and soil organic carbon content will lead to overall decreased soil selenium concentrations, particularly in agricultural areas. These decreases could increase the prevalence of selenium deficiency. The importance of climate-soil interactions to Se distributions suggests that other trace elements with similar retention mechanisms will be similarly affected by climate change. Furthermore suboptimal dietary intake of selenium is found in many parts of Europe. Low Selenium status may contribute for example to colorectal cancer development [4,5].

The trace element selenium has a long history as a cancer preventive agent. A few human trials addressing total cancer incidence have been published [6-9]. Some of these studies show a correlation between low serum selenium levels and increased incidence of mainly breast cancer [10], gastrointestinal cancers [11,12], and prostate cancer [13]. The major effects of supplementation have been observed in the incidences of colorectal-, lung, and prostate cancers along with a drastic decrease in the total cancer mortality

by 50% [14]. There is also a clear correlation to dose and the base line selenium status of the study population [14]. In the case of prostate cancer beneficial effects are clear only in populations with a low baseline selenium level and a low intake [15-17].

A Cochrane review published in 2011 investigated whether there was a relationship between the selenium supply and the risk of cancer, and also the effectiveness of selenium supplements in cancer prevention [18]. The analysis included 49 prospective non-interventional studies and six randomized clinical trials. The epidemiological studies showed that people with a better selenium supply had a reduced incidence of cancer (OR 0.69; 95% CI 0.53–0.91) and a reduced mortality from cancer (OR 0.55; 95% CI 0.36–0.83). The effects on the incidence of cancer was more pronounced in men than in women (OR 0.66; 95% CI 0.42–1.05 and OR 0.90; 95% CI 0.45–1.77, respectively). The randomized clinical trials, however, did not find any effects of selenium supplements, using either selenium yeast to prevent non-melanoma skin cancers or L-selenomethionine to prevent prostate carcinoma. Although an inverse association between selenium exposure and the risk of some types of cancer was found in some observational studies, this cannot be taken as evidence of a causal relation, and these results should be interpreted with caution [18,19].

A critical observation at this point is that the evaluation of the epidemiological data included studies carried out around the world, while merely two studies were considered in the assessment of the preventative effects of selenium, namely the Nutritional Prevention of Cancer Trial (NPCT; selenium yeast for the prevention of non-melanoma skin cancers) [6] and the Selenium and Vitamin E Cancer Prevention Trial (SELECT; L-selenomethionine for the prevention of prostate carcinoma) [20]. It

It is known, however, that the SELECT participants from the USA, Canada, and Puerto Rico had a median selenium serum level of about 135 µg/L at the start of the study and were therefore already adequately supplied with selenium at baseline. This is one reason why the expected effects of selenium supplements were not seen [20]. In Europe, including Germany, healthy people have mean selenium serum levels about 84 µg/L, while the levels in cancer patients are often even below 70 µg/L [10]. The results of a long-term non-interventional study with 13,887 adult USA citizens demonstrated that an optimal selenium supply gives serum levels between about 110 µg/L and 130 µg/L [21,22]. Above and below this range there was a tendency towards increased mortality from cancer and increased mortality in general. This supports the view that serum selenium levels that are too high (>150 µg/L) do not provide any long-term protection against cancer, as was also the case in the SELECT study. A relevant secondary result of the NPCT study, which primarily investigated the effects of selenium supplements on the risk of skin cancer, is that not only the overall incidence of cancer but also the overall mortality was significantly lower after selenium yeast supplements (200 µg/day) in comparison with placebo [6]. The incidence of prostate cancer was also reduced in the selenium group (relative risk 0.51; 95% CI: 0.29–0.87) with the greatest effect being seen in the men who initially had the lowest selenium supplies (serum selenium levels <123 µg/L) [16,23-25].

Against this background, both in healthy patients and in those with cancer, the selenium status should always be checked first whenever supplements are being considered. Only when selenium deficiency has been confirmed should supplements be given until a concentration in the optimal range is achieved (serum selenium level: 130 to 150 µg/L). People whose serum selenium concentration is already 122 µg/L or higher should not supplement with selenium [21, 22]. The converse is also important: there are various health benefits, and more importantly, no extra risk, for persons with serum concentrations less than 122 µg/L associated with rising their selenium status (e.g., selenium containing supplement) to 130–150 µg/L, a selenium level associated with minimal mortality [22].

Use of High-Dose Selenium during Chemo- or Radiotherapy

Five randomized trials have looked at the question of whether the concomitant use of high-dose selenium reduces the toxicity of chemo- or radiotherapy without impairing the main effects of oncological treatment. The five available studies on the use of selenium are all randomized but not blinded or placebo-controlled (Table 3). In a Chinese study by Hu et al. (n = 41), the concomitant use of high-dose selenium significantly reduced the hematotoxicity and nephrotoxicity of cisplatin in the treatment of various solid tumors; survival rates were not given in this publication [26]. Sieja et al. (n = 31) gave selenium to accompany chemotherapy with cisplatin and cyclophosphamide in patients with ovarian cancer, and found a significant reduction in hematotoxicity, as well as alopecia; survival data were not given here either [27]. In patients with non-Hodgkin's lymphomas (n = 50) and chemotherapy according to the CHOP

(cyclophosphamide, doxorubicin, vincristine, prednisone) regimen, the concomitant use of selenium led to a significant reduction in hematotoxicity, a significant improvement in the remission rate, and in the median overall survival [28,29]. A German study (n = 39) in which patients took selenium in parallel to radiotherapy for head and neck cancers showed a significant reduction in the rate of dysphagia in the last week of radiotherapy (week 7) [30].

In another German study (n = 81) on patients with cervical or uterine cancer, taking selenium at the same time as adjuvant irradiation caused a significant reduction in the rate of radio-genic diarrhea (grade ≥ 2) from 44.5% to 20.5% (p = 0.04) [31,32]. After 10 years, the disease-free survival in the selenium group was 81.5%, versus 82.3% without selenium (p = 0.87); the overall survival at this point in time was 58.4% in the selenium group, versus 44.8% without selenium (p = 0.13). We can conclude, therefore, that the administration of sodium selenite is safe and does not reduce the main biological effects of the oncological treatment. In view of its positive effects on RT-induced diarrhea, we consider Se supplementation to be a meaningful and beneficial adjuvant treatment in Se-deficient cervical and uterine cancer patients while undergoing pelvic radiation therapy. All of the selenium studies found a significant increase in the serum selenium concentrations measured after supplements had been taken.

The safety and efficacy of intravenous administered sodium selenite in cancer patients (n = 34, 70% of the patients had lung carcinoma) refractory to cytostatic drugs was assessed in a recent phase I trial (SECAR study). Patients received first line of chemotherapy following intravenous (i.v.) sodium selenite treatment to investigate altered sensitivity to these drugs and preliminary assessment of any clinical benefits. Interestingly, many of the patients in this study responded again to their first line of chemotherapy after i.v. administration of sodium selenite. These results were in support of other findings and indicated that even if sodium selenite in itself might be clinically useful in a subset of cancer patients, its subsequent use with chemotherapy might be therapeutically valuable. Furthermore the findings from this study indicate that sodium selenite might work in three ways against cancer: the antitumor effect by itself, by reversing chemoresistance and by ameliorating toxic effects from chemotherapy. In this trial sodium selenite was safe and well-tolerated when administered up to 10.2 mg/m² under the current protocol [33,34,36].

Recommendation for clinical practice

In routine clinical practice-outside of studies-the idea is to counterbalance any deficiencies, wherever possible after performing the relevant lab tests. This seems particularly important for the trace element selenium. The studies presented here indicate that the toxicity of chemo- and radiotherapy can be reduced by raising the serum selenium concentration without impacting the main anticancer effects. This is also the practical experience with sodium selenite in our group (e.g., 1 mg sodium selenite in 100 mL 0.9% NaCl as pre-medication before chemotherapy). Efforts should be made to achieve a target selenium level between 130 and 150 µg/L [22, 35, 36]. In oncology the selenium salt of choice is sodium selenite.

Table 1. Studies on the use of high-dose selenium during chemo- or radiotherapy

Author	Design	Outcomes
<i>Hu et al., 1997 [26]</i>	Patients with various solid tumors and chemotherapy containing cisplatin (n = 41) Randomized crossover study; administration of selenium (as seleno-kappacarrageenan) 4 mg/day for four days prior to and four days after chemotherapy in the first or second cycle	With selenium supplements: clearly higher leucocyte counts 14 days after chemotherapy ($3.35 \pm 2.01 \times 10^9/L$ vs. $2.31 \pm 1.38 \times 10^9/L$; $p < 0.05$) Less need for granulocyte colony stimulating factor (110.1 IU vs. 723.6 IU, $p < 0.05$) Less need for blood transfusion (0 mL vs. 62 ± 38 mL, $p < 0.05$)
<i>Sieja et al., 2004 [27]</i>	Patients with ovarian cancer on chemotherapy (cisplatin, cyclophosphamide; n = 31): <ul style="list-style-type: none">• Selenium 200 µg/day• Control patients not given any selenium preparations	Significant increases in serum selenium levels, and glutathione peroxidase activity in red blood cells (after 2 and 3 months), and in the leucocyte count (3 months); significant reduction in alopecia, flatulence, abdominal pain, weakness, loss of appetite
<i>Asfour et al., 2006/2007 [28,29]</i>	Patients recently diagnosed with non- Hodgkin's lymphoma (n = 50); Randomized, open-label study: <ul style="list-style-type: none">• Chemotherapy plus sodium selenite 200 µg/kg/day;• Chemotherapy according to CHOP regimen	Significant fall in tumor marker Bcl-2 in the group taking supplements after 30 days (end value: 8.6 ± 6.9 ng/mL vs. 36.9 ± 7.9 ng/mL; $p < 0.05$ for test substance vs. placebo); complete response rate 60% vs. 40%; median overall survival in patients with complete remission 21.9 ± 1.4 months vs. 19.7 ± 2.0 months; $p = 0.01$
<i>Büntzel et al., 2010 [30]</i>	Patients with advanced head/neck cancer and radiotherapy (n = 39) Randomized, open-label study: <ul style="list-style-type: none">• Group A: with sodium selenite (500 µg on radiotherapy days, 300 µg on the other days; n = 22);• Group B: no selenium replacement (n = 17)	Dysphagia (difficulty swallowing): 22.7% vs. 35.3%; alteration in taste: 22.7% vs. 47.1%; dry mouth: 22.7% vs. 23.5%; stomatitis: 36.4% vs. 23.5%; only the decrease in difficulties swallowing in the last week of radiotherapy was statistically significant
<i>Mücke et al., 2010 [31]</i>	Patients with cancer of the cervix or uterus (n = 81) in the radiotherapy phase following surgical removal of the tumor and with a serum selenium concentration below 84 µg/L; randomized, open-label study: <ul style="list-style-type: none">• Group A: with sodium selenite (500 µg on radiotherapy days, 300 µg on the other days; n = 39)• Group B: no selenium replacement (n = 42)	Significantly increased serum selenium concentration in group A at the end of the study; radiogenic diarrhea (grade ≥ 2) at the end of the study 20.5% vs. 44.5% ($p = 0.04$); no difference with respect to blood tests, functional status or quality of life

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone.

Selenomethionine is incorporated non-specifically into proteins in place of methionine and, therefore, accumulate in organs and tissues.

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Author Contributions

All authors contributed writing of this review and approved the text.

Conflicts of Interest

The authors declare no conflict of interest.

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