ANTICANCER RESEARCH *37*: 6497-6509 (2017)
doi:10.21873/anticanres.12106

Review

Optimising Selenium for Modulation of Cancer Treatments

STEPHEN OWEN EVANS[1*], PUTERI FARISA KHAIRUDDIN[2*] and MICHAEL B. JAMESON[2]

[1]*Biomedical Research Unit, School of Science, University of Waikato, Hamilton, New Zealand;*
[2]*Department of Oncology, Waikato Hospital, Hamilton, New Zealand*

Abstract. *Selenium is an essential trace element involved in many biological processes that are mediated through, at least, 25 selenoproteins expressed in humans. Extensive study of selenium compounds has demonstrated growth inhibition of malignant cells in a vast array of experimental models. Moreover combining selenium with conventional cancer therapy has yielded promising results in both pre-clinical studies and a cohort of human trials. The aim of this review is to highlight the current research evaluating the role of selenium compounds in combination with chemotherapy and radiation. Pharmacodymanic mechanisms responsible for the differential effects of the commonly studied compounds on healthy and malignant cells are presented and the pertinent in vitro and in vivo data summarised. The clinical utility of this approach is discussed both in terms of anti-tumour efficacy and toxicity prevention. Finally a case is made for novel trial designs to facilitate rapid progression into pivotal studies.*

Selenium (Se) is one of the most extensively studied trace elements, especially with regard to cancer. Most of this research relates to nutritional doses of Se in healthy people as primary prevention of cancer, with strong evidence that populations with low Se intakes are at higher risk of cancer (1-3); in these groups, supplementation may reduce cancer incidence and cancer-specific mortality (4). However it appears that there can be "too much of a good thing" with Se; not only does supplementing with supranutritional doses of Se in Se-replete populations not confer protection against cancer (5), laboratory and clinical studies suggest this may even increase the risk of cancer (6, 7).

Many patients extrapolate the prevention data and take Se (often at supranutritional doses) to try and control their existing cancer (8, 9). There is very little clinical research relevant to this practice but one study on prostate cancer showed no restraint of prostate-specific antigen (PSA) velocity and, of greater concern, in those with the highest baseline serum Se, supplementation with 800 μg daily of selenized yeast actually significantly increased PSA velocity (10).

While this generates concern about patients using Se as a sole treatment for cancer, especially in those who have adequate Se intakes, there is substantial preclinical research and some early clinical trials suggesting that Se compounds may significantly protect against the normal tissue toxicities of cancer therapies without compromising their anticancer efficacy (or even enhancing it) (11-13). The mechanisms that mediate this are being increasingly explored and understood and, in contrast to primary prevention, the beneficial interactions of Se with cancer treatments appear to be dose-dependent, with maximum efficacy at doses much greater than nutritional requirements (13).

While this is encouraging, considerable uncertainties slow the progress of research in this area. It is not clear what chemical form of Se is most effective, nor at what dose (which has varied from <100 to 90,000 μg/day). While the Se dose has sometimes been guided by preclinical pharmacokinetic (PK) studies, there has not been a clear evaluation of the pharmacokinetic-pharmacodynamic (PK-PD) relationship for various Se compounds, nor comparison of their differential effects on normal and malignant cells at different concentrations for each compound. Furthermore the toxicities of supranutritional doses of the different Se compounds in clinical use have not been systematically evaluated. Of particular concern is the genotoxicity of some forms of Se, particularly the inorganic salts (14), and the possibility that using these in conjunction with other

*These Authors contributed equally to this study.

Correspondence to: Michael B Jameson, Department of Oncology, Waikato Hospital, Private Bag 3200, Hamilton 3240, New Zealand. E-mail: Michael.jameson@waikatodhb.heath.nz

Key Words: Selenium, cancer, radiotherapy, chemotherapy, toxicity and efficacy, review.

genotoxic therapies (such as radiation and alkylating agents) could increase the risk of second malignancies and myelodysplasia. No clinical trials to date have reported on such end-points.

This review focuses on the preclinical and clinical evaluation of the interaction of Se compounds with chemotherapy and radiation, the PK-PD relationship of these compounds and differential effects and thresholds in normal and malignant cells. Ultimately we wish to use this information to inform the rational development of further clinical trials that can definitively assess whether these Se compounds can meaningfully reduce the burden of toxicities of cancer treatments for patients while maintaining or improving their efficacy, as suggested by preclinical studies.

Selenium – Role in Human Health

It is well known that Se intake varies hugely worldwide due to differences in diet and soil content of Se in different geographical locations. Although a recommended dietary intake of Se has been established, it is difficult to give a broad recommendation for a specific dose (6). 'Nutritional' doses ranging from 50-200 μg/day have been used mainly for primary prevention (15), and Se supplementation at these doses for Se-deplete individuals has been associated with lower overall mortality and incidence of certain cancer types (6). However, as alluded to earlier, it is well known that taking Se at supranutritional doses over a long duration can cause adverse effects, a reminder that Se is also recognised as a toxic element (6).

The role of Se in maintaining health is complex and it has many important biological functions including in redox signalling, thyroid metabolism, immune function, detoxification and antioxidant activity (6). These effects are primarily mediated by over 25 specific encoded selenoproteins, in which selenocysteine replaces cysteine. Among the more widely studied selenoproteins are the glutathione peroxidases (involved in antioxidant activity and sperm motility) and thioredoxin reductases (involved in intracellular redox regulation and signalling). The pronounced immunostimulant effects of Se can cause a wide array of effects, from increased proliferation of activated T-cells and natural killer cell activity to enhanced lymphocyte-mediated tumour cytotoxicity (6).

Selenium Compounds – Metabolism, Pharmacology and Toxicity

Se exists in different chemical forms and these compounds can be broadly categorized into organic and inorganic forms. The metabolic pathway of dietary Se is shown in Figure 1.

There is good evidence that the increased Se status attained after supplementation with organic forms of Se such as Se-methyl-selenocysteine (MSC) and L-selenomethionine (SLM), is maintained for a longer period after its discontinuation compared to inorganic forms such as sodium selenate reported whole-body half-lives of SLM and sodium selenate in humans were 252 and 102 days respectively (16). Accordingly, foods or supplements containing SLM can maintain the activities of selenoenzymes during periods of Se depletion for longer than those containing inorganic Se, owing to the recycling of SLM catabolised from protein stores.

Animal laboratory studies have shown that the organic forms of Se are both more effective and safer than the commonly-used inorganic forms such as sodium selenite (SS), which are more genotoxic (14). From 50% lethal dose (LD_{50}) determinations, SS was found to be fourfold more toxic than SLM when administered to mice intravenously and three-fold more toxic than Se-yeast when given orally to rats (17).

In humans safety data is more limited. The No Observed Adverse Effect Level (NOAEL) for Se in humans is variably reported as 400-850 μg/day (18,19). Chronic Se toxicity would be expected after long-term consumption (over months to years) of more than 2,400-3,000 μg/day but is reversible (20). Based on the published literature, likely symptoms of toxicity (due to environmental exposure) include brittle hair and nails and their loss, gastrointestinal disturbances, skin rash, garlic breath odour (caused by volatile selenium compounds) fatigue, irritability, and nervous system abnormalities. Impaired natural killer cell activity and endocrine disturbances may also occur (20).

Three major forms of Se (MSC, SLM and SS) are widely used in supplementation in both preclinical and clinical studies. The organic Se compound MSC is a water-soluble amino acid that is absorbed in mammals from the gastrointestinal tract and is well-tolerated (21). It is readily converted to the active moiety methylselenol through one-stage β-lyase conversion and remains more bioavailable for anticancer effects compared with the other forms (22). Methylselenol can be demethylated to yield selenide or methylated to yield dimethyl selenide, then released in the breath; methylated again, it yields trimethyl selenonium, which is excreted in urine (23). A phase 1, single-dose, dose-escalation study in 15 human subjects evaluated the toxicity and PK profile of MSC, administering 400, 800 and 1,200 μg of MSC orally and measuring Se plasma and urine levels. There was no significant clinical or laboratory toxicity and little difference was seen in PK parameters at the 400 and 800 μg dose levels (23).

The organic Se compound SLM is well-tolerated in humans at a dose of 7,200 μg (or comparable dosing at 3,600 μg/m^2) twice daily for 7 days followed by a once-daily maintenance dose for 10 weeks (24, 25). The only toxicity attribute to SLM was garlic-like odour in breath and urine that was seen more commonly during the induction SLM week and was found to disappear with prolonged treatment. All patients given 4,800 μg

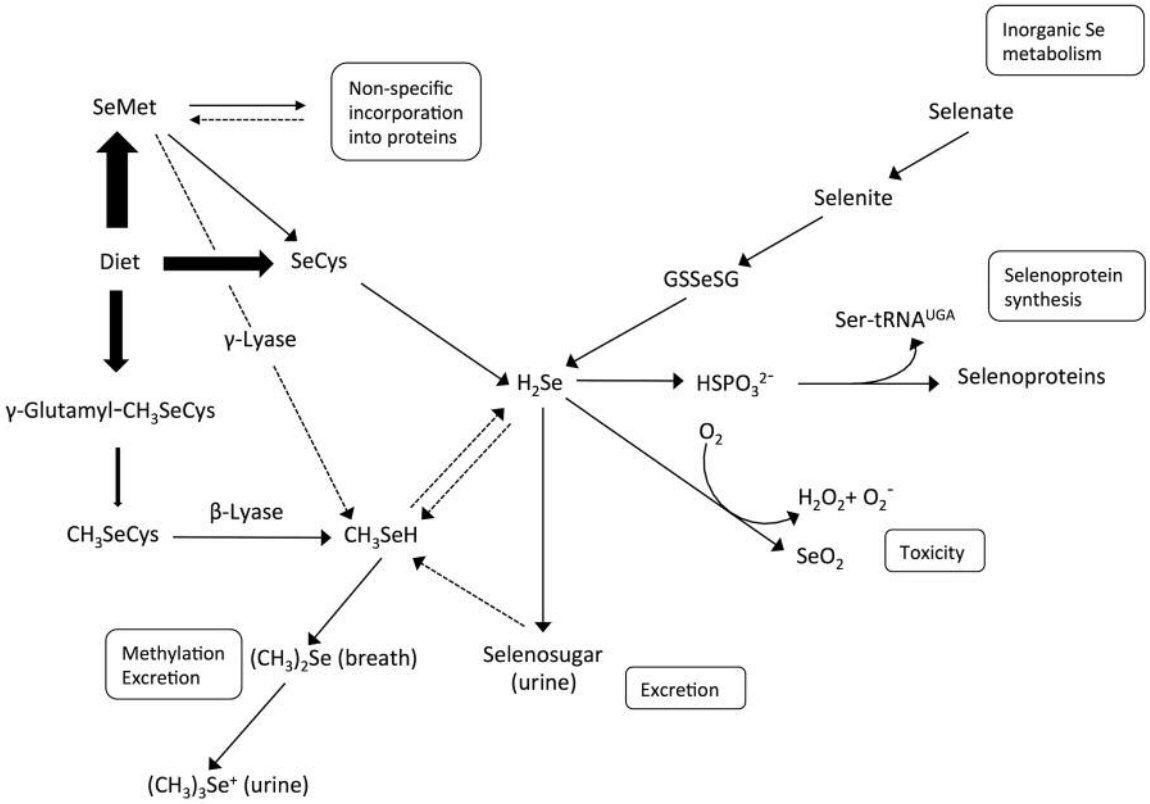

Figure 1. *Metabolic pathway of dietary Se in humans, from Rayman et al. (93). SeMet, Selenomethionine; SeCys, selenocysteine; GSSeSG, selenodiglutathione; γ-glutamyl-CH_3SeCys, γ-glutamyl-Se-methyl-selenocysteine; H_2Se, hydrogen selenide; $HSePO_3$, selenophosphate; CH_3SeCys, Se-methylselenocysteine;CH_3SeH, methylselenol; $(CH_3)2Se$, dimethyl selenide; SeO_2, selenium dioxide; $(CH_3)3Se$, trimethylselenonium ion.*

SLM twice daily achieved plasma Se levels >15 μM, the Se concentration required for reduced chemotherapy-induced toxicity and enhanced antitumor efficacy of chemotherapeutic drugs in preclinical animal models (13). The plasma Se dose levels exceeded 30 μM by day 28, thereby confirming the feasibility of using high-dose SLM in the clinic in this setting. In another study, selenized yeast (which predominantly contains SLM) was given in doses of 3,200 μg daily for up to 24 months in 16 patients with prostate cancer on 'watchful waiting', with five patients reporting minor toxicities, including garlic breath, brittle nails or hair, stomach upset or dizziness, without any correlation with plasma Se levels (18). None of these patients reported symptoms of peripheral neuropathy.

The inorganic compound sodium selenate (which is metabolised to selenite) was evaluated in a recent phase I trial, which established a maximum tolerated dose (MTD) of 60,000 μg daily orally in patients with metastatic castration-resistant prostate cancer (26). Dose-limiting toxicities of fatigue and diarrhoea were seen at 90,000 μg, with adverse events including nail disorders, muscle spasms, alopecia and nausea. Some of these were attributed to the accumulation of selenite, the more potent metabolite of selenate. In the same trial, slowing of PSA velocity was also observed, and one patient had >50% reduction in serum PSA. Another clinical trial adding SS 200 μg/kg/day (equivalent to 14,000 μg/day in a 70-kg adult) to chemotherapy in lymphoma patients reported less toxicity with combination therapy than with chemotherapy alone, including infections and reduction in cardiac function (27).

Pharmacodynamics of Selenium Compounds in Normal and Malignant Cells

Se affects varied cellular processes and molecular pathways that may be involved in the anti-cancer effect of Se [reviewed in (3)] and include:

- Seleno-enzymes involving the reduction of DNA damage, oxidative stress and inflammation;
- Induction of phase II conjugating enzymes involving detoxifying carcinogens and reducing DNA adduct formation;
- Enhancement of immune response including cytotoxic lymphocyte and natural killer cell activity;

• Increase in tumour-suppressor protein p53, which inhibits proliferation, stimulates DNA repair and promoting apoptotic death by acting as a transcription factor for several genes, including the growth arrest and DNA damage-inducible (GADD) genes;
• Inactivation of protein kinase C, a signalling receptor that plays a crucial role in tumour promotion by oxidants;
• Alteration in DNA methylation, as abnormal methylation patterns are associated with neoplasia and inactivation of tumour-suppressor genes;
• Perturbation of the cell cycle, resulting in growth inhibition and may allow DNA repair to take place;
• Induction of apoptosis of cancer cells, which generally involves the sequential activation of the caspases;
• Inhibition of angiogenesis required for the growth and metastasis of tumours.

Reassuringly, there is a significant body of published work demonstrating differential effects of Se compounds in normal *versus* malignant cells or tissues that would be favourable clinically, as summarised in Table I. However, while there is clear evidence from preclinical work that the efficacy and toxicity of Se compounds varies greatly (11,14), European clinical trials mostly use SS and those in the US use SLM, with no direct comparison of Se compounds or their PK-PD dose relationship.

Selenium with Chemotherapy and Radiotherapy

The challenge in using Se compounds in cancer patients in conjunction with chemotherapy and/or radiotherapy lies in being able to reduce normal tissue toxicities of these treatments without compromising their antitumour effects (or preferably enhancing those). However, despite numerous studies on the PD of Se in normal and malignant cells, it is still not known which form and dose of Se can be safely used and has the most favourable differential effect in normal and malignant tissues, especially in conjunction with chemotherapy and radiation. Current doses of Se are empirical or guided by PK, although the PK-PD relationship has not been established in humans, hence the optimal form and dose of Se to be used with chemotherapy or radiotherapy remains unclear. However Joel *et al*. have demonstrated that PD biomarkers of Se effects can be measured in human white blood cells (WBC) *in vitro* and *in vivo* (28), thus enabling the relationship between Se PD and PK to be evaluated in clinical studies and determine the optimal Se compound and dose to be incorporated into potentially pivotal trials.

Antitumour Efficacy

While Se is selectively cytotoxic to cancer cells at higher doses (summarised in Table I), it commonly augments the anticancer efficacy of chemotherapy and radiation in cell culture and tumour xenograft models (summarised in Table II). Therapeutic synergy has been demonstrated between supranutritional doses of Se compounds and chemotherapy drugs, including cisplatin, carboplatin, oxaliplatin, irinotecan, docetaxel, fluorouracil and doxorubicin in human tumour xenografts of colorectal, ovarian, prostate and small cell and non-small cell lung carcinoma, head and neck squamous cell carcinoma and leukaemia (11,13, 29-32).

However the strength of the interaction varied greatly, with differing xenograft models showing up to a 20-fold difference in Se dose potency) (11). Furthermore, the xenograft model and Se dose also influenced the apparent efficacy of the Se compounds. For example, at their MTD of 200 μg/day orally (approximately 8,000 μg/kg/day), MSC and SLM were both superior to SS in combination with irinotecan in head and neck squamous cell carcinoma xenografts (Figure 2) (11) whereas SS and SLM (1,000-1,500 μg/kg/day *i.p.*) were equally dose-potent and effective when combined with cisplatin in an ovarian cancer xenograft model (32).

Attention is also drawn to the schedule-dependency of Se in combination with other cancer treatments: the effects of MSC or SLM were maximal after 7 days pre-treatment, with little or no benefit seen when co-administered without pre-incubation with Se in human colorectal and head and neck squamous cell carcinoma xenograft models in mice (11, 33).

Few clinical studies have been conducted that evaluated the impact of Se supplementation during chemotherapy or radiation on treatment efficacy. Muecke *et al*. randomised 81 Se-deficient women to oral SS (500 μg daily with radiotherapy and 300 μg on non-radiotherapy days) or radiotherapy alone following surgery for gynaecological malignancies (34). At a median follow-up of 67 months, disease-free survival was not significantly different (log-rank p=0.65), though there was there a trend for improved overall survival in the selenium-treated group (log-rank p=0.09) (35).

Mix *et al*. conducted a randomised, placebo-controlled phase 2 pilot study in 18 patients with locally-advanced head and neck squamous cell carcinoma receiving cisplatin concurrently with radiation, administering placebo or 3,600 μg/m^2 SLM twice daily orally for 7 days prior to treatment then once daily until 3 weeks after chemoradiation completion. In this small study, there was no difference observed in disease-free or overall survival (log-rank p=0.39 and p=0.39 respectively) (24).

Asfour *et al*. reported a trial randomising 50 patients with non-Hodgkin lymphoma to either very high doses of SS (200 μg/kg/day) with cyclophosphamide, vincristine, doxorubicin and prednisone chemotherapy or chemotherapy alone (27). A significantly greater tumour response rate was observed in the Se group than controls (60% *vs*. 40% respectively), with correspondingly lower levels of the oncogene B-cell lymphoma 2 (BCL2) in bone marrow aspirates in Se-treated patients compared to controls.

Table I. *Pharmacodynamic mechanisms of selenium supplementation in normal and malignant cells*.

Pharmacodynamic properties	Effects in normal cells (Ref)	Effects in malignant cells (Ref)	Therapeutic significance
Antioxidant effects			
Glutathione peroxidase (GPx)	Se-dependent GPx isoforms 1, 2, 3, 4 and 6 reduce oxidative damage; activity saturates with nutritional doses of Se (6)	Increased GPx1 activity in response to low dose Se (as SS and SLM) in LNCaP cells, resulting in reduced oxidative damage (49)	Mixed
Intracellular glutathione (GSH)	Increased GSH in PBMCs in response to MSA (50)	MSA reduced total GSH in leukaemia cells (50)	Favourable
Thioredoxin reductase (TrxR)	Essential selenoprotein (51), increased TrxR activity in red blood cells with selenized yeast (52)	At low dose SS and SLM increased TrxR activity and apoptosis in LNCaP cells (prostate adenocarcinoma) (49) as did SS in NSCLC cells (53), more so in doxorubicin-resistant compared to doxorubicin-sensitive NSCLC cells (54) Higher concentrations of SS reduced TrxR activity in mesothelioma (55), colorectal cancer (56) and NSCLC (53). Differential effect with increase in TrxR activity and protein in doxorubicin-sensitive NSCLC but the opposite in doxorubicin-resistant NSCLC cells (54)	Mixed
Cell death/cytotoxicity	Minimal effects on normal cells (50, 51, 55)	Marked toxicity and cell death in varied malignant cell lines with dose-dependent and Se species-specific mechanisms of cell death or cell cycle arrest [reviewed in (57)] *e.g*. comparison of MSC, SS and SLM across multiple cancer cell lines showed: i) SLM-induced apoptosis is p53-dependent; ii) MSC instead induced p53-independent caspase activation; iii) ER stress-related signaling was associated with both SS and MSC (58) MSA-induced ER stress provoked a survival response at lower doses and apoptosis at higher doses in prostate cancer cell lines (59)	Favourable
DNA repair	Enhanced DNA repair with SLM in p53 wild-type mouse and human fibroblasts (60, 61)	Increase in base excision repair in colorectal cancer lines by SLM is p53 wild type-dependent (62) Unaltered DNA repair in SLM-treated p53-null human squamous cell carcinoma cell lines (63) Low dose SS or SLM increased DNA repair in prostate cancer cell lines (49)	Mixed
Angiogenesis	In human umbilical vein endothelial cells MSA induced apoptosis *via* p38 MAPK activation whereas SS induced caspase-independent apoptosis (64) MSA inhibited VEGF expression in mammary endothelial cells (65)	MSC and MSA reduced HIF-1α expression and thus angiogenesis in HNSCC and renal cell carcinoma models through inhibition of VEGF signaling mediated by COX-2, iNOS and degradation of prolyl hydroxylases under hypoxia (66-69).	Favourable
		This resulted in improved intratumoral vessel maturation, interstitial fluid pressure and reduced hypoxia (70)	Favourable
Invasion/migration		Reduced cell invasion through inhibiting MMP-2, MMP-9 and UPA by MSA (71) and SS (72)	
Epigenetic		Inhibits DNMT and HDAC resulting in expression of silenced genes by SS (73) and MSA (74)	Favourable
Immunological	1 mg/kg SS for 8 weeks increased antigen-specific $CD4^+$ T-cell responses (75)		Favourable
Drug efflux		Significant reduction in levels of the ABCC1 efflux pump in tumour cells (76).	Favourable

ABCC1: ATP binding cassette C1; COX-2: cyclooxygenase 2; DNMT: DNA methyltransferase; ER: endoplasmic reticulum; GPx: glutathione peroxidase; GSH: glutathione; HDAC: histone deacetylase; HDSCC head and neck squamous cell carcinoma; HIF-1α: hypoxia-inducible factor 1 alpha; iNOS: inducible nitric oxide synthase; MAPK: mitogen activated protein kinase; MMP: matrix metalloproteases; MSA: methylseleninic acid; MSC: Se-methylselenocysteine; NSCLC: non-small cell lung cancer; p53: tumour protein p53; PBMCs: peripheral blood mononuclear cells; Se: selenium; SLM: seleno-L-methionine; SS: sodium selenite; TrxR: thioredoxin reductase; UPA: urokinase plasminogen activator; VEGF: vascular endothelial growth factor.

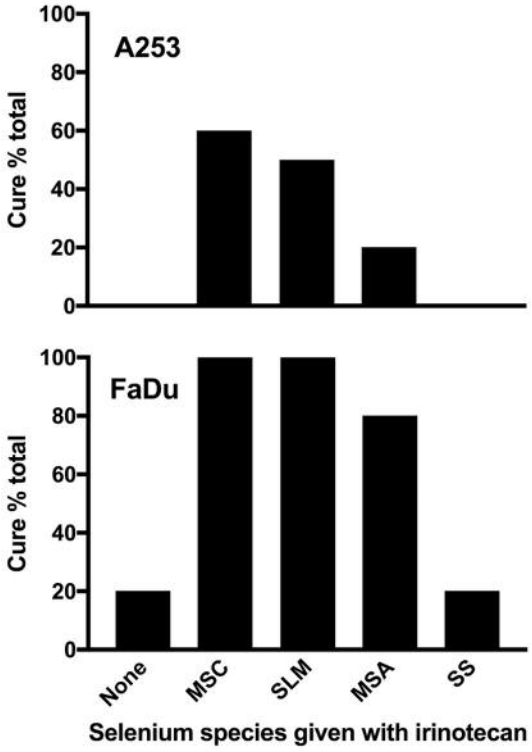

Figure 2. *Tumour cure rates in nude mice with head and neck squamous cell carcinoma xenografts (5 mice per group). Se compounds differ in their ability to improve antitumour activity of irinotecan in xenografts. MSC: Se-Methyl-selenocysteine; SLM: seleno-methionine; MSA: methyl-seleninic acid; SS: sodium selenite. (group means reported) Courtesy of Dr Y Rustum.*

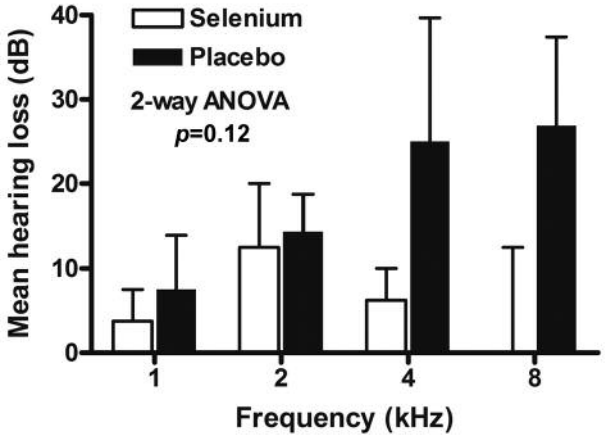

Figure 3. *Hearing loss following chemoradiation in selenium-, and placebo-treated groups. (n=6, 2 Selenium treated, 4 placebo, mean±SEM) Courtesy of M. Jameson.*

Reduction in Toxicity

Table II summarises extensive preclinical work that demonstrated the protective effects of various Se compounds against the toxicities of radiation (12, 36) and organ-specific toxicities of many cytotoxic drugs, including myelo-suppression, mucositis, diarrhoea, alopecia, cystitis and nephrotoxicity (11, 13, 30, 37). Specific toxicities of cisplatin in kidneys, bone marrow and intestine were improved without affecting antitumour efficacy (30, 38-41) or pharmacokinetics (42). Impressive protection from lethal effects of six cytotoxic drugs with 200 μg/day MSC was demonstrated in nude mice (13).

Similar protection by Se compounds from the normal tissue toxicities of chemotherapy has been reported in several clinical trials (Table III). In the setting of high-dose chemotherapy and allogeneic haematopoietic stem cell transplantation, a double-blind randomised placebo-controlled study of oral selenized yeast in 77 patients reported a reduction in the incidence and duration of severe oral mucositis (43). In a trial randomising 41 patients to 4,000 μg Se (as seleno-kappacarrageenan) orally daily for 4 days before and after the first dose of cisplatin-based chemotherapy or to chemotherapy alone, significantly less myelosuppression and nephrotoxicity was seen with Se (44). A double-blind trial involving 62 women receiving cisplatin-based chemotherapy for ovarian cancer randomized patients to Se as selenized yeast, 200 μg per day for 3 months, starting concurrently with chemotherapy (45). Those patients randomized to Se experienced significantly less toxicity at 3 months of treatment, including gastrointestinal, alopecia, weakness and neutropenia. The previously referenced four studies using high-dose SS in patients with non-Hodgkin lymphoma reported the Se group had significantly fewer toxicities (including infection and fall in cardiac left ventricular ejection fraction) and reduced apoptosis of neutrophils (46).

Data from the aforementioned study conducted by Muecke *et al.* reported significantly increased blood Se with SS supplementation (the primary endpoint) but analysis of secondary endpoints showed a significant reduction in the actuarial incidence of grade 2 or more diarrhoea (from 46.6% to 21.0%, p=0.039), without any Se-related side-effects (12). SS has also been assessed as a potential modulator of radiation-related toxicities in 39 head and neck cancer patients in a randomised controlled trial (36). Using the same dosing schedule of SS as the study of Muecke *et al.* (12), there was no statistically significant difference in the incidence of severe toxicities.

More recently SLM has been trialled alongside cisplatin-based chemoradiation for both head and neck squamous cell cancer and non-small cell lung cancer (NSCLC), with

Table II. *Combination of selenium with systemic therapies and radiation.*

Pharmacodynamic properties	Effects in normal cells/tissues (Ref)	Effects in malignant cells/tissues (Ref)	Therapeutic significance
Antioxidant effects - Intracellular glutathione (GSH)	Protective increase in GSH in PBMCs in response to MSA, not compromised by combination with cisplatin, doxorubicin, Ara-C or radiation 2 Gy (50)	Pre-treatment of ovarian cancer xenograft-bearing mice with SLM or SS prevented an increase in intracellular GSH in response to cisplatin or melphalan (77) MSA depletes intracellular GSH in THP-1 leukaemia cells despite combination with cisplatin, doxorubicin, Ara-C or radiation 2Gy (50)	Favourable
Cell death/cytotoxicity	Protects against cisplatin-related renal proximal tubule injury (78) Clinical trial evidence of less gastrointestinal, bone marrow, renal and cardiac toxicity with chemotherapy (43-45, 79) and reduced diarrhoea after radiation (12, 36, 80)	Increased cytotoxicity in combination with chemotherapy, tamoxifen or radiation in several cell lines, including resistant cells *in vitro* (13, 81-85) Therapeutic synergy between supra-nutritional doses of Se (as SLM, SS, MSA and MSC) and cisplatin, carboplatin, oxaliplatin, irinotecan, docetaxel, fluorouracil and doxorubicin in human tumour xenografts of small cell and non-small cell lung carcinoma, colorectal carcinoma, prostate carcinoma, head and neck squamous cell carcinoma and leukaemia (11, 13, 29-32) Clinical trials show either no compromised outcome or improved outcome (12, 27, 45, 46)	Favourable
Angiogenesis	MSC did not cause an increase in chemotherapy drug delivery to normal tissues (86)	MSC resulted in improved tumor blood vessel maturation and hypoxia with improved chemotherapy drug delivery (22, 86)	Favourable
Radiosensitization	No radiosensitization in normal lung fibroblasts by SLM (87). MSA did not increase PBMC death from RT (50).	SLM caused radiosensitization in two human lung cancer cell lines (87).	Favourable

Ara-C: cytosine arabinoside; Gy: gray; MSA: Methylseleninic acid; MSC: Se-methylselenocysteine; PBMCs: peripheral blood mononuclear cells; RT: radiotherapy Se: selenium; SLM: seleno-L-methionine; SS: sodium selenite.

treatment toxicity as the primary outcome (24, 47). In the head and neck trial 18 patients were randomised to pre-treatment with 3,600 μg/m^2 SLM twice daily or placebo before radiotherapy and then daily thereafter. While no significant difference in grade 3 toxicities was observed, 50% of Se-treated patients had grade 0-1 mucositis compared to 25% in the placebo group (24). In addition, a trend for reduced high-frequency hearing loss in Se-treated patients was seen (Figure 3; unpublished data, M. Jameson). The single-arm NSCLC study in 16 patients, administering 4,800 μg/m^2 SLM twice daily for 7 days pre-radiotherapy then daily during chemoradiation, reported no Se-related toxicity but a lower than expected rate of grade III or higher toxicities was observed, particularly for pneumonitis and anaemia (47).

Conclusion

While there have been major advances in cancer therapy in recent years, especially with the development of targeted-therapies, cytotoxic chemotherapy and radiation still remain a mainstay of treatment for many malignancies. The considerable toxicity of these treatments remains a major challenge in cancer management, one that has not been overcome despite extensive research into protective strategies (48).

In this context, Se appears to be unique in terms of its ability to protect against carcinogenesis as well as selectively target existing cancer cells and synergise with other cancer therapies, while protecting normal tissues from the cytotoxic effects of those treatments. These distinctive features enable, at least in preclinical models, administration of higher doses of cytotoxic agents than would be feasible otherwise, with improved cancer outcomes. If this widening of the notoriously narrow therapeutic index of cytotoxic treatments with Se is replicated in the clinical setting, this would represent a very significant advance in cancer management, and further clinical evaluation is clearly justified.

However, before large-scale clinical trials are undertaken to evaluate the ability of Se to modulate the efficacy and toxicity of anticancer therapies, more research is needed to determine which Se compound, and at what dose, can be

Table III. *Clinical trials evaluating outcomes when selenium compounds were given with chemotherapy and/or radiotherapy.*

Author & year of publication	N	Trial design	Cancer treatment	Cancer type	Selenium form & dose	Outcomes - toxicity/efficacy
Hu *et al*. 1997 (44)	41	Randomised to Se with cycle 1 or 2 (not both)	Cisplatin-based chemotherapy (60-80 mg/m^2)	Lung, breast, gastric, colon, oesophagus, liver	Oral kappa-seleno-carrageenan (4000 μg Se/day for 4 days before and after chemotherapy)	• Significantly higher day 14 WBC 3.35±2.01 *vs*. 2.31±1.38×10^9/l (p<0.05) • Less G-CSF and RBC transfusion • less nephrotoxicity
Sieja *et al*. 2004 (45)	62	Randomised to Se or not	Cisplatin (100 mg/m^2) and cyclophosphamide (600 mg/m^2)	Ovarian	Oral selenized yeast 200 μg/day for 3 months	• Significantly less nausea (p<0.001), vomiting (p<0.001), stomatitis (p<0.0292), abdominal pain (p<0.0006), anorexia, weakness (p<0.001), alopecia (p<0.001) • Significantly higher neutrophils • Trend to lower serum CA-125 (93.5±200 *vs*. 228±713 U/ml)
Weijl *et al*. 2004 (88)	48	Randomised to vitamins C, E and Se or placebo	Cisplatin dose intensity (60-100 mg/m^2)	Testicular, bone, gastrointestinal, urogenital, head and neck, melanoma	Oral sodium selenite 100 μg daily	• No improvement in toxicity or response rate • 64% Of supplement group non-compliant due to GI effects • Serum Se did not increase
Gounder *et al*. 2005 (89)	11	Phase I dose escalation	Paclitaxel (175 mg/m^2) and Carboplatin AUC 5 cycle 1 then AUC6	Gynaecologic malignancies	IV sodium selenite 50 μg, 100 μg or 200 μg over 5 hours two days prior to chemotherapy	• Selenite can be safely administered with this chemotherapy • No significant alteration of predicted carboplatin AUC
Asfour *et al*. 2006 (79)	30	Randomised to Se or not	Cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (all day 1) and prednisone 100 mg daily x 5, (CHOP) every 4 weeks	Non-Hodgkin lymphoma	Oral sodium selenite 200 μg/kg/day	• Significantly less apoptosis of neutrophils (67% *vs*. 20%, p<0.05) and reduced infection rate • Significantly better preservation of cardiac ejection fraction (62+/-4% *vs*. 69±5% p<0.05).
Asfour *et al*. 2007 (27)	50	Randomised to Se or not	CHOP (as for Asfour 2006)	Non-Hodgkin lymphoma	Oral sodium selenite 200 μg/kg/day for first 30 days	• Significant decline of *Bcl-2* level in BM aspirate and increase in CD4/CD8 ratio in peripheral blood after 3 cycles (8.6±6.9 ng/ml *vs*. 3 6.9±7.9 ng/ml, p<0.05) • Increased complete response rate in Se group (60% *vs*. 40%)
Fakih *et al*. 2006 (90)	13	Phase I dose escalation study	Irinotecan 125-160 mg/m^2 weekly	Colorectal, lung, pancreatic, gastric, mesothelioma	Oral seleno-methionine 2200 μg Se daily starting 1 week before chemotherapy	• Irinotecan MTD 125 mg/m^2 • No diarrhoea > grade 2 at MTD • Responses seen in irinotecan-refractory population
Fakih *et al*. 2008 (25)	31	Phase I and PK study	Irinotecan 125 mg/m^2 weekly x 4 every 6 weeks	Metastatic or unresectable solid tumour	Oral seleno-methionine; dose escalation from 2800-7200 μg/day maintenance (twice daily loading for 1 week prior to starting irinotecan)	• Prolonged stable disease >6 months in irinotecan-pre-treated patients • SLM well-tolerated at 7200 μg twice daily for 1 week followed by 7,200 μg daily with irinotecan • No reduction in irinotecan toxicity
Asfour *et al*. 2009 (46)	40	Randomised to Se or not	CHOP (as for Asfour 2006)	Non-Hodgkin's lymphoma	Oral sodium selenite 200 μg/kg/day for 5 days	• Significantly greater increase in apoptotic marrow cells on day 8 of cycle 1 in Se group (49.2% *vs*. 29.7%) • Significant increase in tumour reduction • Preservation of cardiac ejection fraction in Se group but not controls (p=0.04)

Table III. *Continued*

Table III. *Continued*

Author & year of publication	N	Trial design	Cancer treatment	Cancer type	Selenium form & dose	Outcomes - toxicity/efficacy
Muecke *et al*. 2010. 2014 (12, 35)	81	Randomized to Se or not in patients with low blood Se (<84 ng/ml)	Radiotherapy (RT) (external beam w/wo brachy-therapy)	Endometrium or cervix	Oral sodium selenite 500 μg on days of RT and 300 μg on days without treatment	• Significant increase in blood Se • Less ≥grade 2 diarrhoea (20.5% *vs*. 44.5%, p=0.04) • 5-Year survival 91.9% *vs*. 83.1% (p=NS) • 10-Year survival 55.3% *vs*. 42.1% (p=NS) • No Se side-effects observed
Buntzel *et al*. 2010 (2 papers with overlapping cohorts) (36, 80)	47 or 39	Randomised to Se or not in patients with low blood Se (not defined)	RT (37/39 adjuvant)	Head and neck squamous carcinoma	Oral sodium selenite 500 μg on days of RT and 300 μg on days without treatment.	• Significantly less dysphagia in the last week of RT • Trend to less acute taste loss • No difference in xerostomia or mucositis • Significant transient increase in serum and whole blood Se
Corcoran *et al*. 2010 (26)	19	Phase I dose escalation	Antiandrogens discontinued >4 weeks before trial; LHRH agonists were continued	Chemotherapy-naïve, castration-resistant prostate cancer	Oral sodium selenate; dose escalation from 5,000-90.000 μg/day for 12 weeks (longer if responding)	• MTD was 60,000 μg/day with linear PK • fatigue, diarrhoea and muscle spasms dose-limiting at 90.000 μg/day • One PSA response >50% and mean PSA doubling time increased (2.18 months before trial to 3.85 months)
Jahangard-Rafsanjani *et al*. (43)	77	Randomised to Se or placebo	High-dose busulfan + cyclophosphamide then allogeneic haematopoietic stem cell transplantation	Acute leukaemia	Oral selenized yeast (200 μg) *vs*. placebo twice daily from day 0 to 14 days after transplant	• Significant reduction in incidence of grades 3-4 oral mucositis (OM) (10.8% *vs*. 35.1%) • Significantly shorter • Significantly shorter duration of grades 2-4 OM (3.6±1.8 days *vs*. 5.2±2.2 days)
Vieira *et al*. 2015 (91)	39	Randomised, placebo-controlled crossover; both placebo periods were grouped for analysis (half had Se first)	Various chemotherapy regimens (timing of Se supplementation not specified)	Paediatric leukaemia or lymphoma (LL) or various solid tumours (ST)	Selenium-glycine age-dependent dosing (27-100 μg/day) for 30 days, 7 days washout then alternate medication for 30 days. Sustained dosing for 12 months in 16 patients.	• No significant change in EORTC QLQ-C30 scores for fatigue, nausea, appetite loss, physical function in LL group • Significant improvement in scores for nausea and appetite loss in ST group with both Se and placebo, for fatigue with placebo and for fatigue at 1 year with Se • Significant decrease in serum AST levels with Se (p=0.045) • General trend to improvement in scores
Mix *et al*. 2015 (24)	18	Randomised, placebo-controlled Study of SLM.	Concurrent chemoradiation (CCRT). RT 70 Gy over 7 weeks; cisplatin 100 mg/m^2 on days 1, 22 and 43 of RT	Stage III-IV head and neck squamous cell cancer	SLM at 3600 μg/m^2 twice daily pre-treatment for 7 days and daily until 3 weeks after chemoradiation completion or placebo.	• No significant change in mucositis or patient reported side effects • No difference in OS or RFS at 12 months
Mix *et al*. 2015 (47)	16	Single arm phase II study of SLM	CCRT with RT 60-66 Gy and weekly paclitaxel 50 mg/m^2 and carboplatin AUC 2 over 6 weeks	Stage III NSCLC	SLM at 4800 μg/m^2 twice daily pre-treatment for 7 days and daily for 6 weeks or completion of chemoradiation.	• No Se-related toxicity observed • Lower than expected rates of grade III or higher toxicities observed particularly for pneumonitis and anaemia

Table III. *Continued*

Table III. *Continued*

Author & year of publication	N	Trial design	Cancer treatment	Cancer type	Selenium form & dose	Outcomes - toxicity/efficacy
Brodin *et al.* 2015 (92)	34	Phase I dose escalation study	Chemotherapy given after intravenous SS (retreated with first-line chemotherapy)	Cancer patients refractory to cytostatic drugs	Intravenous SS given on 5 of 7 days for either 2 or 4 weeks; dose escalation to MTD	• Protocol defined MTD of 10.2 mg/m^2 • DLTs reported to be acute, of short duration and reversible, namely fatigue, nausea, finger and leg cramps

AUC: Area under the curve; BM: bone marrow; DLT: dose-limiting toxicity; AST: aspartate aminotransferase; EORTC-QLQ-C30 The European Organisation for Research and Treatment of Cancer quality of life questionnaire C30; CCRT: Concurrent chemoradiation G-CSF: granulocyte colony-stimulating factor; GI: gastrointestinal; Gy: gray; LHRH: luteinizing hormone-releasing hormone; LL: leukaemia or lymphoma; MTD: maxium tolerated dose; OM: oral mucositis OS: overall survival; PK: pharmacokinetic: PSA: prostate-specific antigen; RBC: red blood cell; RFS: relapse-free survival; RT: radiotherapy; Se: selenium; SLM: seleno-L-methionine; SS: sodium selenite; ST: solid tumours; WBC: white blood cell count.

most safely and effectively used in such trials in patients with cancer. The preclinical data suggest that organic Se compounds (such as MSC and SLM) are safer and likely more effective than inorganic compounds such as SS, particularly at the higher doses that appear to be optimal for anticancer efficacy and beneficial interactions with chemotherapy and radiation.

More rigorous evaluation in clinical trials is needed to characterise the relationship between PK and PD endpoints and comparative safety (including genotoxicity) for the Se compounds in clinical use. Innovative trial designs could include patients selected with malignancies that enable the evaluation of differential effects of Se compounds in normal cells and malignant cells. These trials are critical to inform the selection of the optimal Se compound and dose for future clinical trials and equally to avoid less effective or more toxic forms and doses of Se.

References

1 Shamberger RJ and Frost DV: Possible protective effect of selenium against human cancer. Can Med Assoc J *100*: 682, 1969.

2 Combs GFJ: Selenium in global food systems. Br J Nutr *85*: 517-547, 2001.

3 Rayman MP: Selenium in cancer prevention: a review of the evidence and mechanism of action. Proc Nutr Soc *64*: 527-542, 2005.

4 Clark LC, Combs GFJ, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Lesher JLJ, Park HK, Sanders BBJ, Smith CL and Taylor JR: Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA *276*: 1957-1963, 1996.

5 Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM, Gaziano JM, Hartline JA, Parsons JK, Bearden JD, III, Crawford ED, Goodman GE, Claudio J, Winquist E, Cook ED, Karp DD, Walther P, Lieber MM, Kristal AR, Darke AK, Arnold KB, Ganz PA, Santella RM, Albanes D, Taylor PR, Probstfield JL, Jagpal TJ, Crowley JJ, Meyskens FL Jr., Baker LH and Coltman CA Jr.: Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA *301*: 39-51, 2009.

6 Rayman MP: Selenium and human health. Lancet *379*: 1256-1268, 2012.

7 Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF Jr., Slate EH, Fischbach LA, Marshall JR and Clark LC: Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiology Biomarkers Prevention *11*: 630-639, 2002.

8 Zermann DH: Demand for and clinical practice of complementary selenium therapy in prostate cancer patients. Forsch Komplementmed *19*: 38-42, 2012 (in German).

9 Wagholikar A, Fung M and Nelson C: A pilot study on understanding the journey of advanced prostate cancer patients. Stud Health Technol Inform *168*: 165-171, 2011.

10 Stratton MS, Algotar AM, Ranger-Moore J, Stratton SP, Slate EH, Hsu CH, Thompson PA, Clark LC and Ahmann FR: Oral selenium supplementation has no effect on prostate-specific antigen velocity in men undergoing active surveillance for localized prostate cancer. Cancer Prev Res *3*: 1035-1043, 2010.

11 Fakih M, Cao S, Durrani FA and Rustum YM: Selenium protects against toxicity induced by anticancer drugs and augments antitumor activity: a highly selective, new, and novel approach for the treatment of solid tumors. Clin Colorectal Cancer *5*: 132-135, 2005.

12 Muecke R, Schomburg L, Glatzel M, Berndt-Skorka R, Baaske D, Reichl B, Buentzel J, Kundt G, Prott FJ, Devries A, Stoll G, Kisters K, Bruns F, Schaefer U, Willich N and Micke O: Multicenter, phase 3 trial comparing selenium supplementation with observation in gynecologic radiation oncology. Int J Radiat Oncol Biol Phys *78*: 828-835, 2010.

13 Cao S, Durrani FA and Rustum YM: Selective modulation of the therapeutic efficacy of anticancer drugs by selenium containing

compounds against human tumor xenografts. Clin Cancer Res *10*: 2561-2569, 2004.
14 Valdiglesias V, Pasaro E, Mendez J and Laffon B: In vitro evaluation of selenium genotoxic, cytotoxic, and protective effects: a review. Arch Toxicol *84*: 337-351, 2010.
15 Combs GFJ, Clark LC and Turnbull BW: An analysis of cancer prevention by selenium. Biofactors *14*: 153-159, 2001.
16 Thomson CD, Robinson MF, Butler JA and Whanger PD: Long-term supplementation with selenate and selenomethionine: selenium and glutathione peroxidase (EC 1.11.1.9) in blood components of New Zealand women. Br J Nutr *69*: 577-588, 1993.
17 Rayman MP: Food-chain selenium and human health: emphasis on intake. Br J Nutr *100*: 254-268, 2008.
18 Reid ME, Stratton MS, Lillico AJ, Fakih M, Natarajan R, Clark LC and Marshall JR: A report of high-dose selenium supplementation: response and toxicities. J Trace Elem Med Biol *18*: 69-74, 2004.
19 Aguilar F, Charrondiere UR, Dusemund B, Galtier P, Gilbert J, Gott DM, Grilli S, Guertler R, Cass GEN, Koenig J, Lambre C, Larsen J-C, Leblanc J-C, Mortensen a, Parent-Massin D, Pratt I, Rietjens IMCM, Stankovic I, Tobback P, Verguieva T and Woutersen R: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on Se-Methyl-L-Selenocysteine as a source of selenium added for nutritional purposes to food supplements following a request from the European Commission. EFSA J *1067*: 1-23, 2009.
20 Vinceti M, Wei ET, Malagoli C, Bergomi M and Vivoli G: Adverse health effects of selenium in humans. Rev Environ Health *16*: 233-251, 2001.
21 Ip C: Lessons from basic research in selenium and cancer prevention. J Nutr *128*: 1845-1854, 1998.
22 Bhattacharya A: Methylselenocysteine: a promising antiangiogenic agent for overcoming drug delivery barriers in solid malignancies for therapeutic synergy with anticancer drugs. Expert Opin Drug Deliv *8*: 749-763, 2011.
23 Marshall JR, Ip C, Romano K, Fetterly G, Fakih MG, Jovanovic BD, Perloff M, Crowell J, Davis W Jr., Christy R, Dew A, Coomes M and Bergan RC: Methyl Selenocysteine: single-dose pharmacokinetics in men. Cancer Prev Res *4*: 1938-1944, 2011.
24 Mix M, Singh AK, Tills M, Dibaj S, Groman A, Jaggernauth W, Rustum Y and Jameson MB: Randomized phase II trial of selenomethionine as a modulator of efficacy and toxicity of chemoradiation in squamous cell carcinoma of the head and neck. World J Clin Oncol *6*: 166-173, 2015.
25 Fakih MG, Pendyala L, Brady W, Smith PF, Ross ME, Creaven PJ, Badmaev V, Prey JD and Rustum YM: A Phase I and pharmacokinetic study of selenomethionine in combination with a fixed dose of irinotecan in solid tumors. Cancer Chemother Pharmacol *62*: 499-508, 2008.
26 Corcoran NM, Hovens CM, Michael M, Rosenthal MA and Costello AJ: Open-label, phase I dose-escalation study of sodium selenate, a novel activator of PP2A, in patients with castration-resistant prostate cancer. Br J Cancer *103*: 462-468, 2010.
27 Asfour IA, Fayek M, Raouf S, Soliman M, Hegab HM, El Desoky H, Saleh R and Moussa MA: The impact of high-dose sodium selenite therapy on BCL2 expression in adult non-Hodgkin's lymphoma patients: correlation with response and survival. Biol Trace Elem Res *120*: 1-10, 2007.
28 Stevens J, Juliger S, Summer K, Fitzgibbon J, Lister A and Joel S: Methylseleninic acid demonstrates anti-leukaemic activity and sensitises AML cells to the effects of cytotoxic agents by initiating the unfolded protein response. Congress of the European Hematology Association Copenhagen, Denmark, June 12–15, 2008. Haematologica *93(s1)*: 115-116, 2008.
29 Hu H, Jiang C, Ip C, Rustum YM and Lu J: Methylseleninic acid potentiates apoptosis induced by chemotherapeutic drugs in androgen-independent prostate cancer cells. Clin Cancer Res *11*: 2379-2388, 2005.
30 Cao S, Durrani FA and Rustum YM: Se-(Methyl)selenocysteine (MSC) potentiates the antitumor activity of platinum compounds and protects against drug induced toxicity in rats bearing advanced colorectal carcinoma. Cancer Res *65*: 1209-1209,2005.
31 Frenkel, GD and Caffrey PB:Prevention of carboplatin-induced resistance in human ovarian tumor xenografts. Cancer Res *65*: 351-351,2005.
32 Frenkel GD and Caffrey PB: A prevention strategy for circumventing drug resistance in cancer chemotherapy. Curr Pharm Des *7*: 1595-1614, 2001.
33 Bhattacharya A, Mazurchuk R, Spernyak JA, Tóth K, Magnano CR, Cao S, Azrak RG, Durrani FA and Rustum YM: Tumor vessel maturation by 5-Methylselenocysteine (MSC) results in synergistic antitumor effect in human head and neck squamous cell carcinoma (HNSCC) xenografts. Cancer Res *66*: 413-414, 2006.
34 Muecke R, Reichl B, Glatzel M, Baaske D, Berndt-Skorka R, Buentzel J, Prott F and Micke O: Sodium selenite in gynecologic radiation oncology-final results of a prospective randomized observation study. Int J Radiat Oncol Biol Phys *69*: S393, 2007.
35 Muecke R, Micke O, Schomburg L, Glatzel M, Reichl B, Kisters K, Schaefer U, Huebner J, Eich HT, Fakhrian K, Adamietz IA and Buentzel J: Multicenter, phase III trial comparing selenium supplementation with observation in gynecologic radiation oncology: follow-up analysis of the survival data 6 years after cessation of randomization. Integr Cancer Ther *13*: 463-467, 2014.
36 Buntzel J, Riesenbeck D, Glatzel M, Berndt-Skorka R, Riedel T, Mucke R, Kisters K, Schonekaes KG, Schafer U, Bruns F and Micke O: Limited effects of selenium substitution in the prevention of radiation-associated toxicities. results of a randomized study in head and neck cancer patients. Anticancer Res *30*: 1829-1832, 2010.
37 Francescato HD, Costa RS, Rodrigues Camargo SM, Zanetti MA, Lavrador MA and Bianchi MD: Effect of oral selenium administration on cisplatin-induced nephrotoxicity in rats. Pharmacol Res *43*: 77-82, 2001.
38 Rao M and Rao MN: Protective effects of selenomethionine against cisplatin-induced renal toxicity in mice and rats. J Pharm Pharmacol *50*: 687-691, 1998.
39 Ohkawa K, Tsukada Y, Dohzono H, Koike K and Terashima Y: The effects of co-administration of selenium and cis-platin (CDDP) on CDDP-induced toxicity and antitumour activity. Br J Cancer *58*: 38-41, 1988.
40 Satoh M, Naganuma A and Imura N: Optimum schedule of selenium administration to reduce lethal and renal toxicities of *cis*-diamminedichloroplatinum in mice. J Pharmacobiodyn *12*: 246-253, 1989.
41 Yoshida M, Iizuka K, Terada A, Hara M, Nishijima H, Akinori, Shimada, Nakada K, Satoh Y and Akama Y: Prevention of nephrotoxicity of cisplatin by repeated oral administration of ebselen in rats. Tohoku J Exp Med *191*: 209-220, 2000.

42 Araya Y: Studies on protective effect of selenium on the nephrotoxicity of cis-diamminedichloroplatinum (CDDP) in mice. Hokkaido Igaku Zasshi *65*: 245-253, 1990 (in Japanese).
43 Jahangard-Rafsanjani Z, Gholami K, Hadjibabaie M, Shamshiri AR, Alimoghadam K, Sarayani A, Mojtahedzadeh M, Ostadali-Dehaghi M and Ghavamzadeh A: The efficacy of selenium in prevention of oral mucositis in patients undergoing hematopoietic SCT: a randomized clinical trial. Bone Marrow Transplant *48*: 832-836, 2013.
44 Hu YJ, Chen Y, Zhang YQ, Zhou MZ, Song XM, Zhang BZ, Luo L, Xu PM, Zhao YN, Zhao YB and Cheng G: The protective role of selenium on the toxicity of cisplatin-contained chemotherapy regimen in cancer patients. Biol Trace Elem Res *56*: 331-341, 1997.
45 Sieja K and Talerczyk M: Selenium as an element in the treatment of ovarian cancer in women receiving chemotherapy. Gynecol Oncol *93*: 320-327, 2004.
46 Asfour IA, El Tehewi MM, Ahmed MH, Abdel-Sattar MA, Moustafa NN, Hegab HM and Fathey OM: High-dose sodium selenite can induce apoptosis of lymphoma cells in adult patients with non-Hodgkin's lymphoma. Biol Trace Elem Res *127*: 200-210, 2009.
47 Mix M, Ramnath N, Gomez J, de GC, Rajan S, Dibaj S, Tan W, Rustum Y, Jameson MB and Singh AK: Effects of selenomethionine on acute toxicities from concurrent chemoradiation for inoperable stage III non-small cell lung cancer. World J Clin Oncol *6*: 156-165, 2015.
48 Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, Cohen GI, Emami B, Gradishar WJ, Mitchell RB, Thigpen JT, Trotti A, 3rd, von Hoff D and Schuchter LM: American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol *27*: 127-145, 2009.
49 de R, V, Erkekoglu P, Forestier A, Favier A, Hincal F, Diamond AM, Douki T and Rachidi W: Low doses of selenium specifically stimulate the repair of oxidative DNA damage in LNCaP prostate cancer cells. Free Radic Res *46*: 105-116, 2012.
50 Jameson MB, Lobb RJ, Jacobson GM and Cursons RT: Differential effects of selenium (Se) on normal and malignant cells treated with chemotherapy (CT) and radiation (RT). J Clin Oncol *31*: e13583-e13583, 2013.
51 Selenius M, Rundlof AK, Olm E, Fernandes AP and Bjornstedt M: Selenium and the selenoprotein thioredoxin reductase in the prevention, treatment and diagnostics of cancer. Antioxid Redox Signal *12*: 867-880, 2010.
52 Karunasinghe N, Han DY, Zhu S, Duan H, Ko YJ, Yu JF, Triggs CM and Ferguson LR: Effects of supplementation with selenium, as selenized yeast, in a healthy male population from New Zealand. Nutr Cancer *65*: 355-366, 2013.
53 Selenius M, Fernandes AP, Brodin O, Bjornstedt M and Rundlof AK: Treatment of lung cancer cells with cytotoxic levels of sodium selenite: effects on the thioredoxin system. Biochem Pharmacol *75*: 2092-2099, 2008.
54 Jonsson-Videsater K, Bjorkhem-Bergman L, Hossain A, Soderberg A, Eriksson LC, Paul C, Rosen A and Bjornstedt M: Selenite-induced apoptosis in doxorubicin-resistant cells and effects on the thioredoxin system. Biochem Pharmacol *67*: 513-522, 2004.
55 Nilsonne G, Sun X, Nystrom C, Rundlof AK, Potamitou FA, Bjornstedt M and Dobra K: Selenite induces apoptosis in sarcomatoid malignant mesothelioma cells through oxidative stress. Free Radic Biol Med *41*: 874-885, 2006.
56 Erzinger MM, Bovet C, Uzozie A and Sturla SJ: Induction of complementary function reductase enzymes in colon cancer cells by dithiole-3-thione *versus* sodium selenite. J Biochem Mol Toxicol *29*: 10-20, 2015.
57 Wallenberg M, Misra S, Wasik AM, Marzano C, Bjornstedt M, Gandin V and Fernandes AP: Selenium induces a multi-targeted cell death process in addition to ROS formation. J Cell Mol Med *18*: 671-684, 2014.
58 Suzuki M, Endo M, Shinohara F, Echigo S and Rikiishi H: Differential apoptotic response of human cancer cells to organoselenium compounds. Cancer Chemother Pharmacol *66*: 475-484, 2010.
59 Wu Y, Zhang H, Dong Y, Park YM and Ip C: Endoplasmic reticulum stress signal mediators are targets of selenium action. Cancer Res *65*: 9073-9079, 2005.
60 Fischer JL, Lancia JK, Mathur A and Smith ML: Selenium protection from DNA damage involves a REF1/P53/BRCA1 protein complex. Anticancer Res *26*: 899-904, 2006.
61 Seo YR, Sweeney C and Smith ML: Selenomethionine induction of DNA repair response in human fibroblasts. Oncogene *21*: 3663-3669, 2002.
62 Jung HJ, Kim HL, Kim YJ, Weon JI and Seo YR: A novel chemopreventive mechanism of selenomethionine: enhancement of APE1 enzyme activity via a Gadd45a, PCNA and APE1 protein complex that regulates p53-mediated base excision repair. Oncol Rep *30*: 1581-1586, 2013.
63 Fischer JL, Cao S, Durrani FA, Fakih M, Rustum YM and Smith ML: Chemotherapeutic selectivity conferred by selenium: A role for p53-dependent DNA repair. Cancer Res *66*: 127-128, 2006.
64 Jiang C, Kim KH, Wang Z and Lu J: Methyl selenium-induced vascular endothelial apoptosis is executed by caspases and principally mediated by p38 MAPK pathway. Nutr Cancer *49*: 174-183, 2004.
65 Lu J and Jiang C: Antiangiogenic activity of selenium in cancer chemoprevention: metabolite-specific effects. Nutr Cancer *40*: 64-73, 2001.
66 Chintala S, Toth K, Cao S, Durrani FA, Vaughan MM, Jensen RL and Rustum YM: Se-methylselenocysteine sensitizes hypoxic tumor cells to irinotecan by targeting hypoxia-inducible factor 1alpha. Cancer Chemother Pharmacol *66*: 899-911, 2010.
67 Chintala S, Najrana T, Toth K, Cao S, Durrani FA, Pili R and Rustum YM: Prolyl hydroxylase 2 dependent and Von-Hippel-Lindau independent degradation of Hypoxia-inducible factor 1 and 2 alpha by selenium in clear cell renal cell carcinoma leads to tumor growth inhibition. BMC Cancer *12*: 293, 2012.
68 Jiang C, Ganther H and Lu J: Monomethyl selenium--specific inhibition of MMP-2 and VEGF expression: implications for angiogenic switch regulation. Mol Carcinog *29*: 236-250, 2000.
69 Yin MB, Li ZR, Toth K, Cao S, Durrani FA, Hapke G, Bhattacharya A, Azrak RG, Frank C and Rustum YM: Potentiation of irinotecan sensitivity by Se-methylselenocysteine in an *in vivo* tumor model is associated with downregulation of cyclooxygenase-2, inducible nitric oxide synthase, and hypoxia-inducible factor 1alpha expression, resulting in reduced angiogenesis. Oncogene *25*: 2509-2519, 2006.
70 Bhattacharya A, Toth K, Sen A, Seshadri M, Cao S, Durrani FA, Faber E, Repasky EA and Rustum YM: Inhibition of colon cancer growth by methylselenocysteine-induced angiogenic

chemomodulation is influenced by histologic characteristics of the tumor. Clin Colorectal Cancer *8*: 155-162, 2009.

71 Park JM, Kim A, Oh JH and Chung AS: Methylseleninic acid inhibits PMA-stimulated pro-MMP-2 activation mediated by MT1-MMP expression and further tumor invasion through suppression of NF-kappaB activation. Carcinogenesis *28*: 837-847, 2007.

72 Yoon S-O, Kim M-M and Chung A-S: Inhibitory Effect of Selenite on Invasion of HT1080 Tumor Cells. J Biol Chem *276*: 20085-20092, 2001.

73 Xiang N, Zhao R, Song G and Zhong W: Selenite reactivates silenced genes by modifying DNA methylation and histones in prostate cancer cells. Carcinogenesis *29*: 2175-2181, 2008.

74 Hu C, Liu M, Zhang W, Xu Q, Ma K, Chen L, Wang Z, He S, Zhu H and Xu N: Upregulation of *KLF4* by methylseleninic acid in human esophageal squamous cell carcinoma cells: Modification of histone H3 acetylation through HAT/HDAC interplay. Mol Carcinog *54*: 1051-1059, 2015.

75 Hoffmann FW, Hashimoto AC, Shafer LA, Dow S, Berry MJ and Hoffmann PR: Dietary selenium modulates activation and differentiation of CD4+ T-cells in mice through a mechanism involving cellular free thiols. J Nutr *140*: 1155-1161, 2010.

76 Azrak RG, Yu J, Pendyala L, Smith PF, Cao S, Li X, Shannon WD, Durrani FA, McLeod HL and Rustum YM: Irinotecan pharmacokinetic and pharmacogenomic alterations induced by methylselenocysteine in human head and neck xenograft tumors. Mol Cancer Ther *4*: 843-854, 2005.

77 Caffrey PB and Frenkel GD: Selenium compounds prevent the induction of drug resistance by cisplatin in human ovarian tumor xenografts *in vivo*. Cancer Chemother Pharmacol *46*: 74-78, 2000.

78 Camargo SM, Francescato HD, Lavrador MA and Bianchi ML: Oral administration of sodium selenite minimizes cisplatin toxicity on proximal tubules of rats. Biol Trace Elem Res *83*: 251-262, 2001.

79 Asfour IA, El Shazly S, Fayek MH, Hegab HM, Raouf S and Moussa MA: Effect of high-dose sodium selenite therapy on polymorphonuclear leukocyte apoptosis in non-Hodgkin's lymphoma patients. Biol Trace Elem Res *110*: 19-32, 2006.

80 Buntzel J, Micke O, Kisters K, Bruns F, Glatzel M, Schonekaes K, Kundt G, Schafer U and Mucke R: Selenium substitution during radiotherapy of solid tumours – laboratory data from two observation studies in gynaecological and head and neck cancer patients. Anticancer Res *30*: 1783-1786, 2010.

81 Zhang Y, Zheng S, Zheng JS, Wong KH, Huang Z, Ngai SM, Zheng W, Wong YS and Chen T: Synergistic induction of apoptosis by methylseleninic acid and cisplatin, the role of ROS-ERK/AKT-p53 pathway. Mol Pharm *11*: 1282-1293, 2014.

82 Li S, Zhou Y, Wang R, Zhang H, Dong Y and Ip C: Selenium sensitizes MCF-7 breast cancer cells to doxorubicin-induced apoptosis through modulation of phospho-Akt and its downstream substrates. Mol Cancer Ther *6*: 1031-1038, 2007.

83 Qi Y, Fu X, Xiong Z, Zhang H, Hill SM, Rowan BG and Dong Y: Methylseleninic acid enhances paclitaxel efficacy for the treatment of triple-negative breast cancer. PLoS One *7*: e31539, 2012.

84 Tzeng TJ, Cao L, Fu Y, Zeng H and Cheng WH: Methylseleninic acid sensitizes Notch3-activated OVCA429 ovarian cancer cells to carboplatin. PLoS One *9*: e101664, 2014.

85 Li Z, Carrier L and Rowan BG: Methylseleninic acid synergizes with tamoxifen to induce caspase-mediated apoptosis in breast cancer cells. Mol Cancer Ther *7*: 3056-3063, 2008.

86 Azrak RG, Cao S, Durrani FA, Toth K, Bhattacharya A and Rustum YM: Augmented therapeutic efficacy of irinotecan is associated with enhanced drug accumulation. Cancer Lett *311*: 219-229, 2011.

87 Shin SH, Yoon MJ, Kim M, Kim JI, Lee SJ, Lee YS and Bae S: Enhanced lung cancer cell killing by the combination of selenium and ionizing radiation. Oncol Rep *17*: 209-216, 2007.

88 Weijl NI, Elsendoorn TJ, Lentjes EG, Hopman GD, Wipkink-Bakker A, Zwinderman AH, Cleton FJ and Osanto S: Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. Eur J Cancer *40*: 1713-1723, 2004.

89 Gounder MK, Gibbon D, Kumar CA, Simmons N, Buckley B, Xie R, Lin Y, Shih W, Frenkel GD, Caffrey P, Rubin EH and Rodrigeuz-Rodriguez L: A phase I and pharmacokinetic study of paclitaxel and carboplatin combined with sodium selenite in patients with gynecologic malignacies. Cancer Res *65*: 938-938, 2005.

90 Fakih MG, Pendyala L, Smith PF, Creaven PJ, Reid ME, Badmaev V, Azrak RG, Prey JD, Lawrence D and Rustum YM: A phase I and pharmacokinetic study of fixed-dose selenomethionine and irinotecan in solid tumors. Clin Cancer Res *12*: 1237-1244, 2006.

91 Vieira ML, Fonseca FL, Costa LG, Beltrame RL, Chaves CM, Cartum J, Alves SI, Azzalis LA, Junqueira VB, Pereria EC and Rocha KC: supplementation with selenium can influence nausea, fatigue, physical, renal and liver function of children and adolescents with cancer. J Med Food *18*: 109-117, 2015.

92 Brodin O, Eksborg S, Wallenberg M, Asker-Hagelberg C, Larsen EH, Mohlkert D, Lenneby-Helleday C, Jacobsson H, Linder S, Misra S and Bjornstedt M: Pharmacokinetics and toxicity of sodium selenite in the treatment of patients with carcinoma in a phase I clinical trial: The SECAR Study. Nutrients *7*: 4978-4994, 2015.

93 Rayman MP, Infante HG and Sargent M: Food-chain selenium and human health: spotlight on speciation. Br J Nutr *100*: 238-253, 2008.

Received September 6, 2017
Revised October 3, 2017
Accepted October 12, 2017