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 preclinical 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. Pharmacodynamic 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
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 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 S-methyl-selenocysteine (MSC) and L-selenomethionine (SLM), is maintained for a longer period after its discontinuation compared to inorganic forms such as sodium selenite 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 catalysed 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 (LD50) 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 used in supplementation in both preclinical and clinical studies. 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
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;
doses (summarised in Table I), it commonly augments the anticancer efficacy of chemotherapy and radiation in cell
dose relationship.

with no direct comparison of Se compounds or their PK-PD
clear evidence from preclinical work that the efficacy and
demonstrating differential effects of Se compounds in normal
versus metastasis of tumours.

chemotherapy and radiation. Current doses of Se are
has not been established in humans, hence the optimal form
remains unclear. However Joel
and dose of Se to be used with chemotherapy or radiotherapy
involves the sequential activation of the caspases;
• Induction of apoptosis of cancer cells, which generally
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
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-
icubation with Se in human colorectal and head and neck
squamous cell carcinoma xenografts (Figure 2) (11)
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/m² 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.

http://dx.doi.org/10.21873/anticanres.12143

ANTICANCER RESEARCH 37: 6497-6509 (2017)
Table I. Pharmacodynamic mechanisms of selenium supplementation in normal and malignant cells.

<table>
<thead>
<tr>
<th>Pharmacodynamic properties</th>
<th>Effects in normal cells (Ref)</th>
<th>Effects in malignant cells (Ref)</th>
<th>Therapeutic significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant effects</td>
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<tr>
<td>Glutathione peroxidase (GPx)</td>
<td>Se-dependent GPx isoforms 1, 2, 3, 4 and 6 reduce oxidative damage; activity saturates with nutritional doses of Se (6)</td>
<td>Increased GPx1 activity in response to low dose Se (as SS and SLM) in LNCaP cells, resulting in reduced oxidative damage (49)</td>
<td>Mixed</td>
</tr>
<tr>
<td>Intracellular glutathione (GSH)</td>
<td>Increased GSH in PBMCs in response to MSA (50)</td>
<td>MSA reduced total GSH in leukaemia cells (50)</td>
<td>Favourable</td>
</tr>
<tr>
<td>Thioredoxin reductase (TrxR)</td>
<td>Essential selenoprotein (51), increased TrxR activity in red blood cells with selenized yeast (52)</td>
<td>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)</td>
<td>Mixed</td>
</tr>
<tr>
<td>Cell death/cytotoxicity</td>
<td>Minimal effects on normal cells (50, 51, 55)</td>
<td>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)</td>
<td>Favourable</td>
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<tr>
<td>DNA repair</td>
<td>Enhanced DNA repair with SLM in p53 wild-type mouse and human fibroblasts (60, 61)</td>
<td>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)</td>
<td>Mixed</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>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)</td>
<td>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). This resulted in improved intratumoral vessel maturation, interstitial fluid pressure and reduced hypoxia (70)</td>
<td>Favourable</td>
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<tr>
<td>Invasion/migration</td>
<td>Reduced cell invasion through inhibiting MMP-2, MMP-9 and UPA by MSA (71) and SS (72)</td>
<td></td>
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<td>Epigenetic</td>
<td>Inhibits DNMT and HDAC resulting in expression of silenced genes by SS (73) and MSA (74)</td>
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<td>Favourable</td>
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<tr>
<td>Immunological</td>
<td>1 mg/kg SS for 8 weeks increased antigen-specific CD4(^+) T-cell responses (75)</td>
<td>Significant reduction in levels of the ABCC1 efflux pump in tumour cells (76).</td>
<td>Favourable</td>
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<tr>
<td>Drug efflux</td>
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</table>

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.
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 myelosuppression, 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. (12) 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
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/m² 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/m² 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.

<table>
<thead>
<tr>
<th>Author &amp; year of publication</th>
<th>N</th>
<th>Trial design</th>
<th>Cancer treatment</th>
<th>Cancer type</th>
<th>Selenium form &amp; dose</th>
<th>Outcomes - toxicity/efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al. 1997 (44)</td>
<td>41</td>
<td>Randomised to Se with cycle 1 or 2 (not both)</td>
<td>Cisplatin-based chemotherapy (60-80 mg/m²)</td>
<td>Lung, breast, gastric, colon, oesophagus, liver</td>
<td>Oral kappa-selenocarrageenan (4000 μg Se/day for 4 days before and after chemotherapy)</td>
<td>• Significantly higher day 14 WBC 3.35±2.01 vs. 2.31±1.58×10⁹/l (p&lt;0.05)</td>
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<td>• Less G-CSF and RBC transfusion</td>
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<td>• Significantly less nausea (p&lt;0.001), vomiting (p&lt;0.001), stomatitis (p&lt;0.0292), abdominal pain (p&lt;0.0006), anorexia, weakness (p&lt;0.001), alopecia (p&lt;0.001)</td>
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<td>• Significantly higher neutrophils</td>
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<td>• Trend to lower serum CA-125 (93.5±200 vs. 228±713 U/ml)</td>
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<td>• No improvement in toxicity or response rate</td>
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<td></td>
<td>• 64% Of supplement group non-compliant due to GI effects</td>
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<td>• Se or not controls (60-100 mg/m²)</td>
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<td>• SLM well-tolerated at 7200 μg</td>
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<td>• Responses seen in irinotecan-refractory population</td>
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<td></td>
<td>• Significantly less apoptosis of neutrophils (67% vs. 20%, p&lt;0.05) and reduced infection rate</td>
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<td>• No reduction in irinotecan toxicity</td>
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<td>• Significantly better preservation of cardiac ejection fraction (62±5% vs. 69±5% p&lt;0.05).</td>
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<td>• 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±7.9 ng/ml, p&lt;0.05)</td>
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<td>• Increased complete response rate in Se group (60% vs. 40%)</td>
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<td>• Irinotecan MTD 125 mg/m²</td>
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<td></td>
<td>• No diarrhoea &gt; grade 2 at MTD</td>
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<td>• Responses seen in irinotecan-refractory population</td>
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<td>• Prolonged stable disease &gt;6 months in irinotecan-pre-treated patients</td>
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<td>• SLM well-tolerated at 7200 μg daily for 1 week followed by 7.200 μg daily with irinotecan</td>
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<td></td>
<td>• No reduction in irinotecan toxicity</td>
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<td></td>
<td>• Significantly greater increase in apoptotic marrow cells on day 8 of cycle 1 in Se group (49.2% vs. 29.7%)</td>
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<td></td>
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<td></td>
<td>• Significant increase in tumour reduction</td>
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<td></td>
<td>• Preservation of cardiac ejection fraction in Se group but not controls (p=0.04)</td>
</tr>
</tbody>
</table>

Table III. Continued
<table>
<thead>
<tr>
<th>Author &amp; year of publication</th>
<th>N</th>
<th>Trial design</th>
<th>Cancer treatment</th>
<th>Cancer type</th>
<th>Selenium form &amp; dose</th>
<th>Outcomes - toxicity/efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muecke et al. 2010, 2014 (12, 35)</td>
<td>81</td>
<td>Randomized to Se or not in patients with low blood Se (&lt;84 ng/ml)</td>
<td>Radiotherapy (RT) (external beam w/wo brachytherapy)</td>
<td>Endometrium or cervix</td>
<td>Oral sodium selenite 500 μg on days of RT and 300 μg on days without treatment</td>
<td>• 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 • 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 • MTD was 60,000 μg/day with linear PK • Fatigue, diarrhoea and muscle spasms dose-limiting at 90,000 μg/day • One PSA response &gt;50% and mean PSA doubling time increased (2.18 months before trial to 3.85 months) • 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) • 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 • No significant change in mucositis or patient reported side effects • No difference in OS or RFS at 12 months</td>
</tr>
<tr>
<td>Buntzel et al. 2010 (2 papers with overlapping cohorts) (36, 80)</td>
<td>47 or 39</td>
<td>Randomised to Se or not in patients with low blood Se (not defined)</td>
<td>RT (37/39 adjuvant)</td>
<td>Head and neck squamous carcinoma</td>
<td>Oral sodium selenite 500 μg on days of RT and 300 μg on days without treatment.</td>
<td>• Lower than expected rates of grade 3 toxicities, 3.6%, vs. 8.9% in placebo group (p=NS) • Trend to less acute taste loss • No difference in xerostomia or mucositis • Significant increase in serum and whole blood Se • Significant decrease in serum AST levels with Se (p=0.04)</td>
</tr>
<tr>
<td>Corcoran et al. 2010 (26)</td>
<td>19</td>
<td>Phase I dose escalation</td>
<td>Antiandrogens discontinued &gt;4 weeks before trial; LHRH agonists were continued</td>
<td>Chemotherapy naïve, castration-resistant prostate cancer</td>
<td>Oral sodium selenate; dose escalation from 5,000-90,000 μg/day for 12 weeks (longer if responding)</td>
<td>• Significant reduction in incidence of grades 3-4 oral mucositis (OM) (10.8% vs. 35.1%) • No significant change in mucositis levels compared to placebo (p=NS) • Significant decrease in serum AST levels with Se (p=0.045) • General trend to improvement in scores</td>
</tr>
<tr>
<td>Jahangard-Rafsanjani et al. (43)</td>
<td>77</td>
<td>Randomised to Se or placebo</td>
<td>High-dose busulfan + cyclophosphamide then allogeneic haematopoietic stem cell transplantation</td>
<td>Acute leukaemia</td>
<td>Oral selenized yeast (200 μg) vs. placebo twice daily from day 0 to 14 days after transplant</td>
<td>• Significant reduction in incidence of grades 3-4 oral mucositis (OM) (10.8% vs. 35.1%) • Significantly shorter</td>
</tr>
</tbody>
</table>
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 antitumor 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

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