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Phase I trial of selenium plus chemotherapy in gynecologic cancers

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HIGHLIGHTS

- Selenious acid (5000 μg Se) can be safely combined with carboplatin/paclitaxel.
- Pharmacokinetics of carboplatin on day 3 is not affected by selenious acid on day 1.
- Average plasma half-life of selenious acid/sodium selenite is 25 h.
- Selenious acid administered with carboplatin may downregulate *RAD51AP1*.

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ABSTRACT

Purpose. Preclinical studies performed in our laboratory have shown that high-dose selenium inhibits the development of carboplatin drug resistance in an ovarian cancer mouse xenograft model. Based on these data, as well as the potential serious toxicities of supranutritional doses of selenium, a phase I trial of a combination of selenium/carboplatin/paclitaxel was designed to determine the maximum tolerated dose, safety, and effects of selenium on carboplatin pharmacokinetics in the treatment of chemo-naive women with gynecologic cancers. Correlative studies were performed to identify gene targets of selenium.

Methods. Chemo-naïve patients with gynecologic malignancy received selenious acid IV on day 1 followed by carboplatin IV and paclitaxel IV on day 3. A standard 3 + 3 dose-escalating design was used for addition of selenium to standard dose chemotherapy. Concentrations of selenium in plasma and carboplatin in plasma ultrafiltrate were analyzed.

Results. Forty-five patients were enrolled and 291 treatment cycles were administered. Selenium was administered as selenious acid to 9 cohorts of patients with selenium doses ranging from 50 μg to 5000 μg. Grade 3/4 toxicities included neutropenia (66.7%), febrile neutropenia (2.2%), pain (20.0%), infection (13.3%), neurologic (11.1%), and pulmonary adverse effects (11.1%). The maximum tolerated dose of selenium was not reached. Selenium had no effect on carboplatin pharmacokinetics. Correlative studies showed post-treatment downregulation of RAD51AP1, a protein involved in DNA repair in both cancer cell lines and patient tumors.

Conclusion. Overall, the addition of selenium to carboplatin/paclitaxel chemotherapy is safe and well tolerated, and does not alter carboplatin pharmacokinetics. A 5000 μg dose of elemental selenium as selenious acid is suggested as the dose to be evaluated in a phase II trial.

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1. Introduction

Effective chemotherapy is essential in the treatment of advanced gynecological malignancies. Nevertheless, acquired resistance to platinum-based chemotherapy regimens, the standard-of-care in the treatment of many of these diseases, ultimately occurs in most patients [1–3]. New approaches are, therefore, urgently needed to overcome resistance to cytotoxic therapies [4].

Both platinum agents and taxanes are believed to exert anticancer effects through multiple mechanisms [5–7]. Some of the most well described modes of action of these 2 classes of drugs involve cell cycle arrest resulting in apoptotic cell death [6, 7]. These events are triggered by either the generation of lesions/crosslinks preferentially involving the purine bases of double-stranded DNA in the case of platinum agents, or taxane-induced stabilization of microtubules.

The mechanisms of resistance to these anticancer agents are also believed to be multifactorial in nature. In the case of platinum-based therapy, it has been proposed that these resistance mechanisms may be classified as "pre-target" (e.g., reduced intracellular levels of drug mediated by transporter proteins; increased levels of glutathione which can reduce ROS), "on-target" (e.g., increased proficiency of homologous recombination and other DNA repair mechanisms), "post-target" (e.g., interference in components of apoptotic mechanisms), and "off-target" (e.g., increase in cytoprotective autophagic processes) [6]. Many of these processes are also likely to interfere with the clinical activity of taxanes [7].

Selenium is a nutritionally essential trace element that forms a variety of biologically active organic (e.g., selenomethionine, selenocysteine) and inorganic (e.g., selenite, selenate) compounds, and is cotranslationally incorporated as selenocysteine into various selenoproteins, including glutathione peroxidases [8]. There have been many studies on the use of selenium for the prevention of cancer, but as shown in a recent meta-analysis, a significant effect has not been demonstrated [9, 10]. In contrast, the use of selenium compounds in the treatment of patients with cancer has not received extensive investigation. Nevertheless, a number of rationales exist for the inclusion of selenium in chemotherapy regimens.

Synergistic interactions between high-dose selenium and various cytotoxic drugs, including docetaxel, irinotecan, cisplatin, carboplatin, doxorubicin, and fluorouracil have been reported in a number of preclinical investigations involving in vivo studies of tumor xenografts [11–13]. These findings could be attributed to selenium-related enhancement of therapeutic effect or interference in processes of drug resistance. Regarding the latter possibility, our studies performed in nude mouse xenografts of ovarian cancer show that development of resistance to carboplatin chemotherapy is prevented when high doses of sodium selenite are administered prior to cytotoxic therapy. Furthermore, tumors treated with sodium selenite prior to carboplatin that were reimplanted into new animals maintain chemosensitivity to carboplatin [12]. In addition, proapoptotic effects of high-dose sodium selenite have been reported in studies of a number of different cancers [14]. It has also been proposed that the prooxidant characteristics of high-dose sodium selenite, while unlikely to directly cause DNA damage, can potentiate the action of other DNA damaging agents through induction of oxidative stress [15]. Interestingly, treatment of a xenograft mouse model of ovarian cancer with high-dose sodium selenite alone had no effect on tumor growth [4].

Several clinical studies have shown that addition of selenium-containing compounds to particular cytotoxic drug regimens may decrease toxicity and improve treatment tolerability, although the evidence with respect to this finding is mixed [16–19]. In addition, results from a randomized study of standard chemotherapy with or without high-dose sodium selenite in adult patients with non-Hodgkin's lymphoma showed improved outcomes in the group receiving selenium [20]. However, clinical evidence supporting the safety of administering inorganic selenium compounds at relatively high dosages is limited [9, 13, 20–22], and these studies are critically important given the serious toxicities that have been reported when large quantities of selenium are accidentally ingested [23]. The primary objective of this phase I study is to investigate the safety of selenium as part of a therapeutic regimen for the treatment of women with gynecologic cancers.

2. Materials and methods

2.1. Patient eligibility

Eligible patients had histologically or cytologically proven gynecologic malignancy. They were chemo-naive and a regimen of carboplatin and paclitaxel chemotherapy was considered to be a standard option for their treatment. Other inclusion criteria included age >18 years, estimated life expectancy of at least 6 months, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate hematologic, renal, and hepatic function.

2.2. Study design

A standard 3 + 3 dose-escalating phase I trial evaluating administration of selenious acid followed by chemotherapy in cohorts of eligible patients was followed. Dose escalation was preceded in cohorts of three patients until a dose-limiting toxicity (DLT) was reported during the first cycle of therapy. If one patient out of three experienced a DLT, three additional patients were enrolled at that dose level. The maximum tolerated dose (MTD) was defined as the dose level at which ≥2 of 6 patients experienced a DLT.

The study protocol and amendments for this investigational trial were approved by an institutional review board (IRB) at the Rutgers Cancer Institute of New Jersey in accordance with the Belmont Report. Patients enrolled in this study provided written informed consent prior to study treatment.

2.3. Study endpoints

The primary aim of this study was to determine the safety of selenium, administered intravenously (IV) as selenious acid, with carboplatin/paclitaxel in patients with gynecologic malignancies for whom standard therapy with carboplatin/paclitaxel was planned. This includes determination of the DLT and MTD of selenious acid in combination with carboplatin/paclitaxel. A secondary aim was to describe whether co-administration of selenious acid alters carboplatin pharmacokinetics.

An exploratory outcome measure included assessment of clinical response and progression-free survival (PFS) in the subgroup of patients with advanced ovarian cancer. In addition, correlative studies evaluating the effects of administration of selenious acid plus chemotherapy on gene expression in tumor specimens and ovarian and breast cancer cell lines were also performed.

2.4. Treatment protocol and dose cohorts

Selenium Injection (selenious acid) was purchased from American Regent, Inc. (Shirley, NY). Selenious acid-containing solutions were administered in a total volume of 500 mL, and were prepared by diluting specific volumes of aqueous selenious acid (65.5 μg/mL selenious acid corresponding to 40 μg/mL elemental selenium [Se]) with 5% dextrose in water.

Given the two pK_as of selenious acid (2.7, 8.3) and the pH of blood (7.4), this compound in blood results in a mixture of partially and fully ionized forms of the compound. Treatment consisted of IV administration of these solutions over 5 h on day 1, followed by paclitaxel 175 mg/m^2 IV and carboplatin (area under concentration [AUC] 5 for first cycle; AUC 6 for subsequent cycles) on day 3. A time delay of two days between administration of selenious acid and chemotherapy was

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chosen to approximate the delay between administration of selenium and carboplatin found to be most effective in the mouse xenograft studies [12]. Patients were assigned to 1 of 9 Se escalation dose cohorts ranging from 50 μg/dose to 5000 μg/dose (Table 2). (For reference, the recommended daily allowance of oral selenium for adults is 55 μg/day [24].)

2.5. Clinical toxicity evaluation

All patients who received 1 cycle of protocol therapy were evaluated for toxicity. Adverse events were assessed weekly according to the National Cancer Institute (NCI) Terminology Criteria for Adverse Events (CTCAE) version 3.0. Dose limiting toxicity (DLT) was defined as an adverse event occurring in cycle 1 that met 1 of the following criteria: 1) treatment-related grade 3 or higher non-hematologic toxicity, excluding alopecia, hypersensitivity reactions, injection-site reactions, and dyspepsia, or 2) grade 4 neutropenia for at least 7 days, febrile neutropenia, thrombocytopenia accompanied by bleeding, or grade 3 or higher hematologic toxicity, excluding anemia and lymphocytopenia. The MTD was defined as the dose below the dose at which at least 2 patients out of 6 experienced DLT.

2.6. Clinical response evaluation

Patients were evaluated for response of measurable disease using CT of the abdomen/pelvis at baseline and after 3 cycles of protocol therapy and every 3 cycles thereafter according to RECIST version 1.1 criteria. Progression-free survival (PFS) was defined as the date of registration until disease progression or death, whichever came first (censored by the date of last contact prior to data analysis).

2.7. Statistical analyses

Pharmacokinetic findings were analyzed and parameters were summarized with mean ± SD, and compared with 95% confidence intervals (CIs) between cycle 1 and cycle 2 pharmacokinetic parameters. Confidence intervals at 95% of the mean were determined using OriginPro statistical software (Northampton, MA).

3. Supplementary materials and methods

See Supplementary materials and methods for additional information related to patient eligibility, rationale for use of selenious acid/sodium selenite, treatment protocol and dose cohorts, determination of *BRCA1/2* status, clinical toxicity evaluation, clinical response evaluation, selenium and carboplatin pharmacokinetics, cell lines, cell culture, cell viability and tumor specimens, microarray analysis and immunoblotting experiments, and determination of plasma selenoprotein P levels and plasma glutathione peroxidase activity.

4. Results

4.1. Patient characteristics

Forty-five patients were enrolled in the study; 38 patients had a diagnosis of epithelial ovarian cancer, or cancer of the fallopian tubes or peritoneum, with 28 patients in that group diagnosed with stage III or IV disease. Patient baseline characteristics are represented in Table 1.

Patients received treatment either in the neoadjuvant setting or following surgery (see Supplementary Table S1). For the group of patients with ovarian, fallopian tube, or peritoneal cancer, 12 received neoadjuvant therapy, and 15 and 11 received adjuvant treatment following optimal or suboptimal cytoreductive surgery, respectively. Hence, 23 patients in this group had measurable disease at initiation of treatment.

4.2. Maximum tolerated dose

A total of 291 treatment cycles were administered. A median of 6 cycles was given, with a range of one to 13 cycles per patient. Thirty-three patients (73%) received 6 or more cycles. There were no treatment-related deaths. A summary of the number of cycles in which specific grade 3/4 adverse events were experienced is presented in Table 3. Grade 3 and 4 toxicities, regardless of attribution, from all 291 cycles are shown. Only three cycle 1-related DLTs occurred. Worst grade hematologic toxicities per patient summarized in Supplementary Table S2 show that grade 3/4 neutropenia and thrombocytopenia occurred in 66.7% and 0% of patients, respectively. Rates of grade 3/4 anemia and leukopenia were very low (Supplementary Table S2).

Relatively few patients experienced grade 3 or 4 non-hematologic adverse events. Injection-site reactions are reported as dermatological adverse events, and were noted to occur at a higher rate at the 1200 μg dose of selenious acid. As a consequence, higher doses of selenious acid were subsequently administered through a central venous catheter.

Dose reductions were required in four patients: two patients had a 25% dose reduction of paclitaxel; one patient had a 25% dose reduction of carboplatin; and one patient received AUC 5 for all cycles. Treatment was discontinued early in 6 patients due to treatment-related toxicity (2 bone marrow-related events, 3 grade 3 neuropathy, 1 carboplatin hypersensitivity reaction). Supplementary Table S3 lists reasons for treatment discontinuation in all patients who terminated therapy due to treatment-related toxicity or need for anticoagulation therapy. Interestingly, only one patient receiving the highest dose of selenium terminated treatment early (i.e., after 4 cycles) and this was due to grade 3 neuropathy.

Only one of the first 6 patients receiving selenious acid at the 5000 μg Se dose experienced a cycle 1 DLT and an MTD was not reached in this study. In view of the favorable safety profile seen with selenious acid doses up to and including 5000 μg Se, the protocol was amended to explore a treatment regimen including the 5000 μg dose in a dose

Table 1
Baseline patient and disease characteristics.

Age, years	
Median	54
Range	36–74
Age groups, years (n, %)	
30–49	14 (31%)
50–69	28 (62%)
70–79	3 (7%)
Race (n, %)	
Asian	2 (4%)
Black or African American	4 (9%)
White	39 (87%)
ECOG performance status (n, %)	
0	29 (64%)
1	14 (31%)
2	2 (4%)
Ovarian, Fallopian tube, or peritoneal cancer	
No. of patients	38
Stage (n, %)	
Stage I	2 (5.3%)
Stage II	6 (15.8%)
Stage III	18[a] (47.4%)
Stage IV	10 (26.3%)
Stage unavailable	2 (5.3%)
Uterine cancer	
No. of patients	6
Stage/classification (n, %)	
Stage IV	1 (16.6%)
Recurrent	5 (83.3%)
Cervical cancer	
No. of patients	1
Stage, (n, %)	
Stage IV	1 (100%)

[a] One patient classified as having cancer of both the ovary and the uterus.

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Table 2
Dose escalation schema.[a]

Dose level	Selenious acid IV (μg)	Carboplatin IV (AUC)		Paclitaxel IV (mg/m^2)	No. of pts[b]	Total cycles
		Cycle 1	Subsequent cycles			
1	50	5	6	175	3	14
2	100	5	6	175	6	35
3	200	5	6	175	4	25
4	400	5	6	175	3	24
5	800	5	6	175	7	42
6	1000	5	6	175	3	30
7	1200	5	6	175	7	52
8	2000	5	6	175	3	18
9	5000	5	6	175	9	51

[a] IV-intravenous; AUC-area under the curve.
[b] There were four exceptions to dose escalation rules (dose levels 2, 3, 5, and 7) that were approved by the primary investigator prior to treatment.

expansion cohort (n = 9). Of the additional 3 patients enrolled in the expansion cohort, one patient experienced a cycle 1 DLT (grade 3 leukopenia). In light of these results, a selenious acid dose of 5000 μg Se is suggested as the dose to be evaluated in a phase II study.

4.3. Selenium pharmacokinetics

This study is the first to evaluate the pharmacokinetics of selenious acid in women with gynecologic cancer treated with standard chemotherapy of paclitaxel and carboplatin. In order to describe the pharmacokinetics, the baseline Se concentration at time zero was subtracted from the measured values and the resulting values were subjected to pharmacokinetic estimates. Use of the baseline value to estimate the plasma selenium level over the course of several days is supported by a study conducted in healthy women showing minimal variation in plasma selenium levels over several weeks in nonpregnant women, and over several months in pregnant women [25]. The estimated selenium pharmacokinetic parameters are listed in Table 4. The baseline plasma concentration of selenium ranged from 76 to 141 μg/L, (average ± SD 116.6 ± 21.2), which is similar to values previously reported in the literature for an American population [26]. Plasma Se levels at the initial cohorts 50, 100, 200 μg and 400 μg doses were 'noisy' and almost within the baseline fluctuations. Therefore, the pharmacokinetics of selenious acid was performed only in patients treated with Se doses of 800, 1000, 1200, 2000, and 5000 μg. The average plasma levels of Se in different selenious acid dose cohorts are presented in Supplementary Fig. S1. Selenium concentration in plasma increased steadily until the end of infusion and thereafter declined gradually with an average plasma half-life of 25 h (range 8.2–74.4 h). This finding is similar to the median plasma half-life of 18.25 h reported from pharmacokinetic analyses of data from a phase I trial of IV sodium selenite administered to patients with a variety of advanced cancers [27]. The maximum Se concentration (Cmax) in plasma exhibited a dose-related increase (Supplementary Fig. S1; Table 4). The maximal concentration of plasma selenium observed in patients receiving the 5000 μg dose of Se as selenious acid was 667 μg/L, although this concentration decreased by approximately half within 24 h. The time to maximum concentration (Tmax) corresponded to the time of end of infusion, which was 5–5.2 h. Area under concentration-time curves (AUCs) showed a dose-dependent linear increase during cycle 1 and cycle 2 (Table 4). The average clearance and the 95% confidence intervals (lower, upper) of selenium in cycle 1 and cycle 2 were 478 (279.7, 623.0) L/h and 692.4 (416.4, 898.2) L/h, respectively.

Table 3
Numbers of cycles per se dose level in which grade 3/4 (worst grade) adverse events[a] occurred.

Selenious acid dose (μg)	50	100	200	400	800	1000	1200	2000	5000[b]
Total number of cycles per selenious acid dose	14	35	25	24	42	30	52	18	51

Hematologic toxicities

Grade	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4
Neutropenia		1	1		4	1	2	3	3	3			4	5	2		7	3
Febrile neutropenia																	1	
Leukopenia																	2[c,f]	
Anemia																	1	
Thrombocytopenia																		

Non-hematologic toxicities

Grade	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4
Cardiovascular									2									
Constitutional[d]	1		1						1				1					
Dermatology													2					
Endocrine					1													
Gastrointestinal							1				1		3					
Hepatobiliary													2	2				
Infection								1			1			1[c]			3	
Metabolic											1							
Musculoskeletal																	1[c]	
Neurologic					1				1				1				2[e]	
Pain									1		1		3		1		4	
Pulmonary			1						2		1		1					

[a] Regardless of attribution. More than 1 of the same adverse events occurring during a cycle is reported only once at highest grade level.
[b] Expansion cohort.
[c] One cycle 1 DLT.
[d] Constitutional adverse events include fatigue, fever, anxiety.
[e] Restlessness is a neurologic adverse event.
[f] Occurred in expansion cohort.

4.4. Carboplatin pharmacokinetics

Carboplatin pharmacokinetic parameters were determined during the first two cycles of therapy. The AUC for the first dose was 5, and was increased to 6 for the second dose. The pharmacokinetics parameters associated with carboplatin were evaluated in 33 patients during the first cycle and 27 patients during the second cycle (Table 5). There was variation in AUCs between patients; the average observed AUC in cycle 1 was 4.5 (95% CI, 4.21, 4.80), and 5.74 in cycle 2 (95% CI, 5.31, 6.17) (Table 5). Between cycle 1 (AUC = 5) and cycle 2 (AUC = 6), the estimated pharmacokinetic parameters, average clearance and half-life, showed very little difference (<5%), and the 95% CIs for clearance and half-life were (123, 154 mL/min) vs (120, 147 mL/min) and (253, 371 min) vs (225, 384 min), respectively, thus suggesting that selenium does not affect carboplatin pharmacokinetics.

4.5. Selenoprotein P and glutathione peroxidase determination

Serum glutathione peroxidase levels did not change significantly after selenium treatment compared with pretreatment levels. Similarly, no changes in selenoprotein P levels were detected after each cycle of selenium compared with baseline (data not shown). These results, together with the measured baseline selenium levels (Supplementary Fig. S1), suggest that patients were not selenium deficient prior to study enrollment.

4.6. Clinical response

A summary of the results of the clinical response evaluation is presented in Supplementary Table S4. The median PFS for 28 patients with stage III and IV malignancies was 15 months (95% CI, 10.9–34.5 months; Supplementary Fig. S2). Thirty-three patients had elevated serum CA-125 at initiation of therapy; 21/33 of these patients

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Table 4
Plasma selenium pharmacokinetic parameters.[a]

Dose (μg)	Cmax (μg/L)		AUC (μg/mL*h)		Half-life ($T_{1/2}$ h)		Clearance (L/h)	
	C1	C2	C1	C2	C1	C2	C1	C2
800	101.3 ± 43.9	72.2 ± 18.6	2562.7 ± 2191	1038.9 ± 613.9	19.1 ± 9.3	23.2 ± 19.2	527.7 ± 575.8	841.5 ± 654.1
1000	101.6 ± 11.5	90.3 ± 5.5	2014.2 ± 602.1	1396.3 ± 1225.8	34.4 ± 7.4	17.5 ± 10.6	291.0 ± 114.1	976.9 ± 542.6
1200	162.8 ± 24.9	154.4 ± 47.4	3763.7 ± 2319.9	3000.4 ± 2133.5	35.1 ± 26.4	38.1 ± 25.8	432.8 ± 370.8	552.9 ± 450.3
2000	269.896.5±	230.9 ± 43.9	5090.7 ± 1864.8	4578.5 ± 450.2	28.5 ± 0.1	18.8 ± 1.9	305.6 ± 115.1	390.8 ± 111.3
5000	537.4 ± 90.4	517.9 ± 92.6	10,950.2 ± 3614.7	9552.0 ± 1303.2	21.2 ± 6.7	19.3 ± 6.7	416.8 ± 198.8	443.8 ± 92.3

[a] The pharmacokinetic parameters were estimated using Se concentrations derived after baseline value was subtracted from the measured concentration at each time point (n = 5, 800 μg); (n = 3, 1000 μg); (n = 5, 1200 μg); (n = 3, 2000 μg); (n = 4, 5000 μg). Cmax - maximum selenium concentration; AUC - area under the curve; T1/2 - Half-life; CL - average clearance; C1 - Cycle 1; C2 - Cycle 2.

had normalization of CA-125 (<35 U/mL) after cycle 2 [n = 14], and after cycle 6 [n = 7]).

Twelve patients enrolled in the study were tested for germline deleterious *BRCA* alterations. Of the 3 patients found to have a deleterious mutation in either *BRCA1* or *BRCA2*, one patient experienced a partial response with an overall survival (OS) of 79 months, while two patients receiving adjuvant therapy are alive with disease at 81 and 105 months. Interestingly, seven of the nine patients in this tested group without a deleterious germline *BRCA1/2* mutation experienced prolonged OS ranging from 60 to 120 months. Of those seven patients, three patients remain with no evidence of disease at 62, 69, and 114 months, while one patient is alive with disease at 120 months. Only one patient enrolled in the study subsequently developed another cancer; this patient developed breast cancer in the setting of a deleterious germline *BRCA* mutation.

4.7. Correlative studies

Differential RNA expression in breast and ovarian cancer cell lines, as well as two sets of pre- and post-treatment tumor specimens from patients, were evaluated. The doses of selenious acid and carboplatin used in the cell studies were selected on the basis of results of MTT assays (see Supplementary materials and methods; data not shown). The gene expression analysis was limited to those mRNAs that converged with either over- or under-expression after selenious acid plus chemotherapy exposure in both cell lines and patient tumors compared with the control specimens (Fig. 1A). The downregulation of several genes was of particular interest within the context of chemosensitivity/chemoresistance.

Results of immunoblotting experiments evaluating RAD51AP1 protein expression in lysates from MCF-7/Adr cells pretreated with

Table 5
Plasma carboplatin (ultrafiltrate) pharmacokinetic parameters.[a]

Patient #	Se dose (μg)	AUC (mg/mL*min)		Half-life ($T_{1/2}$ min)		Clearance (mL/min)	
		C1	C2	C1	C2	C1	C2
1	50	3.93	6.24	288	245	187	149
2	50	5.23	4.92	263	257	120	128
4	100	5.65	5.95	383	259	99.8	140
5	100	5.73	4.9	660	344	99.4	107
6	100	6.89	5.51	823.	1302	81.6	73
7	100	4.37	6.69	423	237	152.9	135
9	100	3.86	5.19	209	275	179.4	160
10	200	3.95	5.40	208	252	131.1	132
11	200	4.1	5.10	343	353	95.7	103
12	200	3.7		238		161	
13	200	5.3	6.50	887	277	90	122
14	400	4.7	4.0	239	268	127	168
15	400	4.4	6.5	247	279	159	134
16	400	3.8	4.0	282	254	270	205
17	800	4.0		195		124	
18	800	3.1		270		175	
19	800	4.4	6.1	230	239	113	108
20	800	4.0		291		148	
21	800	4.0	5.1	352	295	186	180
22	800	5.9	4.9	315	291	107	118
23	800	4.6	4.8	277	245	171	170
24	1000	5.4	5.7	290	266	182	158
25	1000	5.2	5.7	217	253	107	107
26	1000	5.1	8.99	266	274	92	82
27	1200	3.58		251		137	
32	1200	4.47		250		104	
33	1200	3.32	4.81	270	243	159	142
35	2000	4.2	4.8	280	257	241	211
36	2000	5.35	7.45	258	261	101	114
37	5000	4.36	6.9	172	242	109	98
38	5000	3.91	6.7	257	254	127	153
39	5000	4.11	6.23	173	247	129	113
40	5000	3.99	5.95	182	254	92	95
Average ± (SD)		4.5 (0.8)	5.74 (1.08)	312 (166)	305 (201)	138 (44)	134 (35)
Median		4.4	5.7	266	257	127	132
95% CI of Mean		(4.21–4.80)	(5.31–6.17)	(253–371)	(225–384)	(123–154)	(120–147)

[a] AUC - area under the curve; C1 - Cycle 1; C2 – Cycle 2. Carboplatin AUC = 5 in Cycle 1 and AUC = 6 in Cycle 2. SD - standard deviation, 95% CI - 95% confidence interval (lower, upper).

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selenious acid followed by chemotherapy compared with no treatment or carboplatin chemotherapy alone showed substantially lower expression of RAD51AP1 at higher concentrations of carboplatin when selenious acid was present vs not. Fig. 1B shows that cells treated with increasing amounts of carboplatin responded with an increase in RAD51AP1 protein expression. However, when they were pretreated with selenious acid, the expression of RAD51AP1 decreased at higher concentrations of carboplatin. This result is consistent with the results of the gene expression profiling studies showing decreased expression of *RAD51AP1* when breast and ovarian cancer cells or patient's tumor were treated with the combination of selenium and chemotherapy compared with controls.

5. Discussion

The results of this phase I trial demonstrate that selenious acid at doses up to 5000 μg can be safely administered to patients with advanced gynecologic malignancies receiving carboplatin and paclitaxel chemotherapy. While none of the patients enrolled in this study had grade 3 or 4 thrombocytopenia, 66.7% experienced grade 3 or 4 neutropenia. For comparison, hematologic toxicities observed in several Gynecologic Oncology Group (GOG) trials of chemo-naive patients with advanced ovarian cancer receiving carboplatin/paclitaxel combination chemotherapy, rates of grade 3 or 4 neutropenia or granulocytopenia were 89% of patients with optimally resected stage III ovarian cancer receiving thrice weekly carboplatin/paclitaxel as reported by Ozols et al. (GOG 0158), and 72% and 83% for patients enrolled in the GOG 0262 as reported by Chan et al. for patients receiving weekly (dose-dense) vs every 3 week regimens, respectively [1, 3]. Burger et al. reported (GOG 0218) grade 4/5 neutropenia rates of 63%, irrespective of bevacizumab use, for patients receiving carboplatin/paclitaxel on a once every 3-week schedule [2]. Reported rates of grade 3/4 thrombocytopenia in these GOG studies varied between 16% and 39%, although they were not included in the GOG 0218 trial report [1–3]. Although it cannot be concluded from these data that selenious acid pretreatment ameliorated the hematologic toxicity of chemotherapy, the observed rates of chemotherapy-associated neutropenia and thrombocytopenia observed in this study are somewhat lower compared with historical controls from the large GOG randomized trials [1–3]. Interestingly, it has recently been reported that administration of relatively low daily doses of selenium glycine over a period of one month was associated with increased neutrophil counts in children with solid tumor cancers [28]. It has also been proposed that simultaneous selenium-induced protection of normal cells from cytotoxic damage and selenium-induced enhancement of cytotoxic damage to *TP53*-mutant cancer cells may be related to p53-mediated upregulation of DNA repair [29]. Such a hypothesis may be reasonable in the setting of gynecologic cancers, many of which are p53 deficient due to inactivating *TP53* mutations.

Some of the reported adverse effects of acute ingestion of very high quantities of selenium include hypotension, tachycardia, cardiac abnormalities, abdominal symptoms such as nausea, vomiting, and pain, pulmonary edema, and neurologic symptoms [23]. Long-term exposure to high dietary levels of selenium has also been associated with brittleness and loss of nails and hair, gastrointestinal disturbances, and neurologic symptoms [30]. In this study, rates of most grade 3/4 adverse events were similar to those reported in several trials evaluating patients with advanced gynecologic malignancies receiving carboplatin and paclitaxel combination chemotherapy [1, 3, 31, 32]. Nevertheless, we cannot exclude the possibility that some of the adverse events observed in this study were associated with administration of sodium selenite.

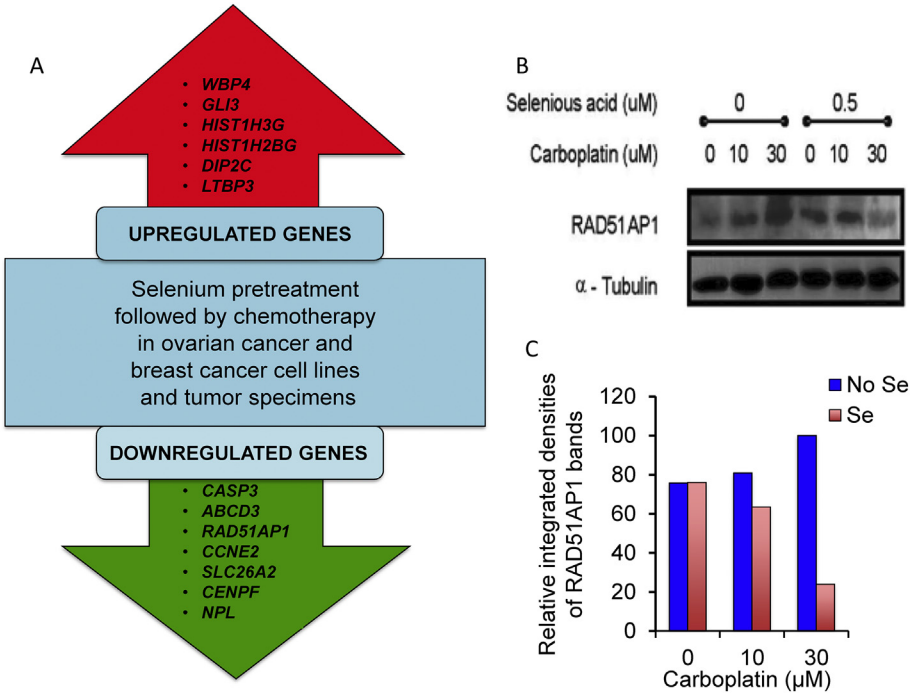

Fig. 1. Alterations in gene and protein expression following treatment with selenious acid plus chemotherapy. A. Genes up- and down-regulated following treatment with selenium plus chemotherapy. Shown are only those genes which exhibited an increase or decrease in expression in all samples tested by microarray analysis (i.e., breast and ovarian cancer cell lines, as well as patient tumor specimens) following exposure to selenious acid plus chemotherapy compared with the control samples. *CASP3:* Caspase 3; *ABCD3:* ATP-binding cassette, sub-family D (ALD), member 3; *RAD51AP1:* RAD51 associated protein 1; *CCNE2:* Cyclin E2; *SLC26A2:* Solute carrier family 26, member 2; *CENPF*: Centromere protein F; *NPL*: *N*-acetylneuraminate pyruvate lyase; *WBP4:* WW domain binding protein 4; *GLI3:* Glioma-associated oncogene family zinc finger 3; *HIST1H3G*: Histone Cluster 1 H3 family member G; *HIST1H2BG:* Histone cluster 1 H2B family member G; *DIP2C:* Disco interacting protein 2 homolog C; *LTBP3:* Latent transforming growth factor beta binding protein 3. B. Downregulation of RAD51AP1 protein expression in the presence of selenious acid plus carboplatin. Western blot of MCF-7/Adr cells showing changes in RAD51AP1 protein expression following treatment with selenious acid, carboplatin, and the combination of selenious acid and chemotherapy. C. Quantification of Western blot image shown in Fig. 1B using ImageJ software (https://imagej.nih.gov/ij/) available from NIH. The corrected (e.g., background subtracted) integrated densities of the RAD51AP1 bands are plotted at three carboplatin concentrations with (red bars) and without selenious acid (blue bars). Results are normalized with respect to the integrated density of the RAD51AP1 band under conditions of 30 μM carboplatin without selenious acid (set at 100%).

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With regard to pharmacokinetic measurements, addition of selenious acid on day 1 did not affect the pharmacokinetics of carboplatin administered on day 3. Given the estimated half-life of plasma selenious acid/selenite, plasma levels of selenium on day 3 were substantially lower than the maximal concentrations observed during day 1 of its administration. Nevertheless, the administration of selenious acid on day 1 is also likely to influence tissue stores of this element [33]. Of note, a study in patients with aggressive non-Hodgkin's lymphoma undergoing their first treatment with chemotherapy, radiotherapy or both showed that a higher serum Se concentration at presentation was a positive predictor for dose delivery, treatment response and long-term survival [34].

Patients with stage III or stage IV ovarian cancer receiving the combination of selenious acid, carboplatin and paclitaxel had a median PFS of 15 months which is similar to the median PFS times of 14.1 and 14.9 months observed for the bevacizumab-containing arms of the GOG 0218 and GOG-0262 (dose-dense) trials, respectively [1–3], although PFS times were shorter in the non-bevacizumab-containing arms of those studies (10.3 months in both studies). Nevertheless, while these data support the conclusion that pretreatment with selenious acid followed by administration of standard chemotherapy did not negatively impact clinical outcomes, it is not possible to conclude that selenium induced an increase in PFS, given that the study was not powered to answer this question. However, the few cases of patients with ovarian cancer exhibiting a long-term response in this trial are noteworthy. Although this finding should be considered anecdotal, it is consistent with a similar observation made in a phase I trial of selenomethionine administered in combination with irinotecan in patients with solid tumors [17], and a phase I trial of sodium selenite in patients with advanced cancers [27].

In this context it is also worth noting that, despite previous findings that patients with germline mutations in *BRCA* are more likely to be sensitive to platinum-based chemotherapy and to achieve better clinical outcomes due to pre-existing impairments in the process of homologous recombination [35], the three patients with deleterious germline mutations in either *BRCA1* or *BRCA2* did not appear to receive greater benefit from platinum-based chemotherapy plus selenium compared with the group without these mutations. It is tempting to suggest that selenium may interfere with DNA repair in a manner similar to BRCA deficiency, particularly in light of the observed changes in gene expression related to the *RAD51AP1* gene, thereby eliminating the advantage of BRCA deficiency in the setting of carboplatin chemotherapy. However, the number of patients with BRCA1/2-related cancers enrolled in this study is too low to draw such a conclusion.

The putative underlying modes of action of selenium as a component of cancer treatment are likely to be multifactorial. Some of the changes observed in the expression of several genes after exposure to selenious acid and chemotherapy are consistent with a selenium-related enhancement of therapeutic effect or its interference in the development of chemoresistance. Genes shown in this study to be downregulated with selenium pretreatment that may enhance sensitivity to chemotherapy and/or decrease disease aggressiveness in ovarian cancer include *RAD51AP1*, *ABCD3*, and *CCNE2*. RAD51AP1, the protein that is encoded for by the gene *RAD51AP1*, interacts with RAD51 and has been shown to have a role in homologous recombination and double-stranded DNA break repair [36]. RAD51AP1 has also been reported to be upregulated in ovarian cancer [37]. Furthermore, knockdown of RAD51 has been shown to increase sensitivity to anticancer agents that cause DNA damage and/or interfere in homologous recombination processes [38]. Another gene shown to be downregulated in this setting is *ABCD3* which encodes for a transporter protein previously shown to be expressed at higher levels in high-grade serous ovarian cancer compared with other subtypes of epithelial ovarian cancer [39]. With respect to *CCNE2*, a known oncogene in many cancers which encodes for cyclin proteins that regulate cell cycle progression, its upregulation has been associated with poor prognosis in ovarian cancer [40].

In conclusion, the results of this study support the safety of adding high-dose selenious acid to the combination of carboplatin and paclitaxel in the treatment of patients with advanced gynecologic malignancies. A phase II trial using selenious acid or sodium selenite at a dose of 5000 μg Se is being planned.

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Author contributions

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Conflicts of interest

The authors have declared that no conflict of interest exists.

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