

Dose Effect of Rhenium (I)-diselenoether as Anticancer Drug in Resistant Breast Tumor-bearing Mice After Repeated Administrations

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Abstract. *Rhenium (I)-diselenoether has shown promising antiproliferative efficacy in both in vitro and in vivo models. However, the maximal tolerated dose and dose-effect relationships have not been fully addressed for this compound. Here, we evaluated the tolerance and efficacy of three dose-levels (namely 10, 40 and 100 mg/kg) intraperitoneally administered daily over 28 days in mice bearing the resistant MDA-MB231 breast cancer cell line. The upper dose was found to be toxic and was reduced to 60 mg/kg. The 10 mg/kg dose well tolerated, whereas 40 mg/kg was associated with 10% mortality (LD₁₀). Both 10 and 40 mg/kg dosing achieved a significantly similar regression of tumor growth compared with untreated animals. This study suggests that 10 mg/kg daily is the recommended dose for rhenium (I) diselenoether.*

Rhenium(I)-diselenoether has been proposed as an anticancer agent (1-6). This compound features a central atom of rhenium bound to 3,7-diselenanonanedioic acid ligand in which the two selenium atoms secure a tight complexation of the Re, while the carboxylic group, as sodium salt, allows water solubility. This amphiphilic

complex is a hydrophilic drug, soluble in water, easy to administer and lipophilic with a good distribution in tissues after oral administration (2).

Re is a heavy transition metal (atomic number 75, atomic mass 186.21 g/mol), with the widest range of oxidation states of any element (-3, -1, +1, +2, +3, +4, +5, +6 +7), providing it with unique properties. It was demonstrated with Re-diselenoether drug that Re formed DNA adducts with one or two guanine bases (3), like cisplatin, but with an octahedral configuration and not a square-planar one. The uptake of Re in the nucleus of malignant cells has also been demonstrated after exposure to Re-diselenoether complex (2). Other Re-based drugs have also shown a high activity against a variety of tumor cell lines, with a good selectivity for cancer cells (7, 8). One common mechanism of action could be related to the binding of Re with guanine and adenine bases of DNA (9-12). In contrast with cisplatin, the binding with the DNA bases is reversible (13). Re also binds with proteins (14, 15). However, other properties of Re compounds have been identified, like the inhibition of some cysteine proteases (16). We hypothesize that the Re atom could be used either for oxidation or reduction of cell components due to its great number of oxidation states. Re cluster compounds were screened for their biological activities as antioxidants (17) and proposed to protect erythrocytes from hemolytic anemia (18). These Re compounds affected the peroxidation level, the activity of superoxide dismutase, the antioxidant factor and the index of resistance of erythrocytes to hemolysis as a function of the concentration range in the pre-incubation medium of erythrocytes (19, 20). Due to these antioxidant properties, Re

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cluster compounds have been proposed for use in avoiding cisplatin-induced anemia (21). This was demonstrated in animal models with tumor-bearing rats, as was a synergism between cisplatin and Re (III) diadamantate (22) and with dichlorotetra- μ -isobutyratodirhenium (III) complex (23) and the cluster Re compound with gamma-aminobutyric acid ligand (24). This synergism was however not observed with the Re (I)-diselenoether complex (4, 3), but the schedule of treatments were different.

Selenium (Se) provides additional biological properties. A non-metal, Se has an atomic number of 34 and atomic mass of 78.96 g/mol. This element also has several states of oxidation (-2, 0, +4, +6). Se is found in selenoproteins (glutathione peroxidases, thioredoxin reductases, selenoproteins P and W, iododeionidase reductase, selenophosphate synthetase) incorporated in the form of selenocysteines (25-30). Selenocysteine is metabolized into methylselenol ($\text{CH}_3\text{-SeH}$), which possesses strong nucleophilicity (31) and stronger potential for inhibiting cell proliferation/survival signals in colon cancer-derived HCT-116 cells when compared to that in non-cancerous colon NCM460 cells (32). Anti-angiogenic properties of Se compounds have been related to the methylselenol derivative (33). Selenol derivatives act as reducing agents to give selenic acid derivatives, which are again reduced by enzymes containing thiols. The oxidation of cysteine, especially its thiol or thiolate groups, has been described as a major event involved in modifying the function of signaling proteins and cysteine redox post-translational modifications affect protein structure and function (34, 35). On the other hand, organo-Se compounds modulate extracellular redox by induction of extracellular cysteine and cell-surface thioredoxin reductase (36). The administration of Se drugs may induce either oxidant or antioxidant effects in the cells (37-39) by oxidation or reduction of thiol-containing proteins, depending on the influence of neighboring groups and redox potential (31). Se is essential for antioxidant activity but may have pro-oxidant properties at higher concentrations. This was clearly shown with Se-methionine in human immortalized keratinocytes by Hazane-Puch *et al.* (40). These cells were exposed for 144 h to Se-methionine and then either to UVA radiation or not. The 10 μM dose was non-toxic, protecting the cells from UVA-induced cell death, while the 100 μM dose was toxic, causing caspase-3-dependent apoptosis. The non-toxic dose was antioxidant, with an increase in selenoprotein glutathione peroxidase 1 (GPX1) activity and an increase in selenoprotein-1 transcript expression. The toxic dose, which did not protect the cells from UVA damage but inhibited cell proliferation through S-G₂ blockage, a decrease in mitochondrial transmembrane potential and a DNA fragmentation, was oxidant with production of hydrogen peroxide. Another study demonstrated that Se yeast selectively inhibited the growth of breast cancer cell lines and not of non-tumorigenic human mammary cells (41). In contrast,

methylselenic acid also inhibited the growth of normal cell lines. It also had greater inhibitory effects, with a higher production of reactive oxygen species (ROS) levels than Se yeast at doses of 1.3 or 9.5 and 19 μM Se, but with a loss of selectivity. The authors proposed the existence of differential redox potential between normal and cancer cells as previously noted by Trachootam *et al.* (42). Selenoprotein antioxidant protection in non tumor cells could explain these results.

Thus, the main mechanism of action of Re and Se on malignant cells could be by interfering with their redox system.

Re-diselenoether was already shown to be active against breast malignant cells in culture and the inhibitory effect persisted after the interruption of the exposure to the drug (3). A dose of 10 μM Re-diselenoether did not inhibit the growth of human hormone-independent breast cancer cell line (MDA-MB231) after an exposure of 48 h, but a dose of 40 μM completely inhibited their growth (3). An experimental animal study in MDA-MB231 tumor-bearing mice showed that an oral daily administration of 10 mg/kg/24 h Re-diselenoether for 4 weeks was very effective and not toxic to the mice (3).

Here we report a new experiment with the same model of MDA-MB231 transplantation in nude mice, using three doses of Re-diselenoether, in order to determine the relationship between dose and the efficacy, as well as toxicity, after repeated intraperitoneal (*i.p.*) injections.

Materials and Methods

This experiment was performed at the Laboratory of Toxicokinetics and Pharmacokinetics at the Faculty of Pharmacy of Marseille University. The protocol was submitted to both the French Ministry of Health and Aix Marseille University local Ethics Committee for approval (number 02151.01).

Triple-negative breast cancer MDA-MB231 cells (Caliper LS, Villebon sur Yvette, France), stably transfected with the luciferase gene (Luc+) to allow the imaging of the primary tumors by bioluminescence, were orthotopically implanted into the mammary gland (fat pad) in nude mice. They were orthotopically inoculated at the dose of 200.000 cells per mouse in 50 six-week-old female Swiss nude mice (Charles River, Ecully, France) with the use of 60% matrigel. Grafting rate was 95%, assessed by a first imaging by bioluminescence at day 6 after the inoculation of the tumor cells. From the mice with positive imaging, 40 mice were randomized into four groups of 10 mice: a control group receiving a saline vehicle and three groups treated by Re (I)-diselenoether complex (Galien Institute, Châtenay-Malabry, France). The treatments were administered to the MDA-M231 tumor bearing-mice, daily. Three doses were initially investigated, 10, 40 and 100 mg/kg and treatments began 9 days after tumor grafting. Initial administration was initially expected to be per os after supplementing food with Re (I)-diselenoether, but observations suggested that the intake could be erratic by this means and it was decided to stop the oral administration at day 16 and to change to *i.p.* injections after a wash-out period of 4 days. The treatments were then continued as *i.p.* injections from day 20 until day 44 for all groups.

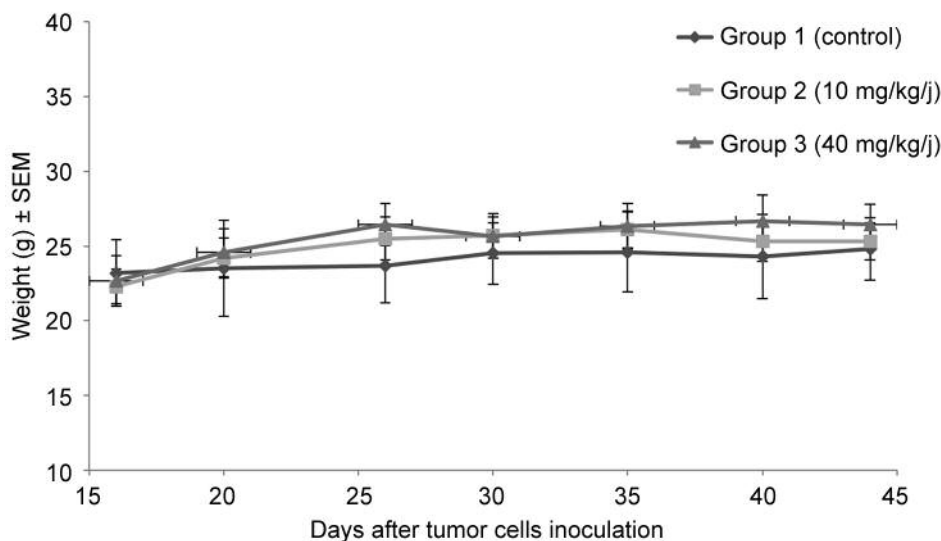


Figure 1. Evolution of mouse weight (mean \pm SEM) after administration of Re (I) diselenoether (10 and 40 mg/kg/d) versus controls. No statistically significant difference was found in carcass weight at study conclusion (one-way Anova, $p=0.108$).

The evaluation of the tumor mass was based on bioluminescence measurements using 2D imaging twice a week. For that purpose, 150 mg/kg luciferin was injected into the mice 12 minutes prior to image acquisition, resulting in a luciferase-induced oxidation of luciferin into oxyluciferin. This oxidation was accompanied by the emission of photons at 560 nm (visible light), which were quantized. The IVIS[®] Spectrum (Perkin Elmer) high-throughput 2D optical imaging system was used to quantitatively evaluate the tumor mass. The evaluation of the toxicity was measured by the weight of the animals, twice a week. Deaths were also reported.

Statistics. Statistical evaluation of the antitumor effect was assessed by ANOVA test (one-way ANOVA on the ranks), using Sigma Stat, USA.

Results

Toxicity. Signs of animal distress were rapidly observed in the group treated with 100 mg/kg as early as the day after the first *i.p.* injection. Despite stopping administration, six out of the 10 animals had to be sacrificed following standard procedures. The four remaining animals were then treated at an intermediary dose of 60 mg/kg with no further death until the end of the experiment. The 60-mg/kg dose can be considered as the maximum tolerated dose (MTD) for 4-week daily *i.p.* administration. After the protocol amendment, a complementary dose-finding study performed on a satellite group of mice not included in the treatment groups confirmed that 75 mg/kg was the 50% lethal dose (LD_{50}) dose after repeated *i.p.* injections (data not shown). Despite no clinical or preclinical sign of distress, one death occurred in the group treated with 40 mg/kg, 6 days after the first *i.p.* injection, thus suggesting this could be the LD_{10}

level. The 10 mg/kg-treated group showed no signs of toxicity and this may represent the no-adversed toxicity level. Monitoring of body weight during the study showed no significant difference in carcass weight between the treated and control mice (Figure 1) at study conclusion (one-way ANOVA, $p=0.108$). However, on day 26, mice from the control group had mean weight significantly smaller than the treatment groups ($p=0.012$).

Efficacy. Because of the change in dosing and reduction of the sample size impacting on statistical power, the group treated with 100 (60) mg/kg was not included in the efficacy study. The experimental data obtained by 2D imaging showed an early statistically significant decrease of the tumor volumes in treated mice, with a 43% reduction for mice treated at 10 mg/kg at day 26 ($p<0.001$) versus controls and a 72% reduction for mice treated at 40 mg/kg versus controls ($p<0.001$) during the early phase of tumor growth, while tumors were in exponential growth (Figure 2). The data indicate the persistence of a statistically significant tumor growth inhibition at both 10 and 40 mg/kg ($p<0.05$) versus controls throughout the experiment. The lack of significant difference between these two doses was evidenced from the growth curves at both dose levels seeming to merge from day 30 until the end of the experiment.

In this study, few metastases were observed: 2/10 in the control group; 1/10 in mice treated at the dose of 10 mg/kg; and 1/9 in mice treated at the dose of 40 mg/kg. It was not possible to perform a statistical test on the incidence of mice presenting with metastasis.

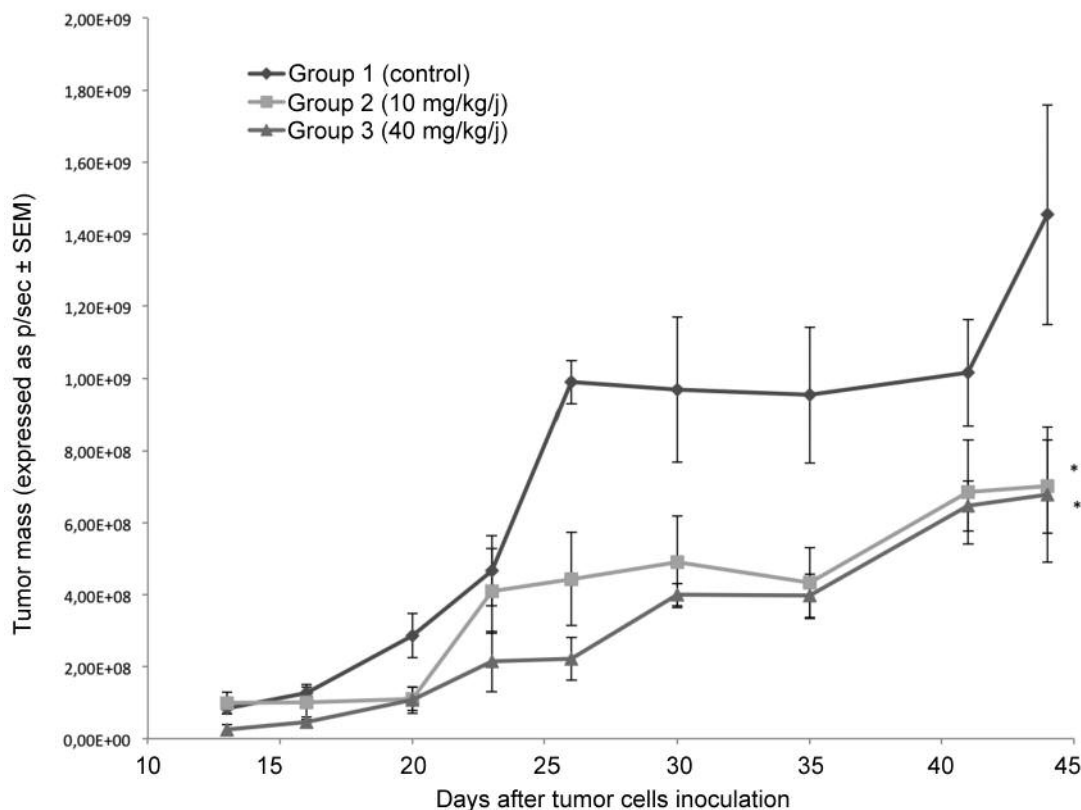


Figure 2. Evolution of the tumor mass as evaluated by 2D bioluminescence (photons/second) after daily *i.p.* administration of Re (I)-diselenoether (10 and 40 mg/kg/d) versus controls. Analysis of the curves by ANOVA tests (one-way ANOVA with Newman Keuls multiple comparison testing) showed that tumor masses were statistically different ($p < 0.05$) in treated groups 2 (10 mg/kg) and 3 (40 mg/kg) versus control group 1, but not between groups 2 and 3. *Statistically different from the control group.

Discussion

In a previous published study, Re-diselenoether complex induced remarkable antitumor activity with nearly complete regression of the tumors at the site of the primary tumors and a statistically significant decrease in the number of pulmonary metastases after a daily oral dose of 10 mg/kg for 4 weeks (3). The aim of this study was to investigate whether increasing the dosing of Re-diselenoether complex would further improve its antiproliferative efficacy. We confirm here the antitumor activity of the Re-diselenoether at the same daily dose of 10 mg/kg for 4 weeks after *i.p.* injection. In this new experiment, matrigel was used to improve the transplantation rate of the primary tumors, but few metastases were noted. It is known that matrigel increases the aggressiveness of transplanted tumors (43) and even the amount of matrigel has a great influence on tumor growth. Matrigel is a basement membrane-like extracellular matrix extract, mainly composed of laminin, collagen IV, heparan sulfate proteoglycan, but also of various growth factors such as fibroblast growth factor,

transforming growth factor beta, epidermal growth factors and others. These components greatly accelerate tumor growth. The use of matrigel can therefore explain why the tumor growth decreased but was not inhibited as it was in the previously published study. Only few metastases were found in this study, probably because of the strain (Swiss nude) of the mice which are not totally immune-compromised.

One important result of this study is the lack of benefit when increasing the dose from 10 to 40 mg/kg. This observation suggests that there was a weak dose–efficacy relationship, at least above the 10 mg/kg dose level. In this respect, treating animals at the MTD (*i.e.* 40 mg/kg) has little relevance. In addition, 75 mg/kg was identified as the LD₅₀ level. In a previous study, three doses of Re-diselenoether were tested in combination with cisplatin and a gallium compound (4): increasing the Re-diselenoether dose from 10 to 50 mg/kg, as an oral administration for 3 weeks, did not improve the efficacy but greatly increased the toxicity. In 1998, it was demonstrated that the protective effects of Se compounds against UV toxicity in keratinocytes and melanocytes were observed at low

concentrations, between 1 and 200 nM, and no protective effects were observed with concentrations higher than 1 μ M (44). These effects were related to the detoxification of free radicals by Se-induced production of glutathione peroxidases. One main objective now will be to investigate if lower doses might also be effective. The toxicity and bioavailability of oral doses will also have to be compared with those resulting from *i.p.* injections. The toxicity may be completely different according to the mode of administration, as well as the metabolism and bioavailability.

Doses may have to be adjusted according to parameters other than the body weight. It is expected that Re-diselenoether could be considered as a modulator of the redox potential. Cancer cells, particularly breast cancer cells, have a pro-oxidant status, resulting from the high production of free radicals (45). Oxidative stress reflects an imbalance between the production of free radicals and anti-oxidant defense. Free radicals include ROS and reactive nitrogen species. Anticancer drugs usually enhance this pro-oxidant status as the high production of free radicals will kill the cancer cells. However, this will also induce toxic effects. This is not the case with the use of trastuzumab, a monoclonal antibody effective against breast cancer overexpressing human epidermal growth factor receptor 2 (HER2), which reduced the redox potential of these cells (46). Studies showed that the molecular subtypes of cancer cells can be determined by their redox status (46). The distinction between luminal type cancer, cells expressing HER2 and triple-negative cancer cells was reportedly related not only to the oxidative status, but also to the markers of inflammation in another publication (47), with high levels of lipidic peroxidation and of nitric oxide for triple-negative cancer. The pro-oxidant status is more pronounced when the cancer stage is more advanced (48) and under the effects of chemotherapeutic agents such as doxorubicin or paclitaxel (49). A decrease of the content of antioxidant enzymes in cancer cells reduces the efficacy of chemotherapy with carboplatin/paclitaxel (50). A relationship was observed between the degree of resistance to cytotoxic drug and the oxidative system in a cisplatin-resistant prostate cancer model (51). All these studies show the importance of investigating oxidative stress in patients with cancer. It could then be proposed to adapt the doses of anticancer drugs according to the redox status. Pro-oxidant doses, expected with the highest doses, will be toxic and the damage induced by free radicals are well known. Antioxidant doses, at lower doses, may actually favor tumor growth if they are not high enough to inhibit the growth of the cancer cells. ROS within cells act as secondary messengers in intracellular signaling cascades, which induce and maintain the oncogenic phenotype of cancer cells, in particular, by ROS activation of activator protein-1 and nuclear factor kappa B signal transduction pathways, which in turn leads to the

transcription of genes involved in cell growth-regulatory pathways (52, 53). Normalizing the level of production of ROS by Re-diselenoether may then reduce these effects.

Plasma Se, copper and zinc may be used to investigate the antioxidant status. These markers could then be useful to define the dose of Re-diselenoether to be administered to patients with cancer. The doses will obviously also be determined by toxicological studies. There are few data on Re toxicity but it seems to be low (54). Se toxicity mainly depends on the chemical form and organic Se compound is less toxic than inorganic salts (55). Most clinical trials with Se compounds are performed with doses of 200 μ g/24 h of Se element, but failed to demonstrate an effect in the prevention of cancer, except in individuals with low plasma Se levels at the beginning of the treatment and this was the case in the Nutritional Prevention of Cancer trial (56). The reduction of the risk of cancer was significantly observed only in those with plasma Se levels lower than 106 μ g/l before the beginning of the treatment with 200 μ g/24 h yeast enriched with Se. In contrast, in those with plasma Se levels higher than 121 μ g/l before treatments, the risk of cancer was significantly increased. The percentage of Se in Re-diselenoether is 23.65%. In 10 mg/kg of Re-diselenoether is therefore 2.4 g of Se. The known toxicity of Se in humans is an additional reason for preferentially investigating doses lower than 10 mg/kg Re-diselenoether, as suggested by our experiment. Plasma Se levels may be also very useful for monitoring toxicity. Plasma Se concentrations may also reflect the effect of the drug on angiogenesis, as it was reported that a decrease in plasma Se levels in breast tumor-bearing mice was associated with a decrease in glutathione peroxidase activity in plasma and was correlated with higher plasma vascular endothelial growth factor and malondialdehyde concentrations (57). The plasma Se concentration could therefore be a simple marker for determining which patients will benefit from Re-diselenoether treatment, monitoring the dose and for controlling efficacy.

Conclusion

A daily dose of 10 mg/kg of Re-diselenoether can be considered safe for Swiss nude mice, by oral or by *i.p.* route for a 4-week treatment period. It allowed a significant antitumor effect and the recommended dose previously published (3) is confirmed. After *i.p.* injections, higher doses will not increase the efficacy but the toxicity. Doses lower than 10 mg/kg/24 h need be tested as they may be as effective, including as part of metronomic scheduling. The schedule of treatment could take into account the redox status noted in patients with cancer. For this, treatment could be monitored by markers of the oxidative system and, among them, the plasma Se concentration. The model of MDA-MB231 transplanted tumor corresponds to the treatment of patients with metastatic non-hormono-sensitive breast cancer, especially triple-negative

cancer, but the treatment could perhaps also be targeted by the redox status level in other types of cancer.

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