Therapeutic Effects of Organic Germanium

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Abstract — Germanium is present in all living plant and animal matter in micro-trace quantities. Its therapeutic attributes include immuno-enhancement, oxygen enrichment, free radical scavenging, analgesia and heavy metal detoxification. Toxicological studies document Germanium’s rapid absorption and elimination from the body, and its safety. Clinical trials and use in private practices for more than a decade have demonstrated Germanium’s efficacy in treating a wide range of serious afflictions, including cancer, arthritis and senile osteoporosis. Germanium’s anti-viral and immunological properties, including the induction of interferon, macrophages, T-suppressor cells and augmentation of natural killer cell activity, suggest its possible efficacy in treating and/or preventing AIDS.

Introduction

Organic Germanium compounds have been used therapeutically within research and clinical practices for almost two decades, yet Germanium is not presently listed as a nutritional trace element, nor are its health-enhancing properties generally known. This report reviews the literature, with particular emphasis upon organic germanium’s therapeutic effects in cancer, which appear to be mediated by immuno-modulation, features which suggest its possible role in the treatment and/or prevention of AIDS.

Historical background, general features of germanium

The element Germanium, atomic number 32, atomic weight 72.60, density 5.36, had been predicted by Mendeleev in his periodic table, but it was not until 1886, that a German chemist, Clemens Winkler, isolated this trace element and named it Germanium. In 1948, it came to be used for its semiconductor properties by U.S. Bell Laboratories, and played a major role in the development of the semiconductor electronics industry. Also around this time, a Japanese scientist Kazuhiko Asai, isolated Germanium from coal, and subsequently demonstrated the existence, albeit in trace amounts, of Germanium in a wide spectrum of plants (1).

In 1967, Schroeder and Balassa (56) documented the presence of Germanium in all biomaterial, plant and animal. Traces of Germanium are found in almost all nutrients, animal and vegetable, with the highest content observed in beans (4.67 ppm), oysters (2 ppm), tunny (2.3 ppm) and dry fish (3.63 ppm). The average daily human intake ranges from 0.9–3.2 mg., on
high protein, low carbohydrate and ovo-vegetarian diets, respectively. Asai had obtained higher Germanium amounts in some plants used in ancient Chinese medicine, such as Ginseng and Shelf Fungus; however, Mino et al. (42), using highly sensitive atomic absorption spectrophotometric technology, found ultra-trace amounts of Germanium in these herbs (below 5 ppb). The highest content was found in green tea (9 ppb).

Germanium thus joins a class of ultra-trace elements, average daily intake by man being less than 1 ppm. The criterion that the essentiality of an element must be proved by a deficiency disease resulting from its withdrawal, is now giving way to the view that the metabolism of silicon and germanium in living systems has a role in limiting and regulating functions in the "carbon metabolism", and can change and influence the living cell over longer periods (68). However, we still know very little about germanium metabolism in living plants and animals.

**Properties of organo-germanium compounds**

Germanium belongs to the fourth group of the periodic table with carbon, silicon, tin and lead. It is intermediate in its chemical properties — oxidation states, affinity for electropositive elements, bond angles with oxygen and basicity of nitrogen compounds — between carbon and silicon. Its atomic number is 32, atomic weight 72.60, specific gravity 5.33 g/cm³, and a melting point of 937.

GE-132, carboxyethyl germanium sesquioxide was originally synthesized by Asai in Japan in 1967, by the hydrolysis of trihalogenopropionic acid, followed by the addition of trihalogenogermane to acrylic acid. This organic germanium compound forms a cubic structure with three negative oxygen ions at the base of a cubic triangle. Two cubic triangles whose bases face each other form one molecule. The three-dimensional array composed of oxygen atoms linked to germanium form a layer network with no definite melting point, which is soluble in water at 1.19 mg/100 ml at 31°C. Its solubility in aqueous solution increases at pH = 7.4. Ge-132 is in a trihydroxyl form in solution.

Sanumgerman, chemical name lactate-citrate-germanate, exists in a ‘quasi-crystalline’ structure, and is soluble in aqueous solution. This compound is the registered trademark of Sanum-Kehlbeck, West Germany.

Spirogermanium, synthesized by Rice et al. (50), is an organic germanium compound being evaluated by Smith, Kline & French Laboratories. It is a member of a class of azaspirane compounds containing a N linked to dimethylaminopropyl substituent.

**Safety of organo-germanium compounds in the body**

Absorption, distribution and elimination of germanium. Organic Germanium compounds are rapidly absorbed and eliminated from the body. In pharmacokinetic C14-labelled studies of absorption, excretion, distribution and metabolism of Ge-132 (43) Ge-132 administered orally, was absorbed about 30%, distributed evenly, with almost no residual concentration after twelve hours. It was excreted, unchanged metabolically, in the urine in 24 hours. In studies performed by Lekim & Kehlbeck (35), after one hour, 50% of the Ge was shown to be in the gastrointestinal tract, which was reduced to only 5% after twelve hours. Germanium is resorbed via the vena portae. One hour after administration, 50% of Germanium is in the vena portae; after eight hours, this figure rises to 85%, and by twelve hours, it is quasi complexed. Plasma levels reach a maximum two hours after administration. In eight hours, Germanium is reduced by 80% of the maximum.

The rate of elimination is also quite high. Germanium is linearly eliminated at approximately 8% of the dose per hour during the first eight hours. Ge is completely eliminated after three days, mainly via the kidneys (85%). Germanium is ubiquitously distributed in all organs — there are no specific target organs, and no differences detected between sexes. Germanium is soluble in the interstitial fluids, and is not protein-bound. Germanium does not accumulate in any organ — no Germanium can be found in animals one week after their removal from treatment.

A single report of Germanium accumulation exists (46). A patient taking 600 mg. of GeO2 daily as an elixir for 18 months died of acute renal failure. The relevance of Ge accumulation to the renal failure remains to be clarified.

**Toxicity studies.** Sanumgerman was investigated for acute and chronic toxicity in mice (CWF/Bog strain) and Wistar rats (52). The LD50 was 275 mg/kg/24 hours, and 250 mg/kg/48 hours. Taken orally, SG was nontoxic up to 3400 mg/kg bodyweight. In studies of Sanumgerman for chronic toxicity, after 24 weeks, 0–50 mg/kg/day.
no symptoms of disease were detected. Compared to the control group the general condition, appearance, behaviour and motor activity were all normal. Appetites were equal, body weight similar and biochemical assays of blood serum showed no abnormalities. There were no abnormalities in hemoglobin, red cells, leukocytes and platelets. The weight of internal organs was similar; there were no pathological changes or differences in macroscopic or microscopic appearance of internal organs. Respiration was unchanged. In orally administered SG, there was no effect on blood pressure; with intravenously administered SG, there was a decrease in the arterial blood pressure of 20–40 mg for 60–100 sec. In the isolated heart determination, there was an increased coronary outflow, but the amplitude and rate were unchanged. In the isolated intestine test, there was no effect on tonus and contractility. In summary, Sanumgerman caused no toxic effects in mice and rats that could be detected by biochemical and morphological studies after prolonged administration.

For Spirogermanium the LD10 in mice (strain CDF1) was determined to be 105–147 mg/m². The highest nontoxic dose in beagle dogs was 12.5 mg/m², the lowest toxic dose was 25 mg/m² and the lethal dose was 800 mg/m² (54). Toxic effects included focal necrosis of lymph nodes, inflammation and necrosis of the gastrointestinal mucosa and abnormal liver function. There was no evidence of bone marrow toxicity. Following acute, subacute chronic toxicity and teratogenicity studies on mice, rats and rabbits, and a chronic study and reproductive study in beagle dogs, Ge-132 was found to be highly safe (43). The acute toxicology findings were as follows:

<table>
<thead>
<tr>
<th>LD50 Sub Cut.</th>
<th>Oral (mg/kg)</th>
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<tr>
<td>Mice (ddN)</td>
<td>6300, 4500, 1800</td>
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<tr>
<td>Mice (ddY) H2O-M</td>
<td>12500, 7550, 2110</td>
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<tr>
<td>Mice (ddY) H2O-F</td>
<td>11400, 8050, 2230</td>
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<tr>
<td>Rats (Wist) H2O-M</td>
<td>11700, &gt;16589, 3500</td>
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<tr>
<td>Rats (Wist) H2O-F</td>
<td>11000, &gt;16589, 3200</td>
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Teratogenic studies. Teratogenic studies of an older formulation of Sanumgerman in rats was performed (11) according to the advises of WHO and the Canadian Ministry of Health. Malformations were found in fetuses of pregnant rats. These were mainly skeleton malformations —

Central nervous studies. The effects of Sanumgerman on central nervous activity in mice were investigated (27, 28). The results indicated that Sanumgerman exerts a positive inhibiting effect (drive-depressant with hyperexcitability, antidepressive) on the central nervous system of the mouse. The mechanism seems to be connected with a depression of the central catecholaminergic and a stimulation of the central serotonergic neurons. These results explain, in part, the mechanism of the transient side-effects observed with Spirogermanium administration (54, 66) — slight lethargy, drowsiness, ataxia, defective vision, paresthesia, with an absence of nausea.

Oncostatic properties of germanium compounds

Cytological evidence. The Allium Test (38) uses changes in the mitotic characteristics of plant meristematic cells, treated with potential cytostatic agents, as a measure of the oncostatic activity of these compounds. Although positive results in the Allium test cannot guarantee a compound's oncostatic activity, all known potent cytostatics show an evident inhibitory or cytotoxic effect in the Allium test, making this a useful tool in prescreening potential cytostatic agents (29). Cytological preparations of Sanumgerman-treated material were analyzed by the Allium procedure (19). The results — lowering of mitotic index values, and changes in other mitotic parameters — indicate that Sanumgerman can be considered as a mitotically active compound.

In vitro. cytotoxicity studies of Spirogermanium with Hela cells (54) and Chinese hamster cells (71) demonstrated highly significant inhibition of DNA, RNA and protein synthesis at micromolar concentrations, and Hill et al. (23) documented the cytotoxic activity of Spirogermanium in NIL 8 hamster cells and a wide range of human cancer lines. Synthesized germanium nucleosides inhibited HSV-1 replication in vitro. blocked 2-deoxyuridine incorpo-
ration into DNA of hepatoma 22A cells and thymidine incorporation into DNA of cancer ovarian cells (41). Various synergistic combinations of Spirogermanium with other drugs are being investigated in vitro (22).

Animal studies. The antitumour activity of Sanumgerman was tested on transplantable neoplasms in mice, according to methods and protocols of the National Cancer Institute, U.S.A. In this study Sanumgerman exhibited moderate antitumour activity against Sarcoma 180, Melanoma B16 and Lewis lung carcinoma (36).

In another study of the effect of Sanumgerman on tumour genesis in mice (5), SG significantly lowered the incidence of tumours from 50% after 4 months in the control group, to 20% after 4 months in the SG-treated group. These results were essentially identical to those reproduced by Lekim & Kehlbeck, (35) strongly indicating a protective influence of SG against fibrosarcoma. In addition, SG prolonged the survival time of mice with carcinoma of the colon (37).

In further studies of Sanumgerman's antineoplastic activity in mice, Sanumgerman showed positive results against Carcinoma of the colon C-26, Madison's lung cancer and Myeloma MP-26a (36, 37).

In studies with rats, Spirogermanium was shown to be effective against Walker 256 Carcinosarcoma, increasing the lifespan by 500%, and resulting in a 50% 45-day survival rate (69). Ge-132 exhibited significant antitumour activity against a wide spectrum of tumours, including Walker 256, Ehrlich Ascites, BC47, Lewis lung, IMC carcinoma, AH 66, AH 43, MH 134 (43, 60, 34). The anti-ascites tumour (syngeneic or allogeneic) activity of Ge-132 appears to be expressed by activation of immune mechanisms, including macrophages and/or T Lymphocytes (53, 58, 59, 61, 62). The augmentation of natural killer (NK) activity and activation of macrophages in mice after oral administration of Ge-132 are mediated by Ge-induced interferon (IFN) (2).

In one study, the administration of IFN-containing sera obtained from Ge-132-treated mice, or the passive transfer of macrophages from Ge-treated mice to mice bearing ascites tumours, resulted in the inhibition of tumour growth (63). The mechanism of Ge-132's antitumour activity was elucidated as follows: 1) Ge-132 stimulated T-cells to produce circulating lymphokines(s); 2) activated macrophages were generated from resting macrophages by these lymphokine(s); 3) the transplanted tumours were inhibited by these macrophages. Studies using combination immunochemotherapy with Ge-132 and 5-fluorouracil demonstrated inhibition of tumour growth, enhanced anti-metastatic effect, prolonged survival time and recovery of loss of delayed type hypersensitivity and body weight in tumour-bearing mice (29).

Human clinical trials
Ge-132 In 1978, a nation-wide organization in Japan was inaugurated to study germanium within research and medical institutions. Numerous controlled studies on Ge-132's effect on cancer have been carried out (17, 43).

A phase I study with Ge-132 was performed with 23 healthy volunteers of both sexes (17). No significant hematological or biochemical changes were found, except for soft stool appearing in several cases. The maximum tolerated dose was between 50–100 mg/kg/day. The absorption and elimination pattern was similar to that in rats. Ge-132 was also observed to induce interferon in humans in a dose-dependent manner.

Clinical trials on lung cancer revealed a statistically significant effect of Ge-132 upon life prolongation, tumour regression in some cases and overall improvement in performance status and immunological parameters (43).

A double-blind controlled study for unresectable lung cancer was commenced in 1980 with Ge-132. The patients were divided into 4 classes, Adenocarcinoma, Squamous, Small and Large Cell, according to the histological type of cancer. The treatments, over 3 months, consisted either of chemotherapy + Ge-132 or chemotherapy + placebo by means of double blind. Effects were evaluated by means of an X-ray assessment committee. Although the study was still ongoing at the time of writing, interim results were disclosed (43). In respect to tumour response, in stage IV patients, there was a significant difference between the placebo and Ge-132, that is, the proportion of partial and complete responses was significantly higher in Ge-132-treated subjects. The survival of Ge-132 patients tended to be longer than in placebo treatments; however the difference was not significant.

Sanumgerman. A phase 1 clinical study of Sanumgerman's effectiveness against ovarian malignancy was conducted (51) with 6 women,
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aged 44–64, post-operative for malignant tumours of ovaries and uterus. The well-being of all these patients improved considerably, and pain alleviation was considerable. In five out of six patients, no exudate formation occurred in the abdominal or inner pelvic cavity; in the remaining patient, only a little exudate was observed. No toxic or side effects were observed.

Detailed patient case histories provide impressive yet anecdotal evidence of Sanumgerman’s therapeutic effects in cancer (31, 48, 51, 72).

**Spirogermanium.** A Phase I clinical trial comprising 35 patients with varying types of cancer, was conducted with Spirogermanium to define a tolerated dose and determine antitumour activity without myelosuppression (54, 70). All had been previously treated with chemotherapy to which their tumours were resistant. The Spirogermanium was administered by intravenous injection, with an initial dose of 8 mg/m, ranging up to 32 mg/m. Several of the patients experienced mild and transient neurologic toxic side effects, such as dizziness, lethargy that lasted for a few minutes to several hours. All signs of neurotoxicity were completely resolved. There was no evidence of cumulative toxicity to the nervous system. There was no evidence of acute or cumulative toxicity, no evidence of bone marrow depression. One patient experienced pain at the injection site and nausea. In this trial one patient showed a partial response in the palpable lymph nodes for 2 months. (Partial response = <50% reduction in the sum of the tumour area). The conclusions drawn from this trial were that Spirogermanium is not toxic to bone marrow, there is no evidence of myelosuppression and no cumulative hematologic toxicity (55).

A Phase II trial for 18 patients with lymphoproliferative disease — 14 non Hodgkin’s lymphoma, and 4 with Hodgkin’s disease was conducted (54). The results — out of 17 patients (one patient withdrew from the study after the first treatment for reasons unrelated to drug toxicity), 5 (30%) demonstrated an objective response, including 2 complete responses. In this study no hematologic toxicity was demonstrated. The conclusions reached were that due to its lack of bone marrow toxicity, Spirogermanium represents a therapeutic option as a single agent or in combination with myelosuppressive drugs for the treatment of lymphoma.

Smith Kline & French Laboratories and other oncology groups have conducted several clinical trials with Spirogermanium as an anticancer therapeutic agent (4, 8, 66). In several Phase II trials with Spirogermanium, there was no hematologic, renal or hepatic toxicity, mild neurotoxicity, limited activity against malignant melanoma (13) and no demonstrated response in heavily pretreated patients with advanced malignant neoplasms and various cancers (5, 6, 9, 12, 14, 25, 33, 49, 56, 65, 66).

**Immunological effects of organic germanium compounds**

*Interferon induction, macrophage, T-cell & NK augmentation.* Organic Germanium compounds demonstrate significant immuno-modulating activities. These include interferon (IFN) induction, activation of macrophages, augmentation of natural killer (NK) cell activity and restoration of impaired immunoresponse (2, 53). As detailed above (see Animal Studies), the anti-tumour activity of Ge-132 appears to be mediated by the orchestrated stimulus and augmentation of various components of the immune system, mainly macrophages and T-suppressor cells (3, 53, 58, 59, 62, 63) and NK activity augmentation and macrophage activation appear to be mediated by IFN induced by Ge-132 (2). Administration of Ge-132 to healthy volunteers was correlated by IFN induction and an augmentation of natural killer (NK) cells (61). In addition to its cell-mediated immunity effects, Ge-132 augments humoral immunity in aged mice with decreased immune response (44). Ge-132 significantly increases plaque-forming cells (PFC) in aged mice and is considered to restore to some extent the impaired immunoresponses in aged mice.

Sanumgerman was shown, in vivo, to stimulate the cytolytic activity of natural killer (NK) cells by 27% and 33% in mice (18). There was a parallel elongation of time of the effect. The cytolytic value of the cells approached normal only on the 8th day. SG seems to stimulate the mechanism of immunological surveillance with NK cells. It is conceivable, however, that the increase of cytolytic activity of NK cells is secondary and takes place through interferon induction.

**Leukemia.** The influence of Sanumgerman (SG) upon experimentally induced leukemia was investigated in mice (18). The two higher doses of SG administered daily to AKR and DBA strain mice produced a statistically significant
prolongation of survival, 168 & 180 days, compared to the control group’s 127 days.

**Effects of germanium treatment upon other diseases**

**Senile osteoporosis.** Clinical investigations have demonstrated the preventive and therapeutic effect of Ge-132 upon senile osteoporosis — (43). In a 12 month study with senile osteoporosis patients, the bone mass of control subjects tended to decrease, while those receiving Ge-132 demonstrated slightly increasing tendencies, with significant differences seen 1 to 3 months after initial treatment. Parathyroid hormone (PTH) levels are negatively correlated with bone mass, and Ge-132 significantly decreased PTH serum levels, thus pointing to the apparent mechanism of Germanium’s therapeutic’s effect on osteoporosis.

**Arthritis.** Oral administration of Spirogermanium to rats resulted in the generation of radiation-resistant (2000 Rad) T suppressor cells, which inhibited the proliferative response of normal spleen cells to Concanavalin A (3). Spirogermanium decreased hindleg inflammatory lesions of adjuvant arthritic rats when administered orally before or after the development of the arthritic lesions (10). The lesions remained significantly suppressed for at least 2 weeks post-drug treatment. Spirogermanium treatment normalized some arthritic response parameters, such as interleukin (IL)-1 production by adherent spleen cells.

**Malaria.** Spirogermanium demonstrated significant in vitro activity against chloroquine-resistant (FCB, FTA, FVO) and sensitive (FSL, FUI, FH) strains of Plasmodium falciparum. (45). Inhibition of growth and maturation of parasites occurred after 36 hours’ exposure to concentrations ranging from 2.48 to 9.9 nm/ml.

**Analgesia.** Ge-132 demonstrated enhancement of morphine analgesia administered both orally and by intraperitoneal injection (20). Twenty-eight species of GE-132 derivatives were examined for inhibitory effects on enkephalin-degrading enzymes from monkey brain, the longitudinal muscle layer of bovine small intestine and human cerebrospinal fluid (CSF) (32). A series of these derivatives strongly inhibited these purified enzymes, particularly from the longitudinal muscle layer, human CSF, and monkey brain.

**Mechanisms of action**

Organic Germanium compounds have been successful in treating a multiplicity of illnesses. The elucidation of germanium’s immunomodulatory activities have started to shed light on these mechanics. But, clearly, there is something intrinsically unique to the element Germanium that facilitates its wide-ranging therapeutic effects.

**Electronic structure.** The electronic structure of organic germanium compounds may be a factor in its therapeutic properties. Germanium has 32 electrons, 4 of which are in the outer shell. These 4 outer shell electrons are negative charge carriers, and if approached by a foreign substance, one will be ejected out of its orbit. This is known as the positive-hole effect in electronics, because when one of these electrons is ejected, a positive-charge hole is created, and the three remaining electrons each seize electrons from other substances to maintain stability.

Germanium compounds function as free radical scavengers by virtue of electrons being available to interact with toxic, unpaired electrons. Germanium, in low doses raises Glutathione (reduced) GSH levels, affording protection against endogenously arising (free) radicals (21).

**Oxygen enrichment, blood purification.** Germanium compounds, complexed in lattice-network structures, bond with negatively charged oxygen atoms which are available to “capture” positively charged hydrogen ions, and heavy metals such as mercury and cadmium (1). Since the germanium compound binds and discharges hydrogen ions (H +), it frees up the body’s extant oxygen supply, and thereby effectively enriches the body’s own supply of oxygen (39). In oxygen multi-step therapy carried out with the administration of Germanium (Sanungerman), the arterial PO₂ may rise 70-140 Torr during O₂ inhalation (40). Germanium’s oxygen enrichment effects may partially explain its far-reaching therapeutic effects upon so many diverse conditions. Studies have linked oxygen deficiency with cancer; an increased provision of oxygen by germanium compounds may in part account for its positive oncogenic activity.

**Possible effectiveness in AIDS?**

Cancer, characterized by uncontrolled proliferation of T cells, and AIDS, by destruction of T cells, seemingly diseases of opposite effects, are
both mediated by retroviruses (15, 16). Germanium compounds have shown effective anti-cancer activity, which appear to be mediated by the mobilization of host immune mechanisms. Recent reports indicate that T-suppressor cells play a role in modulating the appearance of the virus in the blood and the onset of AIDS symptoms (47, 67). There is no literature, known to this author, on the use of germanium to treat AIDS. However, germanium’s anti-viral and cytotoxic activities, along with its abilities to mobilize the immune system, make its suggested effectiveness against AIDS eminently plausible. Moreover, since germanium compounds are virtually nontoxic, there is minimal risk to AIDS patients, and a potential for its efficacy in strengthening AIDS victims’ immune systems.

Conclusions

Organic germanium have been shown to be virtually nontoxic and to possess wide-ranging therapeutic effects in cancer and other serious illnesses. The immuno-enhancement attributes of organic Germanium suggest its testing in AIDS patients.

References

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