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J Gynecol Oncol Vol. 24, No. 1:96-97
http://dx.doi.org/10.3802/jgo.2013.24.1.96

pISSN 2005-0380
eISSN 2005-0399

Journal of Gynecologic Oncology
jgo

Pharmacokinetics and cytotoxic effect of selenium compounds in rodent cancer xenograft model for therapy experiment

To the editor: It has been, currently, acknowledged that selenium, as a chemopreventive agent, reduces considerably the risk of prostate, colorectal, lung, breast or any other cancer. Furthermore, therapeutic application of selenium compounds for several advanced epithelial carcinomas has been tried through translational research. Although the anti-tumor mechanism of selenium was not entirely understood, apoptosis mediated by reactive oxygen species is mainly suggested.

In the volume 23, a research article regarding the therapeutic effects of sodium selenite on epithelial ovarian cancer was very impressive in terms of therapy experiment employing rodent orthotopic ovarian cancer xenograft model [1]. Summarizing the results, *in vitro* growth of selenite-treated cancer cells was significantly decreased; however, *in vivo* treatment with sodium selenite (1.5 mg/kg, intraperitoneal injection, 3 times per week) did not show apparent inhibitory effect against tumor growth.

Various forms of selenium compounds exist. Selenomethionine is synthesized by plants and often used as a supplement in human studies. Selenocysteine represents the proteinogenic amino acid and selenium exerts its biological effects mainly via selenocysteine-containing proteins. Na_2SeO_3 (selenite), Na_2SeO_4 (selenate), and methylseleninic acid are inorganic selenium salts. From an *in vitro* assessment of cytotoxic effects on hepatocyte according to forms of selenium compounds, it was reported that the most powerful and fastest effect was observed in the methylseleninic acid, which is a potent second-generation selenium compound having different biological and pharmacological activity [2]. Additionally, in terms of route-dependent pharmacokinetics of selenium compounds, Willhite et al. [3] reported the high oral bioavailability of organic or inorganic selenium in hamsters. Total absorption of selenomethionine was measured as 73% and that of selenate was 100% in their experiment. Most recently, it was reported that the orally administered methylseleninic acid synergistically enhanced paclitaxel efficacy in a treatment experiment employing breast cancer xenograft model [4]. Therefore, these kinds of issues are needed to be considered for the future design of therapy experiment using selenium in ovarian cancer.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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http://dx.doi.org/10.3802/jgo.2013.24.1.96

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Selenium compounds fall into two categories, organic and inorganic forms. The anticancer activity of selenium is dependent on its chemical form. In general, inorganic selenium compounds, such as selenate or selenite, are known to produce genotoxic effects, and are therefore not preferred for medicinal use especially at high doses. Organic selenium-containing compounds are better tolerated, but are different in their anticancer activity depending on their pharmacokinetic and pharmacodynamics properties. The metabolism of selenium to a monomethylated intermediate, methylselenol, is presumed necessary for the expression of anticancer activity [1-3]. Methylselenol is highly reactive and difficult to formulate. Stable precursors, such as methylselenocysteine or methylseleninic acid, or selenomethionine, which can be converted endogenously to methylselenol, are good selenium precursors for generating methylselenol, the active selenium metabolite that exhibit anticarcinogenic activity. Accumulating evidence suggests that organic selenium-containing compounds have better anticancer activity and are less toxic compared to inorganic selenium compounds. For these reasons, selenomethionine, presumably the major form of selenium in selenized yeast, is selected for the supplement used in SELECT trial. Despite the above advantage of organic selenium, inorganic selenium was also shown to have anticancer activity in prostate cancer [4].

In our study, we tried to evaluate the *in vitro* and *in vivo* effect of inorganic selenium (sodium selenite) on tumor growth and food intake in ovarian carcinoma using animal model [5]. Because we used the partially immunodeficient (nude) mice in this study, the results of *in vivo* study could be different in immune competent models if selenium compound have some effects on immune system. Until now, there are a number of potential mechanisms proposed for the anti-proliferative effects of selenium, including antioxidant effects, enhancement of immune function, stimulation of apoptosis, and induction of cell-cycle arrest [6]. However, there are no conclusive evidences for which selenium compound including inorganic or organic forms is better and which route of administration is effective in treating cancer cells. Further experiments for pharmacokinetics and cytotoxic effect of various selenium compounds should be required to confirm this result.

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No potential conflict of interest relevant to this article was reported.

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http://dx.doi.org/10.3802/jgo.2013.24.1.97