Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

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*.

ARTICLE INFO

Article history:
Received 12 April 2018
Received in revised form 27 June 2018
Accepted 1 July 2018
Available online xxxx

Keywords:
Chemotherapy resistance
Gynecologic cancer
Selenium
Chemotherapy
Carboplatin

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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https://doi.org/10.1016/j.ygyno.2018.07.001
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Please cite this article as: M. Song, et al., Phase I trial of selenium plus chemotherapy in gynecologic cancers, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.07.001

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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