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“Prevention of Carboplatin Drug Resistance by Selenium”

[Selenium may be able to increase the efficacy of chemotherapy by circumventing drug resistance.]

The development of drug resistance is a major problem in the treatment of cancer. Drugs that reverse drug resistance have been used with little success in clinical trials. We have proposed an alternative strategy, prevention of resistance before it occurs. In essence, this would entail the use of specific agents during the initial course of chemotherapy that can prevent the development of resistance. Selenium is a nutritionally essential element that forms a variety of biologically active organic and inorganic compounds. We have obtained evidence that selenium can prevent the rapid development of resistance to cisplatin that occurs in a model of human ovarian tumors growing in immune-deficient mice. As a result, selenium enhances the chemotherapeutic efficacy of platinum in this system. Our ultimate objective is to test the hypothesis that selenium can prevent chemoresistance to platinum compounds, and hence increase their efficacy in the clinical treatment of ovarian and possibly other cancers that are currently treated with platinum compounds. However, we need first to test selenium toxicity when given in combination with platinum compounds, and to decipher how selenium works and inhibits platinum resistance. Accordingly, we propose to:

1. perform a clinical trial to test the safety and efficacy of the use of selenium in patients with gynecologic malignancies.
2. utilize tumor material obtained at surgery to examine three aspects of the status of each patient's tumor prior to beginning chemotherapy:
 - a) The sensitivity/resistance profile *in vitro*. This information will provide the platinum resistance status of the chemo-naïve tumors.
 - b) The behavior *in vivo* of tumors grown in mice, regarding their resistance to platinum.
 - c) The expression of biochemical markers associated with resistance to platinum.

The goal is to define a molecular profile that will predict which tumors will be platinum resistant and/or respond to selenium and not become resistant to platinum treatment.