**NOV-002, a glutathione disulfide mimetic, decreases Cisplatin-induced nephrotoxicity and S-glutathionylates serum proteins in mice.**

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**Abstract**

NOV-002 is a glutathione disulfide (GSSG) mimetic with chemoprotective activity. Clinical studies in the Russian Federation have demonstrated significantly improved survival and decreased tumor progression rates in non-small cell lung (NSCLC) and ovarian cancer patients treated with NOV-002 + chemotherapy compared to those receiving chemotherapy alone. The efficacy of NOV-002 in NSCLC has been confirmed in a recent US randomized Phase 2 clinical trial. The increased efficacy was associated with a lower incidence of chemotherapy-related adverse events. Oral administration of NOV-002 has been found to improve renal function and reduce proteinuria in patients with advanced renal failure. The decreased toxicity of NOV-002 compared to chemotherapy alone may be due to its ability to act as a competitive substrate for γ-glutamyltranspeptidase (GGT). Because oxidized glutathione is an endogenous substrate of GGT, the protective effect of NOV-002 may be partly attributable to its ability to act as a competitive substrate for the enzyme. As such, 8-week old Bl6 mice were treated with a single nephrotoxic dose of Cisplatin (15 mg/kg, ip) and sacrificed on day 5. One group of animals was treated with NOV-002 (15 mg/kg, im) daily. The Cisplatin-treated mice had significantly elevated levels of plasma creatinine compared to mice treated with NOV-002 (4.7 vs 2.9 mg/dL, respectively). Cisplatin-induced weight loss was diminished in the NOV-002 treated animals (22% vs 14.5%). In prior studies, we have shown that NOV-002 treatment of cancer cells leads to S-glutathionylation (glutathione conjugation) of cysteine residues with a low pKa values in redox sensitive proteins. Analysis of blood in drug treated mice showed that NOV-002 causes S-glutathionylation of three distinct proteins in plasma in <30 minutes. Using two-dimensional SDS-PAGE analysis and mass spectrometry, we are identifying these target proteins. S-glutathionylation of one or more of these proteins may prove to be effective biomarkers for following drug pharmacokinetics/dynamics and as plausible surrogates for clinical efficacy.

**Conclusions:**

- NOV-002 is an effective therapy when combined with standard cytotoxic drugs.
- NOV-002 provides protection of normal tissues and permits administration of more cycles of therapy.
- NOV-002 cause S-glutathionylation of a variety of proteins.
- Some of the glutathionylated proteins in the serum may prove to be effective biomarkers for drug effects.
- Induction of the UPR by NOV-002 occurs through redox balance changes and is independent of cell death.