NOV-002, a Glutathione Disulfide Mimetic, Is a Pleiotropic Modulator of Cellular Redox Balance

Danyelle M. Townsend¹, Lin He², Steven Hutchens², Tracy E. VandenBerg², Christopher J. Pazoles³ and Kenneth D. Tew².

Depts. Pharmaceutical Sciences¹, Cell and Molecular Pharmacology and Experimental Therapeutics,² Medical University of South Carolina 173 Ashley Ave., Charleston, SC 29425; Novosel Therapeutics Inc., One Gateway Ctr, Newton, MA 02458³

ABSTRACT

NOV-002 is a novel formulation of oxidized glutathione (GSSG) currently in a pivotal Phase 3 clinical trial in advanced non-small cell lung cancer. In clinical trials conducted to date, NOV-002 administered in combination with standard chemotherapeutic regimens has resulted in increased efficacy (survival, tumor response) and improved toleration (e.g. hematological recovery, immune stimulation). The studies reported here were aimed at further elucidating its cellular and pharmacologic profile. The effects of NOV-002 were assessed on a range of cellular and in vivo endpoints reflecting its key pharmacological actions – modulation of redox balance, NOV-002 affects the intracellular levels of GSH and GSSG, resulting in mild and transient time- and concentration-dependent excitatory signals at the cell surface (reduction in protein thiols) and intracellularly (altered GSSG and GSH levels and ratio). These oxidative signals were associated with an increase in S-glutathionylation of cell proteins, particularly actin, with a concomitant decrease in focal adhesions as detected by fluorescence microscopy. Intravenous administration of NOV-002 in mice also evoked a fingerprint of glutathionylated serum proteins which could represent a wide range of pharmacologic responses. Accumulating evidence supports that NOV-002 is a substrate for GGT and that modulation of cellular redox balance is a feature central to NOV-002's mechanism of action. Such modulation may underlie its clinical actions, including hematological recovery and immunostimulation in the face of hematopoietic stress.

BACKGROUND

NOV-002 is a novel formulation of oxidized glutathione (GSSG) currently in a pivotal Phase 3 clinical trial in advanced non-small cell lung cancer. In clinical trials conducted to date, NOV-002 administered in combination with standard chemotherapeutic regimens has resulted in increased efficacy (survival, tumor response) and improved toleration (e.g. hematological recovery, immune stimulation). The studies reported here were aimed at further elucidating its cellular and pharmacologic profile. The effects of NOV-002 were assessed on a range of cellular and in vivo endpoints reflecting its key pharmacological actions – modulation of redox balance, NOV-002 affects the intracellular levels of GSH and GSSG, resulting in mild and transient time- and concentration-dependent excitatory signals at the cell surface (reduction in protein thiols) and intracellularly (altered GSSG and GSH levels and ratio). These oxidative signals were associated with an increase in S-glutathionylation of cell proteins, particularly actin, with a concomitant decrease in focal adhesions as detected by fluorescence microscopy. Intravenous administration of NOV-002 in mice also evoked a fingerprint of glutathionylated serum proteins which could represent a wide range of pharmacologic responses. Accumulating evidence supports that NOV-002 is a substrate for GGT and that modulation of cellular redox balance is a feature central to NOV-002's mechanism of action. Such modulation may underlie its clinical actions, including hematological recovery and immunostimulation in the face of hematopoietic stress.

SUMMARY

NOV-002 alters redox status resulting in pleiotropic effects on cell functions.