Effect of Methylnaltrexone on Overall Survival in Advanced Illness Patients With Cancer

Background: Methylnaltrexone (MNTX), a peripherally acting μ opioid receptor antagonist (MOR), is FDA-approved for treatment of opioid-induced constipation (OIC) in patients with advanced illness (AI) or chronic pain. MNTX has restricted passage through the blood brain barrier, and is given to cancer patients receiving opioids without affecting analgesia. Recent cellular, molecular, animal, and human data suggest that the MOR may be a target for potential chemotherapeutic agents. Additionally, a polymorphism in MOR which confers opioid resistance shows improved survival for human breast and esophageal cancer. Further, opiate use has been associated with survival in patients with advanced prostate cancer and with recurrence rates in patients undergoing surgery for lung cancer. It was therefore hypothesized that MNTX may improve overall survival (OS) in cancer patients. We assessed pooled data from two Phase 3/4 randomized, placebo-controlled trials (RPCT) to identify whether MNTX given for OIC could influence the survival in AI patients with cancer.

Methods: OS was recorded in two Phase 3/4 trials of MNTX for OIC in patients with advanced illness. Both RPCT studies (2 weeks followed by a 2-week follow-up period), enrolled AI-OIC patients receiving stable doses of laxatives and opioids. In Study 1, patients received MNTX 0.15 Sq mg/kg or placebo (PBO) every other day. In Study 2 patients received MNTX (12 mg based on body weight 38 to < 62 kg or ≥ 62 kg, Sq, respectively) or placebo administered every other day. MNTX responders were those laxating within 4hr after ≥ 2 of the first 4 doses. A modified Royal Marsden Score (RMH) based on albumin (>/= 3.5) was calculated for all patients.

Results: Of 370 patients in the 2 studies, 229 (62%) had a cancer, of whom 116 and 114 were randomized to MNTX and PBO, respectively. Distribution of cancers and RMH was similar between groups. MNTX patients had longer OS than placebo (79 vs. 59 days, $p = 0.019$). 66 patients receiving MNTX responded with laxation while 50 did not. MNTX responders had longer OS than non-responders and placebo (121 vs. 58 days, $p < 0.001$). Multivariate analysis of MNTX response and albumin showed that MNTX (HR = 0.43, $p < 0.001$) and albumin (HR = 0.48, $p < 0.001$) were independent prognostic factors for OS. In non-cancer AI patients, mostly CHF, COPD, and neurologic, response to MNTX was not associated with a significant change in OS.

Conclusion: While limited by the post-hoc nature of the results, our data demonstrate a potential role for MNTX in treatment of patients with advanced cancer. These are the first placebo-controlled human data suggesting that MNTX can influence OS in cancer patients with AI and are consistent with our preclinical observations. Our observations suggest that the MOR may be an important therapeutic target.