RESEARCH PROTOCOL

Intravenous lidocaine for preventing painful oxaliplatin-induced peripheral neuropathy (OIPN)

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Intravenous lidocaine for preventing painful oxaliplatin-induced peripheral neuropathy (OIPN)

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Intravenous lidocaine for preventing painful oxaliplatin-induced peripheral neuropathy (OIPN)

Protocol Revision History

Initial Approval Version	**07/12/2017**
Amendment #1 Version	**08/24/2017**
Amendment #2 Version	**05/23/2018**
Amendment #3 Version	**12/14/2018**
Amendment #4 Version	**1/28/2019**
Amendment #5 Version	**3/4/2019**
Amendment #6 Version	**4/18/2019**
Amendment #7 Version	**10/25/2019**
Amendment #8 Version	**2/12/2021**

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SYNOPSIS

Study Title	Intravenous lidocaine for preventing painful oxaliplatin-induced peripheral neuropathy (OIPN)
Objective	#1: To determine the tolerability of lidocaine co-infusion in colorectal cancer patients treated with oxaliplatin. #2: To determine the initial efficacy of intravenous lidocaine, as a systemic voltage-gated Na^+ channel (Nav) blocker, in preventing oxaliplatin-induced peripheral neuropathy.
Hypothesis	We hypothesize that lidocaine can block the Nav-mediated toxicity of oxaliplatin to peripheral sensory nerves, thus mitigating OIPN.
Study Period	Enrollment: Sep 1, 2017 – December 31, 2018 Completion: August 31, 2019
Number of Patients	Tolerability phase: 8 evaluable patients receiving oxaliplatin treatment by mFOLFOX6 protocol for colorectal cancer. Efficacy pilot study: 30 evaluable patients receiving oxaliplatin treatment by mFOLFOX6 protocol for colorectal cancer.
Study Treatment	Tolerability phase: The proposed dose regimen for this study will be targeting lidocaine plasma Cmax of 2.5 μg/mL with 5.8 mg/kg Ideal Body Weight (IBW) dose infused intravenously over 130 minutes, beginning 10 minutes before oxaliplatin infusion. Efficacy pilot study: subjects will be randomized to receive IV lidocaine as identified in the tolerability study (5.8 mg/kg Ideal Body Weight (IBW) dose infused intravenously over 130 minutes, beginning 10 minutes before oxaliplatin infusion) or placebo for 8 biweekly treatment sessions.
Study Design	Tolerability phase: prospective, open-label Efficacy pilot study: randomized, parallel, double blind, placebo controlled
Inclusion and Exclusion Criteria	Inclusion criteria: 1) Adults ≥18 years old; 2) Stage III and IV colorectal cancer; 3) Scheduled for oxaliplatin treatment in mFOLFOX6-based chemotherapy regimen. 4) Able to understand and sign informed consent Exclusion criteria: 1) Renal insufficiency (calculated Creatinine clearance < 30mL/min); 2) Moderate to severe liver failure (ALT or AST > 3 times upper limit of normal if no liver metastases are present; ALT or AST > 5 times upper limit of normal if liver metastases are present); 3) Presence of brain metastases; 4) Current uncontrolled cardiac arrhythmias (non-sinus rhythm); 5) Contraindication or allergy to intravenous lidocaine; 6) Pre-existing symmetric peripheral painful neuropathy; 7) Treated with chemotherapy within the past 12 months; 8) Pregnancy or breastfeeding; 9) current treatment with medications listed in section 3.2.
Measurements	1. Peripheral neuropathy grading per NCI-CTC. 2. CIPN scoring on QLQ-CIPN20 tool 3. Cold allodynia and dysesthesia measurement on "cylinder test"

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	4. Sensory mapping for cold-, warm-, brush- and pinprick- evoked allodynia. 5. Quantitative sensory testing (QST): Thermal detection and pain thresholds, mechanical detection and pain thresholds, vibration detection thresholds, wind-up ratio. 6. Neuropathic pain descriptors on NPSI (Neuropathic Pain Symptom Inventory). 7. Quality of life assessment using RAND-12 8. Cumulative oxaliplatin dose 9. Lidocaine plasma pharmacokinetics: blood sampling for lidocaine concentration. 10. Genotyping for OIPN susceptibility
Statistical Methodology	Efficacy pilot study: The intensity of stinging/pricking sensation following a 10-second palm contact with a pre-cooled metal cylinder (8°C) will serve as primary outcome measures. We expect that the IV lidocaine intervention will result in a lower intensity of cold-induced stinging/pricking compared to the placebo group. To detect a difference between an intensity of 7(±2.2) in the placebo group vs 4(±2.2) in the lidocaine group, on 0-10 numerical rating scale, thirteen patients per group will allow detecting this difference with 90% power (two-sided t-test, $\alpha = 0.05$, effect size 1.36). We will enroll 30 subjects to account for drop-outs.

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1. BACKGROUND AND SIGNIFICANCE

1.1. Colorectal Cancer

Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer death in both men and women in the United States [1]. It is estimated that more than 130,000 people are diagnosed with colorectal cancer every year in the United States, and more than 50,000 people die annually from the disease. Forty to 50% of patients who undergo potentially curative surgery alone, without chemotherapy, ultimately relapse and die of metastatic disease [2].

1.2. Oxaliplatin

Oxaliplatin is a third-generation platinum derivative, which, when combined with fluorouracil (5-FU) and leucovorin, is among the most efficacious chemotherapies for colorectal cancer. Oxaliplatin differs from earlier platinum compounds such as cisplatin and carboplatin in its lack of nephrotoxicity and hematologic toxicity, respectively. Oxaliplatin is a key drug in many first-line chemotherapy regimens which have demonstrated improved survival in colorectal cancer patients both in advanced disease and in the early stages where the tumor is surgically resected [3-6]. mFOLFOX6 protocol, where 85mg/m^2 oxaliplatin, combined with 5-FU and leucovorin, is administered in 14-day cycles, is among the most commonly used regimens for advanced colorectal cancer [4-6].

Despite being an efficacious drug, and allowing ~80% 6-year overall survival rates in patients with stage II and stage III disease [3], oxaliplatin causes distal symmetric peripheral neuropathy (PN) in about 72% of patients treated with the drug [7]. This neuropathy is typically painful, with additional characteristics of negative neurological signs (i.e. diminished sensation to heat or mechanical stimuli), positive neurological signs (i.e. dynamic mechanical allodynia and profound cold allodynia in the extremities), and impaired proprioception. The acute peripheral neuropathy, which is typically of early onset, is the most common dose-limiting side effect of oxaliplatin [8, 9]. Patients developing PN eventually receive lower cumulative doses of chemotherapy which can increase the rate of treatment failure. As several studies have shown, delivering lower doses of oxaliplatin negatively affects patient survival by impairing drug effectiveness. There is generally 5-14 months difference in overall survival in favor of patients receiving high dose (85mg/m^2 or higher) vs low-dose (<85 mg/m^2) oxaliplatin treatment regimens for colorectal cancer [10, 11].

1.3. Oxaliplatin-Induced Peripheral Neuropathy

Oxaliplatin-induced peripheral neuropathy (OIPN) often persists; one year after oxaliplatin initiation, 21% of patients have painful symptoms [12], which substantially affect their QoL [13]. Once developed, chemotherapy-induced peripheral neuropathy is rather treatment-resistant. With the exception of one randomized controlled study with duloxetine [14], none of the published clinical trials with any of the tested analgesics have demonstrated positive results [15].

The mechanisms of nerve damage in OIPN are not fully understood. Oxidative stress to axonal mitochondria has been suggested as a possible mechanism, and preclinical data suggested that antioxidants may be effective in preventing PN [16]. However, recent clinical trial data indicate that antioxidant agents such as alpha-lipoic acid and acetyl-l-carnitine do not prevent chemotherapy-induced peripheral neuropathy [17]. Additional approaches using serotonin-norepinephrine reuptake inhibitor venlafaxine, or Ca^{++}/Mg^{++} infusions, have not been particularly successful in preventing this peripheral neuropathy [18, 19].

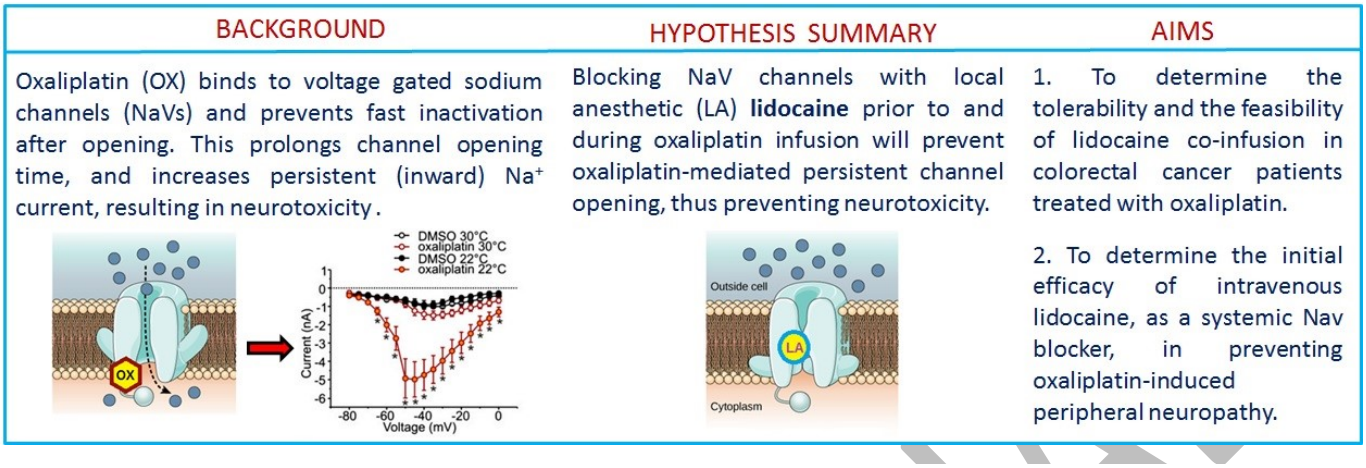
Emerging data suggest that OIPN may be associated with direct toxicity of oxaliplatin to neuronal voltage-gated Na^+ channels (Navs) [20-23]. Oxaliplatin alters the activation and inactivation behavior of voltage-gated Na^+ channels, while not affecting K^+ channels [20]. It is most likely that oxaliplatin acts directly on specific Nav isoforms such as Nav1.6, Nav1.7, or Nav 1.9, as it dramatically lengthens sodium currents and increases refractory time, without being influenced by extracellular calcium concentrations [20]. Interestingly, these changes occur primarily in afferent (peripheral) neurons, and no neurotoxic effect of oxaliplatin was observed in central (hippocampal) neurons in preclinical studies. Moreover, the effect of oxaliplatin on peripheral A-fibers (such as Aδ) was more significant than on unmyelinated C fibers, supporting the clinical evidence of cold (Aδ-mediated) hypersensitivity observed in the acute phase of OIPN [20, 24]. These effects were blocked *ex-vivo* by a non-specific Nav blocker carbamazepine [20], and although emerging data suggest that Nav1.6 might be the primary Na^+ channel isoform mediating oxaliplatin neurotoxicity [22], this requires further investigation. Additional nonspecific Nav blockers such as lidocaine [25] and mexiletine [26] have attenuated established OIPN in rodent models, and case reports suggest that Nav blocking approach may be useful for CIPN prevention [27] or treatment [28]. The data on mitochondrial damage by oxaliplatin in primary afferent neurons [16, 29] may also suggest that the toxicity occurs in more metabolically active primary afferent neurons. Therefore, preventing neuronal depolarization with a local anesthetic, and thus both physically blocking the channel and inhibiting neuronal activity, may diminish the extent of OIPN.

1.4. Lidocaine

Intravenous lidocaine is an FDA-approved intervention for treating cardiac arrhythmias, and the evidence of its effectiveness in treating established neuropathic pain [30-34] [35] and preventing acute postoperative pain [36, 37] supports its neuropathy-preventing potential in the setting of oxaliplatin chemotherapy. The use of intravenous lidocaine for the treatment of neuropathic pain was shown to be effective in multiple studies (reviewed elsewhere [38]). The most common adverse effects include temporary dizziness, drowsiness, and perioral numbness (32). However, no studies have reported arrhythmias due to i.v. lidocaine for neuropathic pain [38]. In a recent retrospective review infusion rates between 4 and 12mg/min were suggested to be tolerable, with toxicities starting above 12mg/min. In our protocol (as described further) the infusion rates are around 3.9 mg/min, depending on patient's weight. Our group has extensive experience with i.v. lidocaine infusions in neuropathic pain. We have recently published on the intervention in patients with neuropathic pain due to symmetric polyneuropathy or peripheral nerve trauma (32). In addition, we are currently conducting a randomized clinical trial of i.v. lidocaine vs placebo in diabetic neuropathy at Washington University (NCT02363803), with minimal side effects using ideal body weight-based dosing.

Overall, there is substantial evidence to support our hypothesis (depicted in Figure 1) that blocking voltage-gated Na^+ channels in the peripheral nerves during oxaliplatin infusion will safely diminish peripheral nerve damage by a dual mechanism: 1) Lidocaine will render the sodium channels less susceptible to conformational modulation by oxaliplatin on the receptor level; and 2) Systemic blockade of Navs will slow down the metabolic activity in primary afferent neurons.

Figure 1. General depiction of study background, hypothesis and aims.



Currently, no established methods exist to prevent OIPN. The contribution of the proposed research is expected to be the novel approach for preventing OIPN. This contribution will be significant because preventing OIPN will substantially reduce the suffering and QoL impairment associated with this painful neuropathy; in addition, in can allow full oxaliplatin dosing in colorectal cancer patients, providing higher treatment success rates and improving survival.

1.5. Preliminary Data

The proposed study is to test, for the first time, the tolerability of intravenous lidocaine intervention in this group of patients undergoing oxaliplatin-based chemotherapy for colorectal cancer. The starting dose regimen of lidocaine in this study (as detailed in Table 1) was derived from intravenous lidocaine pharmacokinetic data from our previously completed study [32]. Maximum plasma concentrations (Cmax) above 3.3 µg/mL, obtained with 5mg/kg (true body weight) 30-min infusion of lidocaine, resulted in peak concentration-related temporary side effects (dizziness, perioral numbness, dry mouth, blurred vision), especially in overweight patients. In a modified dosing regimen of 5mg/kg Ideal Body Weight (IBW) lidocaine (infused over 40 minutes) that we use in an ongoing clinical trial (NCT02363803) to target Cmax below 3µg/mL, minimal side effects have been observed. In the proposed dose regimen for this study, we will be targeting lidocaine plasma Cmax of approximately 2.5 µg/mL. This will be obtained with an initial brief infusion of 1.0 mg/kg IBW over 10 minutes, and a 0.04 mg/kg/min infusion over additional 120 minutes, which was derived using non-parametric pharmacokinetic modeling (WinNonlin, Pharsight, CA).

Lidocaine treatment will start 10 minutes prior to oxaliplatin 120-minute infusion. Oxaliplatin alpha-elimination half-life is about 20 minutes; therefore, one hour after infusion the plasma concentration drops by more than 85% [39]. The longer half-life of lidocaine (90-120 min) is expected to provide sufficient plasma concentrations (>1 µg/mL) for at least two hours after oxaliplatin treatment, to prevent the peak concentration-dependent toxicity of oxaliplatin on the peripheral nerves.

2. OBJECTIVES

1. To determine the tolerability (defined as lack of dose-limiting toxicity – see section 6.4.2) of lidocaine co-infusion in colorectal cancer patients treated with oxaliplatin.

2. To determine the initial efficacy of intravenous lidocaine as a systemic voltage-gated sodium channel (Nav) blocker in preventing oxaliplatin-induced peripheral neuropathy.

3. PATIENT SELECTION

3.1. Inclusion Criteria

1. At least 18 years old
2. Diagnosed with stage III or IV colorectal cancer
3. Scheduled for oxaliplatin treatment in mFOLFOX6-based chemotherapy regimen
4. Able to understand and willing to sign an IRB-approved written informed consent document

3.2. Exclusion Criteria

1. Renal insufficiency (defined as calculated Creatinine clearance < 30mL/min);
2. Moderate to severe liver failure (defined as ALT or AST > 3 times upper limit of normal if no liver metastases are present; ALT or AST > 5 times upper limit of normal if liver metastases are present);
3. Presence of brain metastases;
4. Patients with currently uncontrolled cardiac arrhythmias (non-sinus rhythm) will be excluded. Patients with history of arrhythmias under pharmacological/pacemaker control will be allowed, except if receiving antiarrhythmic medication listed in "contra-indicated medications" below.
5. Contraindication or allergy to intravenous lidocaine;
6. Pre-existing symmetric peripheral painful neuropathy;
7. Treated with chemotherapy within the past 12 months;
8. Pregnant and/or breastfeeding; women of childbearing potential must have a negative pregnancy test within 14 days of study entry
9. Currently treated with any of the following contraindicated medications:
    - Saquinavir, Lopinavir, Amprenavir, Atazanavir, Delavirdine
    - Mexiletine (and other types of sodium-channel blocker antiarrhythmics)
    - Phenytoin, Carbamazepine, Oxcarbazepine, Lamotrigine
    - Amiodarone
    - Dronedarone
    - Dihydroergotamine
    - Cimetidine

3.3. Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

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4. REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1. Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2. Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3. Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4. Randomization

In the 2nd phase of the study (see "Study Design"), patients will be randomly assigned to either intravenous lidocaine or matching placebo of identical appearance. The randomization will be performed in 1:1 ratio, in blocks of 4, with no stratifications, using Research Randomizer (www.randomizer.org).

5. STUDY DESIGN

The study has two phases: 1) a Tolerability phase and 2) a randomized, double-blind pilot phase to evaluate efficacy. In the tolerability phase, we plan to enroll 8 patients with Stage III or IV colorectal cancer treated with oxaliplatin in mFOLFOX6 regimen. In the randomized phase, 30 colorectal cancer patients will be randomized to infusion of intravenous Lidocaine HCl or identical placebo (in D5W-Dextrose 5% in water).

The patients in the mFOLFOX6 regimen receive their routine oxaliplatin treatment sessions every 2 weeks. In both phases, the assessments will be conducted at baseline, and at each of these 2-week visits, prior to oxaliplatin infusions (see summary in Table 2). Two additional visits are planned, the first will occur 2 weeks after the 6th treatment cycle (immediately prior to the 7th cycle) of

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oxaliplatin, and the second will occur 8-10 weeks after the last (or 12th, whichever earlier) oxaliplatin treatment, and several assessment will be performed at both points (Table 2).

Lidocaine pharmacokinetics will be determined by serial blood sampling in both phases, for dose-effect relationship investigation. In the efficacy pilot phase, the full set of blood samples (multiple time-points) will be collected only during first 2 cycles of study drug intervention. A single sample at the end of lidocaine infusion (130 minutes) will be collected during the remaining intervention cycles to obtain the maximum plasma concentration (Cmax).

6. STUDY PROCEDURES

6.1. Pre-Study Period

All subjects will receive comprehensive metabolic panel (CMP) screening to exclude renal or hepatic disorder, blood tests will be ordered for plasma creatinine, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). All subjects will be examined by 12-lead ECG. Blood tests or ECG that have been performed within the last 30 days can be used in lieu of ordering new tests. We will monitor these parameters periodically throughout the study (see study calendar).

Prior to the start of treatment, we will collect data on demographics, cancer diagnosis and staging, and physical and mental quality of life parameters using the RAND-12 questionnaire [40]. Patients' height and weight will be measured. The subjects will be asked to complete the Hospital Anxiety and Depression Scale (HADS), the Brief Pain Inventory (BPI), and undergo brief cognitive testing battery using the Trail Making Test A (TMT A) and TMT B tests, as well as Color Word Matching Stroop Test (CWMST).

We will also perform peripheral neuropathy grading by NCI-CTC (National Cancer Institute – Common Terminology Criteria), Chemotherapy-Induced Peripheral Neuropathy (CIPN) scoring on EORTC (European Organization for Research and Treatment of Cancer) QLQ-CIPN20 tool [41], neuropathic pain characteristics in feet and hands on NPSI (Neuropathic Pain Symptom Inventory), perform sensory mapping (i.e. sensitivity of extremities to cold, warm, brushing and pricking stimuli), and perform quantitative sensory testing (QST) [32] before oxaliplatin treatment. See Table 2 for details. The QST procedure will be performed per established protocol [32, 42], which we routinely utilize in clinical studies. Briefly, we will determine warm detection thresholds (WDT), cold detection thresholds (CDT), heat pain thresholds (HPT), and cold pain thresholds (CPT). For subjects participating at the satellite locations, the CPT test will not be performed (as the specific equipment is non-transportable). We will also determine mechanical detection and mechanical pain thresholds (MDT and MPT, respectively). Also will be assessed wind-up ratio (WUR) and Vibration Detection Threshold (VDT). The tests will be performed bilaterally on dorsal feet, and on a control area (dominant volar forearm). All sensory testing equipment is available in the PI's lab.

6.2. Agent Administration

At each of the intervention visits, an intravenous line used for oxaliplatin administration will be used for lidocaine administration, and a new IV line will be inserted in an arm for obtaining blood samples to evaluate the plasma concentrations of lidocaine. Lidocaine can be infused via Y-site through the same central/peripheral catheter as oxaliplatin, so that only one additional line will be placed for blood collection for the first 2 cycles of study drug administration. During the remaining

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study visits , only a single blood sample will be obtained for lidocaine plasma concentration analysis. This will be done by venipuncture, without the requirement of an additional IV line.

The participants will receive the following mFOLFOX6 treatment regimen:
Oxaliplatin 85mg/m^2 IV over 2h on day 1,
Leucovorin 400 mg/m^2 IV over 2h on day 1,
5-FU 400mg/m^2 IV bolus on day 1, followed by a 1200mg/m^2/day continuous infusion for 46 hours. This cycle is repeated every two weeks for six cycles in the tolerability phase and 8 cycles in the randomized phase with reevaluation for the maintenance therapy.
mFOLFOX6 will be the primary treatment regimen, however, variations of mFOLFOX6 regimen per treating physician (e.g., lack of administration of Leucovorin or 5-FU bolus in metastatic patients, or the addition of bevacizumab or irinotecan), will be acceptable.
In case of development of DLTs after oxaliplatin, dose de-escalation will occur.

mFOLFOX6 dose modification in the case of peripheral neuropathy:
The initial dose of oxaliplatin is 85mg/m^2 every 2 weeks. If a persistent (> 2weeks) Grade II Peripheral Neuropathy (PN) develops, the dose of oxaliplatin in mFOLFOX6 protocol will be reduced to 65mg/m^2. If a persistent Grade 3 PN is present, mFOLFOX6 treatment will be discontinued.
mFOLFOX6 dose changes for reasons other than peripheral neuropathy are subject to treating clinician's decision; however, every dose change will be documented in the CRF.

Intravenous (IV) lidocaine will be dosed as a brief 1 mg/kg infusion (based on Ideal Body Weight (IBW)) over 10 minutes, followed by a 0.04 mg/kg/min infusion over additional 120 minutes. Lidocaine administration will begin 10 minutes prior to oxaliplatin initiation. The study drug administration will begin with the first cycle of oxaliplatin therapy.

IBW will be calculated by B. J. Devine Formula:
IBW = 50.0 + 2.3 kg per inch over 5 feet (man)
IBW = 45.5 + 2.3 kg per inch over 5 feet (woman)

Separate tables (differentially colored for male vs female patients) are added for accurate calculation of IBW based on height (Appendix E).

For subjects with BMI ≤25, lidocaine dose will be calculated per true body weight.
For subjects with BMI ≥25, lidocaine dose will be calculated per ideal body weight.

If this dose is intolerable (details in section 6.4), then dose de-escalation will be performed per regimen outlined in section 6.3, to obtain the maximum tolerable dose, which will be used in the randomized, controlled phase of the study.

The pharmacist (Debra Tesoro) at Center for Advanced Medicine (CAM) Washington University Investigational Drug Service will prepare D5%W infusion bags with the appropriate Lidocaine Hydrochloride dose which is provided by the Principal Investigator (Department of Anesthesiology). D5%W will be first drawn from the infusion bag in a volume equal to the volume of lidocaine 2% solution to be added to the infusion, to keep the same total volume of the infusion bag. The total volume of lidocaine D5W solution to be infused will remain unchanged (at 174mL) for all study subjects. The total lidocaine dose will be limited to 500mg for safety reasons. A study nurse from the Anesthesiology Department (or an Anesthesiology resident physician) will monitor ECG and oxygen saturation by pulse oximetry throughout the infusion and for approximately 60

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minutes after the end of infusion for the first 2 cycles. An attending anesthesiologist from the study team will be on call on the study days (at the Pain Management Center – CAM 14th floor) if assistance is needed for managing lidocaine-related adverse effects. In any case of serious side effects, the study team will follow the American Society of Regional Anesthesia (ASRA) guidelines on systemic local anesthetic toxicity [43]. Administration of agents and conduction of study will take place on the 7th floor of CAM or at the satellite locations (West County Siteman Center, South County Siteman Center, St. Peters Siteman Center and Christian Hospital Siteman Center). Intralipid® infusion for possible local anesthetic systemic adverse effect management will be readily available on the 7th floor of CAM and at the satellite locations.

Subjects can be discharged after a minimum stay of 60 minutes after the end of infusion, and if no neurological or cardiac adverse effects are present, or when any such effects have completely resolved. In case of continuing adverse effects, the subjects will be monitored by the study staff until resolution of these effects as determined by the PI.

Subjects are not allowed to drive or operate machinery for 3 hours after the end of study drug infusion. Intravenous lidocaine infusion may cause dizziness and drowsiness; therefore, there is a risk of falling if the patient attempts to walk without assistance soon after the end of infusion. Subjects will be monitored to ensure they do not stand up or walk without assistance for up to 60 min after the end of infusion. The patients will be required to have a family member escort them home, and transportation will be provided if necessary.

6.3. Dose De-Escalation Schema for Tolerability Phase

If the suggested lidocaine dose is tolerable in four consecutive sessions of mFOLFOX6 in six or more of the eight patients in the tolerability phase, we will initiate the randomized efficacy pilot study with the suggested dose. Tolerability will be defined as lack of dose-limiting toxicities (DLT) associated with lidocaine treatment (defined in Section 6.4.2), and no signs of unanticipated disease progression as evidenced by the routine PET/CT scan (as clinically indicated) performed after 4th cycle of mFOLFOX6. After four cycles of 1st line treatment with mFOLFOX6, approximately 80% of patients respond or remain progression-free [44]. If three or more patients in the tolerability study develop DLT or unanticipated disease progression after 4 consecutive cycles of oxaliplatin, dose de-escalation will occur based on the following table.

Lidocaine dose level	Initial bolus dose over 10 min (based on IBW)	Infusion rate (over 120 min)	Total dose
#1	1.0 mg/kg	0.04 mg/kg/min	5.8 mg/kg IBW
#2	0.8 mg/kg	0.03 mg/kg/min	4.4 mg/kg IBW
#3	0.6 mg/kg	0.02 mg/kg/min	3.0 mg/kg IBW
#4	0.4 mg/kg	0.01 mg/kg/min	1.6 mg/kg IBW

IBW= Ideal Body Weight

6.4. Definition of Maximum Tolerated Dose, Dose De-Escalation Criteria, and Toxicity and DLT Evaluations

6.4.1. Definition of Maximum Tolerated Dose

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Dose escalation will not be performed in this study; therefore no formal maximum tolerated dose (MTD) will be defined. MTD for this study purposes will be defined as either the initial dose regimen (dose level #1, table above), or as the dose level immediately below the dose level at which >2 patients of a cohort experience dose-limiting toxicity over 4 consecutive sessions of mFOLFOX6. Dose de-escalations will proceed if needed until the MTD has been ascertained.

6.4.2. Dose-Limiting Toxicities

Dose limiting criteria for lidocaine include the appearance of any of the following effects during the study drug infusion or up to 60 minutes thereafter:

- Any of the following cardiac arrhythmias:
- Atrial Fibrillation Grade 3+
- Atrial flutter, Grade 3+
- Asystole, any
- Cardiac arrest
- Atrioventricular (AV) block, Grade 3+
- Paroxysmal atrial tachycardia, Grade 2+
- Sinus bradycardia, Grade 2+
- Sinus tachycardia, Grade 3+
- Ventricular arrhythmia, Grade 2+
- Ventricular fibrillation, any
- Seizure, any
- Dizziness, Grade 3+
- Somnolence, Grade 3+
- Syncope, any
- Blurred vision, Grade 3
- Occurrence of any other Grade 3 or higher adverse effect thought to be at least probably associated with lidocaine treatment.

In addition, a dose-limiting toxicity will be an evidence of unanticipated disease progression based on a routinely performed CT, PET or MRI scan (as indicated, and interpreted by the treating physician) at 8 weeks after oxaliplatin initiation – i.e. 4 cycles of treatment. This may indicate that the study drug negatively affects the efficacy of mFOLFOX6 chemotherapy.

6.4.3. Dose De-Escalation Criteria

Dose de-escalations will proceed as follows after the occurrence of dose-limiting toxicity (DLT):

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
Less than three of 8 subjects	Proceed to the randomized phase of the study.
Three or more subjects	De-escalate the dose by entering 8 patients at the next lowest dose level.

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6.5. Toxicity and DLT Evaluations

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving any study treatment until 60 minutes following end of each infusion of lidocaine. There are no concerns with concentration-independent toxicity of lidocaine with intermittent administration such as in this study.

DLT, also defined as drug dose that interferes with oxaliplatin efficacy or otherwise unanticipated disease progression, will be assessed by a CT, PET or MRI scan at 8-weeks, or as clinically indicated .

A patient is evaluable for DLT assessment only if enrolled in the dose-finding portion of the study.

6.6. Randomized Phase

In the randomized phase, 30 colorectal cancer patients will be randomized to infusion of intravenous lidocaine or identical placebo (D5W-Dextrose 5% in water), per regimen established in the dose-finding phase. The blinded infusions will be co-administered with oxaliplatin via Y-site [45] for all cycles of mFOLFOX6 protocol (approximately every 14 days). The patients are initially planned to receive the study drug for 8 of the 12 cycles of mFOLFOX6 treatment; if the treating clinician decides to reduce the number of treatment cycles to less than 8, the number of study interventions will be reduced accordingly.

6.7. Blood for Determining Lidocaine Concentration

Blood samples (4mL tubes) for determining lidocaine concentration will be obtained at baseline and 15, 45, 60, 90, 130, and 180 minutes after initiation of infusion baseline. The samples will be put on ice, centrifuged for 10 min at 3000 rpm, plasma will be separated and transferred to 1.5mL vials and stored at -80°C until analysis by HPLC-MS.

Beginning with the 3rd study visit that included study drug administration, only a single 4-mL blood sample for lidocaine plasma concentration will be obtained at 130 minutes after study drug initiation.

6.8. Concomitant Medications and Supportive Care

The patients will continue their chronic medications; including chronic pain medications, provided the dose have been stable for at least 2 weeks. If any of these medications are discontinued during the study, the changes will be recorded. PRN analgesics will not be limited, but their consumption will be carefully recorded. Addition of new medications for treating painful neuropathy (i.e. gabapentin, pregabalin, duloxetine, venlafaxine, tricyclic antidepressants, opioids) will not be allowed during the study. Patients will be withdrawn from the study if the peripheral neuropathy is severe enough to require pharmacological treatment.
Participation in the study will not be allowed if participants are treated with any of the following medications, which may result in serious drug-drug interaction with lidocaine:

- Saquinavir, Lopinavir, Amprenavir, Atazanavir, Delavirdine
- Mexiletine
- Phenytoin, Carbamazepine, Oxcarbazepine, Lamotrigine

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- Amiodarone
- Dronedarone
- Dihydroergotamine
- Cimetidine

6.9. Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 14 days prior to the first dose of lidocaine.

Female patients are required to use two forms of acceptable contraception, including one barrier method, during participation in the study.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

6.10. Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment will continue for up to 6 cycles in the tolerability phase and 8 cycles in the randomized phase of mFOLFOX6 or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar. On infusion days, those patients who are not receiving study drug will still undergo pre and post-infusion assessments per PI and patient discretion. All subjects will be followed up to two years for the collection of survival data.

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During the tolerability phase the study will continue for 6 cycles of mFOLFOX6. If the patient and the treating physician wish to continue lidocaine co-infusions with additional cycles of oxaliplatin, intravenous lidocaine can be prescribed at the discretion of the treating physician.

6.11. Duration of Follow-up

In the tolerability phase, patients will have a follow-up visit prior to their 7th cycle of mFOLOFX6, and an additional visit at 8-10 weeks after 12th (or last, whichever is earlier) dose of oxaliplatin. In the randomized phase, patients will have a follow-up visit at 8-10 weeks after 12th (or last, whichever is earlier) dose of oxaliplatin. The main purpose of these visits is to compare the development of persistent neuropathy and neuropathic pain between the two study arms. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. One year and again at two years after enrollment in the study, progression-free and overall survival will be assessed by review of the medical record.

7. DOSE MODIFICATIONS

In case of mild (Grade 1 AE) tachy- or brady- arrhythmias, or oxygen desaturation, the infusion will be paused, and attempted to resume 10 minutes after resolution of the adverse effect. In any case of moderate (Grade 2+) to severe tachy- or brady- arrhythmias (except sinus tachycardia, which is defined as DLT if Grade 3+), or oxygen desaturation, the infusion will be stopped, and patient withdrawn from the study.

In any case of serious side effects, the study team will follow the American Society of Regional Anesthesia (ASRA) guidelines on systemic local anesthetic toxicity [43]. Intralipid® infusion for possible local anesthetic systemic adverse effect management will be readily available and carried by the study the team.

The following stopping rules will be applied:
Lidocaine is not known to affect liver or kidney function. However, if the subject develops renal insufficiency (Creatinine clearance <30 ml/min) or liver insufficiency (ALT or AST > 3 times upper normal value in patients with no liver metastases, ALT or AST >5 times upper normal value in patients with liver metastases) for any reason, the study drug will not be administered at that oxaliplatin treatment session for safety reasons. If prior to subsequent cycles of chemotherapy the limiting kidney/liver function improves beyond the above criteria, the study drug can be administered with oxaliplatin, within the same mFOLFOX6 regimen.

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8. STUDY CALENDAR

Required Assessment	Baseline visit	Treatment visit # (concomitant with oxaliplatin cycle)								6th cycle F-U° Tolerability phase	8-10 week F-U	1 year F-U	2 year F-U
								Randomized phase					
		1	2	3	4	5	6	7	8				
Informed Consent	√												
Inclusion/exclusion criteria	√												
Blood tests*	√	√		√			√						
Blood sample for genotyping		√											
Electrocardiogram (ECG) **	√	√	√	√	√	√	√	√	√				
Randomization	√												
Demographic data collection	√												
RAND-12 and BPI questionnaires	√							√		√	√		
Cognitive testing	√										√		
HADS questionnaire	√												

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NPSI questionnaire	√	√	√	√	√	√	√	√	√	√	√		
Sensory mapping	√	√	√	√	√	√	√	√	√	√	√		
QST** *	√			√				√		√	√		
Cold allodynia and dysesthesia	√	√	√	√	√	√	√	√	√	√	√		
PN grading	√	√	√	√	√	√	√	√	√	√	√		
Study drug administration		√	√	√	√	√	√	√	√				
QLQ-CIPN20 assessment		√	√	√	√	√	√	√	√	√	√		
Adverse effect monitoring ‡		√	√	√	√	√	√	√	√				
Serial blood sampling for PK*** *		√	√										
Single PK sample – at 130min				√	√	√	√	√	√				
Progression-free and overall survival (medical record												√	√

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review)													

*Comprehensive metabolic panel (CMP). **ECG will be performed at baseline (12-lead) and monitored during study sessions (3-lead). *** For subjects participating at the satellite locations, the CPT test will not be performed. ‡ Adverse effects will be monitored during and 60 min after the study drug infusion. **** Serial blood sampling for PK collected during first 2 cycles of study drug, then a single PK sample at the remaining cycles. °A scheduled follow-up visit 2 weeks after the 6th treatment visit (immediately prior to the 7th) for patients in the tolerability phase. °° 8-10 weeks after the last cycle (or 12th, whichever earlier), an additional visit will be planned. BPI=Brief Pain Inventory. HADS = Hospital Anxiety and Depression Scale; NPSI = Neuropathic Pain Symptom Inventory; QST = Quantitative Sensory Testing; PK = Pharmacokinetics

9. OBSERVATIONS AND MEASUREMENTS

9.1. Primary Outcome Measures

Efficacy RCT: Oxaliplatin-induced Cold allodynia and dysesthesia as means of the intensity of unpleasantness (stinging and/or pricking) upon holding a pre-cooled (~8°C) metal cylinder (rod test) will serve as primary outcome measure, after the first 8 cycles of mFOLFOX6, and will be compared between Lidocaine and placebo groups.

9.2. Secondary Outcome Measures

1. Occurrence of Grade 2+ peripheral neuropathy during treatment, measured by NCI-CTC Peripheral Neuropathy Grading;
2. Time to event (Grade 2+ peripheral neuropathy)
3. Change in CIPN score (on EORTC QLQ-CIPN20 tool) over time until last follow-up;
4. Magnitude of sensory disturbances on QST (change from baseline to last follow-up);
5. Changes in NPSI descriptors of neuropathic pain over time from baseline to last follow-up (NPSI will be administered separately for pain in feet and for pain in hands).
7. Change in Mental and Physical summary scores on RAND-12 questionnaire [37] from baseline to last follow-up;
8. Pain intensity on 0-10 numerical rating scale at each treatment day, and last follow-up.
9. The cumulative dose of oxaliplatin over the course (up to 12 cycles) of mFOLFOX6
10. Two-year progression-free and overall survival determined by medical record review.

9.3. Exploratory outcome Measures

Determination of a possible association between the development of OIPN and the existence of gain-/ or loss-of-function single nucleotide polymorphisms (SNPs) for the following targets will be conducted in collaboration with the Washington University Genome Technology Access Center:
1. Voltage-gated sodium channels: Nav 1.4 (SCN4A gene), Nav 1.6 (SCN8A gene), (Nav 1.7 (SCN9A gene)), and Nav 1.8 (SCN10A gene), that are associated with painful neuropathies.
2. Glutathione-s-transferase: GST π-gene (GSTP1), GST μ1-gene (GSTM1), and GST θ1-gene (GSTT1), that may affect the development of severe oxaliplatin related neuropathy.

10. STATISTICAL METHODS

Ideally, the primary outcome of the clinical trial would be the comparison of disability caused by painful OIPN between the study arms, or progression-free survival of the patients for the prevention

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of dose-limiting OPIN with lidocaine. However, to have sufficient power to detect these clinically-relevant outcomes of pain and chemotherapy effectiveness, we would require approximately 60 and 78 patients per group, respectively. This would be the goal of the future extramurally-funded clinical trial. In this pilot trial, we have defined our primary outcome as the intensity of unpleasantness of cold-induced stinging/pricking after 6 cycles in the tolerability phase and 8 cycles in the randomized phase of mFOLFOX6 and the study intervention.

Oxaliplatin-induced peripheral neuropathy is associated with characteristic patterns of distal tingling sensations and cold-evoked pain (cold-allodynia), the severity of which is an indicator of long-term neuropathy and neuropathic pain [24]. Conventional nerve conduction studies lack the power to accurately detect early symptoms of cold allodynia. Recently, a cold hypersensitivity method has been developed to determine the severity of oxaliplatin-induced peripheral neuropathy, using the application of standardized pre-refrigerated metal rods on the palmar surface [24] and measuring the severity of cold allodynia after 10 seconds of contact.

Patients will be provided with such rods to place in their home refrigerator, and the results of daily assessment of cold allodynia will be recorded during 6 cycles in the tolerability phase and 8 cycles in the randomized phase of mFOLFOX6 treatment and up to the 2-week follow-up. We will provide patients with scoring sheets and ask to rate the intensity of pricking/tingling and pain after holding the pre-cooled cylinder each day at a standardized time. The intensity will be reported on two separate 0 – 10 numeric rating scales; one for pain (0 = no pain, 10 = worst pain imaginable), and one for pricking/tingling (0= no pricking/tingling, 10 = worst pricking/tingling imaginable).

10.1. Sample Size

To demonstrate a significant difference between Lidocaine and Placebo on oxaliplatin induced cold-allodynia after the first 8 cycles (intensity of pricking/tingling after 10 second contact will 8°C cylinder 7(±2.2) in the placebo group vs. 4(±2.2) in the lidocaine group [24]), with a two-sided t-test, assuming α=0.05 and 90% power (effect size 1.36), 26 evaluable subjects (13 per arm) will be required to participate in the study. We will enroll 30 evaluable subjects to the study due to potential drop-outs.

11. REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 11.2.

11.1. Definitions

11.1.1. Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all

toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

11.1.2. Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

11.1.3. Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

11.1.4. Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

11.1.5. Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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11.1.6. Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

11.1.7. Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

11.1.8. Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

11.2. Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

11.3. Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

11.4. Timeframe for Reporting Required Events

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Adverse events will be tracked for 60 minutes after each lidocaine infusion. For the purposes of this protocol, all adverse events will be collected and documented on CRFs, except the following adverse effects, which are likely to be associated with mFOLFOX6 treatment, and are unlikely to be associated with lidocaine treatment:

- Nausea and Vomiting
- Diarrhea
- Stomatitis
- Hematologic toxicity, e.g. neutropenia
- Loss of appetite
- Fatigue
- Constipation
- Fever
- Generalized pain
- Cough
- Temporary increase in liver functions
- Arthralgia
- Myalgia
- Hair loss

The treatment with 5-FU has been associated with cardiotoxicity in 6-8.5% of colorectal cancer patients receiving FOLFOX chemotherapy [46, 47], particularly due to prolonged (24-hour) infusion of 5-FU. Symptoms of cardiac toxicity appearing later than 1 hour after lidocaine infusion may be attributable to this effect of 5-FU.

12. DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

During the phase I dose de-escalation, the Principal Investigator will review all patient data at least monthly (or before each dose de-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). During the phase II, the Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years

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- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

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APPENDIX A: QST protocol

Quantitative sensory testing will be performed on the dorsal mid-foot, bilaterally. The volar side of the dominant arm will serve as control area.

A description of the QST procedures follows:

Thermal detection and thermal pain thresholds
Equipment: The Thermal Sensory Analyzer (TSA-II platform - Medoc, Ramat Yishai, Israel) will be used to determine thermal detection and pain thresholds. This equipment is used globally for functional assessment of pain and temperature-conducting nerve fibers (C and A-delta fibers).

Method and Background: Using the thermal sensory analyzer, cold and warm detection thresholds (CDT and WDT, respectively), as well as cold and heat pain thresholds (CPT and HPT, respectively) will be determined [48, 49]. The thermode with contact area of 9.0 cm^2 is applied to the tested site, and all thresholds are determined by continuous ramping of temperature from 32°C baseline temperature by 1°C/s until the subject presses the 'stop' button. Cut-off temperatures are 0°C and 50°C, to minimize thermal damage to the skin. The baseline temperature to which the thermode returns before each test is 32°C. The average threshold is calculated from three measurements in each area.

Determination of mechanical detection threshold (MDT)
Equipment: A set of standardised von Frey filaments (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128 and 256mN). The contact area of the hairs with the skin is of uniform size (<1 mm^2) and texture.

Methods and Background: Standardised von Frey filaments will be used in a modified "method of limits" manner using 3 series of increasing and decreasing stimulus intensities to determine the geometric average as the tactile detection threshold of the affected and unaffected skin areas [50].

Von Frey filaments of different stimulus intensities are used to determine the tactile detection thresholds. A filament eliciting 16mN force* is applied first, followed by filaments of consecutively lower intensity until the patient cannot detect the stimulus being applied. This respective force represents the first threshold value. The order in which the stimuli are applied is then reversed and stimuli of consecutively greater intensity are applied until sensation is detected (this intensity becomes the second value). Again filaments with decreasing intensity are applied until in total 3 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

* In case the first von Frey filament with an intensity of 16mN is not detected, the next highest intensity filament which can be detected must be used as a starting intensity. However, the relevant force of this stimulus is not documented. Filaments with consecutively lower intensity are applied until the patient cannot detect the stimulus being applied. The procedure is followed as above; until in total 3 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

Determination of mechanical pain thresholds (MPT)
Equipment: A set of standardized weighted metal probes (Nervetest, MRC systems) exerting pressure of 8, 16, 32, 64, 128, 256 and 512 mN.

Methods and Background:
The standardized metal probes will be used in a modified method of levels manner, 3 series of increasing stimulus intensities to detect the mechanical pain threshold. Beginning with an applied force of 8mN, stimuli increase in intensity until the sensation induced by increased pressure can be described as 'painful'.

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The corresponding force is used to represent the first MPT value. The procedure is then repeated a total of 3 times and until a total of 3 values are obtained, from which the mean MPT is determined.

Determination of vibration detection thresholds (VDT)
Equipment: A standard tuning fork.

Methods and Background:
The tuning fork will be applied at the lateral malleolus, and vibration detection threshold (the moment patient stops feeling the vibration of the tuning fork applied to the skin) will be measured on a scale of 1-8. The test will be repeated a total 3 times. VDT is determined as an average of the three measures.

Determination of wind-up ratio (WUR)
Equipment: A standardized weighted metal probes (Nervetest, MRC systems) exerting pressure of 256mN.

Methods and Background: In this test a pinprick (256mN) is first applied singularly. After that a series of 10 identical pinprick stimuli are applied with a frequency of 1 s^{-1} within an area of 1 cm^2. Immediately following the single stimulus and series of stimuli, an evaluation of the sensation must be provided according to NRS (0-10, '0': 'no pain', '10': 'worst pain imaginable'). A ratio is calculated using these values. This procedure will be repeated 3 times. A geometric average of the 'wind-up' is calculated from the two ratios (Price, Hu et al. 1977, Magerl, Wilk et al. 1998).

Supplements

Table 1: Lidocaine dosing scheme based on IBW

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APPENDIX B: Questionnaires

- Veteran's RAND-12 (VR-12)
- Hospital Anxiety and Depression Scale (HADS)
- Neuropathic Pain Symptom Inventory (NPSI)
- Brief Pain Inventory (BPI)

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APPENDIX C: Cognitive tests

- Trail Making Test A (TMT A) and Trail Making Test B (TMT B)
- Color Word Matching Stroop Test (CWMST).

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APPENDIX D: Neuropathy grading

- Peripheral sensory neuropathy grading by CTCAE
- QLQ-CIPN20 grading

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APPENDIX E: Ideal Body weight (IBW)

- Color-coded Ideal Body Weight (IBW) tables for male and female subjects

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