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Design and rational for the precision medicine guided treatment for cancer pain pragmatic clinical trial

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ABSTRACT

Introduction: Pain is one of the most burdensome symptoms associated with cancer and its treatment, and opioids are the cornerstone of pain management. Opioid therapy is empirically selected, and patients often require adjustments in therapy to effectively alleviate pain or ameliorate adverse drug effects that interfere with quality of life. There are data suggesting *CYP2D6* genotype may contribute to inter-patient variability in response to opioids through its effects on opioid metabolism. Therefore, we aim to determine if *CYP2D6* genotype-guided opioid prescribing results in greater reductions in pain and symptom severity and interference with daily living compared to a conventional prescribing approach in patients with cancer.

Methods: Patients with solid tumors with metastasis and a self-reported pain score ≥ 4/10 are eligible for enrollment and randomized to a genotype-guided or conventional pain management strategy. For patients in the genotype-guided arm, *CYP2D6* genotype information is integrated into opioid prescribing decisions. Patients are asked to complete questionnaires regarding their pain, symptoms, and quality of life at baseline and 2, 4, 6, and 8 weeks after enrollment. The primary endpoint is differential change in pain severity by treatment strategy (genotype-guided versus conventional pain management). Secondary endpoints include change in pain and symptom interference with daily living.

Conclusion: Pharmacogenetic-guided opioid selection for cancer pain management has potential clinical utility, but current evidence is limited to retrospective and observational studies. Precision Medicine Guided Treatment for Cancer Pain is a pragmatic clinical trial that seeks to determine the utility of *CYP2D6* genotype-guided opioid prescribing in patients with cancer.

1. Introduction

Approximately 60% of patients with cancer and up to 80% with metastatic disease report pain [1,2]. Accumulating evidence suggests that survival is linked to pain management and other palliative support measures that improve quality of life [3]. Opioids are the cornerstone of therapy for most patients to relieve moderate to severe pain, with oxycodone and morphine considered first-line treatment options [4]. Unfortunately, only one-third of patients with cancer pain report decreased pain after 1 month of opioid therapy, while one-fifth have

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increased pain, and many patients experience reduced quality of life due to unrelieved pain, opioid side effects, or both; 30% undergo opioid rotation to find relief [5,6].

Although causes are multifactorial, there is evidence of a hereditary basis for inter-individual differences in pain sensitivity and opioid analgesia [7,8]. The CYP2D6 enzyme biotransforms select opioids (e.g. codeine, tramadol, oxycodone, hydrocodone) to metabolites with greater affinity for the μ-opioid receptor than the parent compound [9,10].

The *CYP2D6* gene is highly polymorphic, with over 100 alleles defined. Functional variation within *CYP2D6* includes single nucleotide polymorphisms (SNP), insertions, deletions, and instances where the gene is deleted, duplicated or multiplicated. Individuals with no functional alleles are deemed poor metabolizers (PMs) and have little to no active CYP2D6 enzyme. Intermediate metabolizers (IMs) have one loss-of-function allele and one reduced function allele and significantly impaired enzyme activity compared to normal metabolizers (NMs), which have at least one fully functional allele or two partially functioning alleles [11]. Pharmacokinetic studies have shown lower concentrations of active metabolites of codeine (morphine), tramadol (*O*-desmethyltramadol), oxycodone (oxymorphone), and hydrocodone (hydromorphone) in CYP2D6 PMs compared to NMs [9,10,12–14]. Studies have further shown that lower active metabolite concentrations in PMs lead to decreased analgesia compared to NMs [15,16]. On the other hand, ultra-rapid metabolizers (UMs), with multiple gene copies, are at increased risk for adverse drug effects, including life-threatening toxicities, compared to NMs [13].

The Clinical Pharmacogenetics Implementation Consortium (CPIC) developed guidelines for interpreting and translating *CYP2D6* genotype information into prescribing decisions for codeine. The guidelines recommend considering an alternative opioid for CYP2D6 PMs and UMs, making note that tramadol, oxycodone, and hydrocodone are not good alternatives because their metabolism is affected by CYP2D6 activity. For IMs, the guidelines recommend to monitor codeine use for response [11]. While codeine is not commonly prescribed for cancer pain, oxycodone, hydrocodone, and tramadol are used commonly in this population, and oxycodone is a first line choice for prescribers at our institutions. Despite the evidence that *CYP2D6* genotype plays an important role in the pharmacokinetics and clinical response to opioids, there is a paucity of data on whether incorporating *CYP2D6* genotype information into opioid prescribing decisions improves pain management [10,17–20].

We hypothesize that *CYP2D6* genotype-guided prescribing results in greater reductions in pain severity and interference compared to a conventional prescribing approach in patients with cancer-associated pain. To test this hypothesis, we aim to determine the effect of prospective *CYP2D6* genotype-guided selection of opioid analgesics for cancer patients on pain and symptom severity and interference with daily living.

2. Methods

2.1. Study overview

Precision Medicine Guided Treatment for Cancer Pain is a pragmatic clinical trial being carried out at two independent cancer centers to determine the effect of *CYP2D6* genotype-guided selection of opioid therapy on cancer pain management. Patients are randomized to a genotype-guided or conventional approach to pain management, with patient reported pain-related outcomes (questionnaires) assessed at baseline (enrollment) and 2, 4, 6, and 8 weeks after enrollment (follow-up). The study design flow chart is shown in Fig. 1.

2.2. Study population, location, and personnel

A total of 200 adult patients will be enrolled, with 100 enrolled at University of Florida (UF) Health Cancer Center in Gainesville, FL and 100 enrolled at Moffitt Cancer Center in Tampa, FL. UF Health Cancer Center is a nationally recognized academic cancer center with over 350 researchers and clinicians serving over 10,000 patients, annually, with sites in Gainesville, Jacksonville, and Orlando, FL. Moffitt Cancer Center and Research Institute is a National Cancer Institute (NCI)-designated Comprehensive Cancer Center located in Tampa, Florida. Moffitt collaborates with multiple health care systems across the state serving over 55,000 patients annually. The protocol was approved by the IRB at each institution.

Inclusion criteria for the study are age ≥ 18 years, diagnosis of histologically or cytologically proven solid tumor with metastasis, reported pain score of 4 or higher on a scale of 0–10 on presentation to clinic, and receiving treatment at UF Health Cancer Center or Moffitt Cancer Center for outpatient management of cancer-associated pain. Patients who have undergone major surgery within the last three months or are scheduled to undergo surgery during the study period (8 weeks), have a documented psychiatric or neurological condition that would interfere with study participation, have had a liver transplant, or are allergic to opioids are excluded. Potential participants are identified at the time they present to clinic and are approached by a research team member about study participation.

The research team is composed of pharmacists with expertise in pharmacogenetics, physicians with expertise in cancer pain management, clinical pathologists, research coordinators, nurses, and statisticians. Team members at UF Health and Moffitt maintain bi-weekly telephone calls and email exchanges to consolidate data collection, discuss challenges, and ensure protocol adherence between the two sites.

2.3. Enrollment and randomization

Participants who provide informed consent are randomized in a 1:1 manner to receive *CYP2D6* genotype-guided (n = 100) or conventional (n = 100) selection of pain medication. The randomization schedule was developed in permuted blocks to maintain approximately equal numbers of patients in each group at any point throughout the study [21]. Genotyping remains available clinically, and MDs are not prohibited from ordering a clinical *CYP2D6* test for patients in the conventional group. However, if a *CYP2D6* genotype order is placed for a patient in the conventional group, the patient is withdrawn from the study at that time point.

2.4. Intervention

At baseline, genetic samples are collected via buccal swab from patients in both arms. For the genotype-guided group, samples from both sites are sent to UF Health Pathology Laboratories for *CYP2D6* clinical genotyping. For the conventional pain management group (usual care), the sample is sent to the UF Center for Pharmacogenomics for *CYP2D6* genotyping for research purposes only at the conclusion of the study. Patients in both groups are asked to provide additional consent for the storage of their remaining sample and data for future research to identify additional genetic determinants of opioid response.

Patients in the conventional treatment group will continue to receive standard of care for their cancer related pain [2]. For those randomized to the genotype-guided group, *CYP2D6* results are incorporated into their electronic health record (EHR). A pharmacogenomics pharmacist from the UF Health Personalized Medicine Program or Moffitt Cancer Center Personalized Medicine Clinical Service provides an interpretation of the genotype results and drug therapy recommendation via a consult note in the EHR. The consult note is also sent via email to the treating physician along with instructions on how to locate the results and recommendation in the EHR. For patients with PM, IM, or UM phenotype (based on genotype results), the pharmacist recommends avoiding oxycodone, hydrocodone,