Double Blind Trial Investigating the Role of Sulfasalazine in Decreasing Opioids Requirements in Breast Cancer Patients

Brief Summary

Cancer pain in general, and cancer-induced bone pain in particular, is a significant health problem in the USA and the rest of the world. With the improvement of new surgical approaches and chemotherapies to treat manage cancer, the number of patients with cancer are now living longer. This great achievement created an unexpected problem. For some cancer patients with bone metastases, pain is worse than the cancer itself. The golden standard to manage cancer-induced bone pain is opioids. Patients with cancer-induced bone pain are now are taking ever-increasing doses of opioids to control their pain. Sadly, opioids come with significant side effects. These side effects limit the amount of opioids that can be safely administered. Many attempts have been tried to create better regiments for pain control to lower the need for opioids. There has not been significant success in that area. A better approach to better control cancer-induced bone pain and lower the amount of opioids used would be to add a non-opioid agent that has a different mechanism of action(s). This may create synergism to better control pain while lowering the doses of opioids needed and lowering side effects. Sulfasalazine poses such quality. It is an anti-inflammatory drug with established safety profile. It has been in use for over fifty years for the treatment of inflammatory conditions such as rheumatoid arthritis. In addition to its anti-inflammatory characteristics, sulfasalazine has the capacity in decrease the survival of cancer cells and also to lower the amount of inflammatory mediators released by cancer cells. In short, sulfasalazine inhibits the influx of cysteine into cancer cells and the efflux of glutamate from cancer cells. Cysteine is needed for cell survival against oxidative stress, while glutamate activate pain receptors. Therefore, sulfasalazine will act as anti-inflammatory, an agent to accelerate cancer cells death, and decreasing the released glutamate which activate pain receptors. This one agent with three mechanisms of actions may lower the amount of opioid needed for cancer patients with cancer-induced bone pain while maintaining or improving their pain control. Lowering of opioid dosing may also decrease the side effects associated with opioid use which in turn may improve their quality of life. The objective of this clinical trial is to co-administer sulfasalazine with opioids to patients with cancer-induced bone pain and characterize their pain and their opioid use. Our hypothesis is that adding sulfasalazine to the pain medication regiment will lower the amount if opioids used and lower the side effects. This may improve the quality of life for cancer-induced bone pain patients and decrease the risks of using high amount of opioids for the patients, their families, and society in general. The primary objective of this study is to decrease the amount of opioid pain medication use after addition of sulfasalazine for 12 weeks while controlling pain. The secondary objective is to decrease the intensity of pain and increase the quality of life.

Study Description

This double-blind clinical trial is intended for patients with moderate to severe cancer-induced bone pain on stable doses of opioids. This study is expected to last 12 weeks from the time a

patient first receives the assigned treatment. Each patient will have 7 clinic visits that are related to the study. Initially, we will conduct urine pregnancy test before the start of the study and at week 6 except for patients with documented hysterectomies. If a patient suspects she may be pregnant, additional urine pregnancy test will be conducted. If the results suggest possible pregnancy, the patient will be excluded from the study.

Patients with breast cancer-induced bone pain will be identified and recruited from the chronic pain clinic and from the oncology clinic at the University of Arizona. The consent process as well as the pain evaluation will be conducted at the Chronic Pain clinic at South Campus or at the oncology clinic at main campus. Patients that meet our inclusion criteria and consent to the study will be randomized into either a placebo (sugar pill) or sulfasalazine group. We estimate that a sample size of 16 subjects per group will be necessary based on the power calculations shown below. Because not all subjects will complete the study and provide evaluable data, we will enroll 20 subjects per group. Forty patients will be stratified according to age and randomly assigned to either a placebo or active treatment group in a 1:1 ratio. The randomization sequence will be generated by the Biostatistics Shared Resource of UACC using a computer-generated process. The assignment of patients will be revealed only to the pharmacist. The pharmacist will also not be involved in communicating with patients or analyzing the data. Neither the patients nor the treating physicians will know into which group individual patients will be assigned. Initially, all patients will be given written surveys designed to assess for opioid use, pain level, and quality of life.

The treatment group will receive supplies for 3 months of sulfasalazine at an initial dose of 0.5 gram three times a day for a week then at a dose of 1 gram three times a day for the remainder of the 3 months. Patients will be asked to take their medications with every meal (assuming three meals a day) in addition to their regular pain medications. The placebo group will be asked to take capsules filled with cornstarch three times a day in a similar manner.

The patients will return to the pain clinic or the oncology clinic for follow ups at 2 weeks (+/- 1 week), 4 weeks (+/- 1 weeks), 6 weeks (+/- 1 weeks), and 8 weeks (+/- 1 week), 10 weeks (+/- 1 week), and 12 weeks (+/- 1 week) at which times all follow-up measures from the surveys will be collected. Additionally, a physical exam will be performed on every patient at every follow up appointment. The physical examination will be focusing on the mental status by asking Mini Mental State test. We will also examine the abdomen by light and deep palpation. Any deviation from the normal limits will result in un-blinding the effected patient (to elucidate whether he/she is a control or a treatment group) and withdrawal from the study. If intestinal or urinary obstruction is suspected, the appropriate imaging studies will be conducted and a consultation with the appropriate surgical service will be requested if indicated.

The following is a summery table of safety monitoring and assessments that will be conducted at every follow-up. The pregnancy test will be conducted before the start of the study and at week 6 (not included in the following table) for pre-menopausal patients.

History will focus on symptoms of porphyria, intestinal, urinary obstruction, or blood dyscrasia.

- Neuro exam Mini mental state test
- Abd exam Light and deep palpation of the abdomen
- CBC Complete blood count with differential
- BMP Basic metabolic panel with renal function
- LFT Liver function tests
- UA Urinalysis

Finally, blood and urine samples to monitor for side effects from the study medication. The manufacture of sulfasalazine recommends that blood test be done every two weeks to monitor for side effects. Sulfasalazine may cause anemia and decreased white blood cells. Additionally, it may cause liver and renal damage. Therefore, blood and urine will be collected at every follow up by a phlebotomist who is not part of the study. The collected samples will be labeled by the research team. The blood sample will be used for safety monitoring by analyzing the basic metabolic panel and complete blood count. At the baseline, Week-6, and Week-12, additional blood will be immediately centrifuged and the plasma will be stored in a -80 degrees Celsius freezer for later analysis for inflammatory mediators and tumor markers. The collected urine will be used for urinalysis. Any significant deviation from the baseline values of the CBC, liver function, renal (basic metabolic panel) function, or UA will result in un-blinding of the effected patient, withdrawal from the study, and consultation with the appropriate service.

Patients will be given four paper surveys to assess for pain level, pain medication use, and quality of life. We will utilize a modified pain assessment questionnaire which is used in our pain clinic to assess for pain intensity, frequency, duration, ability to fall and stay asleep, and ability to exercise, this will be completed weekly. We will also utilize the Brief Pain Inventory (short form) for additional pain assessment. The Brief Pain Inventory (BPI) is a valid, clinically useful pain assessment tool that has been used extensively in people with cancer Its purpose would be to assess the severity of pain and the impact of pain on daily functions. It includes a diagram to note the location of pain, questions regarding pain intensity (current, average, and worst using a 0 to 10 rating scale), and items that evaluate impairment due to pain. This would be used to assess their pain in a systematic approach. The short form survey should take about 5 minutes and will be administered at study entry and end of study. There is no scoring algorithm but the arithmetic mean of the four severity items can be used as measures of pain severity and the arithmetic mean of the seven interference items can be used as a measure of pain interference.

We will use the EORTC QLQ-C30 survey which assess global improvement in the quality of life. The EORTC QLQ-C30 version 3.0 will be used to assess quality of life. The questionnaire is multidimensional in structure, brief and easy to complete, and applicable across a range of

cultural settings. This questionnaire would be collected at the start of the trial, week 2, week 4, week 6, week 8, week 10 and the end of the 12 week pilot trial.

Finally, patients will be provided with a pain medication log to document the amount of pain medications needed Subjects will record their opioid pain medication use - both long acting and breakthrough pain. They will be asked to record their opioid pain use daily (both long acting and breakthrough pain meds). In addition, we will also capture data regarding NSAID's, Tylenol and other medications used for pain and document the daily study medication. A research nurse or study coordinator will make weekly calls to the patient to ensure they are taking assigned drug (placebo or sulfasalazine), assess side effects, and recording pain medication use. At the end of study, the drug diary will be collected. Due to the subjective of pain, we chose verified and well accepted surveys that are used in clinical settings to have a more relevant data for better interpretation.

All surveys will be conducted at baseline before starting any treatment. The pain medication log will be done on daily basis. At the end of the study, all data will be gathered and compiled for statistical analysis. The study will be conducted at both the pain clinic at south campus and at the oncology clinic at main campus.

In terms of the blood analysis for inflammatory mediators, ten milliliter blood sample will be collected at the baseline visit, week 6 and at the end of the study (week 12) for all enrolled patients. These three time points will allow us to understand the temporal effect of sulfasalazine on inflammatory mediators. The mid-time point will allow us to maximize the data extraction in case so patients may wish to quit the study before week 12. All samples will be collected from the antecubital fossa. The blood samples will be spun at 12,000 RVM for 10 minutes and the serum will be stored in -80 degree Celsius freezer until analyzed. We will utilize commercially available enzyme-linked immunosorbent assay (ELISA) kits to measure the inflammatory mediators IL-6, and TNF-alpha. Glutamate will be measured using Amplex Red Glutamic Acid Oxidase Assay kit. Additionally, we will measure tumor markers for breast cancer including CA 27.29 and CEA using commercially available ELISA kits, we will also collect tumor measurements from standard of care PET scans to evaluate the tumor size.

The data will be analyzed when all participants complete the trial. At that point we will unblind the subjects and finalize the data analysis.

Inclusion Criteria:

- Adult patients aged >18 and 95< year old.
- Diagnosis of cancer with 3-day average numeric pain rating score (NPRS) for pain of at least 5/10 at baseline evaluation.
- On opioid regiment for at least 3 weeks. This time frame will allow patients to have a stable opioid regiment as it typically takes a few weeks of titration of opioids to reach

an acceptable dosing. Having a stable opioid regiment will allow us to better be able to interpret the effects of sulfasalazine.

- Pain duration of at least 6 weeks or more.
- Prognosis greater than 6 months
- Able to take oral medication.

Exclusion Criteria:

- Patients with intestinal or urinary obstruction or at risk of such disorders.
- History of porphyria
- History of blood dyscrasias, hepatic disease (ALT and AST greater than 2.5X the upper limit of normal).
- History renal disease (serum creatinine greater than 1.5 mg/dl)
- Patients taking Lapatinib or Digoxin.
- No sustained hypercalcemia (blood calcium level greater than 10.4 mg/dl).
- Hypersensitivity to sulfasalazine, its metabolites, sulfonamides, or salicylates.
- The patient is or becomes incarcerated.
- History of addictive behavior, severe clinical depression, or psychotic features.
- Possible pregnancy or lactation.
- Those receiving remuneration for their pain treatment (e.g., disability, worker's compensation).
- Those involved in active litigation relevant to their pain.