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Consent to Participate in Research

Study Title: Double Blind Trial Investigating the Role of Sulfasalazine in Decreasing the Opioid Requirement in Breast Cancer Patients

Principal Investigator: Mohab Ibrahim, MD., Ph.D

Summary of the research

This is a consent form for participation in a research study. Your participation in this research study is voluntary. It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to ask questions before making your decision whether or not to participate.

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. Patients with cancer-induced bone pain 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. 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.

Sulfasalazine acts as an anti-inflammatory, agent and decreases production of glutamate, which activates pain receptor. In addition, it has been shown to accelerate cancer cells death. By different mechanisms of actions Sulfasalazine may lower the amount of opioid needed to treat cancer-induced bone pain while maintaining or improving pain control. Lowering of opioid dosing may also decrease the side effects associated with opioid use that in turn may improve your quality of life.

This is a research study. If you choose to participate in this study, and are eligible to participate. You will be randomly assigned (like the possibility of getting “heads” or “tails” when flipping a coin) to receive either the study medication (Sulfasalazine) or Placebo (a substance that has no therapeutic effect,) (50% change to get one of them). Neither you, nor the study doctor can choose which medication you will receive. Your decision to take part in this study is voluntary, you are free to choose to take part or not.

Why is this study being done?

Breast cancer is a very difficult and complex medical problem. Pain usually comes with cancer. The current drugs available to treat cancer pain are usually strong opioids. Even with high doses of opioids, the cancer pain may not be well controlled. Additionally, high doses of opioid may result in significant side effects. This study is designed to investigate the possibility of better cancer pain control with less opioids by adding the non-opioid medication, sulfasalazine.

What will happen if I take part in this study?

If you decide to participate in this study, you will be asked to sign this consent form. Once you have signed the informed consent form and have met all eligibility criteria to participate, the following procedures will be conducted for your baseline visit. You will be randomly assigned to either a placebo group (a substance that has not therapeutic effect) or the drug group (sulfasalazine). You have 50% chance of being in either group. The study start date and the outcome assessment timeline will begin from the date of your Placebo or drug administration. During your initial visit, we will collect several pieces of data from you that are considered standard of care. Demographics, your work status, disability status, type of work, whether a previous pain physician has evaluated or provided treatment in the past, a detailed description of the pain (burning, electrical, shooting…etc.) and its location. A detailed physical examination assessing the motor strength of the upper extremities, sensations to light touch and reflexes will be completed. You will be asked to give a numerical value for your pain (a scale from 0-10 where 0 is no pain and 10 is the worst pain imagined) and a Mini Mental State test.
We will also ask you to complete the following questionnaires at the beginning of the study, during the study and end of the study (for a total of 12 times.

- EORTC QLQ-C30, this provides an overall assessment of the quality of life
- Modified pain clinic questionnaire, which asks about the intensity and characteristic of your pain and daily activity.
- Brief Pain Inventory questionnaire, this assesses the severity of pain and its impact on functioning.

On a daily basis, you will complete a diary of your daily pain medications, you will also document your study medication on this form.

For the follow up visits, data similar to the information gathered at the initial visit will be collected. The description of the pain (burning, electrical, shooting…etc.) and its location will be reviewed. A physical examination assessing for pain and sensation to light touch that is part of the standard of care will be provided for you. Blood and urine samples will be collected at every follow up visit. We will be performing blood tests to check for your liver and kidney function. We will be collecting your urine sample for monitoring of the, renal (kidney) functions for safety measures only. This is to ensure your safety as the study drug may have rare, but serious side effects. We will not be testing for any illicit drugs from these collected samples. Additionally, we will test for pregnancy at the start of the study and at week 6 into the study unless you have documented hysterectomy (surgical removal of the uterus) or are post-

menopausal. If applicable, we will also document tumor size, from available PET Scans at the beginning and end of the study.

The following is a schedule for the expected visits for this study after your baseline visit is completed:

- Day 0 – Initial dose of placebo or study drug.
- Week 2, 4, 6, 8, 10, 12 follow-up office visit.
- Complete an EORTC QLQ-C30 questionnaire. This provides an overall assessment of the quality of life.
- Complete a modified pain clinic questionnaire, which asks about the intensity and characteristic of your pain and daily activity.
- Hand in your pain medication diary.
- Physical Examination.
- Mini Mental State Test
- Blood work and urinalysis. These are done to check your kidney function and liver function tests, blood counts. These are conducted as routine standard cancer treatments. In addition 10 milliliters (2 teaspoons) of blood will be collected at your baseline visit, 6 week visit and last visit to analysis for inflammatory mediators and tumor markers.
- At the week six follow-up visit, there will also be a pregnancy test performed for those who need to be monitored.
- The 12 week visit will be the END OF STUDY visit.

Throughout the study, you will have normal access to all your pain medications as usual, if needed.

How long will I be in this study?

The study start date and the outcome assessment timeline will begin from the date of your first placebo/drug administration. The study is expected to be 3 months long.

How many people will take part in this study?

Up to forty subjects will be enrolled in this study.

What benefits can I expect from being in this study?

You may or may not benefit as a result of participating in this study. You may notice decreased pain intensity, decreased opioid requirement, or decreased side effects from opioids.

What risks, side effects or discomforts can I expect from being in the study?

Sulfasalazine has been in use for many decades in the United States. The medication is very well tolerated. The most common side effects include anorexia, headache, nausea, and

vomiting. However, on rare occasions, serious side effects have been reported that may result in blood disorder, gastrointestinal reaction (unpleasant or bothersome reaction in the mouth, esophagus, stomach or intestine), central nervous system reaction, renal reaction (reactions involving the kidneys), anaphylaxis (severe and possibly life-threatening allergies), folate deficiency, nephrolithiasis (kidney stones), oropharyngeal pain (pain in the mouth or esophagus), angioedema (severe allergic reaction involving tongue swelling, may be life-threatening), purpura (purple skin rash) , pallor (looking pale), or even death. Your treating physician will discuss with you if there is any concern of taking this medicine and your current ongoing cancer therapies.

What other choices do I have if I do not take part in this study?

You may choose not to participate in this study without penalty or loss of benefits to which you are otherwise entitled. If you choose not to participate you will have access to regular pain management as covered by your medical insurance.

When may participation in the study be stopped?

The study may be stopped by the investigator for any of the following reasons:

1) Violation of any of the inclusion criteria.
2) Aggressive behavior towards the pain or palliative clinic staff.
3) Development of new or discovery of already existing medical condition(s) that was not present during the initial screening if such condition(s) may interfere with the study.
4) Sustaining an injury that may require additional pain medication or may interfere with accurate gathering of the data.
5) Hospitalization for any reason that prevents you from taking the study medication as instructed.
6) Any situation that hinders your access to study medications and follow-up appointment.
7) Refusal to accurately filling pain diaries and reporting them honestly to the pain or palliative clinic staff.
8) Becoming pregnant or expressing desire to become pregnant (the study medications may have adverse effects on a developing fetus or a nursing infant).
9) You decide to stop the study for any reason.
10) Significant deviation from normal blood test values.

What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, we will identify the proper specialist to assist in managing the side effects.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

The University of Arizona and Banner-University Medical Center have no funds set aside for the payment of treatment expenses for this study.

What are the costs of taking part in this study?

There are no anticipated additional costs for you to be in this study, except for your time. Regular medical care performed while participating in study will be billed to you and / or your insurance company as usual. Not all insurance companies are willing to pay for services performed in a clinical trial. Please speak with your insurance company to find out what you may be financially liable for.

Will I be paid for taking part in this study?

You will be compensated for a total of $150 for the completion of the study. You will receive $50 after signing the consent, $50 after week 6 and $50 at the end of the study for a total of $150. If you quite the study or discharged from the study, you will not be asked to pay back the money you received, but you may not receive the subsequent payment.

Compensation for participation in a research study is considered taxable income for you. We are required to obtain your name, address, and Social Security number for federal tax reporting purposes. If your compensation for this research study or a combination of research studies is $600 or more in a calendar year (January to December), you will receive an IRS Form 1099 to report on your taxes.

Will my data or specimens be stored for future research?

A small amount of blood will be stored in a -80 freezer and will be analyzed at a later time point for inflammatory mediators and tumor markers as indicated in this consent form. The sample will be labeled with your study ID number and date of the blood draw.

Will my specimens be sold for commercial profits?

No, your specimens will not be sold for commercial profit.

Will I hear back on any results that directly impact me?

Results from the blood tests may be shared with the subjects if they are clinically significant and have an impact on the study.

Will Whole Genome Sequencing be done with my specimen?

No, there will be no Genome Sequencing done with your specimen.

Will my study-related information be shared, disclosed, and kept confidential?

It is anticipated that there will be circumstances where your study related information and Protected Health Information (PHI) will be released to persons and organizations described in this form. If you sign this form, you give permission to the research team to use and/or disclose your PHI for this study. Your information may be shared or disclosed with others to conduct the

study, for regulatory purposes, and to help ensure that the study has been done correctly. These other groups may include:

- Office for Human Research Protections, Food and Drug Administration, or other federal, state, or international regulatory agencies
- Banner University Medical Group and Banner Health
- The University of Arizona (UA) and the UA Institutional Review Board
- Your primary care physician or a specialist taking care of your health.

If you agree to take part in this study a copy of this signed informed consent form will be saved into your electronic medical record (EMR) at Banner Health. As a result, healthcare providers and staff who are not working on this study, but who may provide you medical treatment in the future, will know that you are taking part or took part in this study.

Your PHI may no longer be protected under the HIPAA privacy rule once it is disclosed by the research team.

What study-related information and PHI will be obtained, used or disclosed from my medical record at Banner?

Information related to this research study that identifies you and your PHI will be collected from your past, present, and future hospital and/or other health care provider medical records.

The PHI you are authorizing to be used and/or disclosed in connection with this research study is:

- Any data collected related to this study.
- Past medical and surgical history
- Current medications
- Age
- Gender

Demographic information to be disclosed may include, but is not limited to, your name, address, phone number, or social security number. If you receive compensation for participating in this research study, information identifying you may be used or disclosed as necessary to provide that compensation.

Your existing health records may include information related to the diagnosis or treatment of sexually transmitted disease (STD), acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), other communicable diseases, genetic information (e.g., genetic testing), and/or alcohol and/or drug abuse. The study staff and study sponsor's monitor may see this information while reviewing your regular health records for this study, but they WILL NOT create, collect, or disclose this type of information for the purposes of this research study.

When will my authorization expire?

There is no expiration date or event for your authorization. Therefore, unless you cancel this authorization (as instructed below) this authorization will continue to be effective.

Do I have to sign this authorization form?

You do not have to sign this authorization. However, if you decide not to sign, you will not be able to participate in this research study; and it will not affect any non-study Banner Health medical treatment or health care, payment, enrollment in any health plans, or benefits.

What do I need to know if I decide to cancel my authorization?

After signing the authorization, you may decide to cancel your previous authorization for the research team to use your PHI. If you cancel the authorization, you will no longer be able to stay in the research study. Please note that any PHI collected before you cancel the authorization may still be used. You may revoke the authorization by contacting the Principal Investigator in writing. Contact information is under "Who can answer my questions about the study" at the end of this document.

Will access be limited to your research study record during this study?

You may not have access to the research information developed as part of this study until it is completed. If you're interested, a brief summary of the results can be mailed to you.

Who can answer my questions about this study?

If at any time you feel you have had a research-related injury, or for questions, concerns, or complaints about the study you may contact t Mohab Ibrahim, MD, PhD at 520-874-7246.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Human Subjects Protection Program at 520-626-8630 or online at https://research.arizona.edu/compliance/human-subjects-protection-program.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact Mohab Ibrahim, MD, PhD at 520-874-7246

If you have questions, concerns, or complaints about the use or sharing of your health information or would like a copy of the Banner Notice of Privacy Practices, you may contact the Banner Research HIPAA Liaison at 602-839-4583 or BHResearchCompliance@bannerhealth.com.

To cancel your authorization for access to PHI you must notify the *Principal Investigator* and/or *Research Team* in writing at the following address:

Research Coordinator
1501 N. Campbell Ave. Suite 4401
Tucson, Arizona 85724-5114

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Signing the consent form

I have read (or someone has read to me) this form, and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study and I authorize the use and/or disclosure of my PHI. I am not giving up any legal rights by signing this form. I will be given a signed copy of this form**.**

Printed name of subject	Signature of subject	Date

Investigator/Research Staff

I have explained the research to the participant or the participant's representative before requesting the signature(s) above. There are no blanks in this document. A signed copy of this form has been given to the participant or to the participant's representative.

Printed name of person obtaining consent	Signature of person obtaining consent	Date