Study Protocol and Statistical Analysis Plan

Title of Study: N-Acetylcysteine Roles in Preserving Renal Function Measured by Urinary KIM-1 (Kidney Injury Molecule-1) and Serum Creatinine on Cancer Patients With Cisplatin Based Chemotherapy: A Randomized Placebo-Controlled Trial

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Study Protocol

Objectives

The goal of this clinical trial is to learn if N-Acetylcysteine drug works to protect kidney function in adults patient with cancer. Kidney function will be measured by laboratory parameter using urine sample (KIM-1 urine) and blood sample (serum creatinine). The main questions it aims to answer are:

1. Does N-Acetylcysteine lower the level of KIM-1 (Kidney Injury Molecule) in patients urine indicating kidney function protection?
2. Does N-Acetylcysteine lower the level of creatinine in patients blood indicating kidney function protection?

Design:

This is an interventional study with a double-blind randomized clinical trial approach focusing on phase 2/ phase 3 treatment study. Subjects that meet the eligibility criteria will be recruited and randomized into two groups, the treatment or the control group.

Methods:

Location. This study will be conducted in Cipto Mangunkusumo Hospital, Central Jakarta, Indonesia, from September 2025 until August 2027.

*Sample and Recruitment.*Patients that meet the eligibility criteria mentioned below will be recruited. Patients with the minimum age of 18 years, with no maximum age, without any sex or gender restriction are allowed to participate in this study.

The Inclusion Criteria:

- Patient with cancer/ malignancy proven by histopathological examination
- Patient with GFR ≥60 ml/mins/1,73 m^2
- Patient with normal complete blood count and liver function test result
- Patient with good performance status (Karnofsky score ≥80)
- Patients with cisplatin based chemotherapy

The Exclusion Criteria:

- Patient that can not tolerate N-Acetylcysteine usage
- Patient with history of hypersensitivity to N-Acetylcysteine
- Patient that given other potentially nephrotoxic drug, such as furosemide, non-steroidal anti-infammatory drugs, aminoglycosides, amphotericin B, cephalosporine
- Patient that given other chemotherapy drug, such as permetrexed, ifosfamide, gemcitabin, bevacizumab, cetuxsimab
- Patient with history of malignant or uncontrolled hypertension
- patient with congestive heart failure, kidney structure abnormality, and acute infection

• Pregnant or lactating women
• Patient refusing to participate in the research

Procedure. Patients that are willing to participate and meet all the eligibility criteria will be given the information about the aims of the study, the procedures they will undergo, and will be asked to fill in the informed consent form. If the participants were unable to read and/or write, or due to their age or other reasons unable to make the decision for themselves, a legal guardian will be informed and will be asked to fill the informed consent form instead. All the participants then will undergo clinical examination including history taking and physical examination. They will also have their sample (blood and urine) taken at three different times: before they received the intervention, 1 week after the intervention, and 3 weeks after the intervention. The urine sample that will be taken is the morning urine and it will be placed in a urine pot. Meanwhile, the blood sample from veins will be placed into two tubes, the purple one that contains EDTA and the green one that contains heparin. All of the samples will be sent to the laboratory for further analysis.

Then, all of the participants will be randomized into two groups, the intervention and the control group. The intervention group will be given N-Acetylcysteine tabs 1200 mg twice a day for 7 days, the day before cisplatin chemotherapy, on the chemotherapy day, and five days after the chemotherapy. Meanwhile, the control group will be given the placebo and cisplatin chemotherapy. All of the participants in the two groups will be given the same hydration regimen before the chemotherapy session, which is 500 mL normal saline 0,9% for 6 hours and will be continued during the session.

The investigator team will be evaluating the adverse effects, hospitalization, and death in all of the participants during the research. If a participant is experiencing adverse effects during the research, they will be asked to come to our hospital for further evaluation. The research team then will treat them as seen appropriate and will evaluate whether they were eligible to continue participating in this study. Another informed consent will be asked if necessary. All of the participants will be asked to come for examination and sample collection 1 week and 3 weeks after the intervention and chemotherapy session.

Statistical Analysis Plan

The participants' data will be recorded in a case report form before it will be uploaded into the electronic database. Data will be analyzed using the SPSS 27.0 version. Descriptive tests using univariate analysis will be conducted for the demographic data. Categoric data will be presented in number and percentage. Meanwhile, numeric data with normal distribution will be presented in mean and standard deviation, and numeric data with abnormal distribution will be presented in median, minimum, and maximum range.

Comparative study will be conducted using bivariate tests of the urinary KIM-1 and serum creatinine data in both groups before and after the intervention. If the data were normally distributed, an independent T test will be conducted, but if the data were not normally distributed, a Mann-Whitney test will be conducted instead. The result will be interpreted as statistically significant if the p value is under 0.05 with confidence interval 95%. All of the data from the participants that were lost to follow up, refused to continue, or died during the study will not be included in the analysis.