Chapter 1

Introduction

1.1 Background

Cancer is known as a deadly disease that altered the signaling and metabolism of cells causing an uncontrolled proliferation and division of cells eventually leading to migration of the cancer cells which is called invasion. Breast cancer is popular as the most frequent cancer that appears in women. Besides, It is also known to be listed second as the most frequent cause of death within women globally.

Breast cancer further divided into several subtypes including luminal A, mesenchymal (M), normal breast like tumors, Mesenchymal stem like (MSL), Luminal B, Immunomodulatory (IM), Human Epidermal Growth Factor Receptor 2 (HER2-), and Basal like which is also known as triple negative breast cancer (TNBC). TNBC is a subtypes of breast cancer that is identified to not have a Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2 (Lehmann et al., 2011; Perou, 2011). With its low expression of HER2, ER, and PR, it is known to be correlated with high expression of other proteins such as CK14, caix, CK5, p63, caveolin, EGFR (Epidermal Growth Factor Receptor)/HER1 (Rakha et al., 2008). According to Goncalves et al, women that are diagnosed with TNBC will have 19% lower overall survival (5 years) and 18% lower in disease free survival compared to other non TNBC (Gonçalves et al., 2018). TNBC is also known to account for 15% of breast cancer worldwide with around 200.000 cases yearly. Furthermore, TNBCs is also known to have a more aggressive and worse prognosis compared to the other subtypes and has higher recurrence rates (Charpentier & Martin, 2013; Malorni et al., 2012).

Breast cancer can be treated with chemotherapy, lumpectomy, mastectomy, and also radiation. The most effective therapy for breast cancer requires good efficacy with minimal side effects (Fisusi &

Akala, 2019). Alternative treatments for TNBC are more limited compared to the other subtypes (non-invasive breast cancer). Several studies show that in treating TNBC, a single treatment such as chemotherapy alone or single drug were shown to be less effective and did not show any significant improvement in patients (Chalakur-Ramireddy & Pakala, 2018). Beside, monotherapy could lead to drug resistance in cancer patients. Combination therapeutics approach could be considered for TNBC treatment as it has been proven to be a more effective way in treating it. With this, drug combination has shown to work well in TNBC patients avoiding any drug resistance and side effects of the drug compared when it's administered as single drugs (Chalakur-Ramireddy & Pakala, 2018). Furthermore, according to NCCN breast cancer guidelines, the drug combinations that are currently being used to treat TNBCs are only useful for limited cases and not all TNBCs cases (*NCCN Guidelines for Patients: Metastatic Breast Cancer*, 2023). However, doing an experiment looking for drug combinations is labor work and requires a lot of resources ,making it inefficient and costly. In this study, Orthogonal Array Composite Design (OACD) was implemented to help reduce the amount of work to optimize drug combinations for TNBC cell lines. An algorithm called Linear Regression was used to optimize the drug combination by showing the prediction of the best drug combination using the regression coefficient equation given from the MATLAB® R2022b native Apple®.

1.2 Objective

The objective of this experiment was to study drug dose combinations in spheroid models TNBC cell lines (MDA-MB-231) using OACD. Other objective of this experiment was also to find more potential drug combinations that could be used in TNBC cases.

1.3 Hypothesis

The expectations of this study is that a potential combination of drugs will be found for TNBC treatment by inhibiting the migration of MDA-MB-231 spheroid.