

Breast cancer, chemotherapy and treatments

Li-Pin Kao^{1,2*}

¹Department of Basic Medical Sciences, Purdue University, West Lafayette, Indiana, USA

²Centre for Cancer Research, Purdue University, West Lafayette, Indiana, USA

Abstract

Breast cancer, the first most common malignant tumor in women worldwide. Many etiological factors such as a wide spectrum of clinical manifestations caused by family clustering, hormonal factors, physiology changed, environmental inducers, and life styles. Although there are many FDA-approval drugs for breast cancers. Tumors are heterogenous and individual has inherited different genetic background. Thus, it is hard to find an effective treatment and it may recurrent after recovery from first treatment.

Introduction

The mortality rate exceeds 144,000 cases and most of the breast cancer (BC) cases are resistant to traditional chemotherapy and radiotherapy. A wide variety of chemotherapeutic agents have been tried and are in use, including tamoxifen, docetaxel, anthracyclines (i.e. doxorubicin, and epirubicin), taxanes (i.e. paclitaxel, and docetaxel), 5-fluorouracil, cyclophosphamide, and carboplatin. No regimen has been proved to be curative. Often, the response rate and prolongation of survival are minimal (a few months or less), and there is a significant morbidity associated with poor treatment effects. Surgical resection is considered the first-line options for early tumors, although there is no agreement on which is the best approach. Interestingly, triple negative has been reported has higher chemo-resistance than other type of breast cancers with low autophagy activity [1,2]. Antiestrogen resistant cell lines exhibit increased basal autophagy when compared with their antiestrogen sensitive parental cells [3]. Study has shown to manipulate transient receptor potential channel 5 (TRPC5), a Ca²⁺ permeable cation channel, which helps in promotes autophagic activity [4]. Studies also demonstrate the breast cancer usually pro-survival after autophagy activity increase by various therapeutics [5-7]. Moreover, Tamoxifen and Faslodex (ICI) both induce autophagy in ER+ breast cancer cells without [3,5,8-11]. There are small molecules which has been in FDA-approval drug lists and applied in clinical trial in different diseases (Table 1 and 2).

Antiestrogen resistant cell lines exhibit increased basal autophagy. Study had demonstrated combination of Tamoxifen or Faslodex (ICI) with hydroxychloroquine (HCQ) had different anti-estrogen responsiveness *in vitro* or *in vivo* which may affect by tumor microenvironment (i.e. chemokines, macrophage development/activity [12]). Inhibiting autophagy via autophagy-related genes (i.e. autophagy-related gene (Atg) 5, Atg7, and p62/SQSTM1) silencing potentiated antiestrogen-mediated cell death, indicating that antiestrogen stimulated autophagy is pro-survival and a critical mechanism of therapy resistance [3]. Overall, it indicated that increased in autophagy activity in early recurring breast cancer when compared with breast cancer that never recurs. Moreover, elevated p62 is significantly

correlated with poor survival in breast cancer patients [12], suggesting a role for autophagy in breast cancer recurrence. Manipulation of autophagy activity can be a potential therapy for chemotherapy *in vitro* or *in vivo*. Therefore, diagnosis or detection at an early stage is crucial to allow the application of treatments for increasing the life expectancy of the patient.

Table 1. Autophagy inhibitors during autophagy pathway. Modified from [13].

Name	Mechanism	
3-Methyladenine	phosphoinositide3-kinase (PI3) inhibitor	Autophagosome formation
Wortmannin	PI3-kinase inhibitor	Autophagosome formation
LY294002	PI3-kinase inhibitor	Autophagosome formation
SBI-0206965	Unc-51-like kinase 1 (ULK1) Inhibitor	Autophagosome formation
Spautin-1	ubiquitin-specific peptidases (USP10) and (USP13) inhibitor	Autophagosome formation
SAR405	Vacuolar Protein Sorting Protein 18 and 34 (Vps18 and Vps34) inhibitor	Autophagosome formation
NSC185058	autophagy-related gene 4 (ATG4) inhibitor	Autophagosome formation
Verteporfin	Unknown	Autophagosome formation and accumulation
ROC325	Unknown	Lysosome
Lys05	Unknown	Lysosome
Chloroquine	Unknown	Lysosome
Hydroxychloroquine	Unknown	Lysosome

Correspondence to: Li-Pin Kao, Department of Basic Medical Sciences, Purdue University, West Lafayette, Indiana, USA, E-mail: kaolipin@gmail.com

Key words: breast cancer, autophagy, autophagy-related inhibitors, chemotherapy

Received: February 03, 2018; **Accepted:** February 20, 2018; **Published:** February 23, 2018

Table 2. Current Hydroxychloroquine (HCQ) clinical trials. Modified from [13].

Treatment	Condition	Phase Trial	Reference # at ClinicalTrials.gov
HCQ + sunitinib malate	Adult solid neoplasm	I	NCT00813423
HCQ + vorinostat	Malignant solid tumor	I	NCT01023737
HCQ + sirolimus or vorinostat	Advanced cancers	I	NCT01266057
HCQ + Protein kinase B (Akt) inhibitor MK-2206 dihydrochloride (MK2206)	Advanced cancers	I	NCT01480154
HCQ as a single agent	Estrogen receptor positive breast cancer	I	NCT02414776
HCQ + gemcitabine	Advanced adenocarcinoma	I/II	NCT01506973
HCQ + Interleukin 2(IL-2)	Renal cell carcinoma	I/II	NCT01550367
HCQ + vorinostat	Colorectal cancer	I/II	NCT02316340
HCQ + gemcitabine/carboplatin	Small cell lung cancer	I/II	NCT02722369
HCQ + capecitabine	Pancreatic carcinoma	II	NCT01494155
HCQ as a single agent	Prostate cancer	II	NCT00726596
HCQ + Abraxane and gemcitabine	Pancreatic carcinoma	II	NCT01978184

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