ABCB1 polymorphisms as prognostic factor for prediction of recurrence risk in TNBC patients undergoing TAC chemotherapy

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Introduction

TNBC and Drug Resistance

- ***Triple Negative Breast Cancer (TNBC),*** accounts 10-14% of breast cancer (Krishnamurthy et al., 2012). TNBC is more aggressive compared to other subtypes and associated with high rate of recurrence, high histological grade and poor prognosis

- Due to genetic heterogeneity, TNBC patients present significant interindividual differences of treatment efficacy.

- TNBC treatment, gap areas:

  1. Lack of clinical biomarkers to distinguish TNBC subtypes
  2. Lack of predictive biomarkers for TNBC that will develop resistance to chemotherapy

Research question: *How to identify TNBC patients who are likely to be chemosensitive and those who are at higher risk for recurrence?*

Introduction

- ATP-binding cassette sub-family B member 1 (*ABCB1*) is drug efflux transporter that play a role in the efflux pump of a variety of environmental carcinogens as well as antineoplastic agents (Kerb, 2006; Zhou, 2008).

- Genetic variations of *ABCB1* had been reported to be responsible for resistance to many anti-cancer drugs and therapeutic failure (Sensorn et al., 2013; Wu et al., 2009; Kim et al., 2015)

- Since report are limited on the impact of *ABCB1* polymorphisms on TNBC patients undergoing TAC chemotherapy regimen, the present study was undertaken.

Main Objective

To investigate whether *ABCB1* polymorphisms have any impact in modulating Taxane, Adriamycin and Cyclophosphamide (TAC) chemotherapy response and treatment outcome in TNBC patients.

Methodology

Study setting and study subjects

- A part of RUT grant (1001/PPSP/853005) and approved by Research Review Board and Ethics Committee (USM) and MOH.

- Cross-sectional study: TNBC patients were recruited from SOPD and Nuclear Medicine, Radiotherapy & Oncology Department, Hospital USM.

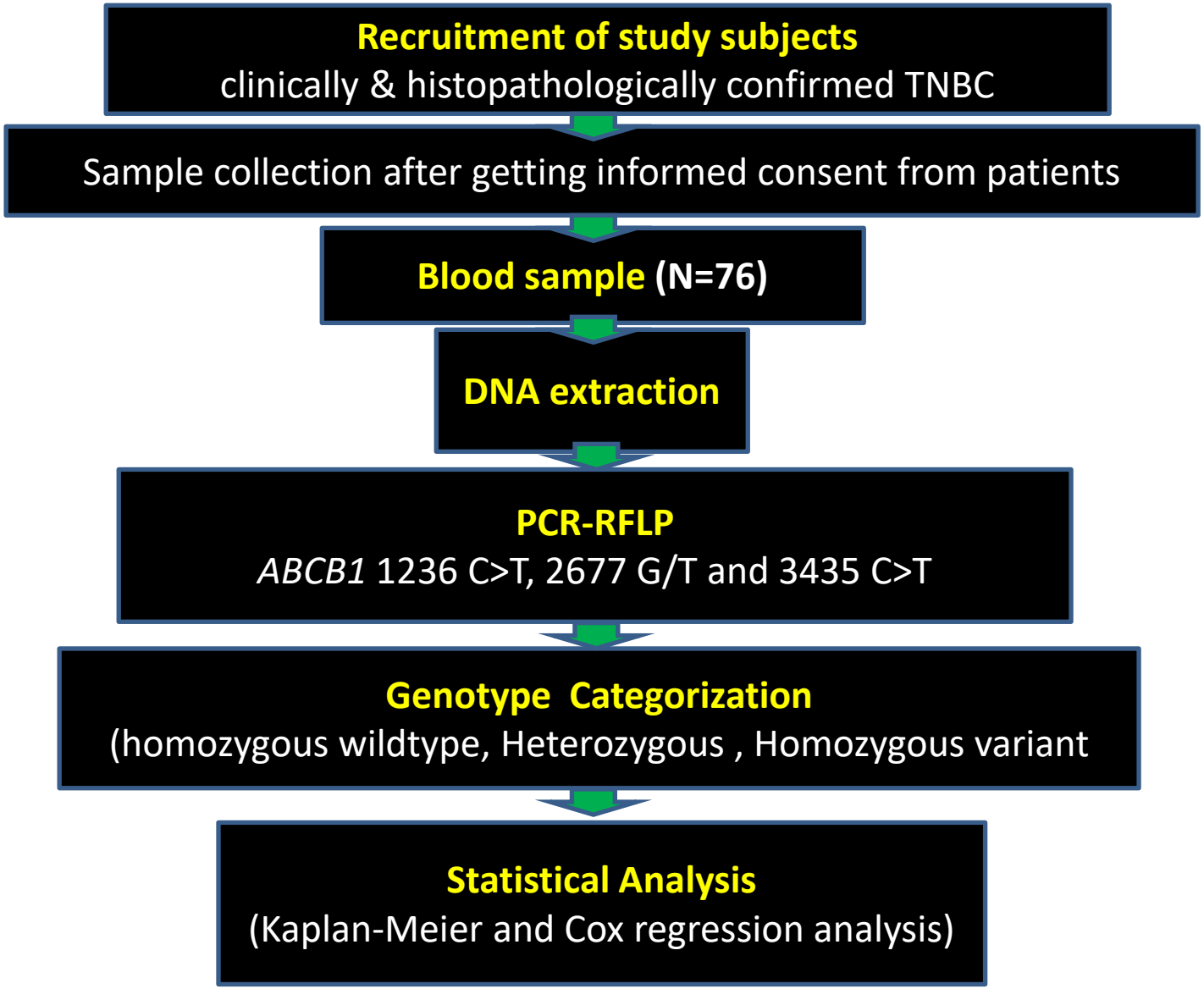
Inclusion criteria

- Clinically and histopathologically confirmed TNBC patients
- TNBC patients, who undergo surgery and complete 6 cycles with adjuvant chemotherapy with TAC protocol

Exclusion criteria

- Breast cancer patients who undergo only surgery

Research Flowchart



Results

Table 1: The genotype frequencies of ABCB1 polymorphisms and clinicopathological characteristics of TNBC patients and its association with treatment response

	Relapsed (n=25)	Non-relapsed (n=51)	p-value
ABCB1 1236 C>T			
CC and CT	23 (92 %)	46 (90 %)	1.000
TT	2 (8 %)	5 (10 %)	
ABCB1 2677 G>T			
GG and GT	20 (80 %)	43 (84 %)	0.639
TT	5 (20 %)	8 (16 %)	
ABCB1 3435 C>T			
CC and CT	17 (68 %)	46 (90 %)	**0.016***
TT	8 (32%)	5 (10 %)	
Histology subtype			
IDC	17 (68 %)	45 (88 %)	**0.033***
Other (medullary & metaplastic)	8 (32 %)	6 (12 %)	
Tumor grade			
Grade 1 and 2	11 (44 %)	22 (43 %)	0.943
Grade 3	14 (56 %)	29 (57 %)	
Stage			
I and II	18 (72 %)	46 (90 %)	**0.041***
III	7 (28 %)	5 (10 %)	
Axillary Lymph node metastasis			
Negative	7 (28 %)	29 (57 %)	**0.018***
Positive	18 (72 %)	22 (43 %)	

- The mean age of TNBC patients at diagnosis was **48.9 ± 9.67 years.**
- ***ABCB1*** **3435 TT, medullary/metaplastic subtypes, Stage III** and **positive ALN metastasis** were found to be significantly higher in relapsed as compared to non-relapsed groups ($p < 0.05$).

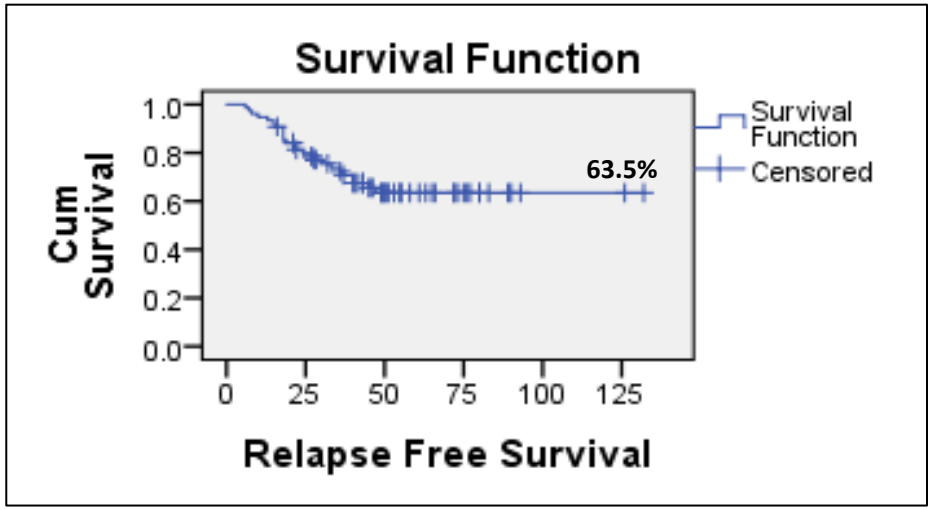


Figure 1: Cumulative 5 year relapse free survival of TNBC patients

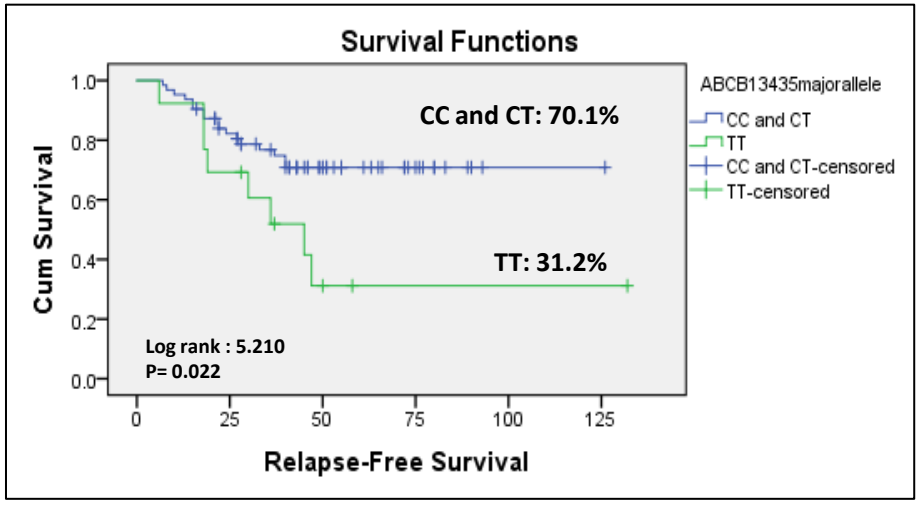


Figure 2: Kaplan Meier curves of RFS probability of TNBC patients according to *ABCB1* 3435 C>T polymorphism

Table 2: Univariate and Multivariate Cox analysis on ABCB1 polymorphisms of TNBC patients and risk of recurrence.

Polymorphism	Frequency (%)	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]	p-value
***ABCB1* 1236 C>T**				
CC and CT	69 (91%)	1 (Reference)	1 (Reference)	
TT	7 (9%)	0.729 (0.172-3.096)	-	-
***ABCB1* 2677 G>T**				
GG and GT	63 (83%)	1 (Reference)	1 (Reference)	
TT	13 (17%)	1.200 (0.450-3.200)	-	-
***ABCB1* 3435 C>T**				
CC and CT	63 (83%)	1 (Reference)	1 (Reference)	
TT	13 (17%)	2.560 (1.103-5.941)	2.560 (1.103-5.941)	0.029*

p<0.05, statistically significant

Discussion

First report to identify pharmacogenetic biomarker for predicting chemotherapy response in TNBC patients undergoing TAC chemotherapy regimen.

- **<u>Results demonstrated that:</u>**

- **Mean age at diagnosis was 48.9 ± 9.67 years**
  -Concordant with two (2) previous studies on TNBC patients in Malaysia (Kanapathy Pillai et al., 2012; Tan et al., 2009) and other populations (Dean and Rhodes, 2014; Dogra et al., 2014; Qiu et al., 2016).

- **Cumulative 5-year of RFS was 63.5%.**
  - In agreement with several other studies that observed a higher DFS in TNBC patients (Buyukhatipoglu et al., 2015; Ovcaricek et al., 2011; Pagoda et al., 2013, Sun et al., 2016 and Yuan et al., 2014)

- **Clinicopathological variables**
  - Positive axillary lymph nodes, other histology subtypes and stage were associated with poor DFS and OS (Sun et al., 2016; Kim et al., 2015; Yuan et al., 2014;).

Discussion

- Previous studies suggest that the TT genotype might lead to decreased *ABCB1* mRNA levels in mammary carcinoma cell lines or in breast tumor (Delou et al., 2017)

- It has been reported to exert impact on protein function by changing mRNA splicing, folding and stability or modification of translation efficiency (Jelen et al., 2015)

- This polymorphism also associated with clinical toxicity and high docetaxel level in the blood of breast cancer patients (Tran et al., 2006). This may cause accumulation of the metabolites within the cells and causes cellular damage or apoptosis alteration (Tazzite et al., 2016).

- Our finding on *ABCB1* 3435 TT genotype associated with higher risk of relapse was contradictory with the previous studies (Chang et al., 2009, Sensorn et la., 2013, Wu et al., 2012, Kim et al., 2015 and Li et al., 2017).

    - Difference in the genetic background of the study subjects
    - Type of treatment
    - Limited number of the study subjects
    - Difference in cancer subtypes
    - Different model for comparison-

      dominant model (CT+TT vs CC) or **recessive model (TT vs CC+CT)**

Conclusion

The present study demonstrates the potential use of ABCB1 3435 TT homozygous variant genotype as a potential biomarker in predicting risk of recurrence in TNBC patients undergoing TAC chemotherapy regimen.

Acknowledgement

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THANK YOU