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Effect of Genetic Polymorphism ABCB1 C3435T on the Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) in Breast Cancer Patients

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Abstract

Background: A hypothesized that inherited polymorphisms in the drug-transporter ABCB1 gene, may interfere with inter-individual variations in quality of life in breast cancer patients treated with Docetaxel.

Methods: Participants included 60 women considering genetic testing to ABCB1 C3435T polymorphism. Functional Assessment of Cancer Therapy – Taxane FACT-Taxane (Version 4) questionnaires were administered in the last cycle of docetaxel treatment. ANOVA and logistic regression were used to estimate correlation of QOL with different single nucleotide polymorphism.

Results: Sixty Egyptian women (mean age, 49.8 y; range, 27–66 y) treated for breast cancer with Docetaxel were recruited. Genotype frequencies in patient were 48.3 % for CC, 40 % for CT and 11.7 % for TT. We found that patients carrying the 3435T/T genotype (11.7%) were the most likely to have a marginal improve in QOL (mean total score=120.56) in comparison with patients carrying the 3435T/C genotype and 3435C/C genotype. The result according to statistical analysis indicated that there is no significant association between ABCB1 C3435T polymorphism and QOL (P=0.544).

Conclusion: Inter-individual variability in QOL breast cancer patients could slightly affected by ABCB1 C3435T polymorphism but is not significant.

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Introduction

Taxanes are a class of chemotherapy agents that promote the polymerization of tubulin into highly stable, intracellular microtubules. These microtubules cause cell death by interfering with normal cell division [1-2]. Docetaxel (DCX; TaxotereTM) is a taxoid derivative that displays high anticancer activity alone or in combination against several common solid tumors, including breast, lung and prostate cancer [3]. Unfortunately, taxane therapy is associated with side effects such as peripheral neuropathy, myelo-suppression, arthralgias, myalgias, and skin reactions that may adversely affect patient-reported quality of life (QOL). Peripheral neuropathy in particular can be severe. This toxicity is cumulative across the course of therapy, can be a dose-limiting toxicity, and may lead to dose reduction or cessation of therapy [4].

Adenosine triphosphate (ATP)-binding cassette (ABC) subfamily B member 1 (*ABCB1*) belongs to a large superfamily of primary active transporters that are present in all kingdoms of life. This gene is also known as multi¬drug resistance gene 1 (MDR1) or cluster of differentiation 243. ABCB1 gene encodes a protein known as permeability glycoprotein (P-gp), which is responsible for energy (ATP)-dependent efflux of drugs. It has broad substrate specificity [5].

The ABCB1 gene encoding P-gp is highly polymorphic. Till date, ~66 coding single-nucleotide polymorphisms (SNPs) in ABCB1 gene have been identified. Out of these, 22 are synonymous and 44 nonsynonymous [6]. Several studies have shown that these polymorphisms alter the functional expres¬sion of the ABCB1 gene [7-8]. The expression, efflux, substrate specificity, and mRNA stability of P-gp are influenced by various SNPs present in ABCB1 gene [9], also shown that genetic variations affecting the function and expression of ABCB1 are responsible for resistance to many anticancer drugs and therapeutic failure [10-12].

Many cancer studies link genetics and treatment outcomes, which then links treatment and QOL outcomes, but not directly between genetics and QOL outcomes To obtain a better understanding of these linkage ,we attempted to investigate the correlate of the quality of life breast cancer patients treated with docetaxel monotherap and ABCB1 genetic polymorphism (C3435T). This information then can be factored into decision-making regarding the value of these chemotherapy agents relative to other options.

Patients and Methods

Study population

The study subjects consisted of a consecutive series of breast cancer patients were admitted to the oncology department at Ain Shams University (ASU) Hospitals, Cairo, Egypt and confirmed cases by the pathologists of the ASU hospital between Marsh 2015 and September 2016. The breast cancer patients, willing to be treated by the chemotherapy of Taxane, which called docetaxel (Taxoter®), were recruited as preliminary subjects.

All eligible participants were treated by docetaxel 3 times in the treatment course. All patients provided written informed consent before inclusion in the study. Anyone that failed to receive the full course of treatment or did not participate by informed consent was

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excluded from this study. The total 60 eligible participants were recruited with their characteristics as shown in table 2.

This study was approved by the Ethics Committee of Clinical pharmacy department, Ain Shams University, Cairo, Egypt.

Quality of life assessment

The Functional Assessment of Cancer Therapy–Taxane (FACT-Taxane) is a self-report instrument that was developed to measure the health-related QOL of patients receiving docetaxel in the end of treatment cycles which include Physical Well-Being (PWB), Social/Family Well-Being (SFWB), Emotional Well-Being (EWB), Functional Well-Being (FWB) and also assessing symptoms related to arthralgia, myalgia, and skin discoloration as shown in Table 1 [13]. The FACT-Taxane is comprised of the FACT-General (FACT-G) plus a 16-item Taxane subscale [14].

Genotype

Genomic DNA was extracted from whole blood (2ml) using QIAamp DNA blood Mini Kit. C3435T (rs1045642) polymorphisms was analyzed using matching primers and TaqMan MGB probes (Thermo Fisher Scientific) labeled with VIC/FAMTGTTGGCCTCCTTTGC TGCCCTCAC[A/G] ATCTCTTCCTGTGACACCACCCGGC for allelic discrimination (assay IDs: C_7586657_20 for C3435T). DNA (5 µl) was amplified with TaqMan PCR Universal Master Mix and Assay Mix in a final volume of 20 µl. Forty cycles with denaturation at 95°C, annealing and extension at 60°C were performed.

Statistical analysis

The collecting data was revised, coded, tabulated and statistically analyzed using SPSS13.0 software program (statistical package for social science). Both descriptive and comparative analyses were done. Different statistical tests were performed for quantitative and qualitative variable the level of significance was taken at p value < 0.05.

Result

Study subjects' clinical characteristics

Table 2, describes the general characteristics of participants. The mean levels of age and weight of the studied patients were 49.8 years (ranged from 27.0 to 66.0) and 82.4 kg (ranged from 50 to 140) respectively. The BMI mean level was 30.8kg/m² (ranged from 19.8 to 45). The BMI were normal 16.7% (10/60), overweight 28.3% (17/60), and obese 55.0 %(33/60). As regards menopausal status, 41.7% (25/60) of patient's group were premenopaused and 58.3% (35/60) were postmenopaused. The tumor grades mean levels were 61.7% (37/60) grade 2, 11.7% (7/60) grade 3, 1.7% (1/60) grade 1, while (13/60) was missed.

Parameter	Mean (range) Or N (%)	
Age	49.8 (27-66)	
Weight	82.4 (50- 140)	
BMI (kg/m²)²	30.8 (19.8-45.2)	
	Normal	10 (16.7%)
	Overweight	17 (28.3%)
	Obese	33 (55.0%)
Menopausal state	Premenopausal	25(41.7%)
	postmenopausal	35(58.3%)
Tumor grade	Grade 1	1(1.7%)
	Grade 2	37(61.7%)
	Grade 3	7 (11.7%)
	Grade4	2 (3.3%)

N= number of patients.
BMI= body mass index.

Table 2: Patient characteristics (n=60).

(FACT-Tax) Scales
FACT-G
Physical Well-Being (PWB)
I have a lack of energy
I have nausea
Because of my physical condition, I have trouble meeting the needs of my
Family
I have pain
I am bothered by side effects of treatment
I feel ill
I am forced to spend time in bed
Social Well-Being (SWB)
I feel close to my friends
I get emotional support from my family
I get support from my friends
My family has accepted my illness
I am satisfied with family communication about my illness
I feel close to my partner (or the person who is my main support)
I am satisfied with my sex life
Emotional Well-Being (EWB)
I feel sad
I am satisfied with how I am coping with my illness
I am losing hope in the fight against my illness
I feel nervous
I worry about dying
I worry that my condition will get worse
Functional Well-Being (FWB)
I am able to work (include work at home)
My work (include work at home) is fulfilling
I am able to enjoy life
I have accepted my illness
I am sleeping well
I am enjoying the things I usually do for fun
I am content with the quality of my life right now
Taxane subscale (Tax)
I have numbness or tingling in my hands
I have numbness or tingling in my feet
I feel discomfort in my hands
I feel discomfort in my feet
I have joint pain or muscle cramps
I feel weak all over
I have trouble hearing
I get a ringing or buzzing in my ears
I have trouble buttoning buttons
I have trouble feeling the shape of small objects when they are in my hand
I have trouble walking
I feel bloated
My hands are swollen
My legs or feet are swollen
I have pain in my fingertips
I am bothered by the way my hands or nails look

Table 1: Functional Assessment of Cancer Therapy-Taxane of Quality of Life questionnaires.

Table 3 provides the overall frequency of different ABCB1 C3435T genotypes. In breast cancer patients, the CC genotype was found in 48 %, CT genotype was found in 40 % and TT genotype was found in 11.7 %.

Polymorphism	Genotypes/SNPs	Number(%)
ABCB1 C3435T	TT	7 (11.7 %)
	TC	24(40.0 %)
	CC	29 (48.3 %)
ABCB1=Adenosine Triphosphate Binding Cassette Sub-Family B Member 1. SNPs=Single-nucleotide polymorphisms.		

Table 3: Number of patients for each genotype.

Relationships between C3435T polymorphism of ABCB1 genes and FACT-TAXAN total score (QOL) after docetaxel treatment in patients with breast cancer (Table 4).

All patients were required to complete the Arabic version of the Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) version 4 scales. The FACT-TAXAN total score were tabulated as mean and range and compared with ABCB1 C3435T genotypes by using ANOVA test in the end of third cycle of docetaxel as shown in table 4 and figure 1. A marginal relationship had been found between the QOL and the homozygous 3435T/T genotype (FACT-Taxan total score mean in TT genotype patients were 120.56/172). But, there were no significant relationship. However, the relationships between the different SNPs of the ABCB1 gene and the quality of life after docetaxel treatment were tested and there were no significant differences (P=0.544) between the ABCB1 (C3435T) SNPs and the patients QOL.

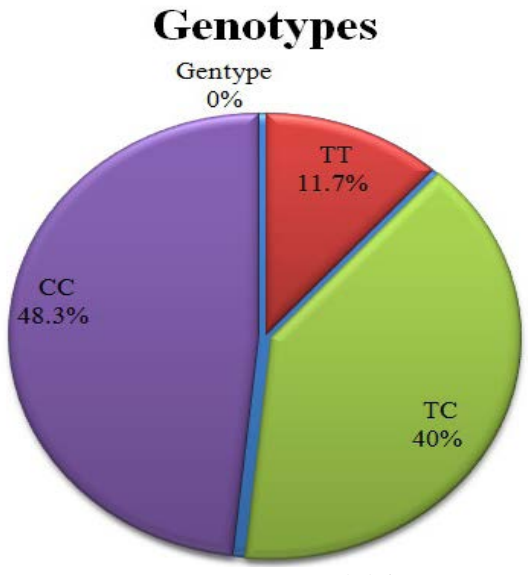

Figure 1: MDR1 expression in patients with different genotypes.

Discussion

In this study, we collected information about the quality of life in the breast cancer patients after they had been treated with docetaxel by using Functional Assessment of Cancer Therapy FACT-Taxane (Version 4) questionnaires. Docetaxel is an anticancer agent that is highly effective in the treatment of breast, non-small cell lung, ovarian, and head and neck cancers [3]. However, it will not only harm normal cells simultaneously when it destroys tumor cells, but also effect on quality of life due to accompanying side effects. Since ABCB1 gene play important role in the metabolism and distribution of docetaxel, the polymorphism of this gene could affect the survival outcome of treatment in breast cancer patients [15].

Further preliminary evidence suggests that a cancer patient's genetic makeup influences how the patient experiences fatigue, one of the most common side effects of cancer. It is believed to be the first finding of a possible link between genetics and a cancer patient's QOL. The North Central Cancer Treatment Group recently completed a hypothesis-generating study which aimed to investigate the existence of a direct link between genetic variation and cancer patient QOL, independent of cancer treatment and outcomes [16].

In current study, There was a slight difference between the 3 SNPS (TT,TC,CC) figure 2 , where the patients who carrying ABCB1 3435TT genotype were better in quality of life scores than other two SNPs (CC,TC). Unfortunately, there was no statistical difference between ABCB1 polymorphism and quality of life outcome in our study, may be due to small sample size, the small sample size in a rare different genotype category caused the statistic power to decrease.
Kafka and colleagues have previously established the association of ABCB1-C3435T gene polymorphism with treatment outcomes in breast cancer patients treated with NACT, which showed a better clinical response in patients carrying the TT genotype of ABCB1-C3435T (p = 0.029) [17].

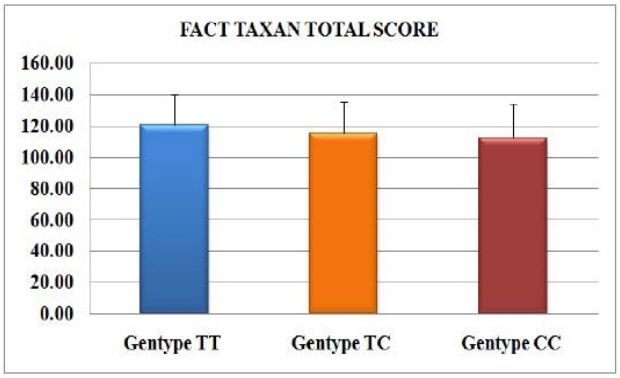

Figure 2: The relation between different genotypes and FACT-taxan score (QOL).

Rodrigues and colleagues did not find a significant correlation between SNPs C3435T and clinical response [18]. Only one study has tried to question the protective role of the ABCB1-3435CT T-allele on breast cancer patients' survival. Patients with ABCB1-3435CT genotype showed a trend to shorter OS compared to patients with ABCB1-3435CC genotype (p = 0.06) in 108 MBC patients treated with anthracycline and paclitaxel [19].

To our knowledge, this study is the first to identify a relationship between ABCB1 C3435T Polymorphism and quality of life in breast cancer patients treated with docetaxel. In conclusion, we studied the relationship between quality of life after docetaxel treatment and ABCB1 C3435T gene polymorphism in Egyptian breast cancer women. The related publication is still limited and uncertain, which could be due to the rare polymorphisms that limited the study sample size. We have recorded the quality of life according to the suggestions of FACT-Taxane scoring. Hopefully, more researchers will follow this study to cumulate more evidence about this issue.

Conclusion

The current data suggested that, there could be correlations between certain side effects of docetaxel treatment and polymorphisms of ABCB1 C3435T, but there was no significant between QOL breast cancer patients and ABCB1 C3435T polymorphism.

Competing Interests

The authors declare that they have no competing interests in this work.

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