

Pharmacokinetic and Pharmacodynamic studies on Docetaxel in Breast Cancer patients: Role of Cytochrome 3A4 in Relation to Activity

Thesis submitted for partial fulfillment the master degree in
pharmaceutical sciences (clinical pharmacy)

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الدراسات الحركية والديناميكية لعقار الدوسيتاكسيل فى مرضى سرطان الثدي : دور انزيم السيتوكروم وعلاقته بفاعلية العقار

رسالة مقدمة من الصيدلانية

ميرفت مصطفى احمد عمران

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معيدة بقسم بيولوجيا الأورام-المعهد القومى للأورام- جامعة القاهرة
للحصول على درجة الماجستير فى العلوم الصيدلية (الصيدلة الاكلينيكية)

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Summary

The present study was conducted to study pharmacokinetic and pharmacodynamic properties of DCX in Egyptian breast cancer patients and the interpatient variability of cytochrome3A4 activity, as estimated using urinary metabolites of exogenous cortisol.

To achieve this goal, fourteen female Patients with metastatic breast cancer, World Health Organization (WHO) performance status 0 to 2, were treated with 100mg/m² single agent DCX, given every 21 days. Hydrocortisone 300 mg was administered intravenously to these patients 2 days before DCX treatment. CYP3A4 activity was determined by estimation of urinary metabolites of hydrocortisone. Pharmacokinetic blood samples were taken after administration of DCX. The correlation between pharmacokinetics, pharmacodynamics and CYP3A4 activity were determined by the following:

- 1- .To phenotype these patients according to the CYP3A4 activity which estimated by the urinary metabolites of exogenous cortisol which detected by HPLC technique.

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قُلْ إِنِّ صَلَاتِي وَنُسُكِي وَمَحْيَايَ
وَمَمَاتِي لِلَّهِ رَبِّ الْعَالَمِينَ

صدق الله العظيم

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Pre-Requisite Postgraduate Courses

Beside the work of this thesis, the candidate has attended the following courses:

General courses:

- 1) Physical chemistry
- 2) Statistics
- 3) Computer science
- 4) Instrumental analysis

Special courses:

- 1) Clinical pharmacokinetic
- 2) Selected topics
- 3) Clinical study design
- 4) Clinical pharmacy practice.

She has successfully passed examination in these courses with a general grade **“very good”**.

Head of Clinical Pharmacy Department
Prof. Osama Ahmad Badary

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Dedication

To my father, who always wanted to see me on that day.

To my beloved, inspiring, and supportive mother; who is always there for me, guiding me to success and making all my dreams come true?

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LIST OF ABBREVIATIONS

AAG	α -1-acid glycoprotein
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
bp	Base pair
6β-OHF	6-beta-hydroxycortisol
BSA	Body surface area
CL	Clearance
FC	Cortisol
C_{max}	Maximum concentration
CYP3A4	Cytochrome P450 3A4
DCX	Docetaxel
ER	Estrogen receptors
FN	Febrile neutropenia
HER2	Human Epidermal growth factor Receptor
PK	Pharmacokinetic
PCR	Polymerase chain reaction
PR	Progesterone receptors
T_{1/2α}	Distribution half life
T_{1/2β}	Elimination half life
V_D	Volume of distribution

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ABSTRACT