CHAPTER I

INTRODUCTION

1.1. Background

Adverse drug reactions or adverse effects contribute to more than 100,000 deaths in the United States each year besides being the fourth leading cause of death following heart diseases, cancer, and stroke. One of the drugs that account for adverse effects is 5-Fluorouracil (5-FU) due to the widespread usage of 5-FU in solid tumor such as colorectal, breast, gastro esophageal, head and neck and other cancers.[1-4] Although 5-FU has benefit in reducing the risk of relapse and prolonging survival[2], 31% to 34% of patients treated experience grade 3–4 toxicity[5-7] with 0.5% of the patients experiencing lethal toxicity.[8] This causes a revision in the benefit/toxicity ratio of 5-FU.[9] Furthermore, based on researches, these patients have low level/deficiency[6] of dihydropyrimidine dehydrogenase (DPD) enzyme, a key enzyme in degradation of 5-FU.[10-14] Consequently, DPD becomes as an important factor for toxicity.[8]

It is likely that a significant proportion of these adverse drug reactions are due to genetically-based differences in gene that encodes DPD enzyme, *DPYD* gene.[5, 9, 15, 16] Consequently, cancer patients carrying mutations in the *DPYD* gene have a high risk to experience severe adverse effects.[16, 17]

Other patient characteristics including gender also have influence in 5-FU clearance, and this is supported by two studies which have shown female

patients experience 5-FU toxicity more frequently and more severely than men.[2, 18, 19]

Although population studies on DPD and *DPYD* gene have been carried out in Caucasian, Chinese, Korean, Japanese, Egyptian, and Turkish population[20, 21], additional study is needed to identify distribution of *DPYD* variants in Malaysian population, especially Malay race due to this is the first study in the world for Malay race based on our literature review.

The identification of patients with an increased risk of severe 5-FU-associated toxicity would allow either dose-adaptation or the application of new non-fluoropyrimidine-based chemotherapeutic drugs.[4, 16]

The understanding of pharmacogenomics can potentially help in the discovery, improvement and finally individualization of anticancer drugs. The identification of genetic variations that predict for drug response is the first step towards the translation of pharmacogenomics into clinical practice.[15, 22]

1.2. Research Questions

What is the distribution of *DPYD* gene variants in Malaysian 5-FU solid tumor patients?

1.3. Research Objectives

1.3.1. General Objective

The objective of this study is to identify and analyze *DPYD* gene variants in Malaysian 5-FU solid tumor patients, also to know the distribution of its variants.

1.4. Research Originality

Our research is the first time study of *DPYD* gene in Malaysian population and this is also the first time study of DPYD gene that study 10 most common variants based on our literature review.

No	Title, Authors, Journal	Research Methodology	Result
1.	Dihydropyrimidine dehydrogenase gene variation and severe 5-fluorouracil toxicity: a haplotype assessment. Amstutz U, Farese S, Aebi S and Largiader CR, 2009. Pharmacogenomics 10(6):931-944.[5]	The first analysis of the DPYD gene at the haplotype level. The entire coding sequence and exon-flanking intronic regions of *DPYD* were sequenced in 111 cancer patients receiving fluoropyrimidine-based chemotherapy. *DPYD* haplotypes were inferred and their associations with severe 5-FU toxicity were assessed.	Association of a haplotype containing no nonsynonymous or splice-site polymorphisms indicates that additional important genetic variation may be located in noncoding gene regions. Comparison with other studies suggests that the relative importance of particular *DPYD* mutations (IVS14+1G>A and c.2846A>T) for predicting severe 5-FU toxicity differs geographically across Europe.

2.	Strong Association of a Common Dihydropyrimidine Dehydrogenase Gene Polymorphism with Fluoropyrimidine-related Toxicity in Cancer Patients. Gross E, Busse B, Riemenschneider M et al., 2008. *PLoS ONE* 3(12): e4003.[16]	Study of entire (23) coding region and comparing DPYD genotype frequencies between cancer patients with good (n = 89) and with poor (n = 39) tolerance of a fluoropyrimidine-based chemotherapy regimen. Analysis using logistic regression.	Showed compelling evidence that, at least in distinct tumor types, a common DPYD polymorphism strongly contributes to the occurrence of fluoropyrimidine-related drug adverse effects. Carriers of this variant could benefit from individual dose adjustment of the fluoropyrimidine drug or alternate therapies.
3.	Mutational spectrum of dihydropyrimidine dehydrogenase gene (DPYD) in the Tunisian population. Fredj RB, Gross E, Chouchen L et al. 2007. C. R. Biologies 330:764–769[23]	Study of 23 exons and its flanking regions of *DPYD* gene by PCR, DHPLC and sequencing methods from 106 healthy Tunisian Arab origins. Analysis by Fisher's Exact test for comparison with other population in Western and Asian.	Tunisian population resembles Egyptian and Caucasian populations with regard to their allelic frequencies of DPYD polymorphisms. New IVS 6–29 G>T was found with allelic frequency 4.7%
4.	Mutations in exon 14 of dihydropyrimidine dehydrogenase and 5-Fluorouracil toxicity in Portuguese colorectal cancer patients. 2004. Salgueiro N, Veiga I, Fragoso M et al. Genet Med 6(2):102–107[24]	Study of 73 Portugese 5-FU treated colorectal cancer patients by PCR, sequencing of exon 14 in *DPYD* gene. Fisher's Exact test for comparison of allelic frequencies between patients with and without gr III-IV toxicity.	Mutations in exon 14 of DPYD gene are responsible for a significant proportion of life-threatening toxicity to 5-Fluorouracil, and screening test before administration is required.

1.5. Research Benefits

Analysis of *DPYD* gene variants in Malaysian 5-FU solid tumor patients is very important. The benefits are:

1. The identification of genetic variations that predict for drug response is the first step towards the translation of pharmacogenomics into clinical practice.
2. Determination of *DPYD* gene variants in Malaysian 5-FU solid tumor patients will provide new important data particularly in Malay race for geneticists and clinicians due to this is the first time in the world based on our literature review.
3. The data will provide preliminary data for next research in Malaysia especially for higher level of association study like case control or cohort.