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Name : Hazwanie Binti Hashim, *PhD*
Title : Integrating Pharmacogenomics-Metabolomics Towards Realising Personalised Medicine For Colorectal Cancer Patients Treated With 5-Fluorouracil
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Colorectal cancer (CRC) is one of the most common cancers among men and women in Malaysia. 5-flurouracil (5-FU)/leucovorin is the standard chemotherapy for colorectal cancer and various other types of cancer including breast, head and neck cancers. However, standard method for dosing 5-fluorouracil (5-FU) still lacks accuracy and reliability. In addition to the body surface area index (BSA) that is currently used in dosing regimen, other factors such as genotype, age, gender and drug-drug interaction needs to be accounted. We explore the value of pharmacogenomics and metabolomics in personalising medicine in patients treated with 5-FU. We intended to profile both the genetics and metabolomics markers that could be useful in the clinical monitoring of patients' responses towards 5-FU and its disease. Genetic polymorphism of DPYD and UGT1A1 show interethnic differences among the populations studied. The frequency of DPYD*5, DPYD 1896 T>C, UGT1A1*28 and UGT1A1*6 was high in this study. Patients who experienced neutropenia had significantly higher serum concentration of 5-FU as compared to those who did not have it (Mann Whitney-U test, p-value= 0.031). Combined regression analysis showed that the predictive power of DPYD*5 and 1896 T>C for serum concentrations of 5-FU in the studied group is 36.6% (p-value= 0.04). However, many factors affecting the efficacy of 5-FU treatment remain to be investigated including optimal drug doses, treatment duration and the synergistic effect between combination of 5-FU with other cytotoxic agents. Current study also highlights the potential use of integrated genotyping and metabolomic tools in monitoring patients' responses towards 5-FU and to pave the way towards personalised medicine (PM). Seven classes of metabolites were found to be potential markers for prognosis of colorectal cancer as well as evaluating the efficacy and toxicity of 5-FU. These biomarkers include acylcarnitines, porphyrins, sphingolipids, eicosanoids, bile acid conjugates and nucleosides. The present data demonstrates the potential use of Quadrupole Time-of-Flight (Q-TOF) LC/MS in profiling serum metabolites which are useful markers for colorectal patients to help achieve better clinical management. Overall, integration of different approaches would enhance the identification of biomarkers which enable the characterization of prognosis as well as response towards chemotherapy. On-going effort to establish personalised medicine (PM) with the help of value added therapeutic drug monitoring using combination of metabolomics and pharmacogenomics approaches is required especially in Malaysia with multiracial community.