CHAPTER I

INTRODUCTION

5-Fluorouracil (5-FU) is one of the most widely used chemotherapeutic agent over four decades. It is absorbed and changed to fluorodeoxyuridine monophosphate (FdUMP) which inhibits thymidylate synthase enzyme in DNA synthesis.[1-3] 5-FU has been used for treatment varieties of solid tumors such as breast, head, neck and colorectal cancer. 5-FU is given at a fixed dosage based either on body surface area (BSA) or body weight. This agent has a narrow therapeutic index and lacks of a simple index of pharmacological effect for monitoring of efficacy and toxicity. Effect of 5-FU in each patient is different as a result of intra- and interindividual variability of its pharmacokinetics. Area under the concentration-time curve (AUC) monitoring is useful for tailoring 5-FU dosage regimen and determining efficacy of cancer treatment.[4]

5-FU pharmacokinetics are different among administration, 5-FU can be given by either intravenous bolus injection, short term infusion methods of 15-30 min or prolonged continuous infusion. After intravenous bolus injection, the 5-FU plasma concentration immediately increases. As a result of saturated metabolism of 5-FU elimination enzyme, 5-FU plasma concentration does not relate to dosage given and shown nonlinear pharmacokinetics. Short-term infusion is then developed in order to prevent high peak level and reduce toxicity. Short term infusion of 500 mg/m^2/day provides lower peak and AUC than bolus injection.[5-6] For continuous infusion, 5-FU plasma concentration rises and shows a linear pharmacokinetic relationship with its dose. Then, one can predict 5-FU plasma concentration at steady state (Css). Plasma clearance rate of various administration methods are also different, after bolus injection of dose ranging from 700-1000 mg/m^2/day total body clearance is 0.39-1.47 L/min whereas total clearance for continuous infusion dose ranging 750-1000 mg/m^2/day for 8 hours is 5.41-57.91 L/min.[7] The dose limiting toxicities of 5-FU are myelosuppression (in intravenous bolus injection and short term infusion) and oral mucositis and hand-foot syndrome (in prolonged

continuous infusion). Continuous infusion provides highest response rate although survival time is not significant different among 3 methods.[8-9]

As it is costly and requires intravenous catheter and ambulatory pump for prolong infusion. Bolus injection is not practical for medical staff because of direct contact to chemotherapeutic agent. Therefore in this trial, patients will receive 5-FU by short term infusion for 15 minute(s).[5,10]

The activity of 5-FU is limited by its short half life approximately 16 minutes and rapid degradation. To increase 5-FU activity, Folinic acid (FA) is the most efficient modulating agent used to enhance the biological effect of chemotherapy. FA is usually prepared in calcium salt form (leucovorin, LV). FA is absorbed and converted to 5,10-methylenetetrahydrofolate binding with FdUMP to inhibit thymidylate synthase enzyme and increasing response rate.[11] A commonly use of 5-FU plus LV regimen is LV 20 mg/m^2/day following by 5-FU 370-425 mg/m^2/day intravenous injection consequently for 5 days every 28 days. This regimen is well tolerated that has become routine in patient and 5-FU was empirical increased to 425 mg/m^2/day. However, this method uses quite low dose of 5-FU compared to other regimen however it still has found toxicity from intervariable metabolism. Gamelin et al.[9,12] found relationships between AUC, Css to predict efficacy and toxicity in patients receiving 5-FU. Patients who responding to the treatment has $AUC_{0\text{-}8hr}$ 960-1440 mg/L.min or Css 2-3 mg/L after 5 day continuous infusion of 5-FU while patients having $AUC_{0\text{-}8hr}$ more than 1800 mg/L.min or Css more than 3 mg/L increase risk in leucopenia and oral mucositis. This study monitor 5-FU pharmacokinetics only one time after first day administration by short term infusion, the Css predicting may be lack of precision so this study will monitor only AUC.

5-FU is mainly metabolized in liver by dihydropyrimidine dehydrogenase (DPD), the rate limiting step enzyme. It has been reported that severe toxicity of 5-FU was seen in patients with lack of enzyme DPD. Etienne MC, et al. and Sohn DR et al. found comparable mean DPD levels in Caucasian and Korean population.[13-14] Morsman JM, et al.[15] evaluated DPD level in South-west Asian, Kenyan and Ghanian populations. They

reported significant difference in median DPD plasma level between Ghanian and Caucasian group and also found that men have higher DPD level than women. However, fatal toxicity by 5-FU in a patient with normal DPD level and DPD activity in liver is variable and difficult to determine.[16] Di Paolo et al. has reported only two from five patients with grade $\geq$ 3 toxicity were abnormally low DPD level while DPD level in the remaining three patients were superior to the value of partial DPD deficiency. Therefore, individual dosage adjustment guide by AUC is commonly used. Normally, low dose 5-FU is started and titrate the dose by therapeutic drug monitoring was used to evaluate efficacy and preventing toxicity from intervariable metabolite of 5-FU.[2] Most studies of 5-FU pharmacokinetics were performed in Caucasian and only few studies provide information about short term infusion. Furthermore, pharmacokinetic of 5-FU in Thai has never been reported. This present study was conducted to determine AUC and pharmacokinetic parameters of 5-FU 425 mg/m^2/day in colorectal Thai patients. AUC level will be used as a guide for monitoring outcomes and adjusting dosage regimen for individual Thai colorectal cancer patients.

Objectives

1. To determine AUC of 15 minute infusion of 5-FU in Thai colorectal cancer patients.
2. To determine pharmacokinetic parameters of 5-FU in Thai colorectal cancer patients.

The significance of the study

1. To determine the average 5-FU AUC in Thai patients after receiving 15 minute infusion of 5-FU 425 mg/m^2/day.
2. To provide useful information for 5-FU plasma therapeutic monitoring.
3. To observe adverse drug reaction including hematological, hand-foot syndrome, diarrhea and oral mucositis in patients receiving 15 minute infusion of 5-FU 425 mg/m^2/day