CHAPTER VI

DISCUSSION

This study was performed to determine wheather AUC of standard mayo regimen of FA 20 mg/m^2/day combined with 5-FU 425 mg/m^2/day in 24 Thai colorectal cancer patients is comparable to AUC of the same regimen given to Caucasian or not. Since it was lacked of AUC data of 15 min infusion 5-FU regimen, although 15 min infusion gave lower response than continuous infusion but it is the most convenience way for nurses to administration and can leave them while continuous infusion, hospital admission and close assessment were necessary for patient monitoring.

This study was the first pharmacokinetics study of 5-FU in Thai patients. Similar to previous reports, we found that 5-FU has great interpatient variations of pharmacokinetics. The 5-FU plasma concentrations in 24 patients were also varied in each sampling time point. The study also confirmed that the same dose administered after adjustment for body surface area led to varying therapeutic intensities. In this study, average AUC was 415.2±121.80 mg/L.min. It was that is lower than AUC reported by Larsson et al after patients received 5-FU 500 mg/m^2 infusion in 20 min. (average AUC 436.48±55.68 mg/L.min)

From two patients who had received 5-FU dose lower than 425 mg/m^2/day. Average AUC after exclude these patient were increased from 415.2±121.80 mg/L.min. to 431.73 ± 113.07 mg/L.min.(p = 0.64) In this study we did not control cycle of chemotherapy to collect blood sample. There were 11 patients had collected blood sample on the first cycle compared to the other group of patients who had collected blood on another cycle of chemotherapy. Mean ± SD of the first cycle group was 427.91± 68.45 mg/L.min. (n = 11) while mean ± SD of the other group was 404.49± 156.26 mg/L.min. (n = 13) (p = 0.65) and 435.54± 148.77 (n= 11, excluding 2 patients had received 5-FU lower than 425 mg/m^2/day. (p = 0.88)

Our findings are different from those of previous reports which determine AUC of 5-FU continuous infusion, assumed for linear elimination. But in this study, we determined AUC in patients who received 15 minute infusion of 5-FU. The peak level of 15 minute infusion and bolus injection were higher than of continuous infusion but 5-FU may not sufficient to reach steady state condition or saturation of enzyme metabolism from interindividual variation.[6] In this study, we found the time to reach maximum concentration is between 15- 20 min after start infusion (average 16.05 ± 2.52 min). Half-life was 8.87± 2.11. Mean± SD of volume of distribution, clearance and constant of elimination were 23.05± 8.85L, 1.72± 0.69 L/min and 0.08± 0.03 min^{-1}, respectively. These are higher volume of distribution and lower clearance than parameters previously reported in a study of 20 min intravenous infusion. Limitations of this study is that we did not control covariables of pharmacokinetic parameters such as age, sex, liver metastases, performance status, patient staging and did not study correlation between covariables and pharmacokinetic parameters of these patients.

Interpatient variations may be result of genetic polymorphism of 5-FU metabolism by DPD. There is a wide range of DPD activities with a Gaussian distribution described among a large population of patients.[14] The median DPD activity was also different by ethnic and never been measured in Thai population. It was largely widespread in tissues and that the degree of DPD activity in tumor cell lines plays a major role in resistance to 5-FU. However, the determination of DPD activity before treatment seems insufficient for predicting 5-FU plasma concentration because the coefficient of correlation between DPD activity in lymphocytes and 5-FU plasma levels is only 0.34. Therefore, it is not a useful indicator for 5-FU dose adjustment. Eventhough, it is important that patients with high enzyme activity have a higher risk of treatment failure.

For the relationship between AUC and toxicity of 5-FU, Thyss et al. have demonstrated AUC of 5-FU over 2,400 mg/L.min for patients with head and neck cancer treated by cisplatin and 5 day continuous infusion of 5-FU. ($p<0.001$) This result confirmed by Gamelin et al. who studied patients with colorectal cancer treated with FA and 8 hours continuous infusion of 5-FU. They reported AUC of 5-FU of higher than 1,440

mg/L.min. In our study, toxicity was monitored in the next visit to the physician for hematological effect, hand-foot syndrome, diarrhea and oral mucositis. We observed the decreasing on hematological parameters in all patients but not different between patients in the first cycle of and another cycle of chemotherapy. There were two patients suffered from grade I hematological toxicity and four patients from grade II hematological toxicity after receiving chemotherapy. Toxicities of 5-FU seen in our patients were lower than those reported previously. This may be because patients who joined join this study were quite healthy. Most of them had performance status level of 0 and 1. Another reason was time to next visit to the physician is 4 weeks while the numbers of white blood cell count usually decreased from day 9^{th} to the 14^{th} after chemotherapy and normally recover in 30 day.[57] Patients may therefore have lowest point of blood cell count in the second week after chemotherapy and recover before the next visit.

Compared with previous studies in Caucasian, there were lower in AUC and toxicity than in Caucasian. After received bolus injection of Mayo regimen, 35% of patients experienced suffer from hematological, diarrhea and oral mucositis toxicities after administration of the full dose of cycle in overall toxicities of 5-FU.[72] Decreased peak concentration and AUC by given short-term infusion of 5-FU may majorly impact on risk of toxicity in these patients.

In this study, tumor response rate in this study is assessed only after completion of chemotherapy course. The efficacy of treatment is monitored in terms of disease free survival and overall survival. There were only nine patients who were evaluated for tumor response after finished their chemotherapy course by computed tomography (CT). We observed that five of them had stable disease and four had progressive disease. One of them had partial response, four had stable disease, one had disease progress, one had no recurrence of liver metastases after 6 months after resection of tumor before start chemotherapy and two had not assessed because they had not finished chemotherapy course.