Evaluation of Efficacy, Toxicity and Pharmacokinetics of Oxaliplatin/5-FU/Leucovorin in Advanced Colorectal Cancers

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**Background** Oxaliplatin (LOHP) is a DACH platinum (Pt) analog. LOHP given with 5-FU/LV showed response rate of 28-65% in adv colorectal cancers (CRCs). Objective of this study was to evaluate 1) therapeutic efficacy, 2) therapy-related toxicity, and 3) pharmacokinetics (PK) of LOHP and 5-FU in adv CRC pts.

**Methods** Pts with histologically confirmed stage IV CRC with ECOG PS 2 or less and renal function in normal range were included. LOHP and 5-FU were given at 130 mg/m² and 425mg/m² on D1 and D1-5, respectively, as 2hr-infusion. Cycles were repeated every 21 days except in cases of progression. Toxicity and tumor response were evaluated according to NCI Toxicity Scale each cycle and by abdomino-pelvic CT scan or MRI every 2 cycles, respectively. Serial blood samples from 10 pts were collected and Pt and 5-FU conc were determined by FAAS and HPLC, respectively.

**Results** Twenty-three pts were enrolled with M : F ratio 14 : 9, and median age 58(36 – 71). Primary sites were rectosigmoid 13, sigmoid 5, ascending 3, and transverse colon 2. The ratio of chemo-naive vs previously treated was 7 : 16. Total 98 cycles were delivered and 21 pts were evaluable for response. PR and SD were observed in 10 pts(47.6%) and 8 pts(38.1%), respectively, and disease progression in 3 pts. Median OS and PFS were 9.3 m and 7.4 m, respectively. In univariate analysis, PS, tumor response, and number of cycles showed significant correlations with OS and PFS (p<0.05). Toxicity was mild except 2 pts(8.7%) who developed grade IV diarrhea. The Pt conc in plasma, RBC and plasma ultrafiltrate (PUF) reached max of 4.66, 5.53 and 0.84μg/ml, respectively, at the end of infusion. The max Pt conc in plasma and PUF showed no significant changes over 3 cycles and were 178% and 77% of previous study (Cancer Chemother Pharmacol 45 : 157,2000) suggesting greater plasma binding of LOHP in our pts. In spite of the increased drug exposure compared to the previous data, i. e., 4.2–5.8 folds higher AUC and 2.4–3.6 fold lower CL calculated based on Pt conc in plasma and PUF, the lower free pt conc indicates that dose reduction may not be necessary in these pts. The max Pt conc in RBC showed 33% increase over 3 cycles indicating drug accumulation consistent with the previous report.

**Conclusion** The present LOHP/FU/LV regimen against adv CRCs may be effective and safe, and dose reduction is not recommended based on free Pt conc comparable to that in previous studies.