Using Novel Monte-Carlo Parametric Expectation Maximization Based Wald’s Approximation Method with Backward Elimination to Develop Disease Progression Model for Metastatic Prostate Cancer Patients Treated with Leuprorelin

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OBJECTIVE: To develop a population model from many patient-specific covariates are both time-consuming and labor intensive tasks. Furthermore, standard FOCE method may produce an unsatisfactory result in the presence of data sparsity and large population variability. In this study, a novel Monte-Carlo Parametric Expectation (MCPEM)-based Wald’s Approximation Method (M-W AM) was proposed as an efficient covariate model selection approach in developing population disease progression (PDP) model for metastatic prostate cancer (PC) patients treated with leuprorelin using routine clinical data from insurance database.

METHOD: 1082 PSA observations from 221 subjects with metastatic PC from Humana clinical database were used to estimate model parameters including $P$, where $[1 - \exp(-P)]$ is proportion of tumor resistant to leuprorelin, tumor growth ($G$) and regression ($D$) rates, and potential “flare-up” in PSA ($FB$). Eleven covariates were included in the analysis. FOCE failed to produce reliable results due to the presence of high degree of data variability. Therefore, full model that included all the covariate effects on model parameters was developed with MCPEM in NONMEM to generate covariate matrix for WAM calculation [1]. A backward elimination (BE) using WAM-derived likelihood was used to efficiently eliminate insignificant covariates, followed by BE with actual NONMEM run to yield the final model.

RESULTS: PSA dynamics in patients with metastatic PC on leuprorelin were well described by the model and parameters were estimated with good precision (%CV<50). Population average of $P$ was $2.66 \times 10^{-2}$ and baseline PSA and ALT were the significant covariates for $P$. Only eleven actual NONMEM model runs were needed to yield the final model while stepwise covariate selection method would require to run >150 NONMEM models to produce similar results.

CONCLUSIONS: The W-WAM approach was able to efficiently develop a PDP for PC patients treated with leuprorelin in the presence of many tested covariates and large population variability.