W-5 [11:50～12:20]

Pharmacokinetic (PK) /Pharmacodynamic (PD) Approach for Molecular Targeting Anticancer Agents (MTAs)

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PK/PD analysis has been recognized as one of the most important research endpoint in the development of anticancer agents. However, clinical application of so-called "Molecular Targeting Agents" sometimes altered the concept of conventional PK/PD analysis. The MTAs contain various types of anti proliferative effects including tumor shrinkage, tumor suppression and tumor growth delay. In addition, pharmacodynamic endpoint is sometimes difficult to be analyzed, because some of these MTA have no dose limiting toxicity such as myelosuppression or major organ toxicities. We have proposed new approach to evaluate PK/PD analysis of cell cycle modulator, Flavopiridol. A Phase I trial of Flavopiridol, a cyclin dependent kinase (CDK) inhibitor, is conducted in patients (pts) with advanced solid tumors to evaluate PK and PD as well as maximum tolerated dose (MTD) and dose limiting toxicities (DLT) by 24 hours intravenous CI. Flavopiridol has been administered at weekly doses of 40, 60, 80, and 100 mg/ m^2 for 4 consecutive weeks. Twenty advanced stage cancer pts have been treated (6 colon, 4 non-small cell lung, 2 ovary and 8 others). Median age: 58 years (range 47-71); median ECOG performance status: 1 (range 0-2). Reversible Grade 3 DLT included multiple colon ulcer and abdominal pain in 2 pts at 100 mg/ m^2 and abdominal distention in 1 pt at 40 mg/ m^2. Linear PK profiles have been observed in 4 dose levels. The mean Cmax and AUC are 718 nmol/L and 19699 nmol hr/L at 80 mg/ m^2 and 924 nmol/L and 22086 nmol hr/L at 100 mg/m^2, respectively. Cmax at all dose levels are above IC_{50} of 300 nM for inhibition of CDKs and IC50 for human cancer cell lines in vitro. Although no tumor shrinkage is observed, 5 pts have had stable disease over 90 days. In addition, significant decreases of tumor markers are found in 4 patients. Biological effects of Flavopiridol are also analyzed by fluorodeoxy- glucose positron emission tomography (FDG-PET) in 7 pts. Significant decrease of standard uptake value (SUV) in 2 pts and stabilization of SUV in 4 pts are observed. In conclusion, Flavopiridol at 80 mg/ m^2, which is biologically active, is recommended for further evaluation.