Influence of Exposure and Infusion Times on Cytotoxicity and Pharmacokinetics of SKI 2053R

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Effect of the exposure time on the in vitro cytotoxicity of a new platinum complex, *cis*-malonato[(*4R, 5R*)-4-,5-bis(aminomethyl)-2-isopropyl-1-1,3-dioxolane] platinum(II) (SKI 2053R), and cisplatin(CDDP) toward two human lung-adenocarcinoma cell lines(PC-9 and PC-14) and two human stomach-adenocarcinoma cell lines(KATO III and MKN-45) was investigated by varying exposure time(1, 4, 12, and 24h) and drug concentration to finally yield a constant product of drug concentration × exposure time (C × T). The inhibitory effect of SKI 2053R on the colony formation of tumor cells at the con- stant C × T values was clearly increased with increasing exposure time; 12-or 24-h exposure of cancer cells to low concentrations of SKI 2053R resulted in a greater killing effect than 1-or 4-h exposure to 24-or 6-fold higher concentration. In contrast, the inhibitory effect of CDDP was generally greater when cells were treated with high concentrations for either 1- or 4-h exposure than with low concentrations for either 12-or 24-h exposure. No significant difference in the inhibitory effect of CDDP on the colony formation of PC-14 cells was noted among exposure times. The intracellular accumulation of SKI 2053R and CDDP was measured under the same condition as those in cell survival assay using MKN-45 cells. The amount of accumulated platinum of SKI 2053R into MKN-45 cells was greater for the treatment of low concentrations and long-term exposures (12 and 24 h) than for that of high concentrations and shortterm exposures (1 and 4 h) at the constant C × T values; however, the increased accumulation of CDDP was more prominent as the concentration was increased even if the exposure time became shorter. The pharmacokinetic studies of SKI 2053R following 1-, 4-, 12-, and 24-h infusions were performed in beagle dogs. A single dose of SKI 2053R(5.0mg/kg) was successively given by various infusion periods to three beagle dogs, with a 3-week interval between infusion. The peak levels of ultrafiltrable platinum observed for SKI 2053R at the 1-, 4-, 12-, and 24-h infusion were 3.10 ± 0.49

(mean ± SD), 1.24 ± 0.06, 0.43 ± 0.07, and 0.25 ± 0.04 μg/ml, respectively. The mean area under the concentration-time curve($AUC_{0 \rightarrow \infty}$) determined for ultrafiltrable platinum of SKI 2053R, as an active component, at the 1-, 4-, 12-, and 24-h infusion were 5.46 ± 1.08, 5.41 ± 0.01, 4.57 ± 0.12, and 5.45 ± 0.66 μg h ml^{-1}.