Effect of administration of 5-(phenylselenenyl)acyclouridine, an inhibitor of uridine phosphorylase, on the anti-tumor efficacy of 5-fluoro-2'-deoxyuridine against murine colon tumor C26-10.

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The effect of co-administration of 5-(phenylselenenyl)acyclouridine (PSAU), a new uridine phosphorylase (UrdPase, EC 2.4.2.3) inhibitor, on the efficacy of 5-fluoro-2'-deoxyuridine (FdUrd) was tested against murine colon C26-10 tumor xenografts. In contrast to our previous results with human tumors, co-administration of PSAU with FdUrd decreased instead of increasing the efficacy of FdUrd against tumor growth. However, co-administration of PSAU with FdUrd (300 mg/kg/day) protected the mice completely from the 83% mortality induced by the same dose of FdUrd alone. Enzyme studies indicated that UrdPase in colon C26-10 tumors is responsible for the catabolism of FdUrd to 5-fluorouracil (FUra), as colon C26-10 tumors do not have thymidine phosphorylase (dThdPase, EC 2.4.2.4). In contrast, colon C26-10 tumors had extraordinarily high UrdPase activity (300 micromol/min/mg protein), which was at least 200-fold higher than the highest UrdPase activity in any of the human xenografts we tested previously. Furthermore, the activities of UrdPase and orotate phosphoribosyltransferase (OPRTase, EC 2.4.2.10) were 192- and 2-fold higher, respectively, while that of dihydrouracil dehydrogenase (EC 1.3.1.2) was 1000-fold lower in the tumor than in the host liver. It is suggested that FdUrd exerts its anticancer effects against colon C26-10 tumors mainly through the catabolism of FdUrd to FUra by UrdPase, which then could be anabolized to 5 fluorouridine 5'-monophosphate (FUMP) by OPRTase and ultimately to other toxic 5-fluorouridine nucleotides, hence inducing the observed FdUrd toxic effects. Co-administration of PSAU with FdUrd inhibited UrdPase and the catabolism of FdUrd to FUra. This would result in the observed reduction of the antitumor efficacy of FdUrd. In addition, the increase in plasma uridine concentration induced by PSAU as well as the catabolism of FUra by the high dihydrouracil dehydrogenase activity in the liver also may have circumvented any residual FUra toxic effects against the host. These results clearly demonstrate that the anticancer efficacy of the combination of UrdPase inhibitors and FdUrd is not general and is dependent largely on the type of tumor under treatment and the mode of FdUrd metabolism in these tumors.

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