Modulation of 5-fluorouracil host toxicity by 5-(benzylolxybenzyl)barbituric acid acyclonucleoside, a uridine phosphorylase inhibitor, and 2’,3’,5’-tri-O-acety luridine, a prodrug of uridine.

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Administration of 200 mg/kg of 5-fluorouracil (FUra) to mice bearing human colon carcinoma DLD-1 xenografts resulted in 100% mortality. Oral administration of 2000 mg/kg of 2’,3’,5’-tri-O-acety luridine (TAU), a prodrug of uridine, in combination with 120 mg/kg of 5-(benzylolxybenzyl)barbituric acid acyclonucleoside (BBBA), the most potent known inhibitor of uridine phosphorylase (UrdPase, EC 2.4.2. 3), 2 hr after the administration of the same dose of FUra completely protected the mice (100% survival) from the toxicity of FUra. This combination also reduced tumor weight by 67% compared with 46% achieved by the maximum tolerated dose (50 mg/kg) of FUra alone. Similarly, administration of BBBA plus TAU 1 hr before or 4 hr after the administration of FUra reduced the tumor weight by 53 and 37%, respectively. However, these schedules were less effective in protecting the host from the toxicity of FUra than when the treatment was carried out at 2 hr after FUra administration. TAU alone did not protect from FUra host toxicity. The efficiency of the BBBA plus TAU combination in rescuing from FUra host toxicities is attributed to the exceptional effectiveness of this combination in raising and maintaining higher plasma uridine concentrations than those achieved by TAU alone or by equimolar doses of uridine (Ashour et al., Biochem Pharmacol 51: 1601-1612, 1996). The present results suggest that the BBBA plus TAU combination can provide a better substitute for the massive doses of uridine required to achieve the high levels of uridine necessary to rescue or protect from FUra host toxicities without the toxic side-effects associated with such doses of uridine. The combination of TAU plus BBBA may also allow the escalation of FUra doses for better chemotherapeutic efficacy. Alternatively, the combination may be used as a rescue regimen in the occasional cases where cancer patients receive a lethal overdose of FUra.

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