POTENTIATION OF ANTITUMOR ACTIVITY OF 5-FLUORO-2'-DEOXYURIDINE BY GUANOSINE-5'-MONOPHOSPHATE

MASAAKI IIGO AND AKIO HOSHI

Pharmacology Division, National Cancer Center Research Institute, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104, Japan

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The antitumor activity of 5-fluoro-2'-deoxyuridine (FUDR) against P388 leukemia was markedly enhanced by addition of guanosine-5'-monophosphate (GMP). With daily i.p. treatment for 5 d, the combination of FUDR at 100 mg/kg/d and GMP at 300 mg/kg/d showed the highest antitumor effect (more than 290% ILS), while maximum ILS of FUDR alone (100 mg/kg/d) was 94%.

Keywords — antitumor activity; 5-fluoro-2'-deoxyuridine; FUDR; guanosine-5'-monophosphate; combination chemotherapy; potentiation

INTRODUCTION

5-Fluorouracil (FU) and 5-fluoro-2'-deoxyuridine (FUDR) have been used clinically for gastro-intestinal cancer. Recently, we found that the combination of FU and guanosine11 or guanosine-5'-monophosphate (GMP)2 potentiates the antitumor activity in various tumor systems without increasing toxicity to the host. These results may be a consequence of an increase in conversion of FU to its ribonucleoside in tumor cells by guanosine.3,4

FUDR is 103 times as active as FU in vitro.5 However, the relatively high anticipated effectiveness of FUDR as compared with FU has not been born out in clinical use. It has been suggested6 that the lower activity observed was due to the in vivo cleavage of FUDR to FU and the phosphorylated sugar moiety. Thus, a large proportion of FUDR is rapidly degraded to FU by pyrimidine nucleoside phosphorylase6 and its enzyme activity in tumor cells is higher than that in normal cells.7 FUDR has been incorporated into RNA in tumor cells at the same rate as after FU administration8 but less toxic to the host than FU. Therefore, the markedly increased incorporation of fluorinated pyrimidine into RNA might be caused by GMP, especially in tumor cells, may produce more enhancement of antitumor activity than did FU.

MATERIALS AND METHODS

1. Drugs — FUDR was kindly supplied by Mitsui Pharmaceuticals, Inc., Tokyo, Japan. GMP was purchased from Sigma Chemical Co., St. Louis, U.S.A. FUDR and GMP were dissolved in physiological saline and 0.5% carboxymethyl cellulose in physiological saline, respectively.

2. Animals and Tumor — Groups of six mice with body weight of 21–23 g were used. Mouse leukemia P388 cells (1 × 108 cells/mouse) were implanted i.p. into male BDF mice (Shizuoka Agricultural Cooperative Association for Laboratory Animals, Hamamatsu, Japan).

3. Antitumor Activity Test — Twenty-four hours after tumor implantation, FUDR or FUDR plus GMP was injected i.p. once a day for 5 d. FUDR and GMP were mixed together and administered simultaneously. Antitumor activity was evaluated by the increase in life-span over that of the controls (ILS = T/C%−100). Data

Abbreviations: FU = 5-fluorouracil, FUDR = 5-fluoro-2'-deoxyuridine, GMP = guanosine-5'-monophosphate.
FIG. 1. Effect of Guanosine-5′-monophosphate on the Antitumor Activity of 5-Fluoro-2′-deoxyuridine against P388 Leukemia

Tumor-bearing mice were given consecutive daily treatments for 5 d, following implantation with 10⁶ leukemia cells.

A: ○, FUdR alone; ●, combination of FUdR and GMP (100 mg/kg/d). Mean survival time of untreated controls was 10.8 ± 1.5 (S.D.) d. Bars represent mean ± S.D. of six mice. a), Significantly greater than corresponding monotherapy (p<0.001) by Student's t test.

B: ×, GMP alone; ●, combination of FUdR (100 mg/kg/d) and GMP. Mean survival time of untreated controls was 10.8 ± 1.5 (S.D.) d. Bars represent mean ± S.D. of six mice. The numbers in parentheses are the cure rates on day 60.

were analyzed for significance by means of the 2 tailed Student’s t test.

RESULTS AND DISCUSSION

The combination of FUdR and GMP markedly enhanced the antitumor activity and caused a greater increase in the life-span than FUdR alone in the P388 leukemia system, but no increase in toxicity to the host. All of the combinations of FUdR at 0.3 – 100 mg/kg/d and GMP at 100 mg/kg/d were more effective than FUdR monotherapy (Fig. 1A), and the antitumor effect of FUdR at 10 mg/kg/d plus GMP at 100 mg/kg/d. Moreover, the combination of FUdR at 100 mg/kg/d and GMP at 300 mg/kg/d showed the highest therapeutic effect including cure (2/6) (Fig. 1B).

It is surprising to find that antitumor activity
of FUdR is markedly enhanced by GMP. The biochemical mechanism of the enhancement in combination treatment is not clear yet, but this result may be due to increase in active metabolites in tumor cells by GMP or guanosine. Analysis of the effect should be proceeded. Thus, the antitumor activity of FUdR was potentiayed by GMP, and the resulted therapeutic effect of FUdR at the optimal dose was also enhanced as shown by the increased maximum ILS.

Further studies on the mechanism of the potentiation of the antitumor activity of FUdR by GMP are under way.

REFERENCES