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Original article

Reversal of 5-fluorouracil-induced toxicity by oral administration of uridine

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Summary

Background: Previous preclinical and clinical investigations have shown that the combined administration of 5-fluorouracil (5-FU) with delayed uridine can reverse side effects induced by 5-FU. This biochemical modulation-based combination may increase the therapeutic index of 5-FU.

Patients and methods: Seven patients with advanced cancer were treated weekly with 5-FU at increasing dosages starting at a dose of 600 mg/m^2. Five patients developed dose-limiting leukopenia, and two patients developed thrombocytopenia. At the dose-limiting toxicity level, 5-FU treatment was repeated and followed after 3 hours by oral uridine (5 g/m^2 q 6 hr) during 72 hours.

Results: 5-FU-induced leukopenia was reversed for several weeks after the administration of oral uridine. However, thrombocytopenia was not reversed. Side effects of the combined treatment consisted of mild diarrhea in five of the seven patients.

Conclusions: These data indicate that oral uridine can reduce the severity of 5-FU-induced myelosuppression.

Key words: biochemical modulation, chemotherapy-induced toxicity, 5-fluorouracil, uridine

Introduction

Treatment with single-agent 5-fluorouracil (5-FU) is still the mainstay in advanced colorectal cancer [1]. However, the chance of an objective response is probably lower than 20%, with no significant influence on survival. The mechanisms of action of 5-FU have been investigated extensively and are complex [2]. 5-FU itself has no antitumor activity. The 5-FU metabolite 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP) inhibits the key enzyme thymidylate synthase (TS), resulting in a decrease of deoxythymidine monophosphate (dTMP) which leads to an inhibition of DNA synthesis. A second mechanism of action of 5-FU is the incorporation of 5-fluoro-uridine-5′-triphosphate (FUTP) into RNA, leading to impaired processing of nuclear RNA. Also, 5-fluoro-2′-deoxyuridine-5′-triphosphate (FdUTP) has been shown to be incorporated into DNA, being a possible third mechanism of 5-FU action.

Biochemical modulation of 5-FU metabolism by the natural nucleoside uridine may enhance the therapeutic index of 5-FU by prevention of its toxicity [3–5].

Martin et al. [6], Klubes et al. [7] and Peters et al. [8] demonstrated that tumor-bearing and non-tumor-bearing mice tolerated much higher doses of 5-FU when administration of the fluoropyrimidine was followed by high doses of uridine. In these studies, prolonged exposure of the mice to uridine appeared to be a prerequisite.

There have been only a few studies evaluating the role of uridine in the biochemical modulation of 5-FU activity in humans. The maximum tolerated dose of i.v.-administered uridine was 10–12 g/m^2 when the nucleoside was given as a 1-hr infusion [9]. Transient shivering was dose-limiting. Low micromolar plasma uridine concentrations increased to millimolar levels, but elimination was rapid with a terminal half-life of about 2 h. Probably because long-term exposure to the tissues was not achieved with this schedule, uridine failed to protect against 5-FU-induced toxicity. Due to the occurrence of high fever, continuous infusion of uridine was not feasible [10]. With an alternative schedule in which 3-h uridine infusions were alternated with 3-h infusion-free intervals during 3 days, fever was no longer dose-limiting and markedly elevated uridine levels could be maintained [10]. The uridine-induced fever may be the result of accumulation of one of its degradation products as has been investigated in rabbits [11]. With this schedule (uridine dose 2 g/m^2 per h), leukopenia induced by escalated doses of 5-FU was reversed, but thrombocytopenia was not [12]. To avoid the drawbacks of parenteral uridine, oral administration of the nucleoside was evaluated; diarrhea was dose-limiting [13]. As compared with i.v. uridine, bioavailability was low (7%) and the same as has been observed in mice [14].

In the present study, the clinical effects of orally administered uridine on 5-FU-induced bone marrow suppression are described.

Patients and methods

Patients

The characteristics of the seven patients with advanced cancer who participated in the study are listed in Table 1. All but one of the patients (No. 2 with locally advanced stomach cancer) had advanced colorectal cancer. The patients had a median performance status (World Health Organization (WHO) standard) of 1, and had normal renal and bone marrow function. The six patients with advanced colorectal cancer all had hepatic metastasis with abnormal liver tests. Informed consent was obtained in each case. None of the patients had received prior chemotherapy.

Treatment schedule

The treatment was given on an outpatient basis. The patients received weekly i.v. bolus injections of 5-FU. The starting dose was 600 mg/m^2. Every 4 weeks the 5-FU dose was escalated by 20% until dose-limiting toxicity occurred, consisting of myelosuppression in all patients. The toxic dose levels of 5-FU and the degree of leukopenia or thrombocytopenia are shown in Table 2. At the nadir values of the white blood cells and the platelets, weekly 5-FU treatment was continued at the dose that produced this myelosuppression. However, 5-FU was now followed after 3 hours by oral uridine at a dose of 5 g/m^2 every 6 hours during 3 days (12 administrations). Continuation of the 5-FU treatment in the same weekly schedule was attempted while maintaining the dose level responsible for the above-mentioned bone marrow toxicity. Patients were removed from the study as soon as dose reduction of 5-FU was required, whatever the reason.

Results

Effect of oral uridine on 5-FU-induced leukopenia

After weekly single-agent bolus injections of 5-FU, patients No. 1–5 developed leukopenia. This occurred at dose levels of 600–864 mg/m^2. The nadirs of the white blood cells ranged from 2.4–3.4 × 10^9/L (Table 2, Fig. 1). At the time of this leukopenia the 5-FU treatment followed by oral uridine for 3 days was continued.

As can be seen in Fig. 1, the white blood cells in all 5 patients increased to maximum values ranging from 3.2–8.5 × 10^9/L despite continued 5-FU administration. Especially in patients 1, 2 and 5, this effect of uridine on 5-FU-induced leukopenia lasted for several weeks, although uridine was administered only after one dose of 5-FU. The effect of uridine on the white blood cells of patients 3 and 4 was much less pronounced. The course of the two patients (Nos. 6 and 7) who did not develop 5-FU-induced leukopenia is also shown in Fig. 1. Especially the white blood cell count of patient 7 was only little or not at all affected by the 5-FU treatment.

Table 1. Characteristics of the patients given 5-FU and oral uridine.

Patient No.	Age (yrs)	Sex M/F	PS (WHO)
1	63	F	2
2	69	M	1
3	65	F	1
4	34	M	1
5	71	F	2
6	76	M	0
7	68	M	1

PS = performance status.

Table 2. Toxic dose of weekly 5-FU and severity of myelosuppression.

Patient No.	Toxic dose (mg/m^2)	Nadir at toxicity	
		WBC (× 10^9/L)	Plts (× 10^9/L)
1	864	3.4	230
2	720	2.4	124
3	720	3.0	118
4	720	2.9	153
5	600	2.4	191
6	720	3.9	85
7	720	6.3	100

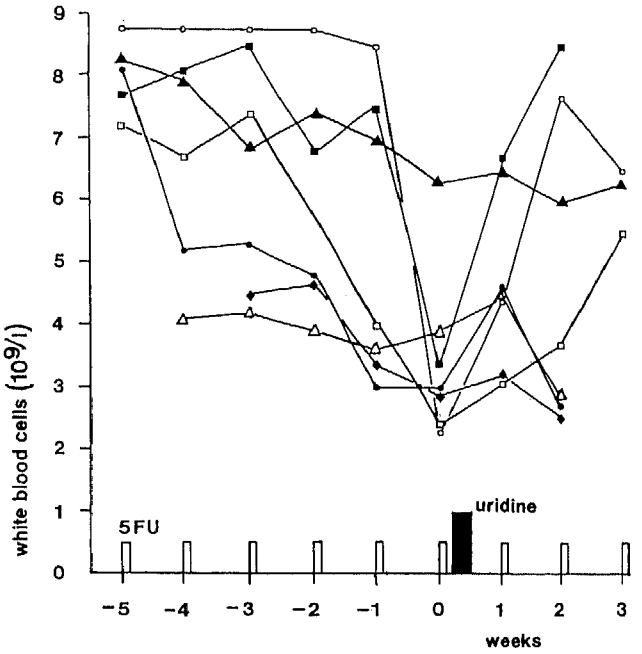

Fig. 1. Course of white blood cell counts in all 7 patients. Patients are indicated by different symbols (■, patient 1; □, patient 2; ●, patient 3; ♦, patient 4; ○, patient 5, Δ, patient 6; ▲, patient 7). Small open bars represent weekly 5-FU treatment. Large closed bar represents oral uridine administration during 72 hours, starting 3 hours after 5-FU injection.

Effect of uridine on 5-FU-induced thrombocytopenia

Patients 6 and 7 developed thrombocytopenia during weekly 5-FU treatment at the dose level of 720 mg/m^2. The platelet counts were 85 and 100 × 10^9/L, respectively, in these patients. Fig. 2 shows that uridine failed to reverse this 5-FU-induced thrombocytopenia; in patient 7 a brief stabilization of the platelet count was observed, while in patient 6 the platelet count continued to decrease. The course of the platelets in patients 1–5 who were not thrombocytopenic at the time of uridine

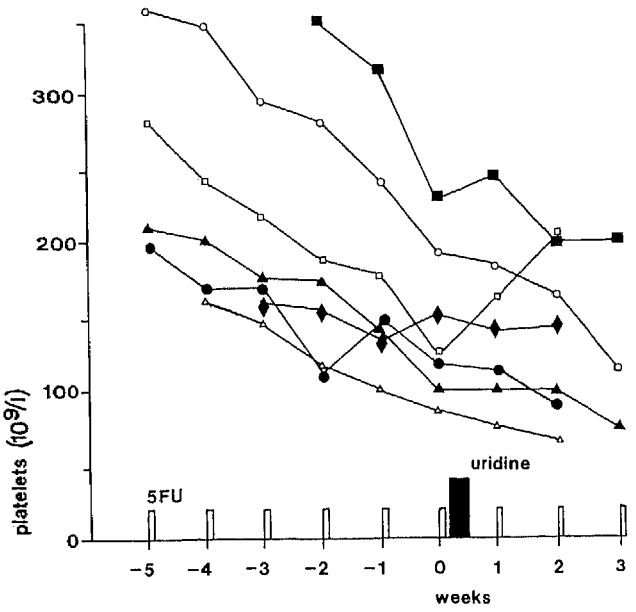

Fig. 2. Course of platelet counts in all 7 patients. Patients are indicated by the same symbols as in Fig. 1. Small open bars represent weekly 5-FU treatment. Large closed bar represents oral uridine administration during 72 hours, starting 3 hours after 5-FU injection.

administration was quite similar to that of the two thrombocytopenic patients, i.e. the platelet count continued to decrease after the uridine (Fig. 2). Remarkably, however, in one patient (2), the platelets showed a significant increase after uridine administration and continuation of the 5-FU treatment.

Toxicity of combined 5-FU/uridine administration

All seven patients tolerated the treatment well. However, five of them developed grade I diarrhea during the administration of oral uridine. Fever was not reported by any of the patients, and no other side effects were observed.

Discussion

The present study is the first to describe the potential value of orally administered uridine in the metabolic modulation of 5-FU activity in cancer patients with advanced disease.

Biochemical modulation of the metabolism of 5-FU may prove to be an effective method to enhance its therapeutic index [3–5]. This is highly desirable because 5-FU is not a very effective drug. 5-FU activity can be modulated by a variety of agents. Most experience has been acquired with leucovorin (LV), especially in advanced colorectal cancer. In this disease, combined LV/5-FU results in higher response rates. However, the effect on survival has been found to be of limited value. There has been much less clinical experience with other biochemical modulators [4, 5].

Uridine is one of the compounds which can modulate the activity of 5-FU [15]. In vivo experiments with tumor-bearing mice have shown that high-dose uridine protects normal tissues against the toxicity of otherwise lethal doses of 5-FU. In previous studies we have evaluated i.v administration of high doses of uridine which resulted in markedly increased plasma uridine concentrations of at least several hundreds of micromolars up to peak levels of approximately 1 millimolar [10]. Initially, it was believed that plasma concentrations of at least 1 mM were necessary to achieve the rescue effect of uridine [6]. Moreover, these high concentrations of uridine should also be maintained for prolonged periods of time. When these two criteria were met, we indeed observed that 5-FU-induced leukopenia could be reversed leading to an increased dose-intensity of 5-FU [12]. However, it was subsequently questioned whether these very high plasma uridine levels were in fact necessary. Therefore, oral administration of uridine has been evaluated in preclinical studies with mice [14]. It became clear that the bioavailability of oral uridine was low in comparison with parenterally-administered uridine. Nevertheless, in mice oral uridine was also effective, at least when combined with benzylacyclouridine (BAU), a uridine phosphorylase inhibitor, to prevent the rapid elimination of uridine and thus increase its bioavailability [16]. In humans the bioavailability of orally administered uridine was also low and similar to that in mice. Steady state plasma levels of approximately 50 μm could be maintained during prolonged periods of time [13]. However, in contrast to humans, in mice the concentration of the breakdown product of uridine, uracil, was 10 times higher than that of uridine.

Our clinical findings are in agreement with the above mentioned preclinical data of Martin et al. [16]. However, in contrast with these mice experiments, oral uridine had a rescue effect in humans without the use of an uridine phosphorylase inhibitor.

In all five patients with 5-FU-induced leukopenia, this side effect was reversed by the oral uridine. Comparable to i.v. uridine, the effect of oral uridine lasted for several weeks despite the fact that uridine was administered after only one course of 5-FU [12]. However, the effect of oral uridine seemed weaker in this respect, which is presumably related to the much lower plasma uridine levels and consequently lesser exposure of the tissues to the nucleoside. Nevertheless, the data support the perception that the high plasma uridine concentrations achieved with the i.v. route are not necessary for the 'rescue' effect.

It is also remarkable that the failure to reverse 5-FU-induced thrombocytopenia was observed for i.v. as well as for orally administered uridine. The reason for this has yet to be found.

Presumably uridine affects the maturation of white blood cells but not of platelets. Culture of 5-FU-treated bone marrow cells, in the presence of the appropriate growth factors, will make it possible to answer this question.

There have been no indications that the toxicity of combined 5-FU and oral uridine is different from that of single-agent 5-FU. Only mild diarrhea was observed in most of these patients and can be contributed to the uridine treatment. However, diarrhea precludes the use of higher doses or oral uridine as concluded from our phase I study [13].

Whether the observed effects of oral uridine on the reversal of 5-FU-induced toxicity can result in enhancement of the therapeutic index of 5-FU is uncertain. As yet, this has not been observed with other combinations based on biochemical modulation in which only one modulator was used. It may be that the concomitant use of more than one modulator will be needed to really enhance the therapeutic index by influencing multiple mechanisms of resistance. Further studies will be necessary to address these questions.

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