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Phase I trials of uracil–tegafur (UFT) using 5 and 28 day administration schedules: demonstration of schedule-dependent toxicities

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We conducted two consecutive phase I clinical trials to identify the qualitative and quantitative toxic effects of uracil–tegafur (UFT) [Taiho Pharmaceutical Co. Ltd, Tokyo, Japan; (BMS-200604) Bristol-Myers Squibb, Princeton, NJ] administered either on a 5 or 28 day schedule and to determine the phase II trial starting doses for both schedules. Nineteen patients were entered on the 5 day schedule and 23 patients were entered on the 28 day schedule; a minimum of three patients were entered at each dose level studied. In both phase I trials, the daily UFT dose was divided into three doses administered every 8 h. Dose levels examined with the 5 day schedule were 360, 720, 900 and subsequent de-escalation to 800 mg/m^2/day. Dose levels studied with the 28 day schedule were 180, 360, 450 and subsequent de-escalation to 400 mg/m^2/day. With the 5 day schedule, the dose-limiting toxicity (DLT) was granulocytopenia, with four of five patients experiencing grade 4 granulocytopenia at the 900 mg/m^2/day dose level. With the 28 day schedule, the DLT was diarrhea, which was noted in three of eight patients treated at 400 mg/m^2/day and in three of six patients treated at 450 mg/m^2/day. At these dose levels, four of these patients required prolonged hospitalizations for their diarrhea. The toxic effects of UFT are schedule dependent, with marked differences in the toxic effect profile (neutropenia versus diarrhea). With the 5 day schedule, the phase II UFT starting dose is 800 mg/m^2/day. On the 28 day schedule, the suggested phase II UFT starting dose is 360 mg/m^2/day. Future clinical trials examining the combination of UFT plus oral folinic acid are being conducted to develop oral regimens of therapy for advanced colorectal carcinoma and adjuvant therapy for colon carcinoma.

Key words: Colon carcinoma, 5-fluorouracil, ftorafur, rectal carcinoma, tegafur, uracil.

Introduction

Tegafur is a 5-fluorouracil (5-FU) prodrug that is hydroxylated and converted to 5-FU by hepatic microsomal enzymes and whose administration may lead to a slow but sustained level of 5-FU in tumor.[1–4] UFT [Taiho Pharmaceutical Co. Ltd, Tokyo, Japan; (BMS-200604) Bristol-Myers Squibb, Princeton, NJ], a combination of tegafur and uracil in a 1:4 molar concentration, was developed by Fujii and coworkers based on the biochemical modulation of tegafur by uracil.[5–7] In preclinical studies, the coadministration of uracil with tegafur enhanced the concentration of 5-FU in tumors and resulted in increased antitumor activity.[8–11] In *in vitro* studies, uracil strongly inhibited the degradation of 5-FU to 2-fluoro-β-alanine.[5,6,8] Tegafur produced comparable concentrations of 5-FU in blood, other normal tissues and tumors, but with UFT, 5-FU concentrations in tumors were five to 10 times higher.[12,13]

Although UFT is commercially available in Japan, a well-defined maximum tolerated dose (MTD) for this drug has not been defined. The dose and schedule most commonly used is 200–300 mg administered two or three times daily until disease progresses. Although UFT has shown activity in colon, gastric, breast and pancreatic cancers, standard response criteria as defined in trials conducted in the US have not been uniformly used in assessing this activity; thus, it has been difficult to draw conclusions about the efficacy of UFT relative to that of i.v. schedules of 5-FU.[14–16]

We chose to study two administration schedules of UFT: 5 and 28 day schedules. The 5 day schedule was repeated every 21 days and the 28 day schedule was repeated every 35 days. The daily dose of UFT was subdivided into three doses administered every 8 h.

Patients and methods

Patient selection

All patients in these trials were required to have histologically proven carcinoma, to have recovered

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from the toxic effects of prior therapies and to have the following laboratory values: absolute granulocyte count $\geq 1500/\mu l$, platelet count $\geq 100\,000/\mu l$, serum creatinine ≤ 1.5 mg/dl and total bilirubin ≤ 1.5 mg/dl. A Zubrod performance status of 2 or less was required. Patients with a history of acute myocardial infarction, congestive heart failure, clinically significant arrhythmias or uncontrolled seizures were ineligible for the study. Written informed consent was obtained from all patients.

No patients treated on the 5 day trial were entered on the 28 day trial.

Study design

UFT was supplied by Taiho Pharmaceutical Co., Ltd (Tokyo, Japan). The drug was provided as 100 mg capsules (100 mg of tegafur). The daily dose of UFT was administered orally with 4–8 oz water at 7 a.m., 3 p.m. and 11 p.m. When doses could not be divided evenly, the highest dose was given in the morning and the lower dose in the evening. The calculated UFT dose was rounded to the nearest 100 mg. Each dose level was evaluated for at least 3 weeks before additional patients were started on escalated doses.

With the 5 day schedule, UFT was administered for five consecutive days; a course of therapy was repeated every 21 days. With the 28 day schedule, therapy was continued for 28 days and a course was repeated every 35 days. The starting doses were selected based on doses previously administered in Japanese studies and demonstrated to be safe.

Dose modification criteria were designed to allow reduction of the dose of UFT. For toxic effects greater than or equal to grade 2, UFT was withheld until the effects had resolved, after which treatment with UFT was resumed at the same dose as before. Days on which therapy was withheld because of drug toxicity were counted as treatment days. For grade 3 or 4 toxic effects, the UFT dose was reduced to the preceding dose level for that course and for subsequent courses.

Dose escalations were planned at 100% increments until biologic activity was observed; subsequent escalations were planned at 50% increments until grade 2 toxic effects occurred. Thereafter, dose increments of 25% were planned until the MTD was established. A minimum of three patients were entered at each level. Subsequent treatment courses were delayed until all toxic effects had resolved.

Compliance to the prescribed therapy was determined by weekly pill counts.

Treatment evaluation

Pretreatment evaluation included a complete medical history, physical examination, lesion measurements, electrocardiogram and chest X-ray. In addition, we performed a urinalysis, a multichannel chemistry evaluation (measuring serum creatinine, bilirubin, calcium, uric acid, alanine aminotransferase, lactate dehydrogenase and alkaline phosphatase levels), and tests to determine complete blood count, platelet count, prothrombin time and partial thromboplastin time. Complete blood cell counts and platelet counts were obtained twice weekly and the multichannel chemistry evaluation was done weekly. All pretreatment evaluations were repeated prior to each course. Appropriate radiologic studies to determine tumor response were performed after at least every two courses.

Evaluation criteria

Toxic reactions could be evaluated in all patients receiving UFT. The drug's toxic effects were graded by the National Cancer Institute's Common Toxicity Criteria.[17] The MTD was defined as that dose level preceding the dose level at which unacceptable toxic effects were encountered in half the study patients. Unacceptable toxicity was defined as grade 4 hematologic toxic effects and grade 3 non-hematologic toxic effects excluding alopecia and nausea and vomiting. Standard response criteria were used.[17] Patients continued therapy at the same dose level without any dose escalations until progressive disease or unacceptable toxic effects were documented. In the event that unacceptable toxic effects occurred, all such effects were allowed to resolve, after which patients continued treatment at the preceding dose level.

Results

Characteristics of the 19 patients who received the 5 day schedule of UFT and of the 23 patients given the 28 day schedule are listed in Table 1. No patients treated on one schedule were subsequently treated on the other schedule and no patients on either schedule had their doses escalated.

Table 1. Patient characteristics by UFT schedule

Characteristics	Schedule	
	5 day	28 day
No. of patients	19	23
Median age (years)	59	54
Performance status (Zubrod)		
0	2	4
1	16	19
2	1	0
Sex		
female	16	9
male	3	14
No. of prior chemotherapy regimens		
1	7	3
2	7	9
3	3	3
> 3	2	8
Primary tumor		
colon and rectum	12	20
lung	1	1
pancreas	1	—
breast	4	1
bile duct	1	—
anal canal	—	1

5 day schedule

The starting UFT dose level for the 5 day schedule was 360 mg/m^2/day. Subsequent daily dose levels were 720, 900 and a subsequent de-escalation to 800 mg/m^2/day. No toxic reactions were observed in patients treated at 360 and 720 mg/m^2/day levels. The toxic effects of the two highest dose levels are listed in Table 2. At 900 mg/m^2, the DLT was grade 4 granulocytopenia, which was noted in four of five patients treated at this level. The median granulocyte nadir, which occurred on day 19, was 2600/μl (range, 0–3900/μl). The median duration of granulocyte suppression was 6 days. Grade 3 toxic effects of fatigue, stomatitis and skin reactions were noted in three patients. Grade 1–2 toxic effects noted at this level included anorexia, nausea, fatigue, alopecia, stomatitis, diarrhea and thrombocytopenia.

Because we believed that 900 mg/m^2/day exceeded the MTD of UFT that should be used to begin phase II trials, we entered patients at a daily dose of 800 mg/m^2/day. Of the eight patients treated at this level, only one patient developed grade 4 granulocytopenia and two patients developed grade 3 toxic reactions (nausea in one patient and thrombocytopenia in the other). Grade 1–2 toxic effects included diarrhea, nausea, vomiting, fatigue, stomatitis and granulocytopenia.

28 day schedule

The starting UFT dose for the 28 day schedule was 180 mg/m^2/day. Subsequent dose levels were 360, 450 and a subsequent de-escalation to 400 mg/m^2/day. No toxic reactions were observed at 180 mg/m^2/day. Table 3 lists the toxic reactions observed in patients treated at the 360, 450 and 400 mg/m^2/day dose levels. At 360 mg/m^2/day, grade 1–2 toxic reactions observed included nausea and fatigue. At the 450 mg/m^2/day level, DLTs of grade 3 and 4 diarrhea were observed in three of the six patients. In addition, grade 3 or 4 diarrhea developed in three of the eight patients treated at 400 mg/m^2/day. The diarrhea generally began during the fourth week of treatment. Patients who developed grade 4 diarrhea experienced abdominal pain. Octreotide (Sandostatin) and conventional antidiarrheal agents [lopera-

Table 2. UFT toxicity for 5 day schedule by dose level

Toxicity by grade	Dose levels							
	900 mg/m^2/day (N = 5 patients)				800 mg/m^2/day (N = 8 patients)			
	1	2	3	4	1	2	3	4
Granulocytopenia	0	0	0	4	1	0	0	1
Thrombocytopenia	1	0	0	0	0	0	1	0
Diarrhea	0	2	0	0	2	2	0	0
Nausea	0	2	0	0	3	3	1	0
Vomiting	0	1	0	0	3	2	0	0
Stomatitis	1	0	1	0	1	0	0	0
Skin rash	0	0	1	0	0	0	0	0
Fatigue	1	1	1	0	3	1	0	0

Table 3. UFT toxicity for 28 day schedule by dose level

Toxicity by grade	Dose levels											
	360 mg/m^2/day ($N = 6$ patients)				450 mg/m^2/day ($N = 6$ patients)				400 mg/m^2/day ($N = 8$ patients)			
	1	2	3	4	1	2	3	4	1	2	3	4
Granulocytopenia	0	1	0	0	0	2	0	1	1	0	0	0
Diarrhea	0	0	0	0	0	1	2	1	3	0	1	2
Nausea	0	2	0	0	1	4	0	0	2	3	0	0
Vomiting	0	0	0	0	0	0	0	0	2	3	0	0
Oral mucositis	0	0	0	0	1	0	1	0	1	0	1	0
Skin rash	0	0	0	0	1	0	0	0	0	0	0	0
Fatigue	1	2	1	0	1	3	0	0	0	2	0	0

mide and dipheno-xylate (Lomotil)] were not effective in controlling diarrhea. Since the appearance of treatment-related diarrhea can be unpredictable and severe in patients receiving UFT doses that exceed 400 mg/m^2/day, we recommend a phase II starting dose of 360 mg/m^2/day for the 28 day schedule.

Antitumor activity

All patients enrolled in these trials had documented carcinoma that had progressed despite prior treatment with 5-FU. One patient who had metastatic rectal carcinoma previously treated with 5-FU, leucovorin and cisplatin achieved a minor response of 4 months' duration in pulmonary and inguinal nodal metastases; the patient received the 28 day UFT plus leucovorin schedule.

Discussion

Tegafur was examined in the US over a decade ago, but the drug's clinical development was discontinued because it was not believed to have a therapeutic advantage over 5-FU. At therapeutic doses, central nervous system toxicity and unpredictable diarrhea were noted, but without improved efficacy. In US clinical trials, the tegafur schedules studied were 4 g/m^2 weekly or 2.5 g/m^2/day × 5 i.v. or 1.5 g/m^2/day orally.[1–4] In contrast, Japanese investigators developed tegafur schedules using smaller doses given orally two or three times a day over several months.[8] In those trials, tegafur had mild toxic effects and showed activity in colorectal, gastric, breast and lung carcinomas. In the clinical development of UFT, the Japanese examined dosing schedules similar to those used with tegafur.[14,15]

Although a variety of 5-FU schedules are used in the US, two schedules commonly used are a short bolus i.v. schedule for five consecutive days repeated every 28 days and a protracted i.v. 5-FU infusion over 28 days followed by a 1 week rest period.[18,19] In our UFT trials, we chose our schedules to resemble those common 5-FU schedules. 5-FU has schedule-dependent toxic effects, with neutropenia more often observed with bolus administration schedules, and diarrhea and oral mucositis the common dose-limiting toxic effects noted with continuous or protracted-infusion schedules.[18,19]

Our clinical trials demonstrated that single-agent UFT possessed schedule-dependent differences. We found granulocytopenia to be the DLT in the 5 day UFT schedule, but it was uncommon in the 28 day schedule, where grade 3–4 diarrhea was the DLT.

Diarrhea has been reported in 20–40% of patients receiving i.v. 5-FU either as a bolus or a protracted infusion schedule; this diarrhea is severe in approximately 5–10% of such patients.[18–20] We noted a steep dose-toxicity relationship with the 28 day UFT schedule: three of the six patients given 450 mg/m^2 and three of eight who received 400 mg/m^2 experienced grade 3 or 4 diarrhea, while no patient at the 360 mg/m^2 dose developed diarrhea. A similar steep dose–toxicity relationship had been reported in our previous trial of UFT plus leucovorin.[21]

Grade 3 or 4 diarrhea generally began during the fourth week of treatment and led to prolonged hospitalizations. Efforts should be made to avoid progression of diarrhea beyond grade 2. Patients should be instructed to discontinue UFT and initiate loperamide in the presence of grade 2 or greater diarrhea. Grade 2 diarrhea generally resolved within 2–3 days, allowing patients to resume UFT treatment without dose reduction.

The diarrhea associated with prolonged administration of UFT may be due to the conversion of tegafur to 5-FU and its subsequent phosphorylation

in the gastrointestinal mucosa, as observed with another oral fluorinated pyrimidine, doxifluridine (Roche Laboratories, Nutley NJ).[22] In rats, oral oxonic acid, an inhibitor of the phosphorylation of 5-FU to 5-fluorouridine-5′-monophosphate, has been demonstrated to markedly reduce both injury to the gastrointestinal tract and the severe diarrhea associated with UFT without influencing that drug's antitumor activity.[23]

Oral mucositis has been observed in approximately 40% of patients treated with intravenous schedules of 5-FU.[18–20] In our trial of the 5 day schedule, mucositis was concurrent with diarrhea and severe granulocytopenia, which probably reflected high maximum plasma drug levels (Cp_{max}) of 5-FU. Of the 14 patients treated at the two highest UFT dose levels (450 and 400 mg/m^2/day for 28 days), serious oral mucositis developed in only two patients (on days 27 and 28) and was associated with the presence of diarrhea.

In early tegafur studies, central nervous system toxic effects were noted with both intravenous and high-dose oral schedules and were associated with plasma tegafur levels above 50 μg/ml.[1,24] In our studies, central nervous system toxicity was not observed; the maximum plasma tegafur level detected was only 26 μg/ml in a patient receiving 900 mg/m^2/day on the 5 day schedule.[25]

Palmar–plantar erythrodysesthesias ('hand–foot' syndrome) has been described in 42–82% of patients receiving protracted i.v. infusions of 5-FU in other studies,[18–20] but we did not observe this effect in patients treated in either of our phase I UFT trials. This toxic effect is generally observed with repeated courses of protracted infusions of 5-FU. However, since the median number of UFT courses administered in our trial was 2, cumulative toxic effects may have been underestimated. Nevertheless, studies in which multiple courses (over 10) of UFT plus oral leucovorin were administered have not reported UFT to be associated with the development of palmar–plantar erythrodysesthesias.[25]

Our recommended phase II doses of UFT (800 mg/m^2/day on the 5 day schedule and 360 mg/m^2/day on the 28 day schedule) were easily administered and well tolerated by patients. A Japanese study of more than 400 patients treated with UFT doses between 300 and 600 mg reported response rates of 25% or greater in patients with stomach, pancreas, gall bladder and breast carcinoma.[14] Our patients had previously received i.v. 5-FU schedules, which made assessments of UFT's activity difficult. In a study conducted in the UK in 40 patients with colorectal carcinoma, a response rate of 16% (95% confidence limits, 6.4–32.8%) with minimal toxic effects was reported.[26] However, in that study all patients received a fixed dose of 200 mg UFT three times a day and prior 5-FU exposure was permitted, which prevented an accurate determination of UFT's activity in a chemotherapy-naive population.[26]

Subsequent UFT development in the US has focused on the 28 day schedule described herein plus oral leucovorin. With the addition of leucovorin to UFT, the UFT dose was reduced from 360 to 300 mg/m^2/day for the 28 day schedule.[21] The regimen's preliminary therapeutic activity is similar to that observed with intravenous 5-FU plus leucovorin.[21,27] The 28 day UFT plus leucovorin schedule demonstrated a favorable toxicity profile without significant neutropenia, mucositis, palmar–plantar erythrodysesthesias, alopecia or central nervous system toxic effects. The current National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant colon cancer therapy trial (CO-6) is comparing a 28 day oral schedule of UFT plus leucovorin with weekly i.v. 5-FU plus leucovorin. In addition, a randomized phase III trial in metastatic colorectal cancer is under way comparing this UFT plus leucovorin regimen with intravenous 5-FU plus leucovorin; this trial is examining the survival, quality of life and pharmaco-economics of these treatments.

Conclusion

The toxic effects of UFT are schedule dependent, with marked differences in the toxic effect profile (neutropenia versus diarrhea). With the 5 day schedule, the phase II UFT starting dose is 800 mg/m^2/day. On the 28 day schedule, the suggested phase II UFT starting dose is 360 mg/m^2/day. Future clinical trials examining the combination of UFT plus oral folinic acid are being conducted to develop oral regimens of therapy for advanced colorectal carcinoma and adjuvant therapy for colon carcinoma.

References

1. Friedman MA, Ignoffo RH. A review of the United States clinical experience of the fluoropyrimidine, ftorafur (NSC 148958). *Cancer Treat Rev* 1980; 7: 205–13.
2. Buroker T, Padilla F, Groppe C, *et al.* Phase II evaluation of ftorafur in previously untreated colorectal cancer: a Southwest Oncology Group study. *Cancer* 1979; **44**: 48–51.
3. Valdivieso M, Bodey GP, Gottlieb JA, Freireich EJ.

Clinical evaluation of ftorafur. *Cancer Res* 1976; **36**: 1821–4.
4. Ansfield FJ, Kallas GJ, Singson JP. Phase I–II studies of oral tegafur (ftorafur). *J Clin Oncol* 1983; **1**: 107–10.
5. Fujii S, Ikenaka K, Fukushima M, Shirasaka T. Effect of uracil and its derivatives on antitumor activity of 5-fluorouracil 1-(2-tetrahydrofuryl)-5-fluorouracil. *Kagaku Ryoho* 1978; **69**: 763–72.
6. Fujii S, Okuda H, Toide H, Watanabe N, Taira K, Hashimoto S. Studies on the fate of FT-207, an antitumor agent: absorption, tissue distribution, and excretion. *Pharmacokinetics* 1974; **8**: 589–95.
7. Taguchi T, Nakano Y, Fujita M, *et al.* Clinical studies of the anticancer activity of FT-207. *Jpn J Cancer Clinics* 1972; **18**: 550–3.
8. Taguchi T, Nakano Y, Jikuya K, Fujii S. Effect of uracil on the antitumor activity of ftorafur. *Jpn J Cancer Chemother* 1978; **5**: 1161–5.
9. Fujii S, Kitano S, Ikenaka K, Shirasaka T. Studies on coadministration of uracil or cytosine on antitumor activity of FT-207 or 5-FU derivatives. *Jpn J Cancer Chemother* 1979; **6**: 377–84.
10. Ikenaka K, Shirasaka T, Kitano S. Effect of uracil on metabolism of 5-fluorouracil *in vitro*. *Gann* 1979; **70**: 353–9.
11. Saitoh T, Kagaya T, Takebe T, Ishii K. The enhancement of the antitumor effect of FT-207 coadministered with uracil on the transplanted ductal adenocarcinoma of the Syrian goldern hamster pancreas. *Jpn J Cancer Chemother* 1982; **9**: 2168–74.
12. Suemasu K, Nomoto C, Higashi Y. Concentration of 5-FU level in the tissue and blood of the patients with breast cancer by preoperative administration of UFT. *Jpn J Cancer Chemother* 1982; **9**: 667–71.
13. Tsujimoto T, Sakai S, Murata M, Sasaki R. Concentrations of 5-FU in the tissue and serum of the patients with head and neck malignant tumors by preoperative administration of UFT. *Jpn J Cancer Chemother* 1983; **10**: 78–83.
14. Ota K, Taguchi T, Kimura K. Report on nationwide pooled data and cohort investigation in UFT Phase II studies. *Cancer Chemother Pharmacol* 1988; **22**: 333–8.
15. Murakami M, Ota K. Clinical results of UFT therapy for malignant tumors under cooperative study. *Jpn J Cancer Chemother* 1980; **7**: 1579–86.
16. Watanabe H, Yamamoto S, Naito T. Clinical results of oral UFT therapy under cooperative study. *Jpn J Cancer Chemother* 1980; **7**: 1588–96.
17. Ajani JA, Welch SR, Raber MN, *et al.* Comprehensive criteria for survival in therapy-induced toxicity. *Cancer Invest* 1990; **8**: 141–53.
18. Dorr RT, Von Hoff DD. 5-Fluorouracil. In: Dorr RT, Von Hoff DD, eds. *Cancer chemotherapy handbook*. Norwalk, CT: Appleton & Lange 1994: 500–15.
19. Leichman CG, Fleming TR, Muggia FM, *et al.* Phase II study of fluorouracil and its modulation in advanced colorectal cancer: a Southwest Oncology Group Study. *J Clin Oncol* 1995; **13**: 1303–11.
20. Hill M, Norman A, Cunningham D, *et al.* Impact of protracted venous infusion fluorouracil with or without interferon alfa-2b on tumor response, survival, and quality of life in advanced colorectal cancer. *J Clin Oncol* 1995; **13**: 2317–23.
21. Pazdur R, Lassere Y, Rhodes V, *et al.* Phase II trial of uracil and tegafur plus oral leucovorin: an effective oral regimen in the treatment of metastatic colorectal carcinoma. *J Clin Oncol* 1994; **12**: 2296–300.
22. Armstrong RD, Diasio RB. Metabolism and biological activity of 5-deoxy-5 fluorouridine, a novel fluoropyrimidine. *Cancer Res* 1980; **40**: 3333–8.
23. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition of oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 1993; **53**: 4004–9.
24. Dindogru A, Vaitkevicius VK, Young JD, Horwitz JP, Baker JH. Pharmacologic studies and phase I evaluation of oral ftorafur. *Proc Am Ass Cancer Res* 1980; **21**: 167.
25. Ho DH, Covington WP, Pazdur R, *et al.* Clinical pharmacology of combined oral uracil and ftorafur. *Drug Metab Dispos* 1992; **20**: 936–40.
26. Malik STA, Talbot D, Clarke PI, Osborne R, Reznek, Wringley PFM, Slevin ML. Phase II trial of UFT in advanced colorectal and gastric cancer. *Br J Cancer* 1990; **62**: 1023–5.
27. Saltz LB, Leichman CG, Young CW, *et al.* A fixed-ratio combination of uracil and ftorafur (UFT) with low dose leucovorin. *Cancer* 1995; **75**: 782–5.

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