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ORIGINAL ARTICLE

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# A phase I study of oral uracil/ftorafur (UFT) plus leucovorin and bis-acetato-ammine-dichloro-cyclohexylamine-platinum IV (JM-216) each given over 14 days every 28 days

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**Abstract** *Purpose*: To determine the feasibility, maximal tolerated doses, and response rates for a combined regimen of the platinum and 5-fluorouracil oral analogues bis-acetato-ammine-dichloro-cyclohexyl-amine platinum(IV) (JM-216) and uracil/ftorafur (UFT) coadministered as a 14 consecutive-day every 28-day schedule. *Methods*: Of 20 patients enrolled in this investigation, 17 on the following dose escalation scheme were evaluable for toxicity and/or response: I UFT 300 mg/day, JM-216 5 mg/day (three patients), II UFT 300 mg/day, JM-216 10 mg/day (four patients), III UFT 300 mg/day, JM-216 20 mg/day (ten patients). *Results*: All 17 evaluable patients were evaluable for toxicity. At dose level III, dose-limiting nausea and emesis were observed in one patient despite maximal antiemetic support. Importantly, neurotoxicity and nephrotoxicity were not observed at the JM-216 dose levels examined in this study. This observation is consistent with results seen with single agent JM-216. *Conclusion*: For JM-216 and UFT administered at 20 mg/day and 300 mg/day over 14 days, nausea and emesis were observed as the principal dose-limiting toxicities. These doses are considerably below the maximally tolerated doses of single agent JM-216 and UFT. Shorter administration schedules should be explored in an attempt to increase the dose intensity and minimize the toxicity of this combination oral regimen.

**Key words** Oral chemotherapy · JM-216 · UFT · Hyperemesis · Advanced cancer

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## Introduction

Therapeutic combination regimens of cisplatin and 5-fluorouracil (5-FU) have been used extensively in the treatment of head and neck, esophageal, gastric, lung and squamous cell skin carcinomas. The effectiveness of such regimens may be due in part to synergy between the two agents. Preclinical models suggest multiple mechanisms for synergism, including (1) 5-FU depletion of intracellular glutathione, which can produce CDDP resistance at high levels, (2) 5-FU incorporation into RNA with subsequent impaired transcription of DNA repair enzymes for cisplatin adducts, and (3) enhanced 5-FU efficacy through a schedule-dependent, cisplatin-mediated increase in intracellular folate levels [2, 3, 14].

Ftorafur (UFT) is an orally bioavailable fluoropyrimidine composed of 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) and uracil complexed at a molar ratio. of 1:4 UFT is a prodrug, metabolized to 5-FU by target tumor tissues and by hepatic cytochrome P450 [1]. Phase I studies of UFT on a 28-day schedule with high-dose leucovorin (150 mg/day) suggest a maximal tolerated dose (MTD) of 350 mg/day, with the principal toxicities being diarrhea, nausea, and emesis [7]. Similarly, UFT has been safely coadministered with low-dose leucovorin (15 mg/day) on a 28-day schedule at a dose of 350 mg/day [13]. UFT has been used extensively in Japan, where pooled phase II data at doses from 300 to 600 mg/day suggest response rates of 25 to 32% in patients with colorectal cancer, cholangiocarcinoma, and gastric and breast carcinomas [8].

Bis-acetato-ammine-dichloro-cyclohexylamine-platinum(IV) (JM-216) is a novel platinum analogue

bioavailable by the oral route. JM-216 is rapidly biotransformed following oral administration into at least six species [12]. Preclinically, JM-118 has been identified as the major cytotoxic species in ovarian carcinoma cell lines [12]. Single-dose pharmacokinetic studies of JM-216 suggest saturable absorption at doses exceeding 200 mg/m$^2$ [5]. Phase I JM-216 studies with 5 and 14 consecutive-day schedules suggest MTDs of 140 mg/m$^2$ and 40 mg/m$^2$, respectively [6, 9]. The dose-limiting toxicity in each study was myelosuppression. Phase II data are notable for a 31% response rate in therapy-naive small-cell lung cancer patients treated on a 120–140 mg/m$^2$/day × 5 schedule [4], while 42% of patients with hormone-refractory prostate cancer had a reduction of serum prostate-specific antigen (PSA) on this schedule [11].

Recognizing the single-agent MTDs of JM-216 and UFT with prolonged administration, we investigated their combination on a 14 consecutive-day every 28-day schedule.

## Patients and methods

This single-institution phase I trial was initiated in November 1996 to determine the MTDs of JM-216 and UFT with leucovorin which could be safely coadministered on a 14-day schedule every 28 days. Disease response was assessed as a secondary endpoint. All patients had pathologic confirmation of a nonhematologic malignancy which was refractory to standard therapies or for which no standard therapy existed. All patients had measurable or evaluable disease. Eligibility requirements, determined within 2 weeks of study entry, included (1) Karnofsky performance status > 70%, (2) adequate bone marrow function (ANC > $2 \times 10^9$/l and platelet count > $100 \times 10^9$/l), (3) serum creatinine < 1.4 mg/dl or calculated creatinine clearance > 60 ml/min, (4) adequate liver function (total serum bilirubin < 1.5 mg/dl, ALT and alkaline phosphatase < 1.25 × the upper limit of normal values, and (4) the ability to swallow pill medications. No patient had received previous chemotherapy or radiotherapy within 4 weeks prior to study entry. Patients with serious concurrent medical disorders, history of gastrectomy, or previous radiotherapy to > 30% of bone marrow were not eligible. This investigation was approved by the investigational review board of the University of Chicago. All patients gave written informed consent prior to study entry.

For each cycle, all patients received a 14-day supply of UFT, leucovorin, and JM-216 tablets. JM-216 (5- or 10-mg tablets) was given as a single daily oral dose. UFT (100-mg tablets) was administered on a three times daily schedule at 7 a.m., 3 p.m. and 11 p.m. Leucovorin was administered concomitantly with UFT at a fixed dose of 30 mg three times daily. Instructions were given to take no food within 1 h before or after UFT or JM-216 dosing. The dose escalation scheme was as follows: I JM-216 5 mg/day, UFT 300 mg/day; II JM-216 10 mg/day, UFT 300 mg/day; III JM-216 20 mg/day, UFT 300 mg/day. The trial design called for three evaluable patients per dose level. Dose escalation proceeded in the absence of dose-limiting toxicities, as defined below. If a dose-limiting toxicity was observed, that dose level cohort was expanded to six patients. The MTD was defined as one dose level below that at which two or more dose-limiting toxicities were observed.

Patients had complete blood counts checked weekly. Dose-limiting toxicities, defined by common toxicity criteria, were as follows: (1) grade 3 or higher GI toxicity with the exception of nausea, diarrhea, and vomiting; (2) nausea, emesis, or diarrhea were dose-limiting *only* if grade 3 or higher following maximal medical intervention (for nausea and emesis, this was defined as symptoms refractory to prochlorperazine and ondansetron given every 6 and 8 h, respectively); (3) grade 3 or higher anemia or thrombocytopenia or grade 4 neutropenia; (4) nonhematologic toxicities grade 2 or higher; or (5) missing four or more doses of JM-216 and/or 12 or more doses of UFT or leucovorin due to toxicity.

Dose delays were allowed in the event of granulocyte or platelet counts less than 1000/mm$^3$ and 50 000/mm$^3$, respectively, at any time during the 14-day period of drug administration. Medications were readministered when granulocytes reached > = 1500/mm$^3$ and platelets > = 100 000/mm$^3$. Dose delays were allowed for nonhematologic toxicities of grade 2 or higher. Medications were readministered only after these toxicities had resolved to grade 1 or less. Medication withheld due to dosage delay was not administered beyond the planned 14-day schedule.

Patients were evaluated for response to treatment after every two courses of therapy. Response criteria were defined according to UICC criteria: CR, complete radiographic disappearance of all tumor lesions for at least 4 weeks; PR, > 50% decrease in the sum of perpendicular diameters of all measurable lesions over two cycles, PD, a > 25% increase in the size of any measurable or evaluable lesions or the appearance of new lesions; SD, a disease assessment not fulfilling any of the above criteria. Patients with stable or responsive disease and acceptable toxicity were eligible for additional treatment cycles.

## Results

A total of 20 patients were treated in this study. Ten patients received at least two complete cycles and were fully evaluable for toxicity and response. An additional seven patients were evaluable for toxicity. Three patients were not considered for toxicity or response, having received only a fraction of their first cycle of therapy. Two of these patients were noncompliant with medication and the third required radiation therapy for spinal metastasis. A total of 40 cycles of JM-216 and UFT with leucovorin were administered to the 17 patients evaluable for toxicity and/or response. Of these evaluable patients, three were treated in dose escalation cohort I, four were treated in cohort II, and ten were treated in cohort III.

### Toxicity

Table 1 summarizes all treatment-related toxicities. Table 2 summarizes gastrointestinal toxicities with respect to dose escalation cohort. Nausea and emesis were the most frequently observed adverse events, occurring in 38% and 28% of all cycles administered, respectively. Although protocol design allowed for prochlorperazine and ondansetron medications, they were utilized by only 1 of 12 patients experiencing grade 1 nausea or emesis. A dose level III patient experienced grade 3 nausea and grade 3 emesis on her first cycle of therapy. She was hospitalized on cycle day 11 for these toxicities, but had taken no antiemetics prior to receiving intravenous prochlorperazine and ondansetron as an inpatient. After a 24-h delay, JM-216 and UFT were restarted with the implementation

**Table 1** Summary of toxicities during 40 treatment cycles

| Adverse event | NCI grade | % of cycles | No. of patients |
|---|---|---|---|
| Gastrointestinal | | | |
| Nausea | 1 | 32.5 | 9 |
| | 2 | 0 | 0 |
| | 3 | 5.0 | 2 |
| Emesis | 1 | 25.0 | 7 |
| | 2 | 0 | 0 |
| | 3 | 2.5 | 1 |
| Anorexia | 3 | 2.5 | 1 |
| Diarrhea | 1 | 2.5 | 1 |
| | 2 | 5.0 | 2 |
| Mucositis | 1 | 2.5 | 1 |
| Hematologic | | | |
| Neutropenia | 2 | 2.5 | 1 |
| Thrombocytopenia | 3 | 5.0 | 2 |
| Hepatic | | | |
| Total bilirubin | 3 | 2.5 | 1 |
| Transaminase | 2 | 2.5 | 1 |
| Renal | | | |
| Creatinine | 2 | 2.5 | 1 |
| Neurologic | | | |
| Dizziness | 1 | 2.5 | 1 |
| Other | | | |
| Fatigue | 1 | 22.5 | 3 |
| | 2 | 15.0 | 1 |
| | 3 | 2.5 | 1 |

of 8 mg ondansetron every 8 h and 10 mg prochlorperazine every 6 h as prophylaxis. Less than 24 h following chemotherapy readministration, the patient experienced recurrent nausea and emesis and was removed from study. Two patients subsequently treated at dose level III received the aforementioned prophylactic ondansetron and prochlorperazine medications at the initiation of therapy. These patients suffered no nausea or emesis in excess of grade 1.

Hematologic toxicity was infrequent, being observed in only 2 of 17 evaluable patients. Each of these patients had comorbid conditions which may have completely or in part contributed to the observed toxicity. A dose level I patient with prostate cancer who experienced grade 3 thrombocytopenia and grade 2 neutropenia following treatment cycle 6 had biopsy-proven tumor infiltration of the bone marrow. A dose level II patient who developed grade 3 thrombocytopenia on the 27th day following the start of treatment cycle 1 had concomitant non-neutropenic sepsis.

Other significant toxicities included fatigue, which was observed in 40% of treatment cycles. One patient treated at dose level II experienced a grade 2 creatinine elevation on the 14th day of his first treatment cycle. This toxicity may have been related to decreased fluid intake during the acute phase of an ongoing cerebrovascular accident. While the renal toxicity was judged as not definitively related to study therapy, it nevertheless prompted an expansion of patient cohort III. No other renal toxicities were observed in the expanded cohort.

One patient treated at dose level III had an isolated episode of grade 3 hyperbilirubinemia (2.1 mg/dl) on day 14 of his first treatment cycle. The serum bilirubin had normalized without intervention by the next analysis of laboratory parameters, on the 27th day following initiation of cycle 1. The patient received cycle 2 of therapy at a reduced dose (level II); no recurrent hyperbilirubinemia was observed.

One dose level III patient had an isolated episode of grade 2 hepatic transaminase elevation during her first treatment cycle, but also had rapidly progressive hepatic-based metastatic disease at that time.

**Table 2** Summary of gastrointestinal toxicities by dose escalation cohort

| Adverse event | NCI grade | Dose level cohort | | |
|---|---|---|---|---|
| | | I | II | III |
| Nausea | 1 | 3 | 2 | 4 |
| | 2 | – | – | – |
| | 3 | – | – | 2 |
| Emesis | 1 | 1 | 2 | 4 |
| | 2 | – | – | – |
| | 3 | – | – | 1 |
| Anorexia | 3 | – | – | 1 |
| Diarrhea | 1 | – | – | 1 |
| | 2 | – | – | 2 |
| Mucositis | 1 | – | 1 | – |

### Response

A patient with hormone-refractory prostate cancer was treated at dose level I for a total of six cycles. The patient had a sustained decrease in serum PSA, which was first noted after the second cycle of therapy. Serum PSA was reduced from 509 ng/ml pretreatment to 67 ng/ml following cycle 6. The patient had a clear improvement in pain symptoms as well, but was subsequently removed from study due to PD (bone marrow metastasis).

Two patients with treatment-refractory malignancies had stabilization of disease on this regimen. A patient with endometrial carcinoma and PD following four previous chemotherapy regimens had stable radiographic disease for four cycles of JM-216 and UFT. A patient with pseudomyxoma peritonei had stable disease over six cycles of therapy.

## Discussion

With this combination of JM-216 and UFT given over a 14 consecutive-day schedule, nausea and emesis were the dose-limiting toxicities at 20 mg/day and 300 mg/day, respectively. These doses are substantially below the 14-day single-agent MTDs of JM-216 (40 mg/m$^2$) and UFT with leucovorin (400 mg/m$^2$) [9, 10]. A relationship between dose escalation and gastrointestinal toxicity was suggested (Table 2). Nausea and emesis did not exceed grade 1 in any dose level I or II patient. No dose level I or II patient utilized prophylactic odansetron or prochlorperazine. All grade 3 nausea and emesis occurred in

dose level III patients. Sustained nausea and emesis were present in one patient treated at this dose level, despite every 8-h ondansetron and every 6-h prochlorperazine prophylaxis initiated after treatment delay. While two other patients treated at this dose level had no nausea or emesis with this prophylactic schedule initiated at the beginning of therapy, it is not clear whether this degree of antiemetic support would be practical in an outpatient schedule. Also, the cost of this intensive prophylaxis would further limit the widespread application of this regimen.

Consistent with previous clinical studies of JM-216 given on 5-d and 14-day schedules, recurrent neurotoxicity and nephrotoxicity were not observed. Hematologic toxicities were significant in two patients, but each had a significant comorbid disease process. Therefore none of the hematologic toxicities observed in this investigation could be definitively ascribed to therapy-induced myelosuppression.

Our results do not demonstrate the feasibility of administration of a concomitant oral regimen of JM-216 and UFT given for 14 consecutive days of a 28-day cycle. The historic efficacy of 5-fluorouracil and cisplatin regimens and the absence of clear myelotoxicity, nephrotoxicity and neurotoxicity observed in this investigation suggest a rationale for additional evaluation of JM-216 and UFT combination regimens. Different dose schedules may be explored in an attempt to increase dose intensity while minimizing significant toxicity, primarily dose-limiting nausea and emesis. Groen et al. noted grade 2/3 nausea and emesis in only 2% (1 of 50) JM-216 cycles administered on a 5-day schedule (120 mg/m$^2$per day) with prophylactic antiemetics [4]. Using an identical dose and 5 consecutive-day schedule, McKeage et al. noted severe (grade 3 or higher) nausea and emesis in up to 13% of JM-216 cycles, despite aggressive antiemetic prophylaxis [6]. These symptoms were routinely delayed, with a median onset at 24 h for nausea and 75 h for emesis. These investigators noted a substantial accumulation of platinum species with this 5-day administration schedule; day 5 platinum ultrafiltrate AUC averaged 1.7 times that observed on day 1 [6]. It was asserted that nausea and emesis may be related to the accumulation of platinum species with repetitive daily dosing. It follows that this effect might be accentuated on the 14 consecutive-day schedule used in our investigation. Given the additive gastrointestinal toxicity manifest with coadministered UFT, it may be valuable to consider a shorter 5-day JM-216 administration schedule for future combination studies of JM-216 and UFT.

## References


1. Au JL, Sadee W (1980) Activation of ftorafur to 5-fluorouracil and gamma-butyrolactone. Cancer Res 40: 2814
2. Dabholkar M, Vionnet J, Bostick-Bruton F, Yu JJ, Reed E (1994) Messenger RNA levels of XPAC and ERCC1 in ovarian cancer tissue correlates with response to platinum-based chemotherapy. J Clin Invest 94: 703
3. Esaki T, Nakano S, Matsumoto N, Fujishim H, Niho Y (1996) Schedule-dependent reversion of acquired cisplatin resistance by 5-fluorouracil in a newly established cisplatin-resistant HST-1 human squamous cell carcinoma cell line. Int J Cancer 65: 479
4. Groen HJM, Smit EF, Bauer J, Calvert AH, Weil C, Crabeels D, Schacter LP, Smith I (1996) A phase II study of oral platinum JM-216 as first-line treatment in small cell lung cancer (abstract). Proc Am Soc Clin Oncol 15: 1128
5. McKeage MJ, Mistry P, Ward J, Boxall FE, Loh S, O'Neill C, Ellis P, Kelland LR, Morgan SE, Murrer B (1995) A phase I and pharmacology study of an oral platinum complex, JM-216: dose-dependent pharmacokinetics with single dose administration. Cancer Chemother Pharmacol 36: 451
6. McKeage MJ, Raynaud F, Ward J, Berry C, O'Dell D, Kelland LR, Murrer B, Santabarabara P, Harrap KR, Judson IR (1997) Phase I and pharmacokinetic study of an oral platinum complex given daily for 5 days in patients with cancer. J Clin Oncol 15: 2691
7. Meropol NJ, Rustum YM, Petrelli NJ, Rodriguez-Bigas M, Frank C, Ho DH, Kurowski M, Creaven PJ (1996) A phase I and pharmacokinetic study of oral uracil, ftorafur, and leucovorin in patients with advanced cancer. Cancer Chemother Pharmacol 37: 581
8. Ota K, Taguchi T, Kimura K (1988) Report on nationwide pooled data and cohort investigation in UFT phase II study. Cancer Chemother Pharmacol 22: 333
9. Pagani O, Bauer J, Bomer M (1996) Phase I study of the oral platinum derivative JM-216 given daily for 14 days. 21st Congress ESMO, Vienna, 1–5 November
10. Pazdur R, Rivera E, Diaz-Canton E, Lassere Y, Bready B, Winn R, Ajani J (1995) Phase I trial of UFT (uracil-tegafur) with leucovin: a 14 day schedule (abstract). Proc Am Soc Clin Oncol 14: 1568a
11. Peereboom DM, Wood L, Connell C, Spisak J, Smith D, Liebwohl D, Bukowski RM (1997) Phase II trial of oral BMS-182751 (JM-216) in hormone refractory prostate cancer (HRPC)(abstract). Proc Am Soc Clin Oncol 16: 339a
12. Raynaud FI, Mistry P, Donaghue A, Poon GK, Kelland LR, Barnard CF, Murrer BA, Harrap KR (1996) Biotransformation of the platinum drug JM-216 following oral administration to cancer patients. Cancer Chemother Pharmacol 38: 155
13. Saltz LB, Leichman CG, Young CW, Muggia FM, Conti JA, Spiess T, Jeffers S, Leichman LP (1995) A fixed-ratio combination of uracil and ftorafur (UFT) with low dose leucovorin: an active oral regimen for advanced colon cancer. Cancer 75: 782
14. Scanlon KJ, Newman EM, Lu Y, Priest DG (1986) Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. Proc Natl Acad Sci USA 83: 8923