Cancer Chemother Pharmacol (1990) 26: 159–162

Cancer Chemotherapy and Pharmacology

Phase I clinical trial of cisplatin given i.v. with 5-fluorouracil and high-dose folinic acid

James L. Abbruzzese, Robert Amato, Susan Schmidt, Martin N. Raber, and Philip Frost

Department of Medical Oncology, Division of Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA

Received 29 August 1989/Accepted 11 January 1990

Summary. We report the results of a phase I study of intravenously administered cisplatin, 5-fluorouracil and high-dose folinic acid. This trial was designed to exploit potential biochemical interactions between these three agents. The maximum tolerated doses were cisplatin, 75 mg/m^2, day 1; 5-fluorouracil, 375 mg/m^2, days 1–5 and leucovorin 500 mg/m^2, days 1–5. The dose-limiting toxic effect of this regimen was myelosuppression. Mild non-hematologic toxic effects were also observed and included nausea, vomiting, stomatitis, and diarrhea. Phase II trial of this regimen are underway, however randomized studies will eventually be necessary to establish whether cisplatin contributes clinically significant activity to this regimen.

Introduction

The low but reproducible activity of 5-fluorouracil (FUra) against a variety of neoplasms has encouraged basic scientists and clinical investigators to exploit this activity through biochemical modulation. The most successful of these approaches have used dl-5-formyltetrahydrofolic acid (calcium leucovorin, dl-CF), which provides an exogenous source of reduced folate and is metabolized to the biochemically active form 5,10-methylenetetrahydrofolate (5,10-CH_2-FH_4). This cofactor augments the cytotoxicity of FUra through stabilization of the ternary complex of 5-fluorodeoxyuridine monophosphate (FdUMP), thymidylate synthase, and 5,10-CH_2-FH_4, and leads to prolonged inhibition of thymidylate synthase [6, 21].

Phase I and II trials based on the principles discussed above have explored a wide variety of doses and schedules for both FUra and dl-CF, and findings have generally supported the hypothesis that the antitumor activity of FUra could be favorably modulated with dl-CF [8]. Subsequently, phase III trials conducted in patients with colorectal cancer have demonstrated improved activity for the FUra/dl-CF regimen over that of FUra alone [5, 14, 15]. In addition, two of these randomized studies suggested a survival advantage for patients treated with FUra and dl-CF [5, 14]. The success of the FUra/dl-CF regimens reported to date has been limited and should not obscure the observations that (a) very few patients treated with this regimen achieve complete remissions and (b) the partial remissions have been of short duration.

In other studies, the combination of FUra and cisplatin (CDDP) has been shown to have synergistic cytotoxicity against murine L1210 leukemia [18] and excellent activity against some human neoplasms [11, 16]. Mechanistic studies by Scanlon et al. [17] showed that exposure of the A2780 human ovarian cancer cell line to 10 μM CDDP for 30 min followed by 5 μM FUra for 30 min resulted in an enhanced cytotoxicity that was thought to be secondary to an increase in the intracellular levels of 5,10-CH_2-FH_4, thereby promoting stabilization of the ternary complex and promoting inhibition of thymidylate synthase.

Based on this information, further modulation of the biochemical pharmacology and cytotoxicity of FUra and dl-CF appeared to be possible by combination of these agents with CDDP. In view of the possibility that this combination could augment toxicity as well as antineoplastic activity, we designed a phase I trial to define the maximal tolerated dose (MTD) and toxicities of CDDP when given in combination with FUra and high-dose dl-CF.

Patients and methods

Patient selection. All patients treated were >16 years of age and had histologically proven recurrent or metastatic solid tumors. Many patients had measurable disease, but this was not a requirement for entry into the study. All patients were ambulatory and had a Zubrod performance status of ≤ 2 and an estimated life expectancy of >12 weeks. Study patients were allowed to have received prior chemotherapy, including CDDP and FUra. Prior radiotherapy or biologic therapy was also allowed; however, patients had to have completed all previous chemotherapy, radiotherapy, or biologic therapy 3 weeks before entry into the study (6 weeks if prior

Offprint requests to: J. L. Abbruzzese

Table 1. Treatment schema

Agent	Day:								
	1	2	3	4	5	8	15	22	(1) 29
CDDP	X								
FUra	X	X	X	X	X				
dl-CF	X	X	X	X	X				

X, treatment given

Table 2. Dose-escalation schedule

Dose level	CDDP	FUra	dl-CF
0	20	300	500
1	20	375	500
2	30	375	500
3	40	375	500
4	60	375	500
5	75	375	500

All doses are expressed in mg/m^2

Table 3. Acute and cumulative hematologic toxicities

CDDP/dose[a] (mg/m^2)	Patients	Total courses	Median nadir × 1,000 (range)			
			AGC-1	AGC-T	Plt-1	Plt-T
20	3	4	4.0 (3.5–5.1)	3.7 (3.4–5.1)	203 (202–291)	224 (202–291)
20	8	15	2.0 (2.0–2.9)	1.4 (0.3–2.9)	208 (172–276)	167 (129–276)
30	5	5	2.3 (1.7–2.4)	1.7 (0.5–2.4)	188 (118–259)	164 (110–259)
40	9	15	0.8 (0.1–2.9)	1.1 (0.1–2.9)	184.5 (81–259)	181 (81–259)
60	7	17	1.6 (0.5–2.2)	1.4 (0.0–2.5)	268 (182–298)	163 (52–293)
75	6	9	0.9 (0.2–2.0)	1.0 (0.2–2.0)	122.5 (43–217)	122.5 (43–217)

AGC-1/Plt-1, absolute granulocyte or platelet count for the first course of therapy; AGC-T/Plt-T, absolute granulocyte or platelet count for *all* courses delivered at a given dose level

[a] The first dose escalation brought FUra to the full dose level – 375 mg/m^2 daily × 5 days

therapy included a nitrosourea or mitomycin C). Concomitant chemotherapy, radiation therapy, or biologic therapy was not allowed.

Hematologic and biochemical requirements for entry into the study included the following values: absolute granulocytes (AGC), >1,500 cells/mm^3; platelets, >100,000 cells/mm^3; bilirubin, <1.5 mg/dl; and serum creatinine, <1.5 mg/dl. All patients were informed as to the experimental nature of this program and signed an informed consent document. Once enrolled in the trial, all patients were followed up and data were analyzed using a computerized patient-data monitoring system at The University of Texas M. D. Anderson Cancer Center. Patients specifically excluded from this trial included pregnant or lactating women and patients with infection, brain metastases, or other serious medical problems. Women of child-bearing age were required to use adequate contraception.

Study design. The major objectives of this study were to establish the MTD and to define the dose-limiting toxicities for the combination of FUra, high-dose dl-CF, and CDDP. The treatment schema and dose-escalation schedule are outlined in Tables 1 and 2. This study design provided for the addition of CDDP to submaximal doses of FUra and high-dose dl-CF, followed by subsequent escalation of FUra and dl-CF to full doses as described by Swain et al. [20]. Subsequently, CDDP alone was escalated until the MTD was reached. A minimum of three patients who had not previously been treated with this regimen were entered at each dose level. Dose escalation was permitted, provided that no toxic effect other than mild nausea or vomiting was encountered. At each dose level, patients were observed for a minimum of 21 days before additional patients were entered at an escalated dose.

To assess the possible cumulative toxicities of this regimen, six patients were evaluated at or near the MTD in an effort to ensure that at least three patients would complete three courses of therapy. Patients who tolerated therapy continued to receive treatment as long as the underlying tumor showed no evidence of progression. Patients received follow-up with twice-weekly blood counts and were formally evaluated for response after every 8 weeks of therapy. Criteria for removal of patients from the study included the development of an intercurrent illness that required discontinuation of the drugs based on the previously outlined eligibility requirements, disease progression, patient noncompliance, a request to withdraw from the study, or the development of unacceptable toxic effects. The MTD was considered to be the doses of CDDP, FUra, and dl-CF that were associated with toxicity more severe than grade 2, as defined by the World Health Organization [13], in >33% of the patients treated at that level.

Drug administration. All three agents were given intravenously. CDDP was infused on day 1 over 1 h and was diluted in 250 ml physiologic saline. Standard pre- and posthydration with normal saline and magnesium supplementation along with intravenous mannitol (12.5 g) were used to promote risk diuresis. All patients received prophylactic intravenous antiemetic therapy with metoclopramide, diphenhydramine, and lorazepam. FUra and dl-CF were given on days 1–5 as follows: dl-CF was diluted in 250 ml physiologic saline and infused over 2 h; after 1 h of dl-CF infusion, the appropriate dose of FUra was given over 15 min. Following the 5 days of drug administration, patients underwent a rest period of 23 days; thus, 28 days defined one course of therapy.

At the start of subsequent courses of therapy, dose modifications were made on the basis of the most severe toxicity encountered during the preceding course. If toxicity more severe than grade 2 was encountered, the dose of CDDP was reduced to the next lower level. Repeat courses of therapy were initiated only if all nonhematologic toxicity had resolved and if hematologic parameters met the original values required for entry into the study.

Response criteria. The definitions of complete response, partial response, minor response, no response, and progressive disease previously published by our group were used [1]. All patients were evaluable for toxic reactions. Patients completing at least two courses of therapy were evaluable for response. Only complete or partial responses were considered to be objective responses.

Results

Patient characteristics

Over a period of 10 months, 22 patients were entered into this study: 14 women and 8 men with a median age of 53 years (range, 22–68 years). The performance status was (Zubrod) 0 or 1 in 21/22 patients. Cancers treated in this broad, phase I trial included colorectal (10), unknown primary (4), breast (4), and esophageal (squamous), appendiceal, pancreatic, and non-small-cell lung cancers (each in 1 patient). Most patients had received some form of prior therapy, the most common being chemotherapy (16 cases) and radiation therapy (9 patients). All patients completed at least one course of therapy. The mean number of courses delivered to the entire patient population was three.

Toxicity

The principle toxic effect encountered with this regimen was myelosuppression. Of all courses delivered in this trial, 72% were associated with leukopenia (white blood cells, <4,000 cells/mm^3); 52%, with granulocytopenia (AGC, <2,000 cells/mm^3); and 9%, with thrombocytopenia (platelets, <100,000/mm^3). Table 3 outlines the nadir values observed as the dose of CDDP was escalated in patients receiving their first course of therapy at a given dose level, as well as the nadir values for all courses delivered at a given level. Although the nadir platelet and granulocyte counts were significant in some patients, there were no hospitalizations for sepsis or bleeding. Table 3 also reflects the apparent cumulative myelosuppression encountered when all courses delivered at a given dose level were analyzed.

Nonhematologic toxic effects were also observed. As anticipated, moderate (grade 1–2) nausea and vomiting were encountered as the dose of CDDP was escalated. There was one episode of grade 3 nausea and vomiting; however, no patient required hospital admission specifically for management of this problem. Other frequently encountered toxic effects included diarrhea and stomatitis. Stomatitis was encountered in 11% of all courses, but only two episodes were classified as grade 3. Grade 1 or 2 diarrhea was documented in 37% of all courses, but there were no instances of grade 3 or 4 severity. Both diarrhea and stomatitis were easily managed using standard measures. Clinically detectable neurotoxicity, ototoxicity, nephrotoxicity, or cutaneous toxicities were not observed in this trial. No other unique or unusual toxic effects were reported.

Response data

Of the 22 patients entered into this trial, 19 completed at least 2 courses of therapy and were eligible for evaluation of response. One of the patients who completed two courses of therapy did not return for follow-up and was counted for study purposes as having progressive disease. Within this heavily pretreated patient population, only one patient (with metastatic colorectal cancer and no prior exposure to CDDP or FUra) achieved a partial response.

Discussion

This study was designed in an attempt to duplicate the in vitro conditions whereby FUra cytotoxicity is enhanced by CDDP and dl-CF. Critical to the design of this trial were data suggesting that optimal modulation of FUra cytotoxicity required exposure to 20 μmol/l dl-CF before exposure to FUra [9, 10]. Trave et al. [21] have shown that a 2-h infusion of 500 mg/m^2 results in a higher peak plasma concentration (96 μmol/l), a greater increase in the intracellular folate cofactor pool, and a higher rate of inhibition of thymidylate synthase than does a 24-h constant infusion of 500 mg/m^2 dl-CF daily. These results suggest that a high peak concentration of dl-CF (rather than a longer total systemic exposure) is essential to the modulation of FUra cytotoxicity with reduced folates and argue for the FUra/dl-CF schedule and doses used in this trial.

Similarly, Scanlon et al. [17] demonstrated enhanced cytotoxicity when A2780 cells were exposed to 10 μM CDDP followed by FUra (5 μM). Further studies by this group showed that CDDP increased intracellular pools of 5,10-CH_2-FH_4 as well as the capacity of cells to form the 5-fluorodeoxyuridylate-thymidylate synthase complex [17]. Other clinical trials of this three-agent combination [2, 4, 7, 19, 22–24] that have used lower doses of CDDP or oral dl-CF may therefore be expected not to demonstrate enhanced efficacy if the modulation of FUra cytotoxicity by reduced folates is the critical determinant for optimal efficacy.

The overall frequency of toxic effects in this trial was comparable with those of other studies using similar (daily × 5) schedules of FUra and high-dose dl-CF [3, 12, 20]. However, the frequency of severe (grade 3 or 4) diarrhea and stomatitis was lower than that reported in other trials. A possible explanation for the variability in reported toxic effects might be subtle differences in the FUra and dl-CF doses and schedules used in each of the studies.

In summary, we demonstrated that these three agents can be safely combined with acceptable and manageable toxic effects and defined the MTD for this combination as: CDDP, 75 mg/m^2, day 1; FUra, 375 mg/m^2, days 1–5; and dl-CF, 500 mg/m^2, days 1–5. On the basis of these data, we are embarking on phase II trials of this regimen against colorectal cancer and unknown primary neoplasms. If there is a suggestion of its improved activity over that of FUra/dl-CF alone, randomized trials will be needed to assess accurately whether CDDP might be contributing significant activity to the combination. In addition, future studies should focus on tissue procurement from patients treated with FUra plus dl-CF, with and without CDDP, in an effort to establish whether there is additional biochemical modulation with enhanced inhibition of thymidylate synthase as the mechanism of interaction between these drugs.

Acknowledgement. The authors thank Linda Trahan for her expert secretarial skills in preparing this manuscript.

References

1. Ajani JA, Abbruzzese JL, Goudeau P, Faintuch J, Yeomans A, Boman B, Levin B (1988) Ifosfamide and mesna: marginally active in patients with cancer of the pancreas. J Clin Oncol 6: 1703
2. Cornfield M, Comis RL, Hudes G, Weiner LM, Catalano RB, O'Dwyer PJ (1988) Phase I study of 5-fluorouracil (5-FU) with leucovorin (LV) and cisplatin (DDP) in patients with advanced cancer (abstract). Proc Am Soc Clin Oncol 7: 67
3. Doroshow J, Leong L, Murgolin K, Flanagan B, Goldberg D, Bertrand M, Carr B, Akman S (1988) Effective salvage therapy for refractory metastatic breast cancer with high dose continuous infusion folinic acid (HDFA) and intravenous bolus 5-fluorouracil (FUra). Proc Am Soc Clin Oncol 7: 33
4. Dreyfus A, Clark J, Fallon B, Miller D, Busse P, Casey D, Costello R, Norris C Jr, Lucarini J, Wright J, Rosowsky A, Frei E (1989) Continuous infusion cisplatin, 5-FU and high-dose leucovorin (PFL) as induction chemotherapy for squamous cell carcinoma of the head and neck (SCHN): preliminary results of a Dana-Farber regimen. Proc Am Soc Clin Oncol 8: 174
5. Erlichman C, Fine S, Wong A, Elhakim T (1988) A randomized trial of 5-fluorouracil and folinic acid in patients with metastatic colorectal cancer. J Clin Oncol 6: 469
6. Evans RM, Laskin JD, Hakala MT (1981) Effects of excess folates and deoxyinosine on the activity and site of action of 5-fluorouracil. Cancer Res 41: 3288
7. Figoli F, Sileni VC, Gulisano M, Maggian P, Fosser V (1989) Leucovorin calcium enhancement of mucositis after continuous infusion fluorouracil and short infusion cisplatin (letter). J Clin Oncol 7: 680
8. Grem JL, Hoth DF, Hamilton JM, King SA, Leyland-Jones B (1987) Overview of current status and future direction of clinical trials with 5-fluorouracil in combination with folinic acid. Cancer Treat Rep 71: 1249
9. Houghton JA, Maroda SJ, Phillips JO, Houghton PJ (1981) Biochemical determinants of responsiveness to 5-fluorouracil and its derivatives in xenografts of human colorectal adenocarcinomas in mice. Cancer Res 41: 144
10. Houghton JA, Schmidt C, Houghton PJ (1982) The effect of derivatives of folic acid on the fluorodeoxyuridylate-thymidylate synthetase covalent complex in human colon xenografts. Eur J Cancer Clin Oncol 18: 347
11. Khater R, Frenay M, Bourry J, Milano G, Namer M (1986) Cisplatin plus 5-fluorouracil in the treatment of metastatic and squamous cell carcinoma: a report of two cases. Cancer Treat Rep 70: 1345
12. Morini G, Simoncini E, Zaniboni A, Gorni F, Marpicati P, Zambruni A (1987) 5-Fluorouracil and high-dose folinic acid as salvage treatment of advanced breast cancer: an update. Oncology 44: 336
13. Miller ABB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207
14. O'Connell MJ (1989) A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. Cancer 63 [Suppl]: 1026
15. Petrelli N, Herrera L, Rustum Y, Burke P, Creaven P, Stulc J, Ermich LJ, Mittelman A (1987) A randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. J Clin Oncol 5: 1559
16. Rooney M, Kish J, Jacobs J, Kinzie J, Weaver A, Crissman J, Al-Sarraf M (1985) Improved complete response rate and survival in advanced head and neck cancer after three-course induction therapy with 120-hour 5-FU infusion and cisplatin. Cancer 55: 1123
17. Scanlon KJ, Newman EM, Lu Y, Priest DG (1986) Biochemical basis for cisplatin and 5-fluorouraccil synergism in human ovarian carcinoma cells. Proc Natl Acad Sci USA 83: 8923
18. Schabel FM Jr, Trader MW, Laster WR Jr, Corbett TH, Griswold DP Jr (1979) *cis*-Dichlorodiammineplatinum(II): combination chemotherapy and cross-resistance studies with tumors of mice. Cancer Treat Rep 63: 1459
19. Scheithauer W, Depisch D, Schiessel R, Karal M, Zielinski C, Muller C, Ludwig H (1988) High dose leucovorin (CF), 5-fluorouracil (5-FU) and cisplatin (DDP) for treatment of metastatic colorectal cancer (abstract). Proc Am Soc Clin Oncol 7: 108
20. Swain SM, Lippman EM, Egan EF, Drake JC, Steinberg SM, Allegra CJ (1989) Fluorouracil and high-dose leucovorin in previously treated patients with metastatic breast cancer. J Clin Oncol 7: 890
21. Trave F, Rustum YM, Petrelli NJ, Herrera L, Mittelman A, Frank C, Creaven PJ (1988) Plasma and tumor tissue pharmacology of high-dose intravenous leucovorin calcium in combination with fluorouracil in patients with advanced colorectal carcinoma. J Clin Oncol 6: 1148
22. Vokes EE, Cho KE, Schilsky RL, Moran WJ, Guarnieri CM, Weischselbaum RR, Panje WR (1988) Cisplatin, Fluorouracil, and high-dose leucovorin for recurrent or metastatic head and neck cancer. J Clin Oncol 6: 618
23. Vokes EE, Moran WJ, Schilsky RL, Weichselbaum RR, Tybor AG, Goldman ME, Awan AM, Panje WR (1989) Cisplatin, 5-fluorouracil (5-FU) and high dose oral leucovorin (LV) for advanced head and neck cancer (HNC) (abstract). Proc Am Soc Clin Oncol 8: 167
24. Zimet AS, Zalcberg JR (1989) A phase II study of cisplatinum, 5-fluorouracil and leucovorin in patients with advanced gastric carcinoma (abstract). Proc Am Soc Clin Oncol 8: 109