Phase I–Phase II Trial of *N*-Phosphonacetyl-L-Aspartic Acid Given by Intravenous Infusion and 5-Fluorouracil Given by Bolus Injection[1,2]

Charles Erlichman,[3,4] Ross C. Donehower,[5] James L. Speyer,[6] Ray Klecker,[7] *and* Bruce A. Chabner[7]

ABSTRACT—A phase I clinical trial of *N*-phosphonacetyl-L-aspartic acid (PALA) and 5-fluorouracil (FUra) was performed on 30 patients. PALA was given as a 15-minute iv infusion once daily for 5 days, and FUra was given as a bolus injection on days 2, 3, 4, and 5. Cycles of treatment were repeated every 3 weeks. Dose-limiting toxicity was manifested by stomatitis and diarrhea. Skin rash was observed also but was not dose limiting. No consistent hematopoietic or renal toxicity was observed. Seventeen patients with disseminated metastatic melanoma and measurable disease were evaluated for response. One partial response was seen; however, the response was associated with significant toxicity, and the treatment could not be repeated. Stable disease was observed in 3 patients with melanoma, 1 patient with colon carcinoma, and 1 patient with ovarian carcinoma. Our findings suggest that the clinical activity of PALA and FUra given according to the above schedule for melanoma is less than 25% ($P<0.05$). Pharmacokinetic studies of FUra revealed no consistent effect of PALA pretreatment on FUra disappearance in plasma. The mean FUra elimination half-life in plasma was 7.11±0.84 minutes (SEM), which is no different from that reported for FUra alone. The recommended doses on this schedule for phase II studies are 1,000 mg PALA/m^2/day iv daily for 5 days and 200 mg FUra/m^2/day iv on days 2, 3, 4, and 5—JNCI 1982; 68:227–231.

The use of combination chemotherapy has become commonplace in the treatment of many neoplastic diseases. In general, drugs have been combined on the basis of their single-agent activity and their lack of overlapping toxicity for normal tissues. Some consideration also has been given to the ability of drugs to act at different phases of the cell cycle. Increasing interest is now being directed to drug combinations designed to take advantage of biochemical interactions at the cellular level. We report here a phase I trial of a combination of PALA and FUra, which was designed with the biochemical mechanisms of these agents in mind.

PALA, a potent inhibitor of aspartate transcarbamylase, acts to inhibit de novo pyrimidine biosynthesis, as demonstrated in several murine solid tumors (*1, 2*). PALA has undergone extensive phase I (*3, 4*) and phase II trials (*5–7*) in humans over the last few years, but this agent has shown little clinical activity. FUra, a synthetic pyrimidine base analog, has been widely used in clinical chemotherapy for more than 20 years. In the cell, FUra is converted enzymatically to nucleotides. 5-Fluorouridine triphosphate is incorporated into RNA, and 5-fluorodeoxyuridine monophosphate potently inhibits cellular thymidylate synthetase. Pretreatment with PALA before FUra administration could result in increased FUra nucleotide formation, inasmuch as PALA has been shown to decrease intracellular pyrimidine nucleotide pool size in some cell lines (*8*), and could result in less competing substrate for FUra conversion to nucleotides, incorporation into RNA, and inhibition of thymidylate synthetase. Additionally, inhibition of the de novo pathway for pyrimidine biosynthesis by PALA might result in increased cellular levels of PRPP because of decreased use by this pathway. Drugs that increase PRPP levels, such as methotrexate, have been shown in vitro to result in enhanced FUra nucleotide formation (*9*).

In support of this hypothesis that pretreatment with PALA would enhance FUra activity, animal studies have shown that PALA and FUra together have greater antitumor activity in CD8F1 mammary carcinoma (*10*), colon 38 and 26 carcinomas, Lewis lung carcinoma, and M5076 carcinoma than do single agents (*11*). On the basis of this hypothesis, a study of PALA and FUra was performed on patients with extensive malignant disease. A dose schedule was chosen that included pretreatment with PALA, to decrease intracellular pyrimidine nucleotide levels before administration of FUra.

MATERIALS AND METHODS

This phase I–phase II trial was conducted cooperatively by the Medicine Branch and the Clinical Pharmacology Branch of the National Cancer Institute. Entered in the study were 30 patients, 26–68 years old. The male:female

Abbreviations used: AUC=area under the curve; FUra=5-fluorouracil; PALA=*N*-phosphonacetyl-L-aspartic acid; PRPP=5-phosphoribosyl-1-pyrophosphate; $t_{\frac{1}{2}}$=half-life; WBC=white blood cell(s).

[1] Received May 4, 1981; accepted September 18, 1981.

[2] Research procedures were in accord with the ethical standards of the Clinical Research Committee, National Cancer Institute.

[3] Fellow of the Medical Research Council of Canada.

[4] Department of Medicine, Princess Margaret Hospital, 500 Sherbourne St., Toronto, Ontario, Canada M4X 1K9.

[5] The Johns Hopkins Oncology Center, 600 North Wolfe St., Baltimore, Md. 21205.

[6] Division of Oncology, New York University Medical Center, 550 First Ave., New York, N.Y. 10016.

[7] Clinical Pharmacology Branch, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Bethesda, Md. 20205.

ratio was 1.6:1. The presence of cancer in all 30 patients was pathologically confirmed: 18 had melanomas, 8 had carcinomas of the colon, 2 had carcinomas of the ovary, 1 had a sarcoma, and 1 had carcinoma of the pancreas. Prior therapy with other chemotherapeutic agents (mean, two drugs) had been administered to 24 patients; 3 patients with carcinoma of the colon and 1 patient with carcinoma of the ovary had had prior FUra chemotherapy. The patient performance status was 30–90 on the Karnofsky scale; 24 of 30 had a performance status greater than or equal to 50.

Every 3 weeks patients received a daily 15-minute iv infusion of PALA for 5 consecutive days. FUra was given as a bolus injection shortly after completion of the PALA infusion on days 2, 3, 4, and 5. This dose schedule was chosen on the assumption that 1-day pretreatment with PALA would significantly decrease the levels of intracellular pyrimidine nucleotides prior to administration of FUra. Dose escalation for new patients was permitted after a minimum of 3 patients had completed 2 therapy cycles. In the absence of known cumulative toxicity for either drug, dose escalation was allowed for patients who had successfully completed a therapy cycle with no toxicity. Two drug escalation programs were used. Initially, the PALA dose was 1,500 mg/m^2/day for 5 days, and FUra was increased from 100 to 150 to 250 mg/m^2/day. The PALA dose was then decreased to 1,000 mg/m^2/day, and FUra was escalated from 150 to 200 to 250 mg/m^2/day. The 6 patients who received 700 mg PALA/m^2/day and 150 mg FUra/m^2/day had developed significant toxicity at a higher dose level in this trial. Patients were considered to be assessable for acute toxicity if they completed one course of therapy.

Skin and gastrointestinal toxicities were graded 1+ to 3+ according to the following criteria: Patchy areas of skin involvement were considered 1+, generalized skin involvement was graded 2+, and patients experiencing generalized exfoliation were assigned 3+. Patients who had loose bowel movements (<4 movements/day and none at night) or minimal stomatitis were considered to have 1+ gastrointestinal toxicity. Frank diarrhea (>4 movements/day) and/or stomatitis, which was uncomfortable but still permitted oral intake of food, was graded 2+. A 3+ gastrointestinal toxicity was assigned to patients having diarrhea with guaiac-positive stool and/or severe stomatitis associated with an inability to ingest any liquids or solids.

Pharmacologic studies were performed on selected patients at dose levels of 100, 200, and 250 mg FUra/m^2. By means of a high-pressure liquid chromatography technique (*12*), drug levels in plasma were monitored for 2 hours after the FUra iv bolus injection (*12*).

RESULTS

Renal function before therapy, as indicated by 24-hour creatinine clearance, was assessed in 22 patients: 14 had normal renal function (clearance ≥70 ml/min), 7 had moderate impairment of renal function (clearance <70 but ≥40 ml/min), and 1 had marked renal impairment (clearance <40 ml/min). In 8 patients for whom information on creatinine clearance was not available, the blood urea nitrogen was normal in all, and serum creatinine was less than 1 mg/100 ml in 6. Serum creatinine values of 1.3 mg/100 ml were recorded for 2 patients. The total bilirubin level in all 30 patients was normal. All patients except 2 had WBC counts of 3,500 or more/mm^3. The WBC counts for these 2 were 3,200 and 3,100/mm^3. All patients had platelet counts greater than 100,000/mm^3.

TABLE 1.—*PALA and FUra dose levels*

Dose level, mg/m^2/day		No. of patients[a]	No. of therapy courses
PALA	FUra		
700	150	6	15
1,000	150	1	3
1,000	200	21	59
1,000	250	2	8
1,500	100	2	4
1,500	150	4	6
1,500	250	3	3

[a] Due to dose escalation in some patients, the total number is >30.

One patient died before completion of 1 cycle of therapy due to progression of the disease and was not included in toxicity evaluations. For the remaining 29 patients, the dose levels evaluated and the number of patients and therapy courses administered at each level are summarized in table 1. Six patients received 1 cycle of therapy only, 17 patients received between 2 and 5 cycles, and 5 patients received between 6 and 10 cycles. One patient received more than 14 therapy cycles.

The major clinical toxicities affected the skin and gastrointestinal tract and are summarized in tables 2 and 3. Skin toxicity was manifested most commonly by a macular, erythematous eruption that occasionally was pruritic. It usually began on days 5–8 of a cycle and was resolved in approximately 10–14 days. Skin toxicity did not occur consistently with each cycle. Prior chemotherapy or radiotherapy did not appear to predispose patients to skin toxicity. Although skin toxicity was a common occurrence, at none of the dose levels evaluated was it dose limiting.

Gastrointestinal toxicity was the dose-limiting toxicity for the PALA–FUra combination used in this study. The major symptoms were mucositis and severe diarrhea. All 3 patients treated at a dose level of 1,500 mg PALA/m^2/day and 250 mg FUra/m^2/day developed severe mucositis and diarrhea with guaiac-positive stool. One patient treated at 1,500 mg PALA/m^2/day and 250 mg FUra/m^2/day became hypovolemic, secondary to fluid loss from diarrhea, and developed renal failure. Careful management of these complications reversed the renal failure and the patient recovered.

TABLE 2.—*Skin toxicity*

Dose level, mg/m^2/day		Toxicity grade			No. of toxic therapy courses/total No. of courses
PALA	FUra	1+	2+	3+	
700	150	1	1	0	2/15
1,000	150	3	0	0	3/3
1,000	200	21	2	0	23/59
1,000	250	3	0	0	3/8
1,500	100	0	0	0	0/4
1,500	150	3	1	0	4/6
1,500	250	3	0	0	3/3

TABLE 3.—*Gastrointestinal toxicity*

Dose level, mg/m²/day		Toxicity grade			No. of toxic therapy courses/total No. of courses
PALA	FUra	1+	2+	3+	
700	150	3	0	0	3/15
1,000	150	0	1	0	1/3
1,000	200	26	7	2	35/59
1,000	250	4	0	1	5/8
1,500	100	3	0	0	3/4
1,500	150	0	1	2	3/6
1,500	250	0	0	3	3/3

At 1,500 mg PALA/m²/day and 150 mg FUra/m²/day, 2 patients developed significant gastrointestinal toxicity manifested by prolonged oral mucositis. At 1,000 mg PALA/m²/day and 200 mg FUra/m²/day, most episodes of toxicity were relatively mild and tolerable. However, 2 of 59 therapy courses were associated with significant mucositis, which varied from angular stomatitis to complete oral mucosal ulceration. The mucositis began most commonly on day 4 and lasted 2–14 days. Diarrhea usually began during the second week of a cycle and was associated with occasional cramping. Gastrointestinal toxicity appeared to depend on the dose of FUra given with 1,500 mg PALA/m², but this relationship was not demonstrated when the PALA dose was 1,000 mg/m². Three patients complained of a gritty sensation in the eyes and photophobia. Two of these had obvious conjunctivitis. None of the three had any visual acuity disturbance, and ophthalmoscopic examination did not reveal any retinal abnormalities.

Hematologic toxicity was assessed by measurement of WBC and platelet counts during the course of therapy (table 4). For 52 of 98 therapy courses, nadir blood counts were available for assessment of hematologic toxicity. No patient developed a platelet count of less than 50,000/mm³. Five courses of therapy were associated with a fall in platelet counts to less than 100,000 but greater than 50,000/mm³. After receiving 1,500 mg PALA/m²/day and 100 mg FUra/m²/day, 1 patient developed a platelet count of 73,000/mm³. A second patient on 2 cycles of 1,000 mg PALA/m²/day and 250 mg FUra/m²/day developed platelet counts of 95,000 and 59,000/mm³. This patient had platelet counts of 74,000 and 59,000 when treated with 2 cycles at 1,000 mg PALA/m² and 200 mg FUra/m²/day. The WBC nadir was less than 2,000 in 2 patients both treated with 1,000 mg PALA/m²/day and 200 mg FUra/m²/day. One of these individuals had been treated previously with cisplatin, chlorozotocin, and BCG. The other patient had received no previous therapy.

While receiving PALA–FUra therapy, 5 patients developed neurologic abnormalities. The 2 patients who had generalized seizures on 1,000 mg PALA/m²/day and 200 mg FUra/m²/day were simultaneously documented to have central nervous system metastases. One patient treated with 1,500 mg PALA/m²/day and 250 mg FUra/m²/day had focal seizures during a period when he was uremic and had a serum creatinine of 12.2 mg/100 ml. In 2 patients in whom bizarre affects and thought disorders were observed, no underlying central nervous system lesions were found. In 1 of these patients treated with 1,000 mg PALA/m²/day and 150 mg FUra/m²/day, the abnormal behavior was resolved when chemotherapy was suspended. However, in the other who received 1,500 mg PALA/m²/day and 150 mg FUra/m²/day, no improvement occurred after therapy was stopped.

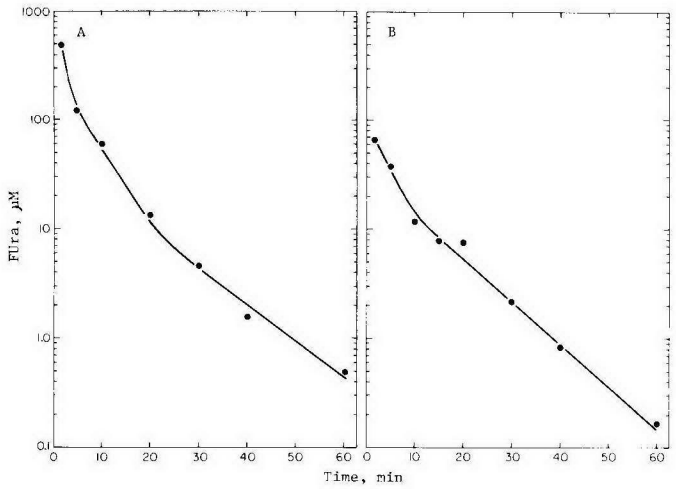
Due to disease progression, 24 patients were removed from the study, and 2 patients died from the disease during the study. Two were removed from the study after they refused further therapy. Two at this writing have stable disease and continue in the study. The 17 patients with pathologic diagnosis of melanoma were treated at adequate doses that produced mild but significant toxicity, and all had measurable disease. No patient had a complete response. One developed a partial response with greater than 50% decrease in a skin nodule and lung metastases. Another patient had a mixed response: a greater than 50% decrease in the size of skin lesions but developed liver metastases on therapy. Three patients with melanoma were considered to have stable disease for 2 and 3 months. None of these patients had had previous FUra therapy. One patient with ovarian carcinoma, who had previously received FUra, was stable for 10 months, and another with colon carcinoma was stable for 4 months.

Pharmacologic studies were performed on 9 patients. Maximum plasma FUra levels were 3.27 m*M* at a dose of 250 mg/m². Plasma FUra levels dropped below the level of assay sensitivity (5×10^{-8} *M*) within 60 minutes. In some patients, a distinct bi-exponential decline could not be

TABLE 4.—*Hematologic toxicity*

Myelosuppression indicator	Dose level, mg/m²/day		No. of therapy courses[a]
	PALA	FUra	
Platelets, <100,000 but >50,000/mm³	1,500	100	1
	1,500	250	2
	1,000	200	2
WBC, <2,000/mm³	1,000	200	2

[a] Hematologic toxicity data were available for 52 of 98 administered courses.



TEXT-FIGURE 1.—Plot of plasma FUra vs. time. A) Patient was treated with 250 mg FUra/m². B) Patient was treated with 200 mg FUra/m².

TABLE 5.—*FUra pharmacokinetics*

Patient	Dose level, mg/m²/day		k, min^{-1a}	$t_{\frac{1}{2}}$, min^b	AUC, mmol·min/liter	r^c
	PALA	FUra				
#1	1,500	100	0.0801	8.65	0.545	−0.893
#2	1,500	100	0.124	5.57	0.047	−0.999
#3	1,500	100	0.0633	10.94	0.029	−0.944
#4	1,500	200	0.0875	7.88	0.360	−0.995
#5	1,000	200	0.0668	10.38	1.800	−0.975
#6	1,000	200	0.1011	6.85	0.550	−0.994
#7	1,000	200	0.1559	4.44	0.319	−0.936
#8	1,500	250	0.138	5.02	1.86	−0.995
#9	1,500	250	0.164	4.24	1.64	−0.983

[a] Plasma FUra elimination rate constant.
[b] Plasma FUra elimination $t_{\frac{1}{2}}$.
[c] Correlation coefficient (r) from linear regression of 10–60 min Log FUra levels vs. time.

clearly defined because of difficulties in obtaining adequate numbers of early samples during this distribution phase (text-fig. 1). Therefore, individual FUra profiles were analyzed in terms of a pharmacokinetic, one-compartment, open model similar to that of MacMillan et al. (*13*). The dose levels, plasma FUra elimination rate constant k, plasma FUra elimination $t_{\frac{1}{2}}$, and the AUC are summarized in table 5. The mean $t_{\frac{1}{2}}$ was 7.11±0.84 minutes (SEM). The mean AUC values obtained in this analysis did not increase linearly with dose, but a rapid nonlinear increase in the mean AUC level was observed for those patients treated with 250 mg FUra/m²/day (text-fig. 2).

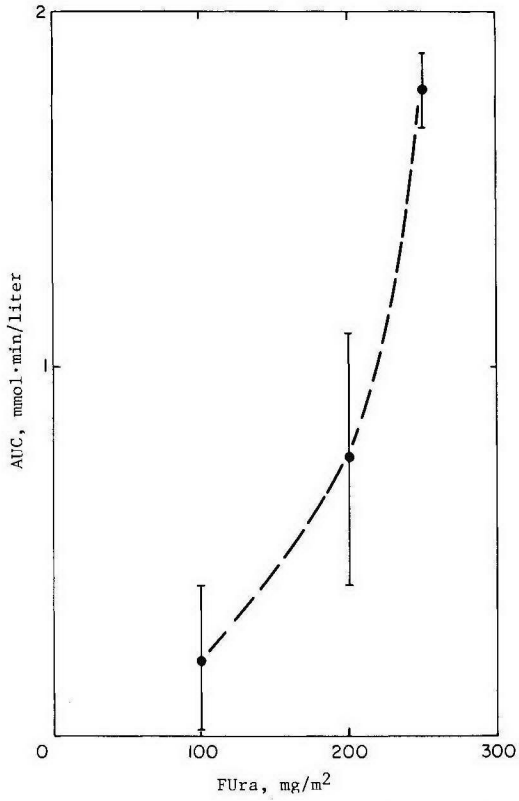
DISCUSSION

An initial trial of PALA given as a 15-minute daily iv infusion for 5 days and FUra on days 2, 3, 4, and 5 as a bolus injection, repeated every 3 weeks, demonstrated dose-limiting toxicity to gastrointestinal mucosa. The major toxicity of PALA as a single agent is manifested in the skin and gastrointestinal organs, whereas FUra when given by bolus injection most commonly results in myelosuppression. However, gastrointestinal and skin toxicity can occur with FUra even when given by bolus injection. Therefore, it is difficult to attribute the toxicity observed in this study to either agent alone. In 2 patients, neurotoxicity occurred that was not explained by causes other than drug administration. Inasmuch as neurologic abnormalities secondary to administration of PALA have been reported (*14*), and because FUra is known to occasionally cause neurologic problems, the neurotoxicity of the 2 patients may be due to both drugs. Conjunctivitis and photophobia after PALA administration, which occurred in 3 patients, previously were not reported (*3, 4*), but these conditions may occur after FUra administration.

This study involved the treatment of numerous patients with melanoma because other clinical trials were being conducted at the time for patients with this diagnosis at the National Cancer Institute. Patients who failed those trials were eligible for our study. A partial response was experienced by 1 of 17 patients with melanoma. However, this patient, treated with 1,500 mg PALA/m²/day and 250 mg FUra/m²/day, developed severe diarrhea with associated hypovolemia and subsequent acute tubular necrosis. Careful management reversed the renal failure and the patient recovered, but subsequent courses of treatment with PALA and FUra could not be administered to him. Our findings suggest that this particular dose schedule for PALA and FUra would result in less than a 25% response rate ($P<0.05$) for patients with melanoma and, therefore, would not be a useful combination for clinical therapy of melanoma.

The FUra pharmacokinetic studies on patients treated with PALA and FUra suggest two points: *a*) The plasma elimination $t_{\frac{1}{2}}$ of 7.11 minutes that we observed is not different from that reported by others in single-agent studies (*13*). This implies that any enhanced toxicity observed for the PALA–FUra combination was not due to a change in plasma clearance of FUra by PALA. Because PALA is excreted primarily by a renal mechanism and is not highly protein-bound and FUra is primarily metabolized, pharmacokinetic interaction between these agents in plasma would not be expected. Such a conclusion is supported by our studies. Therefore, it is more likely that any enhanced toxicity is the result of an interaction at the cellular level. *b*) A saturable mechanism in the elimination of FUra is suggested by the nonlinear relationship between the AUC and the administered FUra dose. This interpretation must be made cautiously because of the small numbers of patients treated at each dose level and the wide variation in the calculated AUC; however, this interpretation agrees with suggestions made in other reports (*15, 16*).

The dose schedule in this study was chosen to take advan-



TEXT-FIGURE 2.—Plot of mean AUC vs. FUra dose level. *Error bars* represent SEM.

tage of the mechanism proposed for PALA and FUra interaction at the cellular level. We had previously noted that on the PALA schedule of a 15-minute infusion daily for 5 days, aspartate transcarbamylase levels in leukocytes were significantly depressed within 24 hours of the first dose (*17*). If similar changes occur in other tissues, pyrimidine nucleotide levels would probably decrease in parallel by 24 hours after the first dose of PALA. Addition of FUra at that time could result in metabolism of this pyrimidine analog to active metabolites at a rate greater than that normally observed. However, a therapeutic benefit of this PALA–FUra dose schedule was seen in only 1 patient with melanoma. Other investigators using other schedules have reported responses in colon carcinoma, large cell carcinoma of the lung, fibrous histiocytoma, and sarcoma (*18, 19*). Although we found very limited activity of this drug combination in patients who had received prior chemotherapy for metastatic melanoma, phase II studies with other dose schedules may be warranted on patients with other malignant diseases responsive to FUra. A schedule that involves PALA and FUra administration by continuous infusion may be more efficacious than the one used in this study. Such a schedule may allow more incorporation of FUra into RNA throughout the cell cycle. For future phase II studies, we recommend 1,000 mg PALA/m^2/day given iv over a period of 15 minutes for 5 days and 200 mg FUra/m^2/day given by bolus injection on days 2, 3, 4, and 5.

REFERENCES

(*1*) Johnson RK, Inouye T, Goldin A, Stark GR. Antitumor activity of *N*-(phosphonacetyl)-L-aspartic acid, a transition-state inhibitor of aspartate transcarbamylase. Cancer Res 1976; 36:2720–2725.

(*2*) Johnson RK, Swyryd EA, Stark GR. Effects of *N*-(phosphonacetyl)-L-aspartate on murine tumors and normal tissues in vivo and in vitro and the relationship of sensitivity to rate of proliferation and level of aspartate transcarbamylase. Cancer Res 1978; 38:371–378.

(*3*) Erlichman C, Strong JM, Wiernik PH, et al. Phase I trial of *N*-(phosphonacetyl)-L-aspartate. Cancer Res 1979; 39:3992–3995.

(*4*) Valdivieso M, Moore EC, Burgess AM, et al. Phase I clinical study of *N*-(phosphonacetyl)-L-aspartic acid (PALA). Cancer Treat Rep 1980; 64:285–292.

(*5*) Carroll DS, Gralla RJ, Kemeny NE. Phase II evaluation of *N*-(phosphonacetyl)-L-aspartic acid (PALA) in patients with advanced colorectal carcinoma. Cancer Treat Rep 1980; 64:349–351.

(*6*) Creagan ET, Ahmann DL, Ingle JN, Purvis JD III. Phase II study of *N*-(phosphonacetyl)-L-aspartate (PALA) in disseminated malignant melanoma. Proc Am Soc Clin Oncol 1980; 21:344.

(*7*) Yagoda A, Watson RC, Blumenreich R, Young CW. Phase II trials in urothelial tumors with Amsa and PALA. Proc Am Soc Clin Oncol 1980; 21:427.

(*8*) Moyer JD, Handschumacher RE. Selective inhibition of pyrimidine synthesis and depletion of nucleotide pools by *N*-(phosphonacetyl)-L-aspartate. Cancer Res 1979; 39:3089–3094.

(*9*) Cadman E, Heimer R, Davis L. Enhanced 5-fluorouracil nucleotide formation after methotrexate: Explanation for drug synergism. Science 1979; 205:1135–1137.

(*10*) Spiegelman S, Sawyer R, Nayak R, Ritzi E, Stolfi R, Martin D. Improving the antitumor activity of 5-fluorouracil by increasing its incorporation into RNA via metabolic modulation. Proc Natl Acad Sci USA 1980; 77:4966–4970.

(*11*) Johnson RK, Clement JJ, Howard WS. Treatment of murine tumors with 5-fluorouracil in combination with de novo pyrimidine inhibitors PALA or pyrazofurin. Proc Am Assoc Cancer Res 1980; 21: 292.

(*12*) Buckpitt AR, Boyd MR. A sensitive method for determination of 5-fluorouracil and 5-fluorodeoxyuridine in human plasma by high pressure liquid chromatography. Anal Biochem 1980; 106:432–437.

(*13*) MacMillan WE, Wolberg WH, Welling PG. Pharmacokinetics of fluorouracil in humans. Cancer Res 1978; 38:3479–3482.

(*14*) Gralla RJ, Kemeny N, Young CW, Sykes MP. Central nervous system toxicity of PALA (*N*-phosphonacetyl-L-aspartate). Proc Am Soc Clin Oncol 1980; 21:350.

(*15*) Collins JM, Dedrick RL, King FG, Speyer JL, Myers CE. Nonlinear pharmacokinetic models for 5-fluorouracil in man: Intravenous and intraperitoneal routes. Clin Pharmacol Ther 1980; 28:235–246.

(*16*) Speyer JL, Collins JM, Dedrick RL, et al. Phase I and pharmacological studies of intraperitoneal 5-fluorouracil. Cancer Res 1980; 40:567–572.

(*17*) Kensler TW, Erlichman C, Jayaram HN, Tyagi AK, Ardalan B, Cooney DA. Peripheral leukocytes as indicators of the enzymic effect of *N*-(phosphonacetyl)-L-aspartic acid on human L-aspartate transcarbamylase activity. Cancer Treat Rep 1980; 64:967–973.

(*18*) Bedikian AY, Valdivieso M, Stroehlein JR, Karlin DA, Bennet RW, Bodey GP. Phase I–II evaluation of PALA–5-fluorouracil combination in patients with colorectal carcinoma. Proc Am Soc Clin Oncol 1980; 21:415.

(*19*) Meshad MW, Ervin TJ, Johnson RK. A phase I trial of combined therapy with *N*-(phosphonacetyl)-L-aspartate and 5-fluorouracil. Proc Am Soc Clin Oncol 1980; 21:341.