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Five-day infusional fluorodeoxyuridine with oral leucovorin and escalating doses of interferon alpha-2b: a phase I study

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Abstract. In a previous phase I study we identified the maximally tolerated dose (MTD) of a continuous intravenous infusion of fluorodeoxyuridine (FUdR) to be 0.3 mg/kg daily for 5 days when combined with oral leucovorin (LV) given at 100 mg q4h. In an attempt to modulate FUdR further, we added escalating doses of interferon alpha-2b (IFN) to FUdR/LV in a phase I cohort study. A total of 36 patients with refractory solid tumors were treated at two dose levels of FUdR and five dose levels of IFN. Although the initial patient cohort was treated with a dose of FUdR lower than that previously identified as the MTD [FUdR at 0.2 mg/kg daily with LV at 100 mg q4h and IFN at 2 million units (MU)/m^2 daily], three of six patients developed grade 3 mucositis, indicating that the toxicity of FUdR/LV was increased in the presence of low doses of IFN. After decreasing the FUdR dose to 0.1 mg/kg daily, we could increase the dose of IFN from 2 to 30 MU/m^2 daily in five additional cohorts of patients. With increasing IFN doses, no increase in mucositis or dermatitis was observed, indicating no further potentiation of FUdR/LV toxicity with higher IFN doses. However, known toxicities of IFN, including transient myelosuppression and hepatic transaminase elevation, were observed more frequently at IFN doses of 15 and 30 MU/m^2 daily, where they became dose-limiting. We conclude that IFN modulates FUdR/LV at low doses, resulting in increased FUdR toxicity. When the dose of IFN is increased, this FUdR/LV toxicity does not appear to be potentiated further and IFN-related toxicities become dose-limiting.

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Introduction

Modulation of fluorouracil (5-FU) with leucovorin (LV) has been shown to result in increased cytotoxicity in vitro due to stabilization of the binding of the 5-FU metabolite 5-fluorodeoxyuridine monophosphate (5-FdUMP) to its target enzyme thymidylate synthase (TS) in the presence of LV [17, 21, 33]. Clinically, increased response rates have been demonstrated in patients with advanced colorectal cancer for the combination of 5-FU/LV as compared with 5-FU alone, although no consistent improvement in overall survival has been demonstrated [1, 9, 11, 28, 30, 31]. In addition, encouraging pilot data have been reported for other types of solid tumors, including head and neck cancer [40, 41, 43–45]. Interferon has also been shown to augment the cytotoxicity of 5-FU in vitro [2, 5, 10, 18, 34, 46, 47, 50]. Clinically, high response rates for 5-FU and interferon have been demonstrated in patients with colorectal cancer [20, 29, 48, 49, 51, 52]; randomized studies comparing 5-FU/interferon with 5-FU alone have not yet been completed.

The mechanisms of interaction between 5-FU and IFN have not yet been conclusively identified. Increased intracellular TS concentrations following exposure to 5-FU have been shown to be a possible mechanism of 5-FU resistance [19]. Interferon may prevent the increase in TS concentrations, thereby resulting in increased 5-FU cytotoxicity. This has been demonstrated in the laboratory setting for interferon-gamma [5]. Increased intracellular conversion of 5-FU to 5-FdUMP has also been described [35]. Finally, alterations in 5-FU pharmacokinetics have been demonstrated in several studies [7, 14, 15, 26, 27, 45, 53].

5-FU can be either sequentially phosphorylated and incorporated into cellular RNA or metabolized to fluorodeoxyuridine (FUdR) and 5-FdUMP. Biochemical modulation of 5-FU by LV affects the latter pathway. Although the mechanisms of interaction between interferon and 5-FU remain to be clearly established, it is possible that they too are focused on the TS pathway [3]. FUdR represents a metabolite of 5-FU on this pathway. Therefore, it may be a more suitable target for biochemical

modulation with LV and/or interferon than is 5-FU [25, 39, 42]. The choice of oral LV was based on previous studies in head and neck cancer that demonstrated a favorable ratio of plasma concentrations of the pharmacologically active L-LV stereoisomer and its major metabolite 5-methyltetrahydrofolate to the inactive D-LV stereoisomer following oral administration of D/L-leucovorin [40, 41]. This is felt to be due to stereoselective absorption of the L-LV isomer during administration of the racemic oral formulation of LV. D-LV has been shown to bind to TS and, thus, might impair the ability of the pharmacologically active L-LV and its metabolites to bind to TS [24]. In a previous phase I study, we combined high-dose oral LV with a 5-day continuous infusion of FUdR [41]. In that study, we identified FUdR given at 0.3 mg/kg daily for 5 days with 100 mg LV given orally q4h during the entire duration of the infusion as recommended doses for phase II testing. Mucositis was the dose-limiting toxicity. Other toxicities included skin rash and hand-foot syndrome; no hematologic toxicity was observed.

We now report the results of a study testing the feasibility of adding interferon alpha-2B (IFN) in escalating doses to this FUdR/LV regimen. We were particularly interested in possible interactions at the high-dose range of IFN with FUdR and LV. Our objectives were to define the maximally tolerated dose (MTD) of IFN given with a 5-day continuous infusion of FUdR and oral LV, to define the pattern of toxicities observed for this regimen, and to establish whether the clinical effects of FUdR modulation with IFN are IFN-dose-dependent.

Patients and methods

This study opened in March of 1990 and was closed to patient accrual in May of 1991. To be eligible, patients had to have histologic or cytologic documentation of neoplastic disease that was refractory to standard therapy or for which no standard therapy existed, a performance status of 0–2 according to Cancer and Leukemia Group B (CALGB) criteria, and a life expectancy of ≥ 8 weeks. Required entry criteria included a total white blood cell count of $\geq 3{,}500/\mu l$, a platelet count of $\geq 100{,}000/\mu l$, total serum bilirubin levels of <1.6 mg/dl, SGOT and SGPT levels of ≤ 3 times the upper normal value, and a serum creatinine value of ≤ 1.5 mg/dl. There was no limitation on prior therapy. The extent of measurable disease was documented when present, but measurable disease was not a requirement for entry into this study. Written informed consent was obtained from all patients.

Treatment plan. Chemotherapy consisted of FUdR given as a continuous intravenous infusion over 5 days. Since we anticipated that the toxicity of FUdR/LV would be increased in the presence of IFN, we initiated this study at an FUdR dose of 0.2 instead of 0.3 mg/kg daily, the previously defined MTD for FUdR/LV without IFN. This dose was decreased to 0.1 mg/kg daily for dose levels 2–6 following the occurrence of dose-limiting toxicity at the first dose level. Racemic D/L-LV (Burroughs-Wellcome) was given orally at 100 mg q4h starting at 4 h prior to the FUdR infusion and continuing until 1 day after the end of the infusion. IFN was injected subcutaneously q24h for a total of six doses; the first dose was given at 4 h prior to the beginning of the FUdR infusion. IFN doses of 2, 4, 8, 15, and 30 million units (MU)/m^2 were evaluated. Cycles were repeated every 21 days until documentation of progressive disease or unacceptable toxicity. Antiemetics were given at the discretion of the treating physician. Placement of a venous access device was recommended. Toxicities were assessed at least once weekly and were graded according to National Cancer Institute Common Toxicity Criteria.

Dose escalation. The dose of IFN was escalated after a minimum of three patients had been evaluated during the first cycle of therapy (21 days) at a given dose level. If toxicity exceeding grade 2 was observed in one of three patients, up to six patients were treated at that dose level until $\geq 50\%$ of the patients (a maximum of three) developed at least grade 3 toxicity. The IFN dose was not escalated in individual patients. Excluded as dose-limiting toxicities were nausea and vomiting, grade 3 or 4 neutropenia resolving to grade 2 or less by day 10 of a cycle and not complicated by a neutropenic fever, and grade 3 or 4 hepatic transaminase elevation resolving to grade 2 or less within 7 days and not resulting in symptoms. The latter has previously been described as being rapidly reversible on the withdrawal of interferon and unassociated with functional sequelae [22]. Patients who experienced dose-limiting therapy but had stable disease or showed a response could continue on the protocol and were given reduced doses during subsequent cycles.

Response evaluation. Response evaluation was performed after the completion of the first two cycles and then every two cycles thereafter. A complete response was defined as the complete disappearance of all detectable tumor for at least 28 consecutive days. A partial response was defined as a reduction of at least 50% in the product of the longest perpendicular diameters of the most easily measurable or largest tumor mass (indicator lesion) in the absence of both the growth of other existing lesions and the appearance of new lesions for at least 28 days. Stable disease (SD) was defined by the same criteria, except that an increase of <25% or a decrease of <50% in the size of the indicator lesion was required. Disease progression was defined as an increase of $\geq 25\%$ in the product of the perpendicular diameters of the indicator lesion or the appearance of new metastatic lesions.

Results

A total of 36 patients were treated in this study. The patients' pretreatment characteristics are outlined in Table 1. One additional patient was registered but taken off study, having received less than 2 days of chemotherapy, after it was discovered that her central venous access catheter had penetrated into the mediastinum. This patient was not included in the analysis. The median age of the 36 evaluable patients was 59 (range, 27–76) years. In all, 11 patients had a performance status of 1 and 17 had a performance status of 2. Thirteen patients had renal-cell carcinoma, and 7 had colorectal carcinoma. Prior therapy included chemotherapy in 17 patients and biological response modifiers in 7 patients.

Toxicity

Patients were treated at six dose levels. All patients were assessed for toxicity (Table 2). The first dose level consisted of 0.2 mg/kg daily of FUdR with LV and 2 MU/m^2 daily of IFN. At this dose, three of six patients developed dose-limiting mucositis despite a decrease in the FUdR dose from 0.3 mg/kg daily as defined in our previous study of FUdR/LV without IFN. Therefore, the dose of FUdR was decreased to 0.1 mg/kg daily for all subsequent dose levels. IFN doses were escalated from 2, 4, 8, and 15 MU/m^2 daily to a maximum of 30 MU/m^2 daily. Doses of 2–8 MU/m^2 daily were tolerated without major toxic events. At daily doses of 15 and 30 MU/m^2 IFN, severe or life-threatening myelosuppression and elevation of hepatic transaminases were consistently observed. Myelosuppression occurred during chemotherapy administration, was of

Table 1. Pretreatment characteristics of 36 evaluable patients[a]

Patients entered	36
Sex:	
M	19
F	17
Age (years):	
Median	59
Range	27–76
Performance status:	
0	8
1	11
2	17
Primary malignancy:	
Renal-cell carcinoma	13
Colorectal carcinoma	8
Ovarian cancer	3
Breast cancer	2
Small-bowel cancer	2
Esophageal cancer	1
Gastric cancer	1
Non-small-cell lung cancer	1
Sarcoma	1
Islet-cell carcinoma	1
Esthesioneuroblastoma	1
Unknown primary, adenocarcinoma	1
Cervical cancer	1
Prior therapy:	
Surgery	24
Radiotherapy	9
Chemotherapy	17
Biologicals	7
Hormones	3
High-dose chemotherapy	1
Number of prior therapies:	
None	3
–1	15
>1	18

[a] One patient who received less than 2 days of therapy is not included

short duration in all patients, and was not dose-limiting as defined in the protocol. In particular, no neutropenic infection was observed. Similarly, transaminase elevation was of short duration and was not a dose-limiting event. Interestingly, FUdR-related toxicities of mucositis, dermatitis, or diarrhea were not found to increase in severity with escalating doses of IFN. This suggested that any interaction of IFN with FUdR/LV was not IFN-dose-dependent and that higher IFN doses merely resulted in increased toxicities usually attributed to IFN as a single agent. Therefore, escalation of the IFN dose beyond level 6 was not attempted.

Other toxicities included repeated episodes of confusion during IFN-related febrile episodes in one patient (dose level 3) and acute pulmonary edema in another patient, which started within 4 h of the FUdR infusion and was felt to be possibly related to the chemotherapy (dose level 4). Another patient developed severe dyspnea and pulmonary edema while receiving his fourth cycle of chemotherapy (level 6); an echocardiogram demonstrated a cardiomyopathy. This toxicity was also felt to be possibly related to the therapy. Headaches were observed in one patient (level 5), and four patients treated on dose level 6 were noted to have grade 3 or 4 anorexia.

Response

Four patients were not evaluated for response. Three of these refused further therapy following cycle 1; one patient developed acute pulmonary edema while receiving her first cycle on level 4 and was not retreated. No partial or complete response was observed in the remaining patients. In all, 12 patients had stable disease following cycle 2; 11 of these continued therapy until disease progression for a maximum of 8 cycles (median, 4), including 6 patients

Table 2. Toxicities, cycle 1[a]

	WBC Grade				Plts Grade		Mucositis Grade			Skin Grade			Hepatic Grade				Diarrhea Grade			Fever Grade			
	0	1,2	3	4	0	1,2	0	1,2	3	0	1,2	3	0	1,2	3	4	0–1	2	3	0–1	2	3	Other
Level 1, $n = 6$ FUdR: 0.2/IFN: 2[b]	6	0	0	0	1	5	0	3	3	3	2	1	5	1	0	0	3	3	0	0	6	0	
Level 2, $n = 6$ FUdR: 0.1/IFN: 2[b]	5	1	0	0	6	0	3	2	1	6	0	0	2	3	0	0	5	1	0	0	6	0	
Level 3, $n = 6$ FUdR: 0.1/IFN: 4[b]	2	3	1	0	5	1	1	3	2	4	1	1	3	3	0	0	4	2	0	0	5	1	Confusion (grade 2)
Level 4, $n = 6$ FUdR: 0.1/IFN: 8[b]	2	3	0	0	4	1	1	4	0	3	2	0	2	2	0	0	4	0	1	0	4	0	Pulmonary edema[c]
Level 5, $n = 6$ FUdR: 0.1/IFN: 15[b]	1	3	2	0	3	3	1	3	2	5	1	0	2	1	2	1	4	1	1	0	6	0	Cardiomyopathy headache
Level 6, $n = 6$ FUdR: 0.1/IFN: 30[b]	0	2	3	1	1	5	2	3	1	5	1	0	2	1	2	1	2	4	0	0	6	0	Anorexia grade 3: 3 patients grade 4: 1 patient

Plts, Platelets

[a] Maximal toxicities seen during cycle 1 in 36 patients. Hepatic enzymes were unavailable from 1 patient each on levels 2 and 4

[b] FUdR dose in mg/m^2 daily; IFN dose in MU/m^2 daily

[c] Other toxicities in this patient were not evaluable due to early discontinuation of the therapy

with renal-cell carcinoma, 2 patients with colorectal cancer, and 1 patient each with ovarian cancer, gastric cancer, non-small-cell lung cancer, and esthesioneuroblastoma. A total of 20 patients developed progressive disease.

Discussion

This study was designed to define the MTD of IFN when added to a previously tested combination of FUdR and LV [41]. A low dose of IFN (2 MU/m^2 daily) appeared to result in increased FUdR toxicity as compared with our previous study. When the FUdR dose was decreased to 0.1 mg/kg daily, corresponding to one-third of the previous MTD without IFN, escalation of the IFN dose to 30 MU/m^2 daily was feasible. At high doses of IFN, toxicities included severe but transient neutropenia and hepatic transaminase elevation, which were attributed to IFN and were not dose-limiting [4, 16, 22, 23, 32, 36]. Interestingly, a further potentiation of FUdR-related toxicities was not observed.

These data suggest that the interaction between FUdR/LV and IFN occurs at low IFN doses and does not increase further at higher IFN doses when an FUdR dose of 0.1 mg/kg daily is used. This statement is specific for FUdR and is based on clinical findings only, since no pharmacologic analysis was performed in this study. Grem et al. [14, 15] and Yee et al. [53] have published different findings regarding the interaction of 5-FU with interferon alpha-2a. These investigators demonstrated an interferon-dose-dependent decrease in 5-FU clearance [14], which appeared to be due to decreased catabolism of the drug [53]. If our data are confirmed by pharmacology studies, low doses of IFN might be sufficient to modulate FUdR cytotoxicity in the clinical setting. The use of IFN at high doses would then be useful only in clinical situations in which single-agent dose-dependent activity of IFN is desired. This may apply to patients with malignant melanoma or renal-cell carcinoma. In this context, it is disappointing that none of the 13 patients with renal-cell carcinoma responded; only 1 of them had received prior treatment with FUdR and LV and 5 had received biological response modifiers, including 3 who had been given interferon. Similarly, a phase II study of this combination at the MTD in patients with advanced renal-cell carcinoma failed to identify any responders [38]. In the more common setting, in which IFN is used as a modulator of fluoropyrimidine activity, its use at a low dose appears to result in clinical effects similar to those observed at higher doses while resulting in fewer IFN-related toxicities. In that setting, it may be possible to use an FUdR dose higher than those explored on levels 2–6 in the present study (e.g, 0.15 mg/m^2 daily).

The toxicities seen in this study at high IFN doses corresponded to those previously described elsewhere [4, 16, 22, 23, 32, 36]. We also observed cardiopulmonary toxicity in three patients. Ischemic heart disease, congestive heart failure, cardiac arrhythmia, and cardiomyopathy have been reported following the use of IFN [6, 8, 37]. In addition, cardiotoxicity has been associated with 5-FU [12, 13], although we are not aware of such reports for FUdR. Therefore, it may be prudent to consider cardiac toxicity as a possible explanation for the cardiopulmonary symptoms that develop in patients receiving combinations including a fluoropyrimidine and interferon.

In summary, we find that IFN enhances FUdR toxicity at low doses (2 MU/m^2 daily). FUdR modulation is not IFN-dose-dependent within the IFN dose spectrum tested in this study (2–30 MU/m^2 daily at low doses of FUdR). Mucositis and dermatitis are dose-limiting FUdR-related toxicities, whereas myelosuppression and hepatic transaminase elevation are severe IFN-related toxicities. The recommended phase II doses are FUdR given at 0.1 mg/kg daily $\times 5$ as a continuous intravenous infusion, LV given p.o. at 100 mg q4h $\times 36$ doses, and IFN given at 30×10^6 units/m^2 $\times 6$ doses where high doses of IFN appear to be useful. In all other clinical situations, low doses of IFN may result in a similar modulatory effect.

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References

1. Advanced Colorectal Cancer Meta-analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10: 896
2. Allegra CJ (1991) Biochemical modulation: a modality that has come of therapeutic age. J Clin Oncol 9: 1723
3. Allegra C, Chu E (1992) Autoregulatory translational control of thymidylate synthase. (Abstract 412, 7th NCI-EORTC Symposium on New Drugs in Cancer Therapy, Amsterdam, The Netherlands) Ann Oncol 3 [Suppl 1]: 162
4. Borden EC (1979) Interferons: rationale for clinical trials in neoplastic disease. Ann Intern Med 91: 472
5. Chu E, Zinn S, Boarman D, Allegra CJ (1990) Interaction of γ interferon and 5-fluorouracil in the H630 human colon carcinoma cell line. Cancer Res 50: 5834
6. Cohen MC, Huberman MS, Nesto RW (1988) Recombinant alpha$_2$ interferon-related cardiomyopathy. Am J Med 85: 549
7. Czejka MJ, Jäger W, Schüller J, Fogl U, Schernthaner G (1991) Pharmakokinetische Aspekte der Kombination von Interferon-α-2b und Folinsäure mit Fluorouracil. Arzneimittelforschung 41: 860
8. Deyton LR, Walker RE, Kovacs JA, Herpin B, Parker M, Masur H, Fauci AS, Lane HC (1989) Reversible cardiac dysfunction associated with interferon alpha therapy in AIDS patients with Kaposi's sarcoma. N Engl J Med 321: 1246
9. Doroshow JH, Multhauf P, Leong L, Margolin K, Litchfield T, Akman S, Carr B, Bertrand M, Goldberg D, Blayney D, Odujinrin O, DeLap R, Shuster J, Newman E (1990) Prospective randomized comparison of fluorouracil versus fluorouracil and high-dose continuous infusion leucovorin calcium for the treatment of advanced measurable colorectal cancer in patients previously unexposed to chemotherapy. J Clin Oncol 8: 491
10. Elias L, Sandoval JM (1989) Interferon effects upon fluorouracil metabolism by HL-60 cells. Biochem Biophys Res Commun 163: 867
11. Erlichman C, Fine S, Wong A, Elhakim T (1988) A randomized trial of fluorouracil and folic acid in patients with metastatic colorectal carcinoma. J Clin Oncol 6: 469–475
12. Forni M de, Malet-Martino MC, Jaillais P, Shubinski RE, Bachaud JM, Lemaire L, Canal P, Chevreau C, Carrie D, Soulie P, Roche H, Boudjema B, Mihura J, Martino R, Bernadet P, Bugat R (1992) Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol 10: 1795
13. Gradishar WJ, Vokes EE (1990) 5-Fluorouracil cardiotoxicity: a critical review. Ann Oncol 1: 409

14. Grem JL, McAtee N, Murphy RF, Balis FM, Steinberg SM, Hamilton JM, Sorensen JM, Sartor O, Kramer BS, Goldstein LJ, Gay LM, Caubo KM, Goldspiel B, Allegra CJ (1991) A pilot study of interferon alpha-2a in combination with fluorouracil plus high-dose leucovorin in metastatic gastrointestinal carcinoma. J Clin Oncol 9: 1811–1820
15. Grem JL, Chu E, Boarman D, Balis FM, Murphy RF, McAtee N, Allegra CJ (1992) Biochemical modulation of fluorouracil with leucovorin and interferon: preclinical and clinical investigations. Semin Oncol 19 [Suppl 3]: 36
16. Gutterman JD, Fine S, Quesada J, Horning SJ, Levine JF, Alexanian R, Bernhardt L, Kramer M, Spiegel H, Colburn W, Trown P, Merigan T, Dziewanowski Z (1982) Recombinant leukocyte A interferon: pharmacokinetics, single-dose tolerance, and biologic effects in cancer patients. Ann Intern Med 96: 549
17. Houghton JA, Maroda SJ, Phillips JO, Houghton PM (1987) Biochemical determinants of responsiveness to 5-fluorouracil and its derivatives in xenographs of human colorectal adenocarcinomas in mice. Cancer Res 41: 144
18. Houghton JA, Adkins DA, Rahman A, Houghton PJ (1991) Interaction between 5-fluorouracil, leucovorin, and recombinant human interferon-α2a in cultured colon adenocarcinoma cells. Cancer Commun 3: 225
19. Johnston PG, Lian C-M, Henry S, Chabner BA, Allegra CJ (1991) Production and characterization of monoclonal antibodies that localize human thymidylate synthase in the cytoplasm of human cells and tissue. Cancer Res 51: 6668
20. Kemeny N, Younes A, Seiter K, Kelsen D, Sammarco P, Adams L, Derby S, Murray P, Houston C (1990) Interferon alpha-2a and 5-fluorouracil for advanced colorectal carcinoma. Cancer 66: 2470
21. Keyomarsi K, Moran RG (1986) Folinic acid augmentation of the effects of fluoropyrimidines on murine and human leukemic cells. Cancer Res 46: 5229
22. Kirkwood JM, Ernstoff MS (1984) Interferons in the treatment of human cancer. J Clin Oncol 2: 336
23. Krown SE (1988) Interferons in malignancy: biological products or biological response modifiers? J Natl Cancer Inst 80: 306
24. Lee PP, Schilsky RL (1990) Inhibition of thymidylate synthase by the diastereoisomers of leucovorin. Cancer Chemother Pharmacol 26: 273
25. Levin RD, Gordon JH, Simonich W, Mellijor A, Sanchez R, Williams RM (1991) Phase I clinical trial with floxuridine and high-dose continuous infusion of leucovorin calcium. J Clin Oncol 9: 94
26. Meadows LM, Walther P, Ozer H (1991) α-Interferon and 5-fluorouracil: possible mechanisms of antitumor action. Semin Oncol 18 [Suppl 7]: 71
27. Neefe JR, John W (1991) Mechanisms of interaction of interferon and 5-fluorouracil in solid tumors. Semin Oncol 18 [Suppl 7]: 77
28. Nordic Gastrointestinal Tumor Adjuvant Therapy Group (1989) Superiority of sequential methotrexate, fluorouracil, and leucovorin to fluorouracil alone in advanced symptomatic colorectal carcinoma: a randomized trial. J Clin Oncol 7: 1437
29. Pazdur R, Ajani JA, Patt YZ, Winn R, Jackson D, Shepard B, DuBrow R, Campos L, Quaraishi M, Faintuch J, Abbruzzese JL, Gutterman J, Levin B (1990) Phase II study of fluorouracil and recombinant interferon alpha-2a in previously untreated advanced colorectal carcinoma. J Clin Oncol 8: 2027
30. Petrelli N, Douglass HO Jr, Herrera L, Russell D, Stablein DM, Bruckner HW, Mayer RJ, Schinella R, Green MD, Muggia FM, Megibow A, Greenwald ES, Bukowski RM, Harris J, Levin B, Gaynor E, Loutfi A, Kalser MH, Barkin JS, Benedetto P, Woolley PV, Nauta R, Weaver DW, Leichman LP (1989) The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. J Clin Oncol 7: 1419
31. Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, Krook JE, Mailliard JA, Laurie JA, Tschetter LK, Wiesenfeld M (1989) Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7: 1407
32. Quesada JR, Talpaz M, Rios A, Kurzrock R, Gutterman JU (1986) Clinical toxicity of interferons in cancer patients: a review. J Clin Oncol 4: 234
33. Santi DV, McHenry CS, Sommer H (1974) Mechanism of interaction of thymidylate synthetase with 5-fluoro-deoxyuridylate. Biochemistry 13: 471
34. Sato M, Yoshida H, Urata M, Yanagawa T, Yura Y, Nitta T, Kobayashi S, Hayashi Y (1984) Effects of 5-fluorouracil and the combination of 5-fluorouracil and human leukocyte interferon on human salivary gland adenocarcinoma cell line in culture. Int J Oral Surg 13: 35
35. Schwartz EL, Hoffman M, O'Connor CJ, Wadler S (1992) Stimulation of 5-fluorouracil metabolic activation by interferon-α in human colon carcinoma cells. Biochem Biophys Res Commun 182: 1232
36. Smith D, Wagstaff J, Thatcher N, Scarffe H (1987) A phase I study of rDNA alpha-2b interferon as a 6-week continuous intravenous infusion. Cancer Chemother Pharmacol 20: 327
37. Sonnenblick M, Rosin A (1991) Cardiotoxicity of interferon: a review of 44 cases. Chest 99: 557
38. Stadler WM, Vogelzang NJ, Vokes EE, Charette J, Whitman G (1992) Continuous infusion fluorodeoxyuridine with leucovorin and high-dose interferon: a phase II study in metastatic renal-cell cancer. Cancer Chemother Pharmacol 31: 213
39. Tevaearai HT, Laurent PL, Saurdet L, Eliason JF, Givel JC, Odartchenko N (1992) Interactions of interferon-alpha 2a with 5'-deoxy-5-fluorouridine in colorectal cancer cells in vitro. Eur J Cancer 28: 368
40. Vokes EE, Choi KE, Schilsky RL, Moran WJ, Guarnieri CM, Weichselbaum RR, Panje WR (1988) Cisplatin, fluorouracil, and high-dose leucovorin for recurrent or metastatic head and neck cancer. J Clin Oncol 6: 618
41. Vokes EE, Schilsky RL, Weichselbaum RR, Kozloff MF, Panje WR (1990) Induction chemotherapy with cisplatin, fluorouracil, and high-dose leucovorin for locally advanced head and neck cancer: a clinical and pharmacologic analysis. J Clin Oncol 8: 241
42. Vokes EE, Raschko JW, Vogelzang NJ, Warfield EE, Ratain MJ, Doroshow JH, Schilsky RL (1991) Five-day infusion of fluorodeoxyuridine with high-dose oral leucovorin: a phase I study. Cancer Chemother Pharmacol 28: 69
43. Vokes EE, Haraf DJ, McEvilly JM, Mick R, Kozloff MF, Goldman MD, Moran WJ, Clendeninn N, Collier M, Weichselbaum RR, Panje WR (1992) Neoadjuvant PFL augmented by methotrexate and piritrexim followed by concomitant chemoradiotherapy for advanced head and neck cancer: a feasible and active approach. Ann Oncol 3: 79
44. Vokes EE, Weichselbaum RR, Mick R, McEvilly J-M, Haraf DJ, Panje WR (1992) Favorable long-term survival following induction chemotherapy with PFL and concomitant chemoradiotherapy for locally advanced head and neck cancer. J Natl Cancer Inst 84: 877
45. Vokes EE, Ratain MJ, Mick R, McEvilly JM, Haraf D, Kozloff M, Hamasaki V, Weichselbaum RR, Panje WR, Wenig B, Berezin F (1993) Cisplatin, fluorouracil and leucovorin augmented by interferon alpha-2b in head and neck cancer: a clinical and pharmacologic analysis. J Clin Oncol (in press)
46. Von Hoff DD (1991) In vitro data supporting interferon plus cytotoxic agent combinations. Semin Oncol 18 [Suppl 7]: 58
47. Wadler S, Schwartz EL (1990) Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: a review. Cancer Res 50: 3473
48. Wadler S, Schwartz EL, Goldman M, Lyver A, Rader M, Zimmerman M, Itri L, Weinberg V, Wiernik PH (1989) Fluorouracil and recombinant alpha-2a-interferon: an active regimen against advanced colorectal carcinoma. J Clin Oncol 7: 1769
49. Wadler S, Goldman M, Lyver A, Wiernik PH (1990) Phase I trial of 5-fluorouracil and recombinant $\alpha_{2\alpha}$-interferon in patients with advanced colorectal carcinoma. Cancer Res 50: 2056
50. Wadler S, Wersto R, Weinberg V, Thompson D, Schwartz EL (1990) Interaction of fluorouracil and interferon in human colon cancer cell lines: cytotoxic and cytokinetic effects. Cancer Res 50: 5735

51. Wadler S, Lembersky B, Atkins M, Kirkwood J, Petrelli N (1991) Phase II trial of fluorouracil and recombinant interferon alpha-2a in patients with advanced colorectal carcinoma: an Eastern Cooperative Oncology Group study. J Clin Oncol 9: 1806
52. Weh HJ, Platz D, Braumann D, Buggisch P, Schmiegel WH, Drescher S, Kleeberg UR, Müllerleile U, Crone-Münzebrock W, Hoffmann R, Müller P, Klapdor R, Pompecki R, Erdmann H, Reichel L, Hoffman L, Mainzer K, Hossfeld DK (1992) Treatment of metastatic colorectal carcinoma with a combination of fluorouracil and recombinant interferon alpha-2b: preliminary data of a phase II study. Semin Oncol 19 [Suppl 3]: 180
53. Yee LK, Allegra CJ, Steinberg SM, Grem JL (1992) Decreased catabolism of fluorouracil in peripheral blood mononuclear cells during combination therapy with fluorouracil, leucovorin, and interferon α-$_{2\alpha}$. J Natl Cancer Inst 84: 1820