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ORIGINAL ARTICLE

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Phase I study of treatment with oral 13-*cis*-retinoic acid, subcutaneous interferon alfa-2a, cisplatin, and 24-hour infusion 5-fluorouracil/leucovorin

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Abstract A combination of oral 13-*cis*-retinoic acid (cis-RA) and subcutaneous interferon alfa-2a (IFN) has been reported to yield high response rates in patients with squamous cell carcinomas (SCCAs) of the cervix and skin. Cisplatin and 5-fluorouracil with leucovorin (5-FU/LV) are chemotherapeutic agents commonly used for SCCAs. *Purpose*: To determine the maximum tolerated doses (MTDs) of cisplatin and 5-FU/LV when combined with IFN and cis-RA, and to define a recommended phase II regimen for testing in cervical cancer and other appropriate tumor types. *Methods*: Phase I cohort design. Cisplatin was administered every 3 weeks. 5-FU and LV were administered together as a weekly 24-h infusion. Cis-RA was given orally twice daily. IFN was initially given subcutaneously at a dose of 3 million units (MU) daily. *Results*: A total of 31 patients were treated. The IFN dose was reduced to 3 MU three times weekly because of patient intolerance. Cytopenias prevented the administration of weekly 5-FU/LV. Single-agent cisplatin with three times weekly IFN and twice daily cis-RA was tolerable. Four partial responses were observed, in patients with adrenal cancer, bladder cancer, gastric cancer, and adenocarcinoma of unknown primary. *Conclusions*: The recommended phase II regimen is cisplatin 100 mg/m^2 every 3 weeks, IFN 3 MU three times weekly, and cis-RA 1 mg/kg daily. This appears to be more toxic than single-agent cisplatin, but the preliminary activity observed warrants further testing.

Key words 13-*cis*-Retinoic acid · Cisplatin · Interferon

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Introduction

The combination of oral 13-*cis*-retinoic acid (cis-RA) 1 mg/kg per day and subcutaneous interferon alfa-2a (IFN) 6 MU/day has been reported to yield a 58% response rate in previously untreated, locally advanced squamous cell carcinoma (SCCA) of the uterine cervix [32]. A similar regimen (cis-RA 1 mg/kg per day, IFN 3 MU/day) has been used in patients with advanced squamous cell cancer of the skin yielding a response rate of 68% with 25% complete responses [33]. Earlier studies of retinoids and interferon as single agents in these two diseases did not show high levels of activity [20, 31]. Cis-RA/IFN regimens have now been studied in a number of other tumors [4, 9, 11, 16, 21, 42, 51]; in renal cell carcinoma a 30% response rate has been observed [40]. Patients with no prior chemotherapy have been reported to have higher response rates [48]. One case report in acute promyelocytic leukemia describes restoration of sensitivity in an all-*trans*-retinoic acid-resistant patient with the addition of interferon alfa-2b [27]. A variety of studies in cell lines have shown additive or synergistic effects of various interferons and retinoids in inducing differentiation or inhibiting proliferation or tumor-induced angiogenesis [10, 13, 17, 18, 28, 30, 35, 36].

Cisplatin and 5-FU are commonly used chemotherapy agents for SCCAs of the skin, cervix, and other

sites. Cisplatin is generally considered the single most active agent against cervical cancer. In large trials involving patients with advanced or recurrent disease, response rates have been in the 18–31% range [41]. There are compelling in vitro and in vivo data to suggest that combining chemotherapy and certain biologic agents may be of value [8, 49, 52]. The combination of two independently active regimens with different toxicity profiles, such as cisplatin/5-FU/LV and cis-RA/IFN is attractive. Since biologic and cytotoxic drugs have different mechanisms of action, they may target different cell populations. IFN potentiates the action of both cisplatin and 5-FU [49, 52]. Retinoids also potentiate the activity of cisplatin in a number of cell systems [1, 6, 7, 12, 46]. This study attempted to combine cisplatin and weekly 5-FU/LV with a regimen of daily cis-RA and IFN using clinically relevant doses of each agent.

Patients and methods

The initial dose level was intravenous cisplatin at 50 mg/m^2 every 3 weeks combined with a regimen of IFN 3MU/day subcutaneously and oral cis-RA 1 mg/kg per day. We then planned to determine the maximal tolerated dose (MTD) of 5-FU (combined with a fixed dose of 500 mg/m^2 intravenous leucovorin), given as a weekly 24-h continuous infusion, that could be combined with the regimen described above, and to subsequently determine whether the cisplatin dose could be further escalated to 100 mg/m^2 every 3 weeks. Both the IFN (recombinant interferon alfa-2a; Roferon-A) and the cis-RA (isotretinoin; Accutane) used on this study were generously supplied by Hoffmann-La Roche.

Eligibility

Patients treated all had a histologically confirmed solid tumor which had failed to respond to standard treatment regimens or for which no standard treatment regimen existed. Eligibility criteria included age $\geq$ 18 years, CALGB performance status 0–2, and life expectancy of $\geq$ 2 months. Required laboratory parameters included a total white blood cell count (WBC) $\geq$ 3000/μl, absolute neutrophil count (ANC) $\geq$ 1500/μl, platelet count (PLT) $\geq$ 100 000/μl, serum creatinine $\leq$ 1.5 mg/dl, serum bilirubin $\leq$ 1.5 mg/dl, serum transaminases up to four times the upper limit of normal, and fasting serum triglycerides up to twice the upper limit of normal. All patients signed informed consent in accord with federal and institutional guidelines.

Treatment schedule

Treatment schedules for dose levels 1–6 are shown in Table 1. Cisplatin was administered as a 6-h intravenous infusion every 3 weeks, and was scheduled to be given 2 h following a dose of IFN. The total dose of cisplatin was mixed with 18.5 g mannitol in 1000 ml 5% dextrose/0.9% NaCl (D5W/NS). Following administration of cisplatin, patients received 3 l D5W/NS with 2 g $MgSO_4$ and 40 meq KCl, each liter given over 8 h. 5-FU and LV were both given as a weekly 24-h infusion, either mixed together in 500 ml NS, or administered simultaneously in separate bags of 500 ml NS. The initial 5-FU/LV infusion was begun immediately following the initial cisplatin infusion. Patients on dose levels 1, 5, and 6 received no 5-FU/LV. IFN was given subcutaneously at a fixed dose of 3 MU; injections were given in the evening to lessen acute side effects of injection, and most patients were premedicated with acetaminophen. Dose levels 1–3 employed daily IFN; this was subsequently reduced to three times weekly (dose levels 4–6) in order to reduce fatigue. Cis-RA was given daily in two equal divided doses with meals for a total dose of 1 mg/kg per day (rounded up to the nearest 10 mg). No patient received hematopoietic colony-stimulating factors while on this study.

Table 1 Treatment schedules for dose levels 1–6

Dose level	Cisplatin (mg/m^2)	5FU/LV (mg/m^2)	IFN (MU)	cis-RA (mg/kg/day)[a]
1	50	0/0	3 daily	1
2	50	1800/500	3 daily	1
3	50	1400/500	3 daily	1
4	50	1400/500	3 three times weekly	1
5	75	0/0	3 three times weekly	1
6	100	0/0	3 three times weekly	1

[a] Taken daily in two divided doses

Dose escalation

At least three patients were treated at each dose level. If one of the first three patients at a dose level experienced dose-limiting toxicity (DLT), up to three additional patients were added at that dose level. DLT was initially defined as any grade 3 or 4 toxicity, or inability to receive all drug doses through day 1 of cycle 2 in full dose on time. For dose levels 6 and 7 low WBC or ANC were considered dose-limiting only if they were grade 4 or if they persisted after IFN and cis-RA were held and treatment delayed for 1 week. If three or more of six patients developed grade 3 or greater toxicity after cycle 1, or if two or more of six patients developed grade 4 or greater toxicity after cycle 1, then the MTD was considered to have been exceeded. For the purposes of this study, the MTD was considered to be equivalent to the recommended phase II dose.

Patients were seen by a physician weekly during the first cycle of therapy, and at least once per cycle thereafter. Blood counts and serum chemistries were obtained weekly. Patients were evaluated every two cycles for tumor response, and could continue therapy if their tumors were responding or stable.

Results

A total of 31 patients were treated between April 1993 and February 1995. Patient characteristics are summarized in Table 2.

Toxicity

Toxicities grade 2 or greater seen after the cycle 1 are summarized in Table 3; toxicities grade 2 or greater seen after any cycle are summarized in Table 4.

Throughout the study, cis-RA-specific dermatologic side effects such as cheilitis and dry skin were mild

Table 2 Patient characteristics

No. entered	31
Male/female	17/14
Median age in years (range)	51 (30–77)
Performance status 0/1/2	16/8/7
Prior therapy	
None	6
Radiotherapy	16
Chemotherapy regimens (range/median)	(0–2)/1
Prior cisplatin or carboplatin	9
Cancer diagnosis	
Colon	4
Lung adeno/squamous	3/1
Cervix adeno/squamous	2/2
Sarcoma	3
Head/neck	3
Esophageal (squamous)	2
Unknown primary (adeno)	2
Renal	1
Mesothelioma	1
Bladder	1
Gastric	1
Endometrial	1
Melanoma	1
Thyroid	1
Adrenal	1
Anal (squamous)	1

Table 3 Toxicities grade 2 or more in first cycle

Level	WBC	PLT	Constitutional[a]	Other
1 ($n = 7$)	2gr2	1gr3	4gr2[b], 1gr3	
				1gr2 headache
2 ($n = 4$)	1gr2[c], 1gr3	1gr2	1gr2	1gr2 mucositis
				1gr3 mucositis
3 ($n = 5$)	–	–	2gr2[b], 2gr3	1gr4 cardiac
4 ($n = 3$)	2gr2[c]	–	1gr2	1gr2 diarrhea
5 ($n = 6$)	1gr2, 2gr3	–	2gr2	1gr3 Na^+
				2Gr2 Mg^{++}
6 ($n = 6$)	1gr2	1gr3	1gr3, 2gr2	1gr2 tinnitus
				1gr4 coagulopathy

[a]Includes fatigue, myalgias, anorexia
[b]One patient refused further treatment after one cycle because of these grade 2 symptoms
[c]Dose-limiting because it prevented administration of full drug dosage

(< grade 1). Elevations in triglycerides were common, but not clinically significant. No patient received lipid-lowering drugs. The median pretreatment triglyceride level was 109 mg/dl (range 48–225 mg/dl), and the median level just prior to cycle 2 was 203 mg/dl (range 83–525 mg/dl). The highest level observed was in a patient at dose level 1 who had an asymptomatic value of 906 mg/dl after two cycles.

Constitutional symptoms, including primarily fatigue, but also anorexia, myalgias, and headache, were the predominant toxicities at the first three dose levels, which employed daily IFN. At dose level 1 (no 5-FU), four patients reported grade 2 and one reported grade 3 constitutional symptoms after just one cycle of therapy. One of those with grade 2 toxicity removed herself from study and refused any further treatment or evaluation for toxicity or response; an additional patient was therefore treated at the dose level. There were seven patients who were evaluable for fatigue among those treated on dose levels 2 and 3 with 5-FU and daily IFN (of the remaining two, one developed a severe cardiac event and was in the intensive care unit, and the other, who had received prior radiation to the oropharynx, developed severe mucositis and refused to come in for evaluation). Three suffered grade 2 and two had grade 3 constitutional symptoms after just one cycle. One of those with grade 2 symptoms stopped his own therapy, and refused further treatment. The IFN at all subsequent dose levels was therefore reduced to three times weekly, which was better tolerated although all patients still developed grade 2–3 fatigue and malaise after multiple cycles.

Table 4 Toxicities grade 2 or more, any cycle

Level	WBC	PLT	Constitutional[a]	Other
1 ($n = 7$)	3gr2	2gr2, 1gr3	2gr3, 4gr2	1↑triglycerides (906 mg/dl)
				2gr2 headache
2 ($n = 4$)	1gr2[c],1gr3	1gr2	2gr2, 1gr3	1gr3 mucositis
				1gr2 mucositis
3 ($n = 5$)	1gr2	1gr2	1gr2, 3gr3	1gr4 cardiac
				2gr2 renal
4 ($n = 3$)	2gr3	–	2gr2	1gr2 diarrhea
				1gr4 cerebellar
5 ($n = 6$)	3gr3	1gr2	4gr2	1gr4 Na^+
				1gr3Mg^{++}
				3Gr2 Mg^{++}
6 ($n = 6$)	2gr2	1gr2,1gr3	4gr2	1gr2 tinnitus
			2gr3	1gr2 headache
				1gr2Mg^{++}
				1gr4 coagulopathy

[a]Includes fatigue, anorexia, myalgias

Hematologic toxicity, although generally mild, prevented the weekly dosing of 5-FU/LV. Some cytopenias were observed even at the first dose level, with one patient experiencing dose-limiting thrombocytopenia. Her nadir PLT was 45 000/μl on day 21. Although IFN and cis-RA had been discontinued on days 12 and 14, respectively, her PLT did not recover to over 100 000/ μl until day 44. Two patients at dose level 2 (daily IFN) and two at dose level 4 (three times weekly IFN) had leucopenia which delayed or prevented 5-FU treatment. Therefore, after dose level 4 we abandoned the attempt to add weekly 5-FU/LV to the regimen, and escalated the cisplatin dose. Patients at dose levels 5 and 6 whose WBC had not recovered sufficiently to receive a second cisplatin dose on day 21 had cis-RA and IFN held, and were considered dose-limiting only if toxicity was grade 4 or if they had not recovered by day 28.

Six patients were treated at dose level 5 (75 mg/m^2 cisplatin). Two patients had grade 3 leucopenia after

the first cycle. Both recovered when IFN and cis-RA were held for a week. Six patients were treated at dose level 6. Only one had significant hematologic toxicity, grade 3 thrombocytopenia after cycle 1. Dose level 6 did not exceed the MTD, but escalation of cisplatin beyond 100 mg/m^2 was not planned since it is well known that this produces increased toxicity [29], and we saw no evidence that cis-RA/IFN protects against such toxicity. The recommended phase II regimen is cisplatin 100 mg/m^2, IFN 3 MU three times weekly, and cis-RA 1 mg/kg daily.

Three patients suffered serious toxicities which were probably treatment-related, but not clearly dose-related. One patient at dose level 3 had a grade 4 cardiac event with chest pain and a marked decrease in ejection fraction, associated with acalculous cholecystitis, during his first 5-FU infusion. Myocardial infarction was ruled out and the patient recovered after cholecystectomy, but he received no further treatment. A woman treated at dose level 4 developed a gradually progressive cerebellar toxicity, which was grade 3 after three cycles of therapy. She had an adenocarcinoma of unknown primary with disease in her supraclavicular and retroperitoneal lymph nodes. Her CA-125 was elevated, but laparotomy showed no evidence of tumor in her abdomen or pelvis. Although ataxia has been reported to be a DLT of 24-h 5-FU infusions, it has been reversible within 3 to 4 weeks after discontinuing therapy [2]. This patient's symptoms were felt by the consulting neurologist to be consistent with a paraneoplastic syndrome, and the patient's serum was positive for anti-YO (anti-Purkinje cell) antibody. It is well known that interferon potentiates or triggers a variety of autoimmune phenomena [43, 44], and although the patient had a significant partial response to treatment, with near complete resolution of adenopathy on CT scan, she was taken off study and treated with single-agent cisplatin with stabilization of her neurologic syndrome and her disease. She remained alive with stable neurologic symptoms 15 months later. A third patient, treated at dose level 6, had an upper GI bleed in association with a large gastric mass, a PT of 48.6 s, a PTT of 79.2 s, a PLT of 45 000/μl, and no evidence of DIC. She recovered and was removed from the study, although her radiologic evaluations showed a partial response in liver lesions and adenopathy after only one cycle. She had been taking warfarin 1 mg/day as prophylaxis against central line thrombosis, and her elevated PT may have been the result of decreased oral intake. However, a decrease in the levels of vitamin K-dependent clotting factors has been reported in patients receiving high doses of lymphoblastoid IFN [39].

Responses

Four partial responses were observed. None of these occurred in patients with prior platinum exposure. One, discussed above, was at dose level 4 in a patient with previously untreated adenocarcinoma of unknown primary. A second, also discussed above, occurred at dose level 6 in a patient with gastric cancer who had failed two prior chemotherapy regimens. A patient treated at dose level 6 with bladder cancer who had failed one prior regimen had a partial response after four cycles, but stopped treatment because of progressive fatigue and malaise. A chemotherapy-naive patient originally thought to have an unknown primary with a right upper quadrant mass and innumerable pulmonary metastases had complete resolution of his pulmonary disease after seven cycles at dose level 5. The residual adrenal mass was resected and felt to be a primary adrenal carcinoma. He remained without evidence of disease 20 months after starting treatment. Two minor responses were observed in patients with previously untreated metastatic SCCA of the esophagus at dose levels 2 and 3. Neither of the two patients with SCCA of the cervix responded; however, one had received prior cisplatin and the other had disease only in a previously irradiated field.

Discussion

This is the first trial to have evaluated the combination of cis-RA, IFN and cisplatin. However, multiple permutations of the combination of interferon, 5-day continuous infusion 5-FU, and cisplatin have been investigated in a variety of tumor types, including bladder, head and neck, esophagus, and cervix with promising results [5, 14, 19, 26, 34, 47, 50].

A weekly 24-h 5-FU/LV infusion was chosen for this trial in an attempt to limit mucosal toxicity [15]. We had anticipated that mucosal toxicities might be worsened by cis-RA, and planned for patients to be able to take a continuous oral medication (cis-RA), while maintaining a reasonable dose-intensity of 5-FU. A weekly regimen of 2600 mg/m^2 5-FU administered concurrently with 500 mg/m^2 LV over 24 h by continuous infusion has been shown to be tolerable, with efficacy in the treatment of metastatic colorectal carcinoma at least comparable to that of other 5-FU-based regimens [3]. The only significant mucositis on this trial was observed in a patient with prior radiation to the head and neck. However, we were unable to deliver weekly 5-FU/LV, primarily because of mild cytopenias, possibly caused by interferon suppression of marrow recovery. It might have been possible to add 5-FU/LV on an every-3-week schedule, particularly if a week off interferon for recovery of counts as needed were permitted, as on dose levels 5 and 6. Because our primary interest was in developing a regimen to test in patients with cervical cancer, in which 5-FU is only minimally active, and because of concern that a 24-h 5-FU/LV infusion every 3weeks was insufficiently dose-intense

for use in those tumors against which 5-FU is highly active, we chose instead to concentrate on dose escalation of cisplatin.

No dose-response data exist for the combination of cis-RA and IFN. Our starting IFN dose of 3 MU/day was lower than that used in the initial study of cervical cancer [32] and equal to that used in the study of squamous cell carcinoma of the skin [33]. The cervical cancer trial reported only one instance of grade 3 fatigue in a group of previously untreated patients with locally advanced disease and a median age in the 40s. The squamous cell carcinoma trial, however, involved patients with a median age of 67 years, some of whom had metastatic disease or prior chemotherapy, and 12 of 32 patients experienced grade 3 fatigue. Fatigue and related constitutional symptoms, although they appeared to be ameliorated by three times weekly IFN dosing, were the most significant problem in our trial and worsened over multiple cycles. We did not routinely use antidepressant medications, which might have moderated some of this toxicity.

Recent mechanistic data has shed some light on the complex interactions between retinoids and interferons. In a variety of cell lines, increased sensitivity to the actions of interferons produced by pretreatment with retinoids has been shown to be associated with an increase of interferon-stimulated transcription [23–25, 38], suggesting retinoid potentiation of the interferon signal transduction pathway. Conversely, interferons have been shown to induce expression of the RA nuclear receptor-γ (RAR-γ) and suppress RA-mediated increases in cellular RA-binding proteins (CRABPs), thus possibly reducing RA degradation as well as augmenting transcription of RA-regulated genes [37].

There is also a good preclinical rationale for the combination of retinoids and cytotoxic agents. Sacks et al. [45] have reported that all-*trans*-RA inhibits growth of squamous cell cancer lines without altering the cell cycle, suggesting that the activity of antineoplastic agents should not be abrogated. A number of in vitro studies have indicated increased activity of cisplatin in combination with retinoids [1, 6, 7, 12]. Enhanced efficacy has been noted using 9-*cis*-RA with cisplatin in a human oral SCCA xenograft model [46]. These authors observed that 9-*cis*-RA suppresses squamous cell differentiation, producing an increased number of basal cells, while cisplatin selectively depletes proliferating basal cells. Retinoids have also been reported to enhance the efficacy of paclitaxel [6] and etoposide [22] in some cell lines, and this may represent a direction for future investigations.

We conclude that doses of 75–100 mg/m^2 of cisplatin with daily cis-RA and three times weekly IFN are tolerable for at least a brief number of cycles. The addition of weekly 5-FU/LV infusions was not feasible. Impressive activity was observed in several patients, and the regimen deserves further testing in appropriate tumor types.

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