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Clinical trial of folinic acid to reduce vincristine neurotoxicity*

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Summary. In a murine model system, folinic acid demonstrated host-protective properties during administration of repetitive and lethal doses of vincristine (VCR). Subsequently, folinic acid was evaluated in patients receiving VCR during an adjuvant chemotherapy program for stage II carcinoma of the breast. The toxicities, cumulative VCR dosage, and percentage of ideal dosage observed in 18 patients receiving folinic acid have been compared with those observed in 70 patients who previously received VCR without folinic acid in the same chemotherapy program. All patients ideally were intended to receive VCR 1.0 mg/m^2 weekly for 6 weeks, with dose modification for neurotoxicity. Treatment patients received folinic acid 800 mg PO daily in three divided doses during the 6-week course. The degree of neurotoxic manifestations of VCR was similar in the treatment and comparison patients. Absent to mild neurotoxicity was observed in approximately 70% of patients in both groups; moderate or greater neurotoxicity occurred in about 30% of patients in both groups. Full dosage (6.0 mg/m^2) was attained in 7 (39%) treatment patients and 17 (24%) comparison patients ($P=0.21$). The mean percentage of the ideal dosage of VCR was 73.7 ± 28.7 in patients receiving folinic acid and 76.1 ± 20.5 in those given only VCR ($P=0.69$). Hematologic toxicities were similar in both groups, but nausea occurred more frequently in the folinic acid group. Folinic acid in this dose and schedule afforded no protection from the neurotoxic side effects of VCR.

Introduction

The principle side effect limiting the clinical use of the antitumor agent vincristine (VCR) is neurotoxicity [7]. It is dose-related, occurs to some degree in most of the patients receiving repeated injections, and may be observed within the first few weeks of therapy [3, 6, 8, 16].

Currently, there are no known methods of routinely preventing or decreasing the toxicity associated with the use of this agent, other than its discontinuation and/or dose modification. Trials of thiamine and vitamin B_{12} [16] and pyridoxine [13] have been unsuccessful. A preliminary clinical trial of glutamic acid [10], based on results observed in a murine model [11], appears somewhat promising.

Folinic acid has been used as an antidote in a patient experiencing severe neurotoxicity following a large single dose of VCR [5], but several reports have disclaimed its value [14, 19] or shown no apparent benefit [17, 20]. Use of folinic acid stems from laboratory investigations performed over two decades ago. In 1963 Johnson et al. reported host protection of normal mice against a single lethal dose of VCR by administration of folinic acid [15]. Recently, somewhat similar experiments have confirmed the host-protective effect of folinic acid during VCR administration to normal mice [9]. In these experiments, repetitive small ($< LD_{10}$) doses of VCR were given to mimic the situation in the clinic; injections were continued until death. Folinic acid 140 mg/kg was given daily IP, which resulted in a significant increase in survival compared with animals receiving VCR alone. Subsequent experiments in a tumor-bearing model (P-388 murine leukemia) revealed no inhibition of the antitumor effect of VCR by folinic acid [9]. These data led to the current trial of folinic acid as a potential modifier of VCR toxicity in the clinic [12].

Materials and methods

The trial was begun in August, 1983. The treatment group consisted of 18 consecutive patients who received folinic acid during an adjuvant chemotherapy program containing VCR for stage II carcinoma of the breast. Historical controls were used for comparison; this group was comprised of 70 consecutive patients with stage II breast cancer, who were in the same general condition at the start of treatment as those in the treatment group and who had previously received VCR under the same adjuvant chemotherapy protocol, which had been initiated in July, 1980. To minimize the differences in the subjective assessment of neurotoxicity, the comparison group consisted of patients whose physicians were the same ones as were involved in caring for the patients in the treatment group.

Patients in the treatment group received folinic acid (25-mg tablets kindly provided by A. Guaspari, Burroughs Welcome Co., Research Triangle Park, NC) 800 mg daily PO in three divided doses during the 6-week induction phase of the adjuvant chemotherapy program, in which VCR 1.0 mg/m^2 IV was given weekly. Pyridoxine was started on the day of the first dose of VCR. The dosage of

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folinic acid approximated the dosage found to be effective in the previous murine study [9] by using a conversion factor of 1/12 from mouse to man [4]. Other agents administered weekly during induction therapy included doxorubicin 10 mg/m^2 IV, cyclophosphamide 400 mg/m^2 IV, and 5-fluorouracil 400 mg/m^2 IV; prednisone 40 mg/m^2 was administered PO daily for 3 weeks and then gradually discontinued by the 4th week of induction.

Differences between the treatment and comparison groups in the cumulative VCR dosage and toxicity during induction therapy were compared. A previously defined grading scale [10] was used to define the level of neurotoxicity. This scale was used during assessment of both control and treatment patients and was not applied retrospectively in a case review. The dosage of VCR was not to be modified for grade 1 neurotoxicity. Neurotoxicity ≧ grade 2 required omission of VCR until neurologic recovery, at which time 50% dosage was administered. Patients in the treatment group underwent careful neurologic examination weekly during induction therapy, just prior to the next planned dose of VCR. Evaluation of toxicity in the comparison group had been performed every 2 weeks.

Since VCR could be with held due to neurotoxicity, cumulative VCR and percentage of ideal dosage of VCR during induction were considered to be toxicity indicators. But there were cases in both the folinic acid and the comparison groups where one or more whole cycles of treatment were omitted for reasons other than neurotoxicity, such as failure to come to clinic or low blood counts. Therefore, an "adjusted" percentage of ideal dosage was calculated in which these cycles were ignored. Since the exclusion of these cycles of treatment was directly related to the percentage of drug dose given, this resulted in an upward adjustment of percentage ideal dosage.

The Chi-square test and the Wilcoxon rank sum method were used in analysis of the data, on the assumption that the treated and comparison groups were from the same population. The study was designed to detect a 40% decrease in neurotoxicity with 90% power at a 5% level of significance.

Results

Patients in the treatment and comparison groups were comparable (Table 1) with respect to overall age distribution, but there were more patients aged ≧50 in the comparison group ($P=0.04$) and more postmenopausal patients in the comparison group ($P=0.04$). Estrogen receptor status and the distribution of the number of positive axillary nodes were comparable in the two groups. The median age of folinic acid (treatment) patients was 46 years (range 30–66 years), as opposed to 52 years (range 29–67 years) for comparison patients.

The neurologic side effects by grade are detailed in Table 2; no differences between treatment and comparison groups were observed. No neurotoxicity (grade 0) was reported in 11% of treatment patients and 31% of comparison patients ($P=0.08$). Moderate to severe neurotoxicity (grade 2–3) occurred in 34% of the treatment group and 31% of the comparison group. Severe (grade 3) neurotoxicity occurred in 17% and 4% of the treatment and comparison patients, respectively ($P=0.06$).

Cumulative VCR dosage during induction therapy is given in Table 3. Attainment of full dosage during induction therapy is indicated by a cumulative VCR dosage of 6.0 mg/m^2. Seven (39%) of the patients given folinic acid received the full dosage of VCR, as against 17 (24%) of the comparison patients, who did not receive folinic acid during induction therapy ($P=0.21$). The mean (±SD) cumu-

Table 1. Patient characteristics

	VCR + folinic acid (n = 18)		VCR only (n = 70)	
	No.	(%)	No.	(%)
No. of patients	18	(100)	70	(100)
Median age, years (range)	46	(30–66)	52	(29–67)
No. of pts. ≧50 years	8	(44)	49	(70)
Race				
White	15	(83)	63	(90)
Black	3	(17)	7	(10)
Menopausal status				
Pre-	11	(61)	28	(40)
Post-	6	(33)	42	(60)
ER status				
Positive	7	(39)	43	(61)
Negative	11	(61)	27	(39)
Positive nodes				
1–3	11	(61)	32	(46)
4+	6	(33)	38	(54)
Unknown	1	(6)	0	–

Table 2. Neurotoxicity during induction adjuvant chemotherapy for stage II breast cancer

	VCR + folinic acid (n = 18)		VCR only (n = 70)	
	No.	(%)	No.	(%)
Not recorded	0	(0)	17[a]	(24)
None	2	(11)	5	(7)
Mild	10	(56)	26	(37)
Moderate	3	(17)	19	(27)
Severe	3	(17)	3	(4)
Life-threatening	0	(0)	0	(0)

[a] Omission of ratings for neurotoxicity was assumed to have indicated absence of neurotoxicity

Table 3. Cumulative VCR dosage during induction adjuvant chemotherapy for stage II breast cancer[a]

	VCR + folinic acid (n = 18)		VCR only (n = 70)	
	No.	(%)	No.	(%)
1.0–2.0 mg/m^2	2	(11)	1	(1)
>2.0≦3.0 mg/m^2	1	(6)	6	(9)
>3.0≦4.0 mg/m^2	5	(28)	14	(20)
>4.0≦5.0 mg/m^2	1	(6)	13	(19)
>5.0<6.0 mg/m^2	2	(11)	19	(27)
6.0 mg/m^2	7	(39)	17	(24)

[a] Vincristine (VCR) 1.0 mg/m^2 was given IV weekly for 6 weeks during induction; full dosage was 6.0 mg/m^2. Patients receiving FA were administered 800 mg po three times daily in divided doses during induction

Table 4. Non-neurologic toxicity

	VCR + folinic acid ($n = 18$)		VCR only ($n = 70$)	
	No.	(%)	No.	(%)
Nausea reported	15	(83)	34	(49)
Vomiting reported	8	(44)	22	(31)
WBC < 3000/mm³	8	(44)	24	(34)
Platelets < 150 000/mm³	2	(11)	11	(16)

lative VCR dosage (mg/m²) during induction therapy was 4.3 ± 1.8 in treatment patients and 4.6 ± 1.2 in comparison patients. After adjustment for missing cycles for reasons such as failure to come to clinic or low blood counts, the percentage who attained 100% of the ideal dosage was not significantly different (56% in the treatment group and 50% in the comparison group). The mean (± SD) "adjusted" percentage of ideal dosage of VCR was 73.7 ± 28.7 in patients receiving folinic acid and 76.1 ± 20.5 in controls ($P = 0.6$). Cumulative VCR dosage during induction was not affected by relapse of breast cancer, since there were no such cases in either group.

Administration of folinic acid was not associated with any increased hematologic toxicity compared with controls (Table 4), but more patients experienced nausea in the treatment group (83% vs 49%; $P = 0.008$).

Discussion

Except for an increase in nausea, the large daily dosage of folinic acid was well tolerated; there was no enhanced myelosuppresion such as might be expected with co-administration of 5-fluorouracil [1, 2, 18]. Unfortunately, with the dose and schedule used in the current trial, folinic acid did not appear to reduce the neurotoxicity associated with the administration of VCR. Since this was not a randomized trial, some elements of bias, both positive and negative, could be operative in this study. In an attempt to produce a positive outcome, perhaps physicians would have attempted to use higher doses of VCR. Obviously, this did not occur. On the other hand, the prospective careful neurologic evaluation performed at weekly intervals in treatment group, compared with the nonprospective, routine neurologic evaluation done every 2 weeks in the comparison group, would perhaps bias the study in a negative fashion.

However, in this study, analysis of a number of parameters, including degree of neurotoxicity experienced, cumulative dosage of VCR delivered, and adjusted percentage of ideal dosage of VCR delivered, showed no positive trends suggestive of a potential benefit for use of folinic acid to ameliorate VCR-induced neurotoxicity. Perhaps the very intensive use of VCR in the current study (six weekly doses of 1.0 mg/m²) masked any potential benefit that folinic acid might have produced. Many combination chemotherapy regimens for neoplastic disease employ a less intense schedule, such as every 3–4 weeks.

Certainly, the clinical benefit for patients receiving folinic acid prior to the development of symptoms and signs of neurotoxicity following an overdose of VCR has been unimpressive (Table 5). At least five such cases have been reported [5, 14, 17, 19, 20], and in only one of these did there appear to have been any benefit [5]. In this last case, neurotoxic manifestations, including neuropathy, paresthesias, changes in sensorium and gait, and development

Table 5. Reported cases of folinic acid administration after an overdose of vincristine

Reference	Age/Sex	Diagnosis	VCR	Folinic acid	Time folinic acid given after VCR	Neurotoxicity outcome
Wakem and Bennett (1975) [20]	14/M	Leukemia	15.0 mg	12 mg IM q 6 h x6	"Immediate"	Symptoms – signs 12 days after VCR; recovered partially (confusion, ataxia, seizures, SIADH[a]) 18 days after VCR: and fully 5 months after VCR; course not improved
Kaufman et al. (1976) [17]	7/F	Leukemia	13.5 mg	? mg IV	1 h	Symptoms – signs 4 h after VCR; died 68 h after VCR
Grush and Morgan (1979) [5]	14/M	Sarcoma	10.0 mg	15 mg q 3 h x24 (route not given)	48 h	Symptoms – signs 1 day after VCR; recovered partially (SIADH) in 8 days after VCR and fully 1 month after VCR; course shortened
Thomas et al. (1982) [19]	24/M	Lymphoma	25.0 mg	12 mg IM q 6 h x20	24 h	Symptoms – signs 4 days after VCR; recovered partially (SIADH) in 16 days after VCR and fully by 80 days; course not improved
Jochimsen (1982) [14]	60/F	Colon	9.5 mg (1.9 mg/ d × 5d)	15 mg IV q 3 h x24	On day 5 of 5 VCR bolus injections	Symptoms – signs 7 days after last of 5 daily VCR injections; recovered partially (neuropathy) in 21 days after VCR but still had deficits 3 months later; course not improved

[a] Syndrome of inappropriate antidiuretic hormone secretion

of the syndrome of inappropriate antidiuretic hormone secretion, still occurred, but were said to have cleared more rapidly than expected.

The results of the current trial and a review of the reported cases of prophylactic administration of this agent following an overdose of VCR cast some doubt on the potential clinical usefulness of folinic acid given to prevent or ameliorate VCR-induced neurotoxicity.

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