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Hepatic intra-arterial infusion of vincristine

Don V. Jackson, Jr.[1], Frederick Richards II[1], Charles L. Spurr[1], Tony R. Long[1], Duff A. Rardin[1], David A. Albertson[2], and J. Michael Sterchi[2]

Departments of [1]Medicine and [2]Surgery, Oncology Research Center, Bowman Gray School of Medicine, of Wake Forest University, Winston-Salem, NC 27103, USA

Summary. *Currently the chemotherapeutic agents available for intra-arterial infusion in metastatic liver cancer are limited to only a few. The recent demonstration of the feasibility of prolonged IV infusion of vincristine led to exploration of hepatic intra-arterial infusion of this agent. A continuous infusion of 0.4 mg total dose was administered daily for 5 days via a hepatic artery catheter to each of six patients with metastatic liver cancer. Transient but life-threatening toxicity principally involving the nervous and gastrointestinal systems occurred in five of them. Future investigation of hepatic intra-arterial infusion of vincristine should be based on dose-schedules other than that employed in the current trial.*

Introduction

The antitumor agent vincristine (VCR) is usually administered by rapid IV bolus injection in a dose range of 1.4–2.0 mg/m^2. Recently we have demonstrated that continuous IV infusions for 5 days in a dose range of 0.25–0.50 mg/m^2/day are well tolerated [2, 6]. In view of the growing need to identify active agents for the treatment of metastatic liver disease, we have investigated prolonged hepatic intra-arterial infusions of VCR.

Material and methods

Patients with refractory metastatic hepatic cancer were the subjects of this investigation. All patients had one or more abnormal serum liver function test and scan evidence of metastatic disease. Patient characteristics are listed in Table 1. All the patients with adenocarcinoma of the colon had eventually failed to respond to intra-arterial infusion of FUDR, and four of them had also received mitomycin C intra-arterially. The single patient with lymphoma had previously received several antitumor agents but no hepatic intra-arterial therapy. No patient had evidence of portal hypertension and patients were not excluded from entry into the trial because of extent of metastatic disease in the liver. Following informed consent, VCR 0.4 mg/day was administered daily by continuous hepatic intra-arterial infusion for 5 days. A total dose of 2.0 mg was selected, since that is the usual maximum IV dose of VCR. Repeat infusions were planned at 3-week intervals in the absence of progressive disease and/or prohibitive toxicity. No cytotoxic agents other than VCR were administered during this trial. Supportive medications were given according to the discretion of the attending physician. Prior to treatment the catheter position was determined radiographically, usually with the aid of a radiolabel (99mTc macroaggregated albumin). The infusion pumps used were Infusaid (Infusaid Corp. Norwood, Mass) in patients 1 and 3, Cormed (Cormed Inc., Medina, NY) in patients 2, 4, and 5, and IVAC-600 (IVAC, Inc., San Diego, Calif) in patient 6. Permanent hepatic artery catheters were used in the patients with the Infusaid and Cormed pumps, whereas a temporary percutaneous catheter provided arterial access for infusion with the IVAC-600. Infusates consisted of 5% dextrose in water, to which were added heparin (1,000 U/ml in the Infusaid and Cormed pumps and 0.3 U/ml in the IVAC pump) and VCR (to provide a daily dose of 0.4 mg). The infusate was continuously delivered over a 5-day period in patients with portable infusion pumps, whereas it was changed daily in the patient whose infusion was delivered by the IVAC system. The stability of VCR in these solutions for 1 or 5 days has been documented by high-pressure liquid chromatography [2, 5].

Patients were hospitalized during the first infusion, during which time they were observed for toxicity and daily liver function tests were performed. Daily serum samples for VCR concentration were obtained in three patients; the details of the radioimmunoassay have been described previously [9]. Stool samples were not obtained.

Results

Of the six patients treated, in whom 13 courses were administered, five experienced life-threatening toxicity (Table 2). Central nervous system toxicity was observed in three patients, all of whom had transient periods of severe confusion and disorientation which lasted for 7, 11, and 19 days, respectively. Computerized cranial tomography was performed in two of them and was normal. Autonomic neuropathies were observed in two patients (ileus and postural hypotension in one each). Gastrointestinal toxicity was present in four patients, one of whom (No. 2) experienced profuse watery diarrhea in addition to nausea and vomiting, which rapidly produced dehydration. A second infusion using 50% dosage did not produce diarrhea but resulted in a marked decrease of motor strength. A brief episode of right upper quadrant abdominal pain associated with local tenderness to palpation occurred in one patient soon after the start of an infusion; a radiographic study (labeled macroaggregated albumin scan) showed dislodgement of the hepatic arterial

Offprint requests to: D. V. Jackson, Jr.

Table 1. Patient characteristics

Patient no.	Metastatic liver disease	Age/sex	PS[a]	Prior chemotherapy[b]	Biochemical abnormality[c]
1	Adenocarcinoma of the colon	76/M	2	FUDR IA, M–C IA	B 2.1 AP 381 SGOT 68
2	Adenocarcinoma of the colon	38/M	2	FUDR IA, M–C IA	AP 687
3	Adenocarcinoma of the colon	64/F	3	FUDR IA, M–C IA	AP 548 SGOT 48
4	Adenocarcinoma of the colon	58/F	2	FUDR IA, M–C IA	AP 187
5	Adenocarcinoma of the colon	34/F	2	FUDR IA,	AP 246
6	Poorly differentiated lymphocytic lymphoma	69/M	3	CTX, A, CL, VCR, Pred	AP 181

[a] Performance status: 2, with symptoms but bedridden < 50% of the time; 3, bedridden > 50% of the time but capable of self-care

[b] Abbreviations: FUDR, fluorodeoxyuridine; M–C, mitomycin C; CTX, cyclophosphamide; A, Adriamycin; VCR, vincristine; Pred, prednisone; CL, chlorambucil; IA intra-arterial

[c] Normal laboratory values: B (bilirubin), ≦ 1.0 mg%; AP (alkaline phosphatase), ≦ 110 U/l; SGOT (serum glutamic-oxaloacetic transaminase), ≦ 40 U/l

Table 2. Toxicity

Patient no.	Intra-arterial VCR infusion dose	No. of courses	Toxicity	Reason for stopping treatment
1	0.4 mg/day × 5 days	1	Confusion, disorientation, anorexia, urinary incontinence	Toxicity
2	0.4 mg/day × 5 days 0.2 mg/day × 5 days	1 1	Profuse diarrhea, nausea, vomiting, weakness, paresthesias	Toxicity
3	0.4 mg/day × 5 days	2	Confusion, aphasia, weakness, anorexia	Toxicity
4	0.4 mg/day × 5 days	1	Confusion, weakness, nausea, vomiting, ileus	Toxicity
5	0.4 mg/day × 5 days	6	Diarrhea, weakness	Catheter dislodgement
6	0.4 mg/day × 5 days	1	Postural hypotension weakness, nausea, vomiting	Toxicity

catheter with perfusion of a portion of the peritoneal cavity. In this patient discontinuation of the infusion and delivery of a steroid solution through the catheter resulted in rapid disappearance of the symptoms. Hepatic intra-arterial infusions of VCR were not clearly associated with worsening hepatic function; a mild but transient rise in SGOT was observed in one patient (No. 4) during infusion and 10-fold increase in the serum bilirubin concentration occurred in a patient (No. 3) who had progressive disease. White blood cell and platelet counts were not affected.

Serum concentrations of VCR during hepatic intra-arterial infusion approximated the lower range of sensitivity of the assay ($\sim 1 \times 10^{-9} M$) in one patient (No. 5) and were undetectable in the two other patients examined (Nos. 1 and 4).

No suggestive antitumor activity was noted during this limited trial, other than stable disease for 4 months in a single patient. However, the generally severe toxicity precluded an adequate trial with repeated infusions.

Discussion

The toxicity involving the nervous and gastrointestinal systems prohibits future trials of VCR administered by hepatic intra-arterial infusion with this dose and schedule. It is of interest that IV infusion of a comparable or a two-fold greater dose of VCR given over the same period of time appears to be much better tolerated than hepatic intra-arterial infusion [2, 6]. Central nervous system toxicity and nausea and vomiting have not been observed in patients receiving daily IV infusions of 0.25–0.50 mg/m^2 for 5 days [2, 6]. The greater toxicity following intra-arterial delivery than after IV administration may be due to the derangement in liver function as a consequence of metastatic disease in the patients in the current trial, since the biliary system appears to be the principal route of excretion of this agent [1]. Indeed, neurotoxicity associated with VCR has previously been observed to be increased in patients who have had abnormal liver function [8]. The occurrence of gastrointestinal toxicity following intra-arterial

administration of VCR might be related to direct mucosal effects of high concentrations of the drug and its products in the bile, which might persist for long periods of time. The presence of VCR and its products in the bile can be observed for several weeks following IV injection in the dog [4].

Given the greater toxicity with intra-arterial infusions of VCR, it might be expected that serum concentrations would exceed those previously observed during IV infusions [3]. That this is not the case might be accounted for in part by an alteration of systemic distribution and subsequent tissue binding of this agent and its metabolic products as a result of direct hepatic injection, Perhaps a greater arterial concentration of unaltered drug reaches the central nervous system and gastrointestinal system following direct hepatic injection due to saturation of hepatic metabolic pathways. However, little is known about the metabolic products of this agent and the differences in their capability to produce toxicity compared with the parent drug.

The tolerance to hepatic intra-arterial delivery of VCR may be dependent on total dose and schedule of administration. Other than development of duodenal ulcers in two patients, Lise et al. reported very little toxicity in 14 patients with primary or metastatic carcinoma following hepatic intra-arterial chemotherapy which included VCR [7]. In the trial conducted by Lise et al. patients were given 0.25 mg VCR by bolus injection into a hepatic arterial catheter on four occasions at 2- to 4-day intervals. In the current trial, however, 0.4 mg daily for 5 days by continuous infusion has been poorly tolerated and other dose schedules should be employed if hepatic intra-arterial VCR is to be further investigated.

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