Chemotherapy for malignancy of the liver by short-term direct infusion of the hepatic artery

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SYSTEMIC chemotherapy with primarily 5-fluorouracil (5Fu) has achieved significant palliation in only about 20 percent of cases of advanced gastrointestinal malignancy.[1, 2] The low percentage of successful results has led to a search for other means of effective therapy. Catheterization of the hepatic artery with direct infusion of 5Fu and other drugs has been utilized for hepatic malignancies. This technic has been used on a long-term program by means of a permanently indwelling catheter,[3-5] and also for short-term courses of therapy.[6-8] Beneficial results of chemotherapy by infusion of the hepatic artery have been reported by Sullivan and associates,[3, 4] by Nora, Kukral, and Preston,[7] by Ariel and Pack,[8] by Brennan and associates,[5] and by Fletcher, Chandler, and Donaldson.[9]

Because of the favorable reports, in August 1964 we began a study of the chemotherapy of hepatic malignancy by direct arterial infusion of 5Fu on a short-term basis. This is a report of the first 16 patients treated by this method.

PROCEDURE

All patients with primary or metastatic malignant neoplasms confined to the liver were considered to be eligible for the study. Histologic verification of the hepatic malignancy was obtained in all cases. This was done by means of laparotomy in 10 patients, and by percutaneous liver biopsy in six patients. No patient had evidence of spread of the malignant lesion beyond the liver at the time the treatment was instituted. All patients had undergone previous operation for the primary malignant lesion.

The series comprised 11 men and 5 women, whose ages ranged from 32 to 73 years at the time of chemotherapy via intrahepatic arterial infusion (*Table 1*). The interval between diagnosis and infusion chemotherapy ranged from just shortly after, to as long as seven years after, the original

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Table 1.—*Clinical data of 16 patients treated with intrahepatic arterial cancer chemotherapy*

Patient no.	Sex	Age at time of diagnosis, years	Date of diagnosis, month, year	Previous X-ray treatment	Previous chemotherapy	Date of chemotherapy, month, year	Agent used*	Duration of intra-arterial treatment, days
1	F	44	9-64	No	No	11-64	5Fu	10
2	M	38	4-63	No	No	3-65	Cyp., Mtx.	8
3	M	58	8-61	No	No	12-65	5Fu	10
4	F	56	2-63	No	No	11-65	5Fu	10
5	M	44	10-62	No	Yes	8-64	5Fu	10
6	F	37	11-64	No	No	11-64	5Fu	10
7	M	66	11-64	No	No	1-65	5Fu	10
8	F	50	2-59	No	No	6-65	5Fu	10
9	M	45	12-65	No	No	12-65	5Fu	10
10	M	71	?-63	No	No	12-65	5Fu, Cyp., Mtx.	7
11	M	25	?-57	No	No	12-64	5Fu	9
12	M	39	3-63	No	No	12-64	5Fu	10
13	M	50	3-65	No	No	3-65	5Fu	10
14	M	47	4-65	No	No	4-65	5Fu	11
15	F	67	?-60	No	No	11-65	5Fu	10
16	M	47	5-64	Yes	No	11-64	5Fu	10

* 5Fu = 5-fluorouracil; Cyp. = cyclophosphamide; Mtx. = Methotrexate.

diagnosis. The most common primary lesion was carcinoma of the colon (seven patients, *Table 2*).

Clinically, all patients had lost weight, had jaundice, abdominal pain, or hepatomegaly at the time of their selection for study. Nine patients had lost more than 10 pounds, and 11 patients had persistent upper abdominal pain. All patients except one had hepatomegaly; four were jaundiced; and none had demonstrable ascites, lymphadenopathy, or evidence suggestive of distant metastases. The most consistent pretreatment laboratory test suggesting hepatic malignancy was the serum alkaline phosphatase value, which was abnormal in all but one patient (*Table 2*). Hepatic scintiscan, performed on 12 of the patients, was abnormal in each, and was compatible with hepatic neoplasm (*Fig. 1*). Other laboratory studies were not consistently helpful. Roentgenography did not demonstrate evidence of spread beyond the liver. Only one patient had received previous systemic chemotherapy, and none had received prior infusion therapy. One patient had received roentgentherapy several months before being included in our study. The progress of each patient was consistently followed.

Table 2.—*Clinical and laboratory data of 16 patients before intrahepatic arterial cancer chemotherapy*

Patient no.	Site of primary malignancy	Weight lost	Abdominal pain present	Jaundice present	Serum alkaline phosphatase, units*	Anemia present	Abnormal liver scintigram	Diagnosis by	
								Liver biopsy	Laparotomy
1	Gallbladder	Yes	Yes	No	134	Yes	Yes	—	Yes
2	Stomach	No	No	No	17	No	Yes	—	Yes
3	Colon	No	No	Yes	60	No	Yes	Yes	—
4	Colon	No	Yes	No	Normal	No	Yes	—	Yes
5	Colon	No	Yes	No	28	No	Yes	—	Yes
6	Colon	Yes	Yes	No	98	Yes	†	—	Yes
7	Lung	Yes	Yes	No	29	Yes	Yes	—	Yes
8	Colon	No	Yes	No	36	Yes	Yes	Yes	—
9	Liver	Yes	Yes	No	40	No	†	—	Yes
10	Melanoma	Yes	No	No	20	No	Yes	Yes	—
11	Melanoma	Yes	Yes	Yes	123	No	Yes	Yes	—
12	Colon	No	Yes	No	30	No	Yes	Yes	—
13	Liver	Yes	Yes	No	27	No	Yes	—	Yes
14	Liver	No	No	Yes	62	No	†	—	Yes
15	Colon	Yes	Yes	No	19	No	Yes	Yes	—
16	Pancreas	Yes	No	Yes	100	No	†	—	Yes

* Serum alkaline phosphatase measured in King-Armstrong units.
† Not evaluated.

Hepatic arterial catheterization was performed in the hospital. Open arteriotomy was performed and a single-end-hole radiopaque polyethylene Ödman-Ledin catheter with a molded tip was introduced into the left brachial artery. Under fluoroscopic control, the catheter was advanced into the abdominal aorta and manipulated into the celiac axis. To determine the arteriolar anatomy of the liver, 10 ml of contrast medium (sodium diatrizoate) was injected into the celiac artery. (According to Stulberg and Bierman[10] in approximately one quarter of the persons studied by hepatic arteriography a portion of the hepatic blood is supplied by arteries other than the hepatic artery, usually the aorta and superior mesenteric artery. These considerations make a preinfusion arteriogram of the liver necessary.) When the predominant blood supply of the liver originated from the celiac artery, the catheter was further manipulated and advanced into the hepatic artery, and, when possible, to a position just beyond the origin of the gastroduodenal artery (*Fig. 2*). A loose ligature was placed about the left brachial artery at the site of entrance of the catheter, and the skin was sutured.

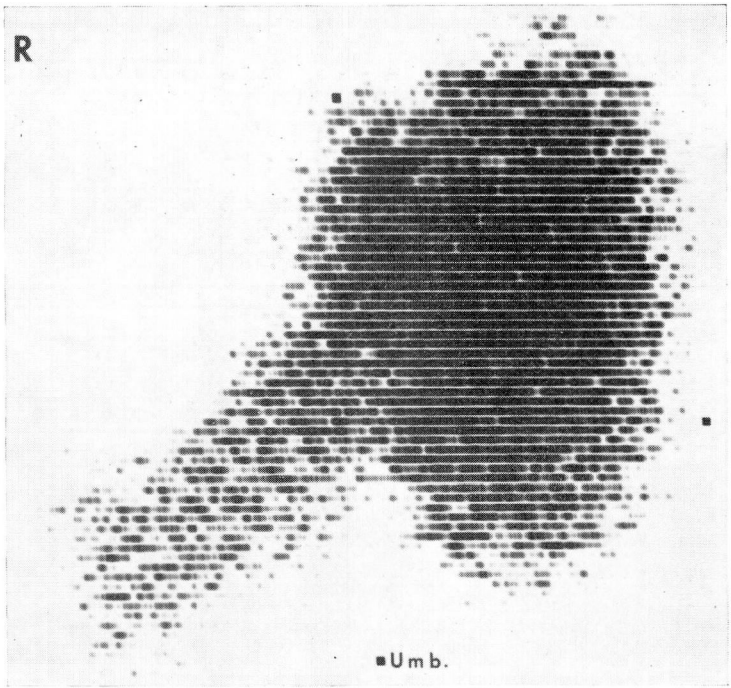

Fig. 1. Hepatic scintigram showing diffuse neoplastic involvement.

Because it was believed that the catheter should not remain in the patient for longer than 10 days, this time was arbitrarily chosen for the period of treatment. The cancer chemotherapeutic agent used for 14 patients was 5Fu in a dosage of 15 mg per kilogram of body weight daily, given as a slow drip over a 12-hour period, using a Fenwall pressure-infusion apparatus. The other two patients (one with malignant melanoma and one with leiomyosarcoma of the stomach) received a combination of 4-amino-n_{10} methyl pteroylglutamic acid,* 5 mg daily, and cyclophosphamide, 1.5 mg per kilogram of body weight administered by the same technic for seven and eight days, respectively. In general, all the patients tolerated infusion therapy satisfactorily, and nausea and vomiting were infrequent side effects. Systemic toxicity was minimal; there were no deaths during the period of infusion therapy or in the immediately posttherapy period. Each patient was discharged from the hospital after completion of the course of infusion therapy. Those who showed no evidence of progressive disease after six weeks were advised to continue long-term maintenance intravenous 5Fu therapy.

* *Methotrexate, Lederle Laboratories.*

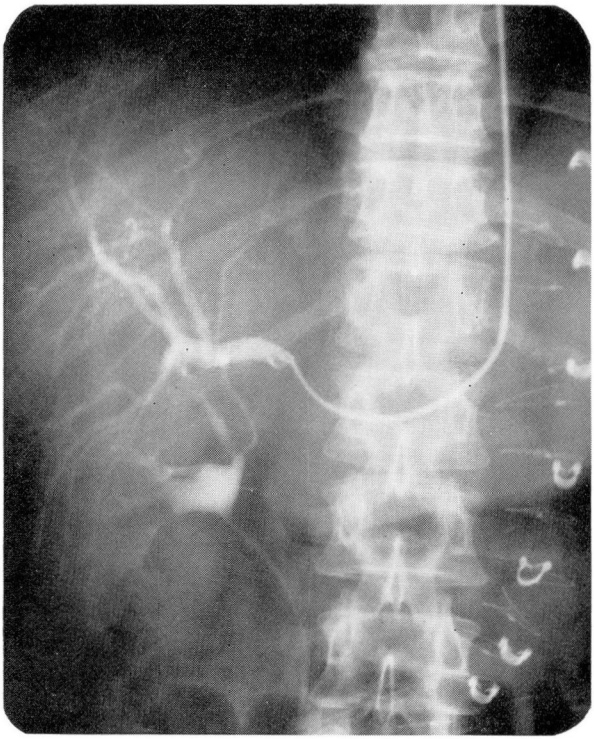

Fig. 2. Angiogram demonstrating ideal position of catheter in the hepatic artery before infusion of cancer chemotherapeutic agent.

RESULTS

An adequate trial period was considered to be approximately six weeks after completion of intraarterial chemotherapy. The criteria for response are those generally accepted in regard to treatment of solid tumors. A *complete remission* is the attainment of a state of no apparent disease; *a moderate remission* is a 50 percent decrease in the size of the liver, and significant improvement of results of liver function studies to normal or nearly normal values; *no remission* means there has been no change in the state of the disease during the trial period; *failure* means that the disease progressed during the trial period.

Pertinent factors in judging effects of therapy included size of the liver, scintigraphic pattern, liver function studies including determinations of serum glutamic oxaloacetic transaminase (SGOT), serum alkaline phosphatase, serum bilirubin, and sulfobromophthalein retention values. Subjective response was measured by improvement in performance status.

Information in regard to response by all patients is available from the

period of institution of therapy to the present time or to death. No patient had a complete or partial, objective remission during the six-week period after therapy. Eight patients each had a subjective response, with relief of pain and improvement in performance status. The range of follow-up periods is from 2 to 14 months; the mean follow-up period for all patients is 6.5 months. Eight (of the 16) patients survived longer than six months after therapy. None had a significant decrease in size of the liver, although five had transient improvement in liver function tests. Only one of the six patients of whom numerous hepatic scintigrams were made showed a decrease in the size of the hepatic lesions during the course of treatment, and this was only temporary. In regard to the other five patients with numerous scintigrams, ranging from 2 to 14 months after initial examinations, there was no scintigraphic evidence of regression of the disease.

COMMENT

The results of therapy in this study are discouraging, and indicate that short-term intrahepatic arterial infusion chemotherapy for hepatic malignancy has not been beneficial. A subjective response was achieved in 8 of the 16 patients, who survived longer than six months. However, these eight patients all received subsequent maintenance chemotherapy and it is not possible to state whether infusion therapy was primarily responsible for prolongation of life. There were no significant complications associated with the therapy and there were no deaths immediately after infusion therapy attributable to the drug. Objective clinical evaluation during the follow-up period did not demonstrate improvement judged on the basis of the criteria mentioned. For this reason, it is our opinion at this time that short-term intrahepatic arterial cancer chemotherapy offers no more than does conventional intravenous chemotherapy. It is believed that chemotherapy by direct infusion of the hepatic artery for malignancy confined to the liver is feasible, but that the results of such therapy on a short-term basis are largely unsatisfactory at the present time.

SUMMARY

Sixteen patients with malignant neoplasm, either primary or metastatic, confined to the liver, were treated by means of hepatic arterial infusion of cancer chemotherapeutic agents. No patient achieved a true objective remission from the disease, but eight survived longer than six months after chemotherapy and achieved a subjective clinical improvement. It is concluded that, whereas the technic of administering intrahepatic artery chemotherapy on a short-term basis is satisfactory, the results are not.

ACKNOWLEDGMENT

The authors herewith thank their colleague, James S. Hewlett, M.D., Department of Hematology and Medical Oncology, for his advice and suggestions in the preparation of this paper.

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