ABSTRACT

We have evaluated the degree to which hepatic arterial infusion of Adriamycin produces higher hepatic and lower systemic drug concentrations than are achieved with corresponding peripheral venous infusion. Hepatic arterial catheters were placed in seven patients with primary or metastatic liver cancer. Temporary hepatic venous catheter placement allowed direct sampling of drug levels in the hepatic venous effluent. Adriamycin and metabolites were measured by a highly sensitive, unambiguous, high-performance liquid chromatographic system with sensitivity in the 2- to 10-pmol/sample range.

Hepatic extraction of Adriamycin was demonstrated with an extraction ratio (hepatic arterial level minus hepatic venous level/hepatic arterial level) of 0.45 to 0.50, depending upon the dosage of Adriamycin chosen. The systemic Adriamycin levels during hepatic arterial infusion were 25% lower than the corresponding systemic levels with peripheral venous infusion. Hepatic venous anthracycline levels, which are one measure of intrahepatic drug concentration in the hepatic and tumor capillary bed, were consistently higher when drug was given by the hepatic arterial route. Plasma levels of Adriamycin correlated well with the subsequent development of myelosuppression.

Four of five patients with breast adenocarcinoma metastatic to the liver demonstrated significant tumor regression lasting 1 to 7 months. A clinical complete response was seen in one patient, and three demonstrated partial responses. One of two patients with primary adenocarcinoma of the bile duct achieved a partial response lasting 1 month.

These results support hepatic arterial infusion as a means to improve the therapeutic index of Adriamycin and provide a sound pharmacological justification for its use in the treatment of cancer of the liver. This therapeutic modality may best be suited for the treatment of those metastatic tumors of the liver which are known to respond to Adriamycin administered systemically.

INTRODUCTION

Hepatic involvement by metastatic cancer can be the major cause of morbidity and mortality in patients with disseminated cancer (16). This is most often seen in the natural history of breast, colon, and gastric cancer and primary adenocarcinoma of the bile duct (8). Conventional treatment with systemic chemotherapy has been generally ineffective in the treatment of metastatic liver involvement. Modalities attempting to increase the therapeutic effectiveness of antineoplastic agents have included the use of regional arterial administration of chemotherapeutic agents targeted directly to the organ containing metastatic disease (5, 9, 12, 17, 21). Conceptually, the delivery of chemotherapy would have the pharmacological advantage of achieving higher drug concentration delivered to the tumor than would be possible with conventional peripheral i.v. administration. If the particular chemotherapeutic agent chosen underwent hepatic extraction and hepatobiliary metabolism, systemic regional arterial administration might be accompanied by lower systemic drug exposure to target organ areas such as the bone marrow, mucous membranes, and thus minimize toxicity. A recent pharmacokinetic analysis has demonstrated that these objectives can be achieved and that higher hepatic and lower systemic drug concentrations pertain with hepatic arterial administration of 5-fluoro-2'-deoxyuridine and 5-fluorouracil (10).

Based upon these considerations, a pharmacological study using intrahepatic arterial administration of ADR3 was performed in patients with predominant hepatic metastases. ADR was selected for several reasons: (a) the drug exhibits a broad antineoplastic spectrum of activity, especially in tumor types which may demonstrate metastatic hepatic involvement; (b) it is metabolized principally by the hepatobiliary route (3, 4, 20); and (c) recent analytical methodology using HPLC permits unambiguous measurement and identification of the parent molecule and specific metabolites in the 2- to 10-pmol/ml range (14, 15).

MATERIALS AND METHODS

Five patients with histologically proven breast cancer with predominant hepatic metastases and 2 patients with primary adenocarcinoma of the bile duct were entered into the study. The liver was the predominant site of disease involvement in all patients. The patients with breast cancer had demonstrated progressive hepatic disease while receiving conventional chemotherapy. Of the 5 patients, 2 had received prior ADR therapy, either as a single agent or as part of combination chemotherapy. The 2 patients with primary adenocarcinoma of the bile duct were treated initially with hepatic arterial ADR. All patients satisfied the following criteria: (a) recovery from prior surgery or chemotherapy; (b) progressive hepatic disease demonstrated by at least 2 of the following: physical examination, rising carcinoembryonic antigen titer, progressive abnormalities in serum liver function tests, liver nuclide scans, and/or hepatic ultrasound; (c) anticipated sur-

1 This paper was presented in part at the 14th Annual Meeting of the American Society of Clinical Oncology, Inc., in Washington, D. C., April 3 and 4, 1978 (11). These investigations were supported in part by NIH Grants CA-17979, N01-CM-87037, and CA-19118.

2 To whom requests for reprints should be addressed, at Sidney Farber Cancer Institute, 44 Binney St., Boston, Mass. 02115.

Received April 5, 1979; accepted July 18, 1979.

The abbreviations used are: ADR, Adriamycin; HPLC, high-performance liquid chromatography; AMNOL, adriamycinol.
vival of at least 2 months; (d) performance status allowing
ambulation at least 50% of the time; (e) absence of significant
cardiovascular disease; (f) normal hematological and renal
function. Written informed consent was obtained from all pa
tients.

Catheter Placement

All patients were hospitalized in the Dana Cancer Center of
the Sidney Farber Cancer Institute. Hepatic arterial catheters
were placed either percutaneously, through the left axillary
artery, or surgically, through the gastroduodenal or gastroepi-
ploic arteries. Hepatic venous catheters were placed angi-
ographically through the femoral vein and were removed within
32 hr after initial placement. Hepatic arterial and hepatic ve-
nous catheters were maintained with 5% dextrose in water
solutions containing 1000 units of heparin per liter of solution.
Constant infusion pumps (IMED Corp., San Diego, Calif.) were
used on all lines. Three-way stopcocks were attached to cath-
eters for blood sampling. The unattended lines were protected
with one-way valves to prevent back-flow bleeding from inad-
vertent disconnection or failure of the pumping system.

All lines and solutions were shielded from light during the
period of administration.

Protocol for ADR Infusion

Several schedules of ADR infusion were used for the pur-
poses of this investigation. A total of 15 pharmacological studies
were performed.

Schedule 1. Five patients and 7 pharmacological studies. A
4-hr hepatic arterial infusion began on Day 1. Anthracycline
levels were monitored from the hepatic vein and peripheral vein
during the infusion procedure. Following the 4-hr administra-
tion, anthracycline values were monitored in the hepatic artery,
hepatic vein, and peripheral vein. On Day 2 (24 hr after initiation
of hepatic arterial infusion on Day 1), ADR was administered
via a peripheral vein for a 4-hr infusion. Anthracycline levels
were monitored at the same time points in the hepatic artery,
hepatic vein, and peripheral vein for the next 24 to 36 hr.
However, the hepatic venous catheter was usually removed 1
to 2 hr following completion of the peripheral venous infusion
on Day 2 (i.e., 30 to 32 hr following initial placement).

Schedule 2. Two patients and 7 pharmacological studies. A
72-hr continuous infusion of ADR via the hepatic artery was
administered. Anthracycline levels were monitored from pe-
ripheral venous samples. During this 3-day infusion, hepatic
venous effluents were not monitored.

Schedule 3. One patient and one pharmacological study. In
one patient, an 8-hr continuous hepatic arterial infusion of ADR
(80 mg/sq m) was administered, accompanied with anthracy-
cline level measurement during the same times as in Schedule
1 in the hepatic vein and peripheral vein. Following drug
infusion, hepatic arterial levels were determined for the next
48 hr.

Anthracycline measurements in timed urine collections
were performed during all 3 schedules.

Anthracycline Analyses by HPLC

Heparinized plasma samples were immediately separated,
adjusted to pH 8.5, extracted with chloroform and methanol,
dried under N₂, and analyzed immediately or frozen, protected
from light. Aliquots of extracts were reconstituted in methanol
and monitored according to an analytical scheme previously
published (14, 15).

RESULTS

Pharmacology Studies

Schedule 1: Comparison of Hepatic Venous with Periph-
eral Venous Anthracycline Values during Hepatic Artery In-
fusion. A composite profile of anthracyclines present in the
hepatic vein and peripheral vein, determined simultaneously
during hepatic arterial infusion at a dose of 45 mg of ADR per
sq m given over 4 hr (Day 1 of Schedule 1) is illustrated in
Chart 1. Total anthracycline fluorescence, calculated as the
sum of ADR, AMNOL, and aglycones (expressed as adriamy-
cinone equivalents), reached a plateau level between 1 and 2
hr following the drug infusion, hepatic arterial levels were determined for the next 48 hr.

Anthracycline measurements in timed urine collections
were performed during all 3 schedules.

Anthracycline Analyses by HPLC

Heparinized plasma samples were immediately separated,
adjusted to pH 8.5, extracted with chloroform and methanol,
dried under N₂, and analyzed immediately or frozen, protected
from light. Aliquots of extracts were reconstituted in methanol
and monitored according to an analytical scheme previously
published (14, 15).

RESULTS

Pharmacology Studies

Schedule 1: Comparison of Hepatic Venous with Peripheral Venous Anthracycline Values during Hepatic Artery Infusion. A composite profile of anthracyclines present in the hepatic vein and peripheral vein, determined simultaneously during hepatic arterial infusion at a dose of 45 mg of ADR per sq m given over 4 hr (Day 1 of Schedule 1) is illustrated in Chart 1. Total anthracycline fluorescence, calculated as the sum of ADR, AMNOL, and aglycones (expressed as adriamycinone equivalents), reached a plateau level between 1 and 2 hr following the drug infusion, hepatic arterial levels were determined for the next 48 hr and was maintained for the duration of the infusion. ADR levels paralleled total fluorescence. AMNOL concentration in-

Chart 1. Simultaneous anthracycline levels in the hepatic vein (A) and peripheral vein (B) during a 4-hr hepatic arterial (H.A.)-infusion of ADR (45 mg/sq m over 4 hr). Heparinized plasma samples were immediately separated, adjusted to pH 8.5, extracted with chloroform and methanol, dried under N₂, and analyzed immediately or frozen, protected from light. Aliquots of extracts were reconstituted in methanol and monitored according to an analytical scheme previously published (14, 15).

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increased both during the infusion and shortly thereafter in both the peripheral vein and the hepatic vein. The plateau level of ADR in the peripheral vein was 30% lower (see Table 1) than that measured simultaneously in the hepatic vein.

The anthracycline levels obtained during hepatic arterial infusion in Schedule 1 at 30, 40, and 45 mg/sq m, respectively, over the 4-hr period are presented in Table 1 and represent individual pharmacological studies on 3 different patients. Similar profiles of ADR and anthracyline metabolites in the peripheral vein and hepatic vein were seen during the lower dosage administrations.

One patient received a hepatic arterial dosage of 80 mg/sq m (10 mg/sq m/hr) during an 8-hr continuous infusion to further characterize steady-state parameters (Schedule 3). With ADR administration at 80 mg/sq m over this 8-hr period, the plateau hepatic venous ADR and total fluorescence levels were reached between 2 and 3 hr. The peripheral venous plateau level of ADR was 20% lower than that determined in the hepatic vein.

**Anthracycline Extraction from the Liver.** Evidence for hepatic extraction of ADR and metabolites was sought in vivo. The capacity of the liver to extract ADR and its principal metabolite, AMNOL, was demonstrated by monitoring hepatic arterial and hepatic venous levels during peripheral venous infusion on Day 2 (4-hr continuous infusion via the peripheral vein) of Schedule 1. Simultaneous hepatic arterial and hepatic venous values during peripheral venous administration are seen in Chart 2. Higher hepatic arterial ADR levels were achieved when compared to hepatic venous levels in all dose ranges in addition to the 40 mg/sq m demonstrated in Chart 2. Immediately after the peripheral venous infusion had been discontinued, hepatic venous levels surpassed hepatic arterial levels, indicating potential continued drug release from the hepatic parenchyma. To express this in another fashion, the difference between hepatic arterial and hepatic venous levels for the 30- and 40-mg/sq m dosage, respectively (given during the 4-hr peripheral infusion on Day 2 of Schedule I), is illustrated in Chart 3. During peripheral venous administration, hepatic arterial ADR levels were 1.3 to 2 times greater than those of hepatic venous levels.

The hepatic extraction ratio, defined as the hepatic arterial value minus the hepatic venous value divided by the hepatic arterial concentration (HA – HV/HV), is shown in Table 2. During a 4-hr peripheral venous infusion, the extraction ratios of ADR and total anthracyline ranged between 0.5 and 0.05. The negative extraction ratio for AMNOL probably reflects hepatic metabolism of ADR to this derivative, and its subsequent release into the systemic circulation from the hepatic parenchyma.

**Schedule 2 Studies.** In 2 patients with continuous hepatic arterial infusion of ADR in Schedule 2 (72-hr continuous infusion), there appeared to be a threshold dose rate before plasma levels of either ADR or its metabolites became detectable. At dose levels of 15 and 20 mg/sq m/day for 3 days via continuous infusion, plasma levels were undetectable; ADR was detectable at doses of 25 mg/sq m/day on this schedule.

**Clinical Response and Toxicity**

Five patients with metastatic adenocarcinoma of the breast with predominant hepatic metastases were treated with hepatic arterial infusion of ADR. The clinical characteristics of these patients are seen in Table 2. A complete clinical response (defined as complete disappearance of all signs of hepatic metastases measured by physical examination, radiographic and nuclear examination, and lasting a minimum of 1 month), was seen in one patient (R. P.), which lasted 7 months. At postmortem examination, 2 microscopic foci of carcinoma were noted. Extensive fibrosis and hepatic cell regeneration were noted throughout the remainder of the liver parenchyma. Pathologically, this was consistent with the dead tumor being re-

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**Table 1**

<table>
<thead>
<tr>
<th>Time (hr)</th>
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<td>ADR AMNOL</td>
<td>ADR AMNOL</td>
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<tr>
<td></td>
<td>Agly-cones</td>
<td>Agly-cones</td>
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<tr>
<td>12</td>
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**Peripheral venous anthracycline values during 4-hr hepatic arterial infusion at various dose ranges (x 10^-7 M)**

<table>
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<tr>
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<th>45 mg/sq m</th>
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<td>ADR AMNOL</td>
<td>ADR AMNOL</td>
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<td>Agly-cones</td>
<td>Agly-cones</td>
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<td>Simultaneous hepatic venous anthracycline values (x 10^-7 M)</td>
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<tr>
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<td>0.38</td>
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</table>
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Chart 2. Simultaneous hepatic arterial (A) and hepatic venous (B) anthracycline levels during peripheral venous (P.V.) infusion of ADR (40 mg/sq m over 4 hr). Hepatic arterial levels of ADR were consistently higher than the corresponding hepatic venous levels. Shaded area, duration of ADR infusion.

Chart 3. Differences between hepatic arterial and hepatic venous levels of ADR during peripheral venous (P.V.) infusion at 2 doses. Shaded area, duration of ADR infusion at 2 dose levels.

placed by fibrosis with surrounding regenerating hepatic cells. Three additional patients demonstrated clear-cut partial responses of the liver (defined as greater than 50% reduction in tumor mass, as demonstrated by serial liver-spleen scans, a fall in the carcinoembryonic antigen titer to normal, and diminution in palpable hepatomegaly), which lasted 4, 3, and 1 months, respectively. One patient (W. S.) died within 1 month of initiation of hepatic arterial ADR infusion and showed no demonstrable antitumor effect in this short time. Two of these 5 patients had received ADR treatment via peripheral venous infusion prior to receiving hepatic arterial ADR and had demonstrated progressive hepatic disease. One of the 2 patients with primary adenocarcinoma of the bile duct demonstrated a partial response, lasting 1 month.

The toxicity of hepatic arterial ADR was predictable, usually reversible, and tolerable. All 7 patients demonstrated myelosuppression (a WBC of less than 2000/cu mm) 12 to 14 days following drug administration, with recovery by Day 21. One patient developed irreversible leukopenia and thrombocytopenia, which was accompanied with a sudden deterioration of liver function studies shortly after the infusion had ended. Infectious complications resulted and the patient died of hepatic failure and sepsis.

The relationship between peripheral blood ADR levels and anthracycline toxicity in a patient receiving multiple courses of therapy (on Schedule 2) via the hepatic artery demonstrated no detectable anthracycline levels at a dose of 20 mg/sq m for 3 days. This total dose of 60 mg/sq m during the 3-day period resulted in a WBC nadir of 2800 cells/cu mm. A total of 75-mg/sq m (25 mg/sq m/day for 3 days) infusion which led to a sustained plasma ADR level of $1.4 \times 10^{-7}$ M was twice unassociated with any toxicity. 120 mg/sq m (40 mg/sq m/day for 3 days) resulted in sustained ADR levels of $2.75 \times 10^{-7}$ M and was associated with significant myelosuppression. A subsequent course of 90 mg/sq m total over 3 days (30 mg/sq m/day for 3 days) did not produce myelosuppression. Myelosuppressive courses using Schedule 2 were uniformly associated with plasma ADR levels of greater than $2 \times 10^{-7}$ M.

Although these data are preliminary, there is a suggestion that systemic toxicity (myelosuppression) may be prevented if lower doses and prolonged infusion schedules through the hepatic artery are chosen. However, the number of observations and patients studied are too small to draw conclusions.

Liver function studies improved in those patients demonstrating an antitumor response to ADR. None of the patients entered in this study developed evidence of anthracycline-induced cardiac damage.

DISCUSSION

These studies provide a pharmacological rationale for regional hepatic arterial administration of the anthracycline antibiotic, ADR, and present in detail the pharmacokinetics of ADR and metabolites, as determined by a highly sensitive, unambiguous, HPLC assay. The pharmacology of standard ADR therapy (i.e., bolus peripheral venous infusion every 21 days), which
has been studied by several methods of detection including thin-layer chromatography (3, 4, 20), has provided the rationale for single-dosage, intermittent schedule. Similarly, the results obtained during this pharmacological study, comparing peripheral venous and hepatic venous anthracycline values during hepatic arterial infusion, provide a sound pharmacological justification for hepatic arterial administration of this drug. Over a range of concentrations, peripheral venous levels of ADR were lower than hepatic venous levels during hepatic arterial administration. These higher hepatic venous drug concentrations presumably represent drug effluent from the neoplastic liver and are one measure of drug concentration in the hepatic and tumor capillary bed. The data also indicate that the liver is able to efficiently extract and metabolize ADR over a range of concentrations, and is a predominant site of catabolism and excretion of the potentially active ADR metabolite, AMNOL.

A major goal for hepatic arterial chemotherapy in the palliation of hepatic metastases is to provide high concentrations of antineoplastic agents directly to the tumor, as it derives its blood supply primarily from the hepatic artery (1, 6, 7, 13, 19). From cell culture data, it is known that ADR produces dose-dependent cytotoxicity which is partially cell cycle and phase dependent (18). In some systems, cell kill with increasing ADR concentration does not increase to any great extent above 2 to 5 μg of ADR per ml. However, exponentially growing cells are 100-fold more sensitive than are plateau phase cells to the cytotoxic effects of ADR (2). Hence, in the management of liver disease, one would like to utilize hepatic extraction processes in order to maintain ADR concentrations at the tumor capillary bed at cytotoxic levels, and at noncytotoxic levels in the periphery. Maintenance of this concentration differential in a prolonged infusion would kill tumor cells selectively as they entered exponential growth.

The correlation of plasma levels of ADR with toxicity was a new finding. Continuous 72-hr infusion of low doses via the hepatic artery was unaccompanied by significant myelosuppression and allowed one patient to receive 1150 mg of ADR per sq m via the hepatic artery intermittently for almost 1 year. In this instance, there was no evidence of anthracycline cardiotoxicity. The potential importance of dose rate in determining cardiotoxicity is suggested by a recent study showing markedly decreased cardiotoxicity with weekly, as compared

---

**Table 2**

Clinical characteristics of patients treated with hepatic artery ADR

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Schedule</th>
<th>Dose (mg/sq m)</th>
<th>Response</th>
<th>Duration of response (mos)</th>
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<tbody>
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<td>Breast</td>
<td>1</td>
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*a Schedule 1, 4-hr hepatic artery infusion on Day 1; 4-hr peripheral vein infusion on Day 2; Schedule 2, 72-hr continuous infusion through hepatic artery; Schedule 3, 8-hr continuous infusion through hepatic artery on Day 1.

*b Dose administered per day for 2 days on Schedule 1, 3 days on Schedule 2, and 1 day on Schedule 3.

*c Each value indicates a full course of therapy for that schedule.

*c Measured from initiation of response to progressive disease or death.

*d PR, partial response; CR, complete response; NR, no response. Further definitions given in text.
to triweekly, ADR administration (22). Thus, by extrapolation, it seems probable that hepatic arterial ADR infusions at sufficiently low dose rates may also allow appreciably more ADR to be given over an extended time. Similarly, correlation of peak plasma levels during a 4-hr hepatic arterial infusion with resultant myelosuppression allowed subsequent modification of drug dose with less systemic toxicity. The results complement those of Bern et al. (5), in which marrow and gastrointestinal toxicity during hepatic arterial infusion was noted with drug plasma levels of $1.2 \times 10^{-7} \text{ M}$. Although we did not observe anthracycline toxicity with ADR levels at less than $2 \times 10^{-7} \text{ M}$, these differences may in part be due to methodological variations, since a radioimmunoassay was used in the former study, while we used a HPLC assay.

Complications of catheter insertion did not occur in this study. Although enthusiasm for hepatic arterial infusion therapy has been countered by those who cite the large effort, potential morbidity, and hospitalization requirement, it should be considered as a palliative modality in selected patients. Of 5 patients with breast carcinoma metastatic to the liver, 4 achieved an antitumor response following treatment with hepatic arterial ADR. ADR can be used as an antineoplastic agent for regional arterial hepatic administration, based upon both the pharmacological and the clinical data of this report. Our data, along with previous studies, suggest that ADR at low dose rates by the hepatic arterial route may be effective without significant myelosuppression. Its use might best be restricted to those metastatic tumors which are known to respond to ADR administered systemically. However, it is conceivable that continuous low doses of the drug might prove to be efficacious for other tumor types.

The authors acknowledge Vinod Khelarpal, Dr. William Pegg, and Matt Thompson for skillful technical assistance and Martha J. Sack for manuscript preparation. The assistance of the medical and nursing staff of the Dana Cancer Center is also appreciated. We are thankful to Dr. George P. Canellos and Dr. Emil Frei, Ill, for support in this study.

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A Clinical-Pharmacological Evaluation of Hepatic Arterial Infusion of Adriamycin

Marc B. Garnick, William D. Ensminger and Mervyn Israel


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