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Perspectives and Commentaries

The Rationale for Intra-Arterial Chemotherapy

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(A COMMENT ON: Pannuti F, Camaggi CM, Strocchi E *et al.* Intrahepatic arterial administration of 4'-epidoxorubicin (epirubicin) in advanced cancer patients. A pharmacokinetic study. *Eur J Cancer Clin Oncol* 1986, **22**, 1309–1314.)

THE intra-arterial (i.a.) use of chemotherapeutic agents to treat an organ involved with tumor was initiated by Bierman *et al.* and Klopp *et al.* in 1950 [1]. Subsequently, long-term continuous infusion i.a. chemotherapy was popularized by Sullivan *et al.*, Clarkson *et al.* and Brennan *et al.* in the 1960's. Further studies have shown that delivering chemotherapy drugs directly into the tumor through its arterial supply was more effective than systemic intravenous (i.v.) therapy while others doubted its advantages. The rationale of i.a. chemotherapy can be discussed from three different aspects:

ANATOMICAL AND THEORETICAL REASONS

As the tumors grow, they develop their own arterial blood supply. In both primary and metastatic liver tumors, there are ample anatomic and clinical studies in experimental animals and patients to show that the tumors receive their nutritional and blood supply almost exclusively from the hepatic arterial system, whereas non-malignant live parenchyma has a double supply, the hepatic artery and the portal vein.

Regional and continuous chemotherapy via the arterial to the blood supply of the tumor has the potential advantages of achieving higher local concentration of drug, prolonging the contact of drug with tumor cells, and reducing systemic toxicity. In principle, i.a. chemotherapy can produce a greater biologic effect on the limited anatomical area containing the neoplasm sensitive to a specific drug or combination of drugs (i.e. a regional advantage). For this to take place, one must assume that the chemotherapeutic agent is largely extracted on initial contact, that is, a 'first pass' effect. Fluorouracil (5-FU) and floxuridine (FUDR) are particularly attractive from this standpoint with hepatic extractions of about 80 and 95%, respectively. Mitomycin (MMC) has a lower hepatic extraction, ranging from 4 to 18% [3]. Furthermore, since most cytotoxic drugs exhibit a steep dose–response curve (that is, the higher the concentration, the greater the antitumor effects and side-effects) [4], this differential would be operative during the infusion until the tumor's 'drug receptor sites' are saturated.

Cancer cells are most vulnerable to an antimetabolite during deoxyribonucleic acid (DNA) synthesis (G_2), and prolonged exposure of the tumor to such drugs would affect most of the susceptible cells of the tumor population as they enter this synthetic phase. The exposure should exceed the doubling time of the tumor [2]. Thus long-term infusion chemotherapy has the theoretical advantage of sequential destruction of tumor cells as they randomly enter their vulnerable metabolic phase.

PHARMACOKINETIC STUDIES OF i.a. VS. i.v. ADMINISTRATION

Many pharmacokinetic studies have shown that there is increased drug delivery via arterial route

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compared to i.v. route. With a 1 hr infusion of cisplatin, hepatic arterial administration produced a 4-fold to 7-fold higher hepatic level of free drug [5]. However, no difference between hepatic arterial and i.v. administration was noted with bolus injections.

Considerations based on direct blood level determinations and area under-the-curve calculations indicated at least an 8-fold to 10-fold advantage for 5-FU and a 400-fold advantage for FUDR for hepatic i.a. over system i.v. infusion [6]. Athough the data are limited, increased exposure with hepatic arterial infusion is also seen for a number of other agents, including *bis*-chlorethylnitrosourea, dichloromethotrexate, MMC (all 6–8 fold), and cisplatin (4–7-fold).

Doxorubicin (adriamycin) is also of interest for i.a. infusion since it is metabolized by the liver. It has been widely used in patients with hepatoma, hoping for a greater therapeutic effect without a concomitant increase in systemic toxicity [7, 8]. No randomized studies of i.a. vs. i.v. adriamycin have been performed, but the response rate and toxicity of hepatic i.a. infusion appears to be similar to that of i.v. therapy. Pharmacologic studies suggest some differences for i.a. administration of adriamycin. Following an i.v. bolus dose, adriamycin disposition in man is triphasic with mean half-lives for the 3 phases of 9.2, 91, and 1556 min [9]. In patients who underwent ligation of their hepatic arteries and catheters placed distally, the plasma disappearance curves of adriamycin were similar whether the drug was administered by bolus directly into the hepatic artery or peripheral vein. However, the concentration of metabolites after hepatic i.a. route was definitely higher than that after i.v. administration [10].

In patients with progressively growing neoplasms in their livers, Garnick *et al.* [11] demonstrated that hepatic extraction of adriamycin was about 45–50% when 30–45 mg/m^2 of the drug was infused into the hepatic artery. Among patients with hepatoma associated with cirrhosis or chronic hepatitis, the extraction ration is less than 10% [12]. The systemic adriamycin level during hepatic i.a. infusion was 25% lower than the corresponding levels with peripheral i.v. infusion, while hepatic venous adriamycin levels, which reflect the drug concentration in the hepatic and tumor capillary beds, were consistently higher with i.a. administration [11].

Animal experiments also suggest a local advantage for hepatic i.a. administration. In rats, at 24 hr after bolus administration, the concentration of doxorubicin in the liver was much higher in those that received the drug injected directly into the hepatic artery than in those that had the drug via peripheral vein [13].

The toxicity of adriamycin when given by infusion is also changed. In patients receiving adriamycin as a 3-day i.a. or i.v. infusion every 21 days (20–30 mg/m^2/day), increased myelosuppression and severe stomatitis developed at 1.2×10^{-7} M adriamycin serum level, though not present when given by flow i.v. infusion. Another study observed leukopenia and stomatitis in 50% of the courses when the drug was given at 4 mg/m^2/day for a mean of 28 days [14].

Epidoxorubicin, a new anthracycline derivative, seems to have the same pharmacokinetic characteristics as doxorubicin [15]. After i.v. or hepatic i.a. bolus administration, it has a triexponential decrease in the plasma levels in normal as well as in patients with impaired renal functions. Blood levels are consistently higher than plasma levels. Furthermore, in patients with advanced liver metastases or hepatopulmonary shunt, the hepatic first-pass effect is decreased yielding higher than normal plasma drug levels as shown in the paper by Pannuti *et al.* [21].

CLINICAL STUDIES OF i.a. VS. i.v. DRUG ADMINISTRATION

Although some workers, especially those using short-term i.a. infusion therapy, reported nearly equivalent responses of hepatic metastases with hepatic i.a. infusion and systemic i.v. chemotherapy, others indicated at least a 2-to-1 superiority for hepatic i.a. infusion [1]. For advanced gastrointestinal cancers, the objective response rate with 5-FU by systemic administration varies from 13% without prior loading to 33% with an initial loading course, whereas it was 36–71% when the drug was given directly into the hepatic artery. Among patients who had progression of liver metastases after systemic i.v. 5-FU therapy, subsequent hepatic i.a. infusion of 5-FU produced response rates of 46–68%. The median survival of responders is generally at least twice as long as that of non-responders.

Despite higher response rates for i.a. therapy, the overall mean or median survivals of the i.a. group has not been improved, particularly for patients with colorectal metastases [16]. In patients with head and neck cancers, the overall response rates are also not substantially different between the i.v. and the i.a. groups [17]. Lokich [18] noted that patients who responded to i.a. chemotherapy were the ones who responded to systemic i.v. 5-FU before. Thus he postulated that higher response rate to i.a. therapy over systemic i.v. bolus therapy was related to the constant infusion schedule.

Despite more than 2 decades of clinical research, it remains difficult to assess the merits of hepatic i.a. chemotherapy due to the inadequate design of

past trials. Grage *et al.* [19] carried out the first prospective randomized clinical trial of hepatic arterial infusion vs. systemic i.v. treatment for colorectal cancer metastatic to the liver. Their result failed to demonstrate any improved survival for the regional infusion, but the experimental design was not optimal and there were many technical problems [1].

In the last 5 years the treatment of hepatic metastases by regional infusion chemotherapy has enjoyed increasing popularity because the availability of the totally implantable pump. Kemeny *et al.* [20] attempted to randomize patients with multiple unresectable liver metastases into systemic i.v. 5-FU vs. continuous hepatic artery FUDR infusion before laparotomy. Among 31 such patients, only 7 were randomized into the i.v. therapy arm; many patients were excluded because they had positive portal lymph nodes or extrahepatic disease. Progressive disease developed in all patients who were started on i.v. therapy. Six of the 7 patients who failed i.v. 5-FU were switched over to i.a. FUDR and 2 had partial responses. That study is still ongoing, and the preliminary results suggest that i.a. hepatic infusion therapy in patients with unresectable disease have increased survival over historical controls. However, many new and serious complications also appeared with long-term infusion chemotherapy using the implantable pump, including chemical hepatitis, sclerosing cholangitis, gastritis, peptic ulcers, diarrhea, and pump pocket problems.

In summary, theoretical reasons, pharmacological and retrospective non-randomized studies suggest that i.a. use of chemotherapeutic agents might be more effective than i.v. treatment. However, to date, no definitive advantage has been reported with i.a. chemotherapy over systemic therapy in prospective randomized studies.

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