Hepatic chemoembolization : clinical and experimental correlation

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Abstract

Chemoembolization has become the preferred treatment for patients with inoperable, hypervascular hepatic malignancies in the Far East, but controversial elsewhere. In vivo microscopy in addition to other experimental procedures are used in this presentation to better understand the mechanisms involved in chemoembolization. In chemoembolization Lipiodol acts as a contrast material, a vehicle for chemotherapy and an embolic agent. Although not optimal, Lipiodol injected into the hepatic artery, traverses the peribiliary plexus to the portal veins resulting in a dual embolization. Chemoembolization creates ischemia, slows arterial flow and increases the contact time between the infusate and the neoplasms, increasing the tumor cell kill. However, the vascular occlusion also produces infarction and fibrosis compounding the already existing cirrhosis frequently associated with hepatocellular carcinoma.

Lipiodol/ethanol (3:1) injected into the segmental or lobar hepatic artery supplying the neoplasm also gains access to the associated portal venous branches causing focal ablation. This preoperative approach is easier to perform than direct portal vein occlusion, with less parenchymal damage and comparable hypertrophy of the remnant liver frequently necessary for adequate hepatic function following resection.

Polymer-drug conjugates, e.g. PG-TXL, have considerable potential for intra-arterial delivery especially with the dramatic increase in concentration of the drug in the tumor and its efficacy. Using in vivo microscopy especially with green fluorescent protein (GFP) gene as an efficient and non-toxic tumor cell marker, the events leading to hepatic metastases can be documented which will serve to better evaluate these varied techniques of chemoembolization. (Acta gastroenterol. belg., **2000**, 63, **169-173**).

Introduction

Hepatic blood supply originates from the portal vein (70-80%) and the hepatic artery (20-30%). Hepatic tumors are primarily nourished by arterial blood flow, with varying supply from the portal vein. This allows more specific treatment via the hepatic artery while preserving adequate liver function. Collateral pathways contribute especially in the event of hepatic artery occlusion. Chemoembolization creates ischemia, slows arterial flow and increases contact time between the infusate and the tumor cells which increases tumor cell kill and accelerates programmed cell death (apoptosis) or tumor necrosis (1). Several techniques have been considered to be chemoembolization including : (1) balloon occlusion during intra-arterial infusion ; (2) the injection of cytotoxic agents with or without iodized oil and with embolic particles ; (3) the intravascular or direct parenchymal injection of (a) sclerosing solutions ± iodized oil ; (b) genes ; (c) growth factors ; (d) microcapsules, microspheres or liposomes ; (c) polymer-drug conjugates ; and (4) chemoembolization combined with focal ablation. Tumor "new" vessels (angiogenesis) seen in most neoplasms exhibit *enhanced permeability* of macromolecules (MW > 30,000) compared to normal vessels coupled with a lack of lymphatics results in *retention* (EPR) (2). This may explain in part the accumulation of iodized oil and the increased concentration of polymer-drug conjugates in the neoplasms, e.g. SMANCS (styrene maleic acid- neocarcinostatin) and PG-TXL (poly-l-glutamic acid paclitaxel).

The purpose of this presentation is to correlate clinical experience with experimental data to better understand the mechanisms of action of chemoembolization, its complications and side effects. *IN VIVO MICROSCOPY* of small animals and the green fluorescent protein (GFP) gene allows direct visualization of these events in an attempt to improve diagnostic accuracy and therapeutic efficacy.

Materials and methods

Tumor cell marker : Green fluorescent protein (GFP) gene, cloned from the genome of the jellyfish *Aequorea victoria*, within an expression vector (Clontech Laboratories, Palo Alto, CA) is transfected in tumor cells as a tumor cell marker and passed to subsequent generations through cell division. This In Vivo marker does not require cofactors, substrate, or additional gene products (3).

IN Vivo Microscopy : A modified standard compound binocular microscope (Zeiss Axioplan, Carl Zeiss Inc., Germany) is equipped with trans- and epi-illumination with magnification up to X1500 (4). The images are recorded on a Sony U-Matic videotape recorder (Sony Electronics, Inc. Medical System Division ; Montvale, NJ).

For studies of the hepatic microcirculation, animals are anesthetized ; a midline incision is made and a liver lobe is gently exteriorized and positioned on the tray in

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Presented at the Société Royal Belge de Gastro-entérologie, May 29, 1999, Brussels, Belgium

This work is supported in part by the John S. Dunn Research Foundation Fund (SW, ZK, CL), Cesare Gianturco Fund (SW), M. D. Anderson Cancer Center PRS Grant (ZK), National Institutes of Health (NIH) FIRST Award (CL), Small Business Technology Transfer (STTR) (CL, SW), and Sponsored Research from Cell Therapeutics, Inc., Seattle, Washington, which has licensed PG-TXL.

the window of the microscopic stage. The liver lobe is covered with a plastic wrap (Saran Wrap, Dow Chemical Co., Midland, MI) and irrigated with Ringer's solution (Baxter, Travenol, Morton Grove, IL) at body temperature.

The gastroduodenal artery (GDA) and/or vein (GDV) are catheterized after a midline laparotomy and dissection. Silastic tubing (ID/OD 0.15/0.30mm for mouse GDV, 0.30/0.60 mm for rat GDA ; 0.60/0.90 mm for rat GDV and rabbit GDA ; and 0.90/1.20 mm for rabbit GDV) is inserted into the lumen through a small cut proximal to the ligature ; care is taken not to advance the tip of the tubing beyond the lumen of the proper hepatic artery or the portal vein. Because the GDA of mice is too small, a plastic catheter (0.15/0.30 mm) is inserted into the aorta via the mesenteric or femoral artery and advanced so that the tip is above the celiac artery.

As Kupffer cell markers, *fluorescent latex particles* (50 nm–1 μm) (Fluoresbrite noncarboxylate, Polysciences Inc., Warrington, PA) are injected into the femoral vein using a 30 g needle 20 min. before in vivo microscopic examination. Stainless steel coils (Cook Inc., Bloomington, IN) and Gelfoam (surgical gelatin) (Pharmacia & Upjohn, Kalamazoo, MI) powder and segments are utilized for embolization. Poly-dl-lactic microcapsules (100 um diam.) are formulated by solvent evaporation of the polymer and cisplatin (40-42%) and used for a Phase I/II clinical trial in 20 patients with neuroendocrine hepatic metastases to be treated by chemoembolization. If additional embolization is necessary, microcapsules without cisplatin are injected with water-based radiographic contrast material (1:1) to complete the obstruction.

Lipiodol/Ethanol embolization : Five groups of rats (n = 6) were treated with a mixture of iodized oil/ethanol in ratios of 5:1, 4:1, 3:1, 1:1, and 1.0 which was injected during surgery into the right hepatic artery until saturation. Another group (n = 6) was studied using in vivo microscopy to observe the distribution of the mixture in the liver and changes in the hepatic microcirculation. Similar studies were performed in pigs (5).

Polymer-drug conjugate : Poly (L-glutamic acid) paclitaxel (PG-TXL) is water soluble compared to paclitaxel (TXL) which contained 6 mg/ml of Cremophor EL (polyoxylated castor oil and ethanol 50% V/V). Several toxic effects have been attributed to the cremophor including "hypersensitivity" reactions treated with corticosteroids and antihistamines. The present clinical protocols call for an infusion (IV) over 3-24h. PG-TXL is delivered as a bolus over 10 min. with less toxicity.

PG-TXL is administered as a single intravenous dose in C3Hf/Kam with an ovarian (OCA-1) cancer at 160 mg eq./kg while paclitaxel is given at 80 mg (MTD) ; for rat breast carcinoma, 13762F, 40 mg eq/kg PG-TXL and 20 mg/kg TXL are delivered intravenously (6). Other murine tumors HCa (hepatocellular carcinoma), MCa4 and MCa35 (breast cancer), SKOV3 ip (ovarian) in nude mice and MDA-MB435 Lung2 (breast cancer) were also tested for response to PG-TXL and TXL.

Other Tumor models : Hepatic metastases of Friend erythroleukemia cells (FTC) are studied in DBA/2 mice ; hepatic metastases of CT-26 colon adenocarcinoma in BALB/C mice ; and breast cancer metastases to the liver in female Fischer 344 rats. Swine and rabbits are also examined for the effects of embolization of the liver by a variety of particulate materials.

Results

GFP : GFP allows real time observations of tumor growth and spontaneous metastases. In vivo microscopy combined with GFP demonstrates the distribution, adherence, extravasation, and migration of cancer cells in the microvasculature (3).

Lipiodol injection : In vivo microscopy reveals the Lipiodol (iodized oil), injected into the portal vein, instantly filled the terminal portal venules in the form of an oil column. When Lipiodol is injected into the hepatic artery, a series of droplets appeared within two minutes in the terminal portal venules in all rats, mice, rabbits and swine (Fig. 1). The amount of oil in the portal vein is dose dependent. Lipiodol entered the initial portal venules and slowly traverses the sinusoids into the hepatic veins. Although the Lipiodol causes temporary obstruction, the oil is cleared by the re-established arterial circulation and Kupffer cell phagocytosis.

In vivo microscopy demonstrates that Lipiodol flowed through the peribiliary plexus into the portal vein.

Lipiodol, Microfil, other plant oils and CO_2 enter the portal vein in large quantities following hepatic arterial administration. Solid particulate materials including microspheres (25-200 μm), Gelfoam powder (75-200 μm) ; and starch microspheres (40 μm) injected into the hepatic artery never appear in the portal vein. The

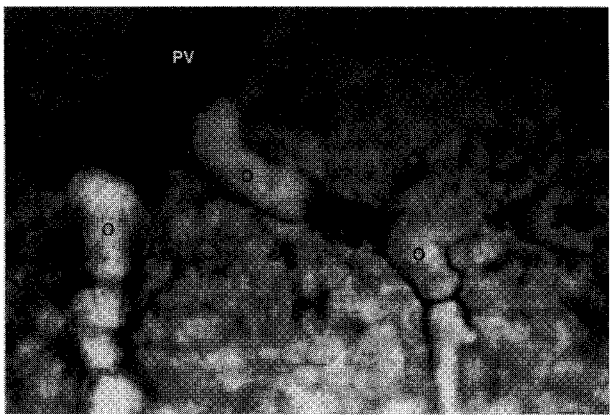

Fig. 1. — In vivo micrograph (500 ×) of a rat 4 minutes after injection of 0.2 ml/kg of iodized oil into the hepatic artery. The oil droplets (O) reached and accumulated in a terminal portal venule (PV).

blood flow in the portal system and the sinusoid was not significantly affected. Smaller particles (50-100 nm) traverse the hepatic artery, portal venules, sinusoids and hepatic veins only to be phagocytosed within 20 min. by the Kupffer cells narrowing the sinusoids and disturbing flow. A phenylalanine coat on the 50-100 nm particles allowed recirculation for 4h before phagocytosis. Particulate materials, latex particles, poly-dl-lactic acid microcapsules, Gelfoam powder and segments, polyvinyl alcohol foam granules even in sizes as small as 1 μm cause proximal hepatic artery occlusion, fibrosis and necrosis. The necrotic and fibrotic areas are bypassed by collateral sinusoids and vessels similar to "capillarized" sinusoids observed in cirrhotic liver of humans. These vessels act as sinusoidal shunts around embolized areas (7).

Lipiodol/ethanol embolization : In both rats and pigs segmental atrophy and diffuse hypertrophy of the residual liver is accomplished by chemoembolization of a lobar or segmental branch of the hepatic artery ; a 3:1 and 4:1 ratios of Lipiodol to absolute ethanol mixture are optimal in pigs and rats respectively (Fig. 2). Hepatic artery injection of Lipiodol/ethanol gains rapid access to the portal vein primarily through the peribiliary plexus, i.e. the dual embolization of the hepatic artery and portal vein (5).

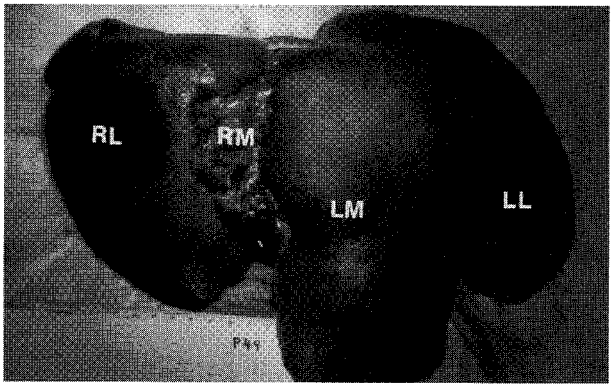

Fig. 2. — Photograph of a pig liver showing ablative result of the right segment of middle lobe (RM) by selective infusion of 13.5 ml of a mixture of iodized oil and absolute ethanol (3:1) into the RM artery. The residual liver, especially the left segment of middle lobe (LM), became markedly hypertrophied. LL = left lobe ; RL = right lobe.

Poly-dl-lactic acid/cisplatin microcapsule chemoembolization : Of the 20 patients treated 17 patients had hepatic metastases due to carcinoid tumors and 3 with islet cell metastases. The median percentage of liver replacement was estimated at 50%. Fifteen of the 20 patients had prior therapy and 17 patients had elevated peptide markers that could be followed serially. Six patients received encapsulated cisplatin at 50 mg/m^2, 4 patients at 75 mg/m^2 and 10 patients at 100 mg/m^2 (MTD) of body surface area. The median number of vascular occlusions was 3 per patient. All patients were accessible for the evaluation of toxicity and 18 patients for response (two were lost to follow-up). The median follow-up was 14 months. Twelve (67%) of the 18 patients had a median reduction in symptoms of 50%. Eleven (73%) of 15 patients with elevated 24 h urine levels of 5 hydroxyindole acetic acid and had a median reduction of 64% ; 14 (77%) of 18 had an objective reduction in the tumor ; 6 of 14 patients had a partial response (PR) and 8, had a minor response (MR). One treatment related death occurred from a hepatorenal syndrome. Other complications included hepatic pain (100%), fever (100%), nausea (100%) and vomiting (95%). All patients had transient elevations of liver enzymes and 5 of 20 patients died of disease during the study (8).

Polymer-drug conjugate : PG-TXL injected intravenously in murine ovarian cancer (OCa1) resulted in a complete response (CR) in 25 of the 26 mice and in rats with breast cancer (13762F), a CR in 13 of 13 animals (6). The therapeutic activity of PG-TXL was evaluated in syngeneic murine tumors (MCa-4, MCa-35, HCa1 and FSa II inoculated i.m. into C3Hf/kam ; a human SKOV3 i.p.I ovarian tumor injected ip into nude mice and a human MDA-MB435 Lung2 breast tumor grown in the mammary fat pad of nude mice). Two paclitaxel-responsive murine tumors MCa4 and MCa-35 showed significant growth delay with PG-TXL given as a single i.v. injection at its MTD of 160 mg equiv. paclitaxel/kg or even at 120 mg equiv./kg. HCa1 and FSaII did not respond well to paclitaxel although there was a significant growth delay with PG-TXL. In SKOV3 i.p., the median survival time for mice treated with paclitaxel alone (60 mg) was 43d, while PG-TXL at 60 mg equiv. and 120 mg equiv. it was 61d, and 75d, respectively. In MDA-MB435 Lung 2, PG-TXL (120 mg equiv.) produced a 50% regression and marked reduction in pulmonary metastases.

Discussion

When injected into the hepatic artery, the Lipiodol rapidly entered the portal vein primarily through the peribiliary plexus, creating a dual embolization. Nakamura *et al.* demonstrated improved results in their patients with inoperable hepatocellular carcinoma (HCC) who were treated with Lipiodol, doxorubicin and Gelfoam embolization (9). The survival rates of their 443 patients were at 1 yr., 56.3% ; 2 yrs., 11.8% ; and 5 yrs., 8.0%, slightly better than the control group embolized with Gelfoam and doxorubicin. Ohishi *et al.*, described their experience in over 500 patients with inoperable HCC with a 4 yr. survival rate at 20.4% utilizing anticancer drugs, Gelfoam and Lipiodol (10). From the same group, Uchida *et al.* reported a 3 yr., survival rate of 55% in their series of 99 nodular HCC (5cm diam.) treated by subsegmental Lipiodol chemoembolization (11). More recently they have employed SMANCS soluble in Lipiodol, followed by Gelfoam. Matsui *et al.* reported that subsegmental

chemoembolization with Lipiodol and anticancer drugs followed by Gelfoam or a mixture of Lipiodol and absolute ethanol in 82 patients with nodular HCC (< 4 cm diam.). Childs A and B yielded 1 yr. survival rates of 100% and 67% (12). Shiina *et al.* treated 146 patients by chemoembolization followed by percutaneous injection of ethanol (PEI) into the residual lesion and had survival rates of 1 yr., 79% and 5 yrs., 38% (13). Livraghi *et al.* compared radiofrequency ablation (RF) vs. PEI in the treatment of small HCC (3 cm diam.). Complete necrosis was achieved in 47 (90%) of 52 tumors in 1.2 sessions with RF and 48 (80%) of 60 tumors in 4.8 sessions under PEI (14).

In the study of 38 consecutive patients with HCC, 35% Stage I, 62% Stage II, and 3% Stage III, 51% with cirrhosis, Solomon *et al.* (15), reported the results of chemoembolization with cisplatin, doxorubicin, mitomycin C, Lipiodol and polyvinyl alcohol particulates. The lesions became resectable in 7 patients. Among 25 patients evaluable for morphologic response, 36% had a partial response (PR) 32% had a minor response (MR) and 32% remained stable. No patient had progression of disease while receiving therapy. The cumulative survival was 60% at 1 year, 41% at 2 years and 16% at 3 years. Two patients developed progressive hepatic failure. The 30-day mortality was 8%. These results compare favorably to the response and survival rates for chemoembolization of more advanced HCC from Asia.

Three randomized studies of groups of patient summarized in the French and American Literature (16,17,18) with unresectable HCC without severe liver cirrhosis were treated by Lipiodol chemoembolization with epi- or doxorubicin and/or cisplatin and Gelfoam particles or powder. This approach definitely reduced tumor growth, but often caused liver damage and/or hepatic failure which increased hospitalization and was definitely more expensive. These groups were randomized against supportive therapy with no chemoembolization ; there was no significant improvement in survival. In one of these studies cisplatin was used at a total dose of 70 mg which was considerably less than the 2 mg/kg used at MDACC. Undoubtedly the patient selection criteria employed in these randomized studies differed from those in Japan where the tumors are more frequently nodular, encapsulated, hypervascular and positive for Hepatitis B or C antibody. In Japan selection of patients for chemoembolization is done earlier in the course of the disease because of their aggressive screening program and therefore better results.

Utilizing Lipiodol/ethanol (3:1) chemoembolization, Cheng, Kan *et al.* (19), treated 200 patients with HCC by injection of the segmental or lobar hepatic artery supplying the lesion. Twenty patients were subsequently subjected to segmental or lobar hepatectomy after 6 weeks. All biochemical tests reverted to normal in 2 weeks. Preoperatively 6 patients were estimated to have insufficient residual liver volume which after chemoembolization hypertrophied adequately for resection. In 7 patients there was complete necrosis of the HCC. All patients survived without major associated complications and the 1 year survival was 95%. They reported that transarterial Lipiodol/ethanol administration was a safe and efficacious method for treatment of HCC. It effectively decreased tumor size, caused hepatic hypertrophy, improved liver function and allowed a wide range of patients to undergo hepatectomy with a better survival rate.

Complications : Undoubtedly with chemoembolization, there is an increase local effect along with local toxicity. Sakamoto *et al.* (20) reported an incidence of 102 (4.4%) complications in 2300 chemoembolization procedure for hepatic neoplasms. Of those related to the chemoembolic agents, 63 (1.8%) produced injury to the liver including acute liver failure, liver abscess, intrahepatic biloma, liver infarction and multiple intrahepatic aneurysms. Injury to extrahepatic structure, probably due to inadvertent chemoembolization of adjacent arteries occurred in 28 episodes (0.9%)caused severe cholecystitis, gallbladder and splenic infarctions, gastrointestinal mucosal lesions (ulcers along the lesser curvature of the stomach), pulmonary embolism or infarction, tumor rupture and variceal bleeding. In 39 (1.7%) the complications were due to catheter or guide wire trauma leading to iatrogenic dissection, occlusion or vascular perforation.

Similar experience occurred with hepatic metastases. Hypervascular metastases as with HCC responded better than hypovascular metastases to chemoembolization including neuroendocrine tumors, leiomyosarcoma, ocular melanoma and at times breast carcinoma (1). Further experimental data should be gathered with the use of GFP (3) by which the fate of one metastatic cell can be evaluated in relation to chemoembolization (Fig. 3).

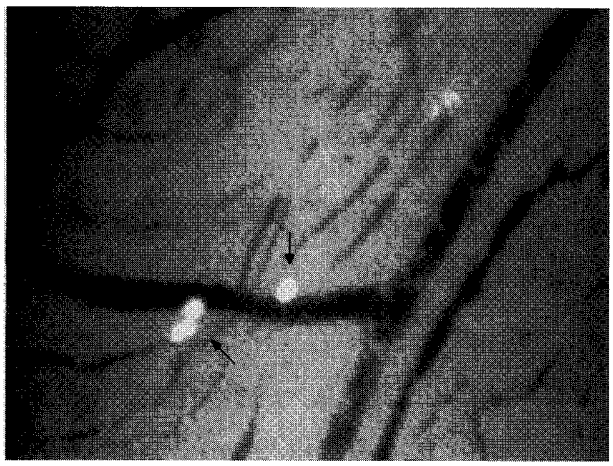

Fig. 3. — In vivo fluorescent micrograph (250 ×) of the mesentery in a rat inoculated in mammary fat pad with GFP-labeled breast cancer 25 days earlier. The fluorescent metastatic cells (arrows) have extravasated from a blood vessel.

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