Liver and Tumor Uptake and Plasma Pharmacokinetic of Arterial Cisplatin Administered With and Without Starch Microspheres in Patients With Liver Metastases

Dario Civalleri, MD,* Mauro Esposito, PhD,† Rosa Anna Fulco, PhD,† Maria Vannozzi, PhD,† Nadia Balletto, MD,* Franco DeCian, MD,* Pier Luigi Percivale, MD,§ and Franco Merlo, PhD‖

Arterial chemoembolization of liver tumors should improve regional treatment by reducing native blood flow of the whole organ and redistributing residual flow toward hypovascular masses. Plasma cisplatin pharmacokinetics and its tissue uptake and relative tumor and liver vascularity were studied during surgical placement of arterial catheters in four patients and in four patients with colorectal metastases given intraoperative arterial cisplatin (DDP, 25 mg/m^2), with and without coadministration of 600 mg degradable starch microspheres (DSM). Mean (± standard deviation) filterable plasma platinum levels peaked later (2 minutes) and were significantly lower after DDP with DSM (1.23 ± 0.69 μg/ml) than after DDP alone (2.13 ± 0.43 μg/ml, *P* less than 0.05), with the area under the curve ($AUC_{0-30\ min}$) values of 15.8 ± 5.5 and 25.1 ± 3.8 μg × min/ml (*P* less than 0.05), respectively. No differences in urine excretion, total body clearance, or plasma protein binding of platinum were observed. Tissue biopsies were started 15 minutes after DDP administration and completed in all cases within 5 minutes. Tumor platinum concentrations were significantly higher after DDP with DSM (3.03 ± 1.60 μg/g) than after DDP alone (0.67 ± 0.49 μg/ml, *P* less than 0.05). Liver concentrations and tumor-liver ratios of platinum also were higher, although not significantly, after DDP with DSM. Preoperative vascularization, studied with arterial perfusion scan, influenced individual tissue drug uptake in cases given DDP alone, with the lowest tumor levels in cold masses. Very high and almost superimposable liver and tumor concentrations were measured in those receiving *DDP and DSM*. The latter phenomenon was irrespective of native vascularization, indicating that DSM administration induced both an increased whole-liver extraction of the drug and a redistribution of blood flow and flow-dependent tissue uptake of platinum. *Cancer* 68:988–994, 1991.

THE PRIMARY AIM of arterial cancer chemotherapy is to increase tumor delivery of regionally administered drugs while maintaining tolerable systemic exposure as a result of first-pass extraction. Both animal and human studies show that liver tumors, unlike liver parenchyma, are supplied mainly by the hepatic artery.[1,2] Moreover, pharmacokinetic studies relative to intraarterial therapy indicate that the increase in drug concentration at the target site is related inversely to the regional blood flow and directly to the total body clearance of the drug.[3,4] Low arterial blood flow rate along with high total body clearance would ensure a high regional drug exposure. Therefore, the whole-organ blood flow, and tumor vascularity, studied with ^{99m}Tc-macroaggregated albumin (MAA) hepatic artery perfusion scans, are crucial factors in regional treatment of liver cancer.[5–7] For these reasons,

From the *Department of Surgery, University of Genoa, and the Departments of †Pharmacotoxicology, ‖Epidemiology and Biostatistics, and §Surgical Oncology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.

Supported in part by a grant of the Associazione Italiana per la Ricerca sul Cancro and Consiglio Nazionale delle Ricerche, Italy.

The authors thank Pharmacia AB, Uppsala, Sweden for supplying degradable starch microspheres (Spherex).

Address for reprints: Mauro Esposito, PhD, Servizio di Farmacologia Tossicologica, Istituto Nazionale per la Ricerca sul Cancro, viale Benedetto XV, 10-16132 Genova, Italy.

Accepted for publication January 16, 1991.

arterial chemoembolization was devised as a means of reducing regional blood flow and targeting the drug to virtually unresponsive hypovascular tumors.[5,8-12] Various materials have been mixed or loaded with selected drugs,[11-13] including absorbable gelatin, glutaraldehyde-stabilized collagen, polyvinyl alcohol particles, ethylcellulose microcapsules, albumin, and starch microspheres (DSM).

The bolus administration of 90×10^6 parts of DSM into the proper hepatic artery can induce a mean reduction of blood flow by 80%.[14] This short-term block of the arterial flow can be exploited to improve the extraction of drugs by the liver as a whole. Several studies investigated whether DSM infusion can affect the pharmacokinetics of antineoplastic drugs such as carmustine,[14] mitomycin C,[15] 5-fluorouracil (5-FU),[16] and doxorubicin.[17] These indicate that intraarterial coadministration with DSM results in increased uptake by the liver and reduced systemic drug exposure. Moreover, as DSM have a tendency to go preferentially to high-flow areas,[18] the capillary blockade should prevail in the latter, thus producing an increased arterial back pressure that would forcibly redistribute the residual arterial flow toward previously ischemic areas. Personal experiences[5,10,19] indicated that native arterial vascularity of both hypervascular (hot) and hypovascular (cold) areas of the liver in humans can be modified by means of arterial embolization with DSM.

Cisplatin (DDP) is an inorganic platinum complex whose clinical activity against many human cancers is well recognized.[20] Its activity also has been reported in colorectal cancer patients receiving hepatic artery infusion of DDP alone.[21] An additive effect was reported between DDP and 5-FU, with up to 34% response rate after intravenous infusion.[22-23] However, the clinical use of DDP frequently is associated with severe side effects such as nephrotoxicity, neurotoxicity, emesis, and ototoxicity. Pharmacokinetic studies comparing intraarterial and intravenous DDP routes of administration indicate a decrease in circulating drug levels but no difference in tumor concentrations.[24,25]

The extraction of DDP after arterial infusion is rate dependent, with longer infusion times resulting in a whole-liver uptake of 40% to 50%.[26-29] However, in the case of hypovascular tumors and/or lack of local response to regional treatments, it is desirable to induce a further selective increase of tumor exposure. This could be obtained with bolus injections of the drug mixed with DSM. Little has been published on the hepatic uptake,[30] distribution, and excretion of platinum after hepatic arterial administration of DDP with DSM. To define the possible benefits of DSM chemoembolization further, pharmacokinetic parameters, changes of native vascularity, and tumor and liver concentrations of platinum were investigated in patients with disseminated colorectal liver metastases after intraarterial administration of DDP given alone or with DSM.

Materials and Methods

Degradable Starch Microspheres

The DSM (Spherex, Pharmacia AB, Uppsala, Sweden) consist of glucose polymers cross-linked with epichlorohydrine bridges to form spheres with a mean diameter of 40 ± 5 μmol/l; they are degraded by serum amylases with a $t_{1/2}$ of 15 to 30 min at 37°C *in vitro*. The spheres are stable in a dry state and can be stored at room temperature. Once injected into an artery, they cause a block of flow at the arteriole–capillary level that is fully reversible even after repeated administration.[16] We chose DSM because their small size and short half-life allowed repeated chemoembolization at the arteriole–capillary level with distal entrapment of the drug and limited risk of permanent vascular occlusion.

Treatment

Eight patients (four men and four women) undergoing surgical implantation of arterial catheters for regional treatment of disseminated colorectal liver metastases were studied. For all patients, preoperative examinations showed typical hepatic arterial anatomy and absence of arteriovenous shunts, normal blood values of creatinine, bilirubin, albumin, prothrombin time, and liver enzymes, with the exception of alkaline phosphatase. The clinical staging included computed tomographic scan for the assessment of liver involvement. At surgery, the gastroduodenal artery was cannulated with implantable ports,[31] the catheter tip being threaded up to its confluence with the hepatic artery.

Four patients were infused through the arterial catheter with a 30-second bolus of DDP, corresponding to a DDP dose of 25 mg/m^2; the other four patients received the same dose of DDP mixed with 60×10^6 parts of DSM. Relatively low doses of DSM and DDP were chosen for the kinetic study to prevent unwanted side effects during the anesthesia and the immediate postoperative period and because even low doses of DSM can induce substantial and easily detectable hemodynamic changes in the liver.[5] The total amount of DSM and DDP was suspended in 50 ml of normal saline, and to avoid sedimentation, the syringe containing the mixture was shaken for 30 seconds before and continuously during the injection.

Blood samples of all patients were collected in heparinized tubes before administration of DDP, at the end of the infusion, and 1, 2, 4, 8, 15, 30, and 45 minutes and 1, 2, 4, 8, and 24 hours after infusion. Blood samples were taken daily (24-hour intervals) for at least 1 week. Urine

collection was started just before DDP administration and from 2, 4, 8, and 24-hour pools during the first 24-hour period; 24-hour samples were collected for 5 days thereafter. Blood samples were centrifuged immediately, and the plasma was removed. For all patients 4-ml plasma samples were filtered through Amicon Centriflo CF 25A cones (molecular weight cutoff, 25,000; Lexington, MA), and the ultrafiltrate fraction was used for determining the filterable platinum concentration. The concentration of platinum in the plasma, plasma ultrafiltrates, and urine were determined by flameless atomic absorption spectroscopy,[32] using an Hitachi Model Z-9000 simultaneous spectrophotometer (W. Pabish, Milano, Italy). Biopsy specimens of about 0.5 g were taken in random sequence starting 15 minutes after drug injection and stored in dry plastic tubes at −20 °C until processing. Whenever possible, more than one biopsy specimen was obtained from different areas of both liver and tumor, care being taken to complete sampling in less than 5 minutes. Tumor samples were taken from the peripheral portions of the lesions; parenchyma was sampled far away from the tumor. Tissue samples were digested with 14 mol/l nitric acid; after digestion and evaporation to near dryness, the residue was eluted in 10 mmol/l nitric acid. All tissue samples were assayed for platinum using both flameless atomic absorption spectroscopy and neutron activation analysis, as previously described.[33]

The vascularity of tumors was studied by means of low-flow ^{99m}Tc-MAA arterial perfusion scans, according to the method described in details elsewhere.[5,10] Briefly, native vascularity was determined in all cases 7 to 14 days after surgery with a plain MAA scan. The distribution of MAA in the obvious tumor masses, as identified by conventional sulfur colloid scan, was indicated as either hot or cold according to tumor uptake compared with normal parenchyma. In cases of gross coexistence of the two vascular patterns, tumors also were indicated as mixed type. Two to 7 days after the first examination, an additional MAA arterial scan was done in all patients who had undergone intraoperative infusion of DDP with DSM. The MAA scan was done immediately after the infusion of 60 × 10^6 parts of DSM through the arterial catheter. Differential patterns of tumor vascularity were noted in each patient, and the individual changes were attributed to the arterial flow redistribution caused by DSM arterial embolization. Because the gamma camera was not available in the operating room, the MAA perfusion scans were done postoperatively. Theoretically, this could be increase the risk of overlooking possible changes in tumor vascularity as a result of tumor responses after the intraoperative DDP infusion.[34] The perfusion scans, however, were done after an echoscan had shown no substantial changes in tumor dimensions. In addition, although modifications of tumor vascularity have been reported during chemotherapy even in the absence of gross changes of tumor masses,[35] they essentially are chronic in nature and unlikely to occur in short periods of time. Tumor vascularity appears to be fairly stable during several months in over 80% of cases even with substantial tumor progression or treatment response.[36]

The patients subsequently were treated according to a prospective clinical study of regional chemotherapy[37] including plain intraarterial infusion of DDP (40 mg/m^2 on days 1 to 3 every 21 days) with intravenous 5-FU (200 mg/m^2 on days 1 to 5 every 21 days).

Data Analysis

To analyze the data, a Fortran program was developed on a HP-1000 and HP-150 (Hewlett-Packard, Milano, Italy) computer according to the linearization method for nonlinear least-squares cases.[38] Plasma decay of total and filterable platinum was fitted to a one-compartment and two-compartment open model, and pharmacokinetic parameters were derived using standard equations. All differences between patients treated with DDP alone and DDP with DSM were evaluated using the Mann-Whitney test (Wilcoxon) at the 0.05 level of significance.[39]

Results

Effect of Starch Microspheres on Systemic Platinum Exposure

Table 1 shows the systemic pharmacokinetic parameters of platinum in patients after injection of DDP alone or DDP with DSM into the hepatic artery. At early times (≤8 minutes) after administration of DDP alone, the plasma total platinum levels were approximately twofold higher than those observed after administration of DDP with DSM, and there were no differences in total area under the plasma concentration time curve (AUC, Table 1).

TABLE 1. Systemic Pharmacokinetic Parameters of Platinum in Patients Receiving Cisplatin Alone (n = 4) and Cisplatin + Degradable Starch Microspheres (n = 4)

	DDP alone	DDP with DSM
Total platinum		
Maximum (Pt) (μg/ml)	2.13 ± 0.43	1.23 ± 0.69
$AUC_{0-\infty}$ (mg/ml × min)	2.52 ± 2.22	2.73 ± 1.47
Filterable platinum		
Maximum (Pt) (μg/ml)	1.40 ± 0.43	0.70 ± 0.32*
AUC_{0-120} (mg/ml × min)	0.0326 ± 0.0046	0.0385 ± 0.0047
Cl_{Tb} (ml/min)	663 ± 89	699 ± 61

DDP: cisplatin; DSM: degradable starch microspheres.
Values are mean ± SD.
Cl_{Tb}: clearance rate of filterable platinum from systemic circulation.
* $P < 0.05$.

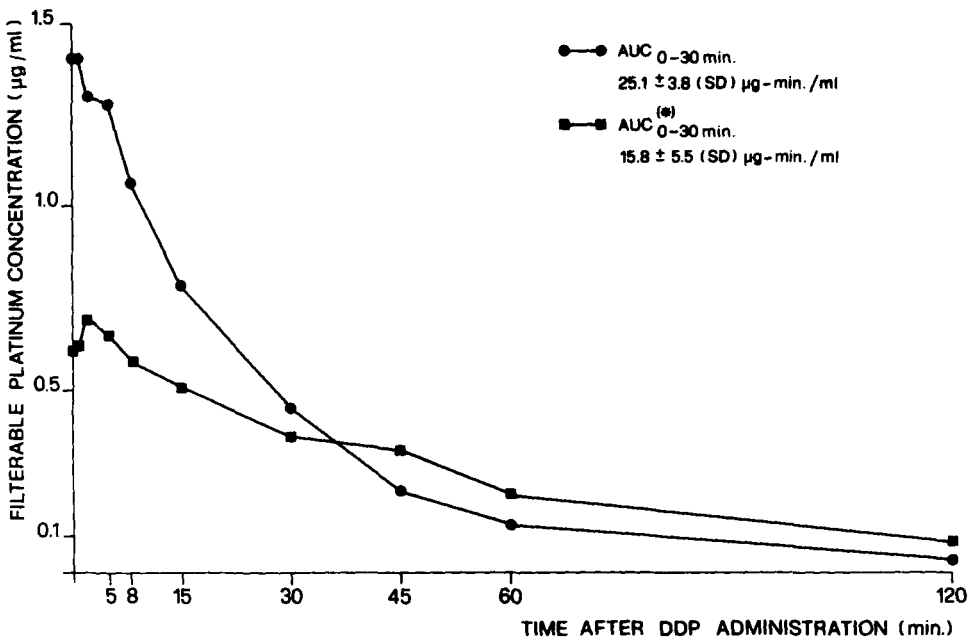

FIG. 1. Mean plasma concentrations of filterable platinum in patients treated with DDP alone (●: n = 4) and DDP with DSM (■: n = 4) (*) $P < 0.05$.

Plasma disappearance of filterable platinum after treatment with and without DSM was best fitted to a one-compartment model (Fig. 1). Sharp differences in the systemic concentrations of filterable platinum were observed from 0 to 30 minutes after administration of DDP alone or with DSM (Fig. 1 and Table 1). The mean peak concentration of filterable platinum determined at early times (≤8 minutes) after administration of DDP alone (2.13 ± 0.43 μg/ml [standard deviation]) was significantly higher (P less than 0.05) than that observed in patients given DDP with DSM (1.23 ± 0.69) μg/ml, Table 1). The AUC mean value of filterable platinum over 30 minutes after administration of DDP alone (25.1 ± 3.8 μg-min/ml) was significantly higher (P less than 0.05) than that measured after DDP with DSM (15.8 ± 5.5 μg-min/ml, Fig. 1). No difference in total body clearance was observed between the two groups of patients (Table 1).

The rate constant for the protein binding of platinum to fixed metabolite in plasma (determined by dividing the concentration of bound platinum at 120 minute by the AUC of filterable platinum) was 0.0146 ± 0.0055 and 0.0149 ± 0.0048 min^{-1} in patients administered DDP alone and DDP with DSM, respectively. The percentage of platinum excreted in the urine for the 5-day period after treatment was 29 ± 7% and 20 ± 10% for patients treated with DSM and without DSM, respectively.

TABLE 2. Tumor and Liver Platinum Concentrations (ng/mg wet tissue) Determined 15 Minutes After Intra-arterial Injection of DDP: Tumor Vascularity

	Tumor	Liver	Tumor/liver ratio	Vascularity	
				Native	After DSM
DDP alone (patient no.)					
5	0.10 —	0.19 —	0.54	Cold	—
6	1.43 —	0.92 —	1.55	Hot	—
7	0.61 0.45	4.08 2.73	0.16	Cold	—
8	0.78 —	1.64 —	0.48	Cold	—
Mean (SD)	0.67 (0.49)	1.91 (1.53)	0.68 (0.61)		
DDP + DSM (patient no.)					
1	1.29 —	1.68 1.70	0.76	Cold	Mixed
2	3.06 2.26	3.43 2.16	0.95	Hot	Hot
3	4.09 5.59	3.79 6.14	0.97	Cold	Hot
4	1.88 —	1.85 —	1.02	Hot	Mixed
Mean (SD)	3.03 (1.59)*	2.96 (1.64)	0.93 (0.11)		

SD: standard deviation.

* $P < 0.02$ compared with DDP alone.

Effect of Starch Microspheres on Tissue Uptake of Platinum and Tumor Vascularity

Table 2 shows tissue uptake and tumor–liver ratios of platinum in each patient undergoing intraoperative biopsies. Tumor vascularity with and without DSM also are reported in this table.

The DSM chemoembolization compared with the administration of DDP alone appeared significantly to increase the uptake of the coinjected drug by the tumor (P less than 0.02), with mean concentrations of platinum of 3.03 ± 1.59 and 0.67 ± 0.49 μg/g in patients given DDP with DSM and DDP alone, respectively (Table 2). Higher mean platinum concentrations also were observed in the liver parenchyma as were higher tumor–liver ratios after DDP with DSM compared with DDP alone (Table 2). Relative tumor and liver uptake of platinum was influenced by native tumor vascularity in the individual patients given DDP alone. The tumor–liver ratio of platinum was low in the three cases with cold tumors (Patients 5, 7, and 8) and high in one case with hot lesions (Patient 6). In a case with cold lesions (Patient 5), the uptake of platinum was very low both in the tumor and liver parenchyma. In turn, high platinum levels were found after DDP with DSM both in cold and hot tumors and in liver parenchyma. This was related not only to the DSM-induced reduction of blood flow to the whole organ but also to the reversal of tumor vascularity caused by DSM in the two patients with native cold lesions receiving intraoperative DDP chemoembolization (Patients 1 and 4).

Discussion

High liver toxicity and poor control of systemic progression seem to be the major problems limiting the efficacy of the most widely used drugs for intraarterial treatment of colorectal liver metastases, such as 5-FU and 5-fluor-2′-deoxyuridine (FUdR).[13,40,41] Thus, modified FUdR-based regimens or alternative drugs are being investigated by several groups in an attempt to improve clinical results.[13,40] For this purpose, DDP has potentially useful characteristics: most of the arterially administered drug reaches the systemic circulation[26–29] without producing serious liver toxicity. Moreover, the association of intraarterial DDP and intravenous 5-FU in colorectal liver metastases[37] resulted in an overall objective response rate almost superimposable on that achieved with FUdR alone (55%) but with a lower incidence of systemic progression. In nonresponsive cases, whose tumors mainly are hypovascular in nature, the lack of response could be related, at least in part, to the poor perfusion of the lesions and, consequently, to a low tumor uptake of the drug. Arterial chemoembolization could help overcome these problems through a reduction and a redistribution of regional blood flow.

Our results indicate that higher tumor and liver concentrations of platinum are achieved after intraarterial infusion of DDP with DSM than after DDP alone, with minimal alteration of systemic pharmacokinetics. No differences were observed between the two groups in the total and filterable AUC, in the total body clearance, and in the urinary platinum excretion. Because only nonprotein-bound platinum species are filtered by the kidney, these findings are consistent with the similar rate constant for the biotransformation of DDP to fixed metabolite observed in the two groups of patients.

Despite the general similarities in pharmacokinetics after the administration of DDP alone and DDP with DSM, both peak plasma concentrations of filterable platinum and filterable platinum exposure determined up to 30 minutes after treatment were significantly lower in the group receiving DDP with DSM than in the group receiving DDP alone (Fig. 1). These differences were consistent with the half-life of DSM (15 to 30 minutes) and cannot be explained by differences in drug doses or patient characteristics. Therefore they are likely to reflect an enhanced local diffusion of DDP at early times when the drug is combined with DSM.

Tumor vascularity has been identified as a prominent prognostic factor in regional treatment of liver tumor.[5–7] In one report,[6] MAA scan provided a good positive correlation between tumor perfusion and treatment responses in 47 patients with colorectal metastases undergoing hepatic arterial infusion of FUdR. Our data concur with this prediction, suggesting that platinum distribution to both tumor and liver is influenced by tumor vascularity in patients without DSM embolization (Table 2). This agrees with the findings of others[42,43] on intraarterial infusion in humans. Although the uptake of FUdR generally was lower in the tumor than in the liver parenchyma, a direct correlation was observed in these two studies between tumor vascularity (MAA retention) and tumor FUdR levels.

Patients treated with DDP plus DSM showed higher platinum levels both in the tumor and liver parenchyma than did those treated with DDP alone. Only one patient (1) with native cold lesions, treated with DDP and DSM, had a tumor concentration of platinum that was similar to the highest platinum levels detected in the only patient with native hot lesions (6) in the group receiving DDP alone (Table 2). This could be a result of the DSM-induced reduction of total blood flow to the liver, causing increased first-pass extraction of the drug. However, DSM arterial embolization can increase not only tumor doxorubicin levels but also tumor–parenchyma doxorubicin ratios in experimental VX2 tumor transplanted in rabbits' liver.[44] Higher tumor–liver ratios of FUdR have been reported in patients receiving arterial embolization with FUdR plus DSM compared with those receiving FUdR alone.[45] Sub-

stantial changes in tumor perfusion patterns can be induced by DSM in most patients undergoing MAA arterial perfusion scans with and without DSM embolization.[5,10] Our data show that patients receiving DDP with DSM had tumor–liver ratios of mean platinum concentration (0.93 ± 0.11) similar to that observed in patients receiving DDP alone (0.68 ± 0.61). Moreover, each patient receiving DDP with DSM showed almost superimposable platinum levels both in the tumor and liver parenchyma; diverging values were measured in patients receiving DDP alone. This contrasts with the behavior we would expect if tissue uptake of platinum were increased uniformly by DSM without changing the relative blood flow toward the tumor and liver. In the latter case, although increased, the tumor platinum uptake would be related to the native tumor vascularity as found in the group treated with DDP alone. Therefore, the observed tissue levels of platinum after DSM suggest a redistribution of blood flow in the liver toward native hypovascular areas resulting in an increased platinum uptake.

In turn, although changes in vascularity were been investigated in the previous studies with arterial DSM plus doxorubicin[44] and FUdR,[42,43,45] the reported data could be explained, at least in part, by a DSM-induced redistribution of blood flow to the tumor. However, FUdR has very high first-pass extraction into the normal liver;[3,4] whereas the extraction of doxorubicin, although not extensive, cannot be increased by the DSM-induced reduction of flow.[44] For these two drugs, the effect of DSM could only be related to the DSM-induced slow-down of arterial flow to the entire organ. Even in these cases where DSM embolization does not induce changes in tumor vascularity, first-pass extraction could be increased to a greater extent in the tumor than in the parenchyma. This phenomenon could be magnified by a substantial washout of normal parenchyma due to the portal flow.

In summary, our data show that intraarterial injection of DDP combined with DSM resulted in enhanced exposure of local tumor to the drug, compared with that achieved when DDP was given alone, without any substantial alteration of systemic pharmacokinetics. Bolus intraarterial DDP has a low first-pass liver extraction,[26–29] but our data indicate, contrary to doxorubicin and FUdR, that substantial improvement of tissue platinum uptake can be achieved by DSM-induced blood flow reduction. Moreover, because the specific uptake of platinum in normal condition is similar in the liver and tumor, relative changes in tissue platinum levels appear to be closely related to the DSM-induced blood flow redistribution. The net result of this phenomenon is a more homogeneous tissue uptake of DDP in both cold and hot areas of tumor-bearing livers. This is also supported by the DSM-induced changes of tumor vascularity observed in the two patients with native cold lesions receiving intraoperative DDP combined with DSM (Patients 1 and 4). Parallel changes of blood flow targeting and tissue uptake of platinum appear to have occurred in these patients. It follows that DSM chemoembolization may be useful in the administration of drugs with either high or low specific first-pass extraction, even without necessarily increasing the tumor–liver ratio. However, DSM chemoembolization variously can influence blood flow reduction, tumor vascularity, and drug uptake, depending on DSM dose, native vascularity, specific liver uptake of the given drug, and total capillarity of the organ, which can vary widely between individuals.[46] Hence, with the aim of optimizing the beneficial effects of chemoembolization, DSM doses should be individualized to obtain similar hemodynamic effects with different doses. For this purpose, different methods of monitoring the hemodynamic effects of DSM are available including nuclear medicine[46] and digital subtraction angiography.[47] Finally, the short-term effect of the DSM can be exploited fully only with bolus infusions of these drugs. Therefore, the drugs of choice for chemoembolization appear to be those agents whose best schedule is represented by bolus infusion and/or those agents, such as mitomycin C, known to be preferentially toxic to cells under the hypoxic condition occurring after DSM embolization.[48] Specific questions that remain to be answered for each drug suitable for DSM chemoembolization deal with the chemical structure of the substance taken up by the tumor and whether it is localized at intracellular or extracellular levels.

REFERENCES

1. Ackerman NB. Experimental studies on the circulatory dynamics of intrahepatic blood flow supply. *Cancer* 1972; 29:435–439.
2. Healey JE Jr. Vascular patterns in human metastatic liver tumors. *Surg Gynecol Obstet* 1965; 129:1187–1193.
3. Collins JM. Pharmacologic rationale for regional drug delivery. *J Clin Oncol* 1984; 2:498–504.
4. Ensminger WD, Gyves JW. Regional cancer chemotherapy. *Cancer Treat Rep* 1984; 68:101–115.
5. Civalleri D, Scopinaro G, Balletto N *et al.* Changes in vascularity of liver tumours after hepatic arterial embolization with degradable starch microspheres. *Br J Surg* 1989; 76:699–703.
6. Daly JM, Butler J, Kemeny N *et al.* Predicting tumor response in patients with colorectal hepatic metastases. *Ann Surg* 1985; 202:384–393.
7. Rodari A, Bonfanti G, Garbagnati F, Marolda R, Milella N, Buraggi GL. Microspheres angiography in hepatic arterial infusion of cancer. *Eur J Nucl Med* 1981; 6:673–677.
8. Iwaki A, Nagasue N, Kobayashi M, Inokuchi K. Intra-arterial chemotherapy with concomitant use of vasoconstrictors for liver cancer. *Cancer Treat Rep* 1978; 62:145–146.
9. Tuma RF. The use of degradable starch microspheres for transient occlusion of blood flow and for drug targeting to selected tissues. In: Davis SS, Illum L, McVie JG, Tomlinson E, eds. Microspheres and Drug Therapy: Pharmaceutical, Immunological and Medical Aspects. Amsterdam: Elsevier, 1984; 189–203.
10. Civalleri D, Scopinaro G, Simoni G *et al.* Starch microsphere-induced arterial flow redistribution after occlusion of replaced hepatic arteries in patients with liver metastases. *Cancer* 1986; 58:2151–2155.
11. Lee YTN. Regional management of liver metastases: II. *Cancer Invest* 1983; 1:321–332.

12. Willmott N. Chemoembolisation in regional cancer chemotherapy: A rationale. *Cancer Treat Rev* 1987; 14:143–156.

13. Vanook A. Novel treatments for unresectable liver tumors. Presented at the Educational Symposia, Twenty-Sixth Annual Meeting of the American Society of Clinical Oncology, Washington DC, May 20–22, 1990; ASCO Educational Booklet 81–85.

14. Dakhil S, Ensminger WD, Cho K, Niederhuber J, Doan K, Wheeler R. Improved regional selectivity of hepatic arterial BCNU with degradable microspheres. *Cancer* 1982; 50:631–635.

15. Ensminger WD, Gyves JW, Stetson P, Walker-Andrews S. Phase I study of hepatic arterial degradable starch microspheres and mitomycin C. *Cancer Res* 1985; 45:4464–4467.

16. Lindell B, Åronsen KF, Nosslin B, Rothman U. Studies in pharmacokinetics and tolerance of substances temporarily retained in the liver by microsphere embolization. *Ann Surg* 1978; 187:95–99.

17. Teder H, Nilsson B, Jonsson K, Hellekant C, Aspergren K, Åronsen KF. Hepatic arterial administration of doxorubicin (Adriamycin) with or without degradable starch microspheres: A pharmacokinetic study in man. In: Hansen H, ed. Anthracyclines and Cancer Therapy. Amsterdam: Excepta Medica, 1983; 166–174.

18. Yipintsoi T, Dobbs WA, Scanlon PD, Knopp TJ, Cassingthwaigthe JB. Regional distribution of diffusible tracers and carbonized microspheres in the left ventricle of isolated dog hearts. *Circ Res* 1973; 33:573–587.

19. Civalleri D, Rollandi GA, Simoni GA, Mallarini G, Repetto M, Bonalumi U. Redistribution of arterial blood flow in metastases-bearing livers after infusion of degradable starch microspheres. *Acta Chir Scand* 1985; 151:613–617.

20. Prestayko AW, Crooke ST, Carter SK, eds. Cisplatin: Current Status and New Developments. New York: Academic, 1980; 317–509.

21. Lehane DE, Zubler MA, Lane M, Smith FE. Intra-arterial cisplatin in metastatic or recurrent colon cancer. *Proc Am Soc Clin Oncol* 1982; 1:C-365.

22. Loehrer PJ, Einhorn LH, Williams SD, Hui SL, Estes NC, Pennington K. Cisplatin plus 5-FU for the treatment of adenocarcinoma of the colon. *Cancer Treat Rep* 1985; 69:1359–1363.

23. Kemeny N, Niedzwiecki D, Riechmann B *et al.* Cisplatin and 5-fluorouracil infusion for metastatic colorectal carcinoma: Differences in survival in two patient groups with similar response rates. *Cancer* 1989; 63:1065–1069.

24. Gouyette A, Apchin A, Foka M, Richard JM. Pharmacokinetics of intra-arterial and intravenous cisplatin in head and neck cancer patients. *Eur J Cancer Clin Oncol* 1986; 22:257–263.

25. Hcquet B, Vennin P, Fournier C, Poissonnier B. Evaluation of the pharmacological benefit and determination of the influencing factors of intraarterial cis-diamminedichloroplatinum administration in patients with uterine cervical cancer. *Cancer Res* 1987; 47:6134–6137.

26. Campbell TN, Howell SB, Pfeifle CE, Wung WE, Bookstein J. Clinical pharmacokinetics of intraarterial cisplatin in humans. *J Surg Oncol* 1983; 1:755–763.

27. Kelsen DP, Hoffman J, Alcock N *et al.* Pharmacokinetics of regional infusion of cisplatin. *Proc Am Assoc Cancer Res* 1980; 21:746.

28. Stewart DJ, Benjamin RS, Zimmermann S *et al.* Clinical pharmacology of intraarterial cis-diamminedichloroplatinum (II). *Cancer Res* 1983; 43:917–920.

29. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. *Semin Oncol* 1983; 10:176–182.

30. Müller H, Walther H, Aigner KR. Time dependent hepatic tissue levels of cisplatinum (CDDP) after HAI versus HAI and degradable starch microspheres (Spherex) (Abstr). Presented at the Fourth International Conference on Advances in Regional Cancer Therapy, ICRCT 89, Berchtesgaden, West Germany, June 5–7, 1989, F6:72.

31. Civalleri D, Cafiero F, Cosimelli M *et al.* Regional arterial chemotherapy of liver tumours: I. Performance comparison between a totally implantable pump and a conventional access system. *Eur J Surg Oncol* 1986; 12:277–282.

32. Pera MF, Harder HC. Analysis for platinum in biological material by flameless atomic absorption spectrometry. *Clin Chem* 1977; 23:1245–1249.

33. Esposito M, Collecchi P, Oddone M, Meloni S. Platinum assay by neutron activation analysis and atomic absorption spectroscopy in cisplatin treated pregnant mice. *Journal of Radioanalytical and Nuclear Chemistry* 1987; 113:437–443.

34. Gyves JW, Ensmiger WD, Thrall JH *et al.* Dependence of hepatic tumor vascularity on tumor size. *Clin Res* 1982; 30:747A.

35. Bledin AG, Kim EE, Chuang VP, Wallace S, Haynie TP. Changes of arterial blood flow patterns, as monitored by intra-arterially injected technetium 99m macroaggregated albumin. *Br J Radiol* 1984; 57:197–203.

36. Ziessman HA, Thrall JH, Yang PJ *et al.* Hepatic arterial perfusion with Tc-99m-MAA: Use of a totally implanted drug delivery system. *Radiology* 1984; 152:167–172.

37. Cosimelli M, Mannella E, Anzà M *et al.* Two consecutive clinical trials on cisplatin (CDDP) hepatic arterial infusion (HAI) and i.v. 5-fluorouracil (5-FU) chemotherapy for unresectable colorectal liver metastasis: An alternative to FUdR based regimens? *J Surg Oncol* 1991 (in press).

38. Draper NR, Smith H. Applied Regression Analysis, ed. 2. New York: John Wiley and Sons, 1981; 458–529.

39. Dixon JW, ed. BMDP Statistical Software. Berkeley: University of California Press, 1983.

40. Levine B. Hepatic arterial chemotherapy: Results of clinical trials. Presented at the Educational Symposia, Twenty-Sixth Annual Meeting of the American Society of Clinical Oncology, Washington DC, May 20–22, 1990; ASCO Educational Booklet. 74–76.

41. Hohn D. Hepatic arterial chemotherapy. Presented at the Educational Symposia, Twenty-Sixth Annual Meeting of the American Society of Clinical Oncology, Washington DC, May 20–22, 1990; ASCO Educational Booklet. 77–80.

42. Ridge JA, Sigurdson ER, Daly JM. Distribution of fluorodeoxyuridine uptake in the liver and colorectal hepatic metastases of human beings after arterial infusion. *Surg Gynecol Obstet* 1987; 164:319–323.

43. Sigurdson ER, Ridge JA, Daly JM. Fluorodeoxyuridine uptake by human colorectal hepatic metastases after hepatic artery infusion. *Surgery* 1986; 100:285–291.

44. Sigurdson ER, Ridge JA, Daly JM. Intra-arterial infusion of doxorubicin with degradable starch microspheres: Improvement of hepatic tumor drug uptake. *Arch Surg* 1986; 121:1277–1281.

45. Thom AK, Sigurdson ER, Bitar M, Daly JM. Regional hepatic arterial infusion of degradable starch microspheres increases fluorodeoxyuridine (FUdR) tumor uptake. *Surgery* 1989; 105:383–392.

46. Starkhammar H, Håkansson L, Morales O, Svedberg J. Effect of microspheres in intra-arterial chemotherapy: A study of arterio-venous shunting and passage of a labelled marker. *Med Oncol Tumor Pharmacother* 1987; 4:87–96.

47. Lorenz M, Herrmann G, Kirkhova-Reimann M *et al.* Temporary embolization of hepatic malignancies with degradable starch microspheres: DSM: Technique and Results. In: Kreidler J, Link KH, Aigner KR, eds. Proceedings of the Third International Conference, "Advances in Regional Cancer Therapy," Ulm, West Germany, 1987. Basel: Karger, 1988; 49–66.

48. Teicher BA, Lazo JS, Sartorelli AC. Classification of antineoplastic agents by their selective toxicities toward oxygenated and hypoxic tumor cells. *Cancer Res* 1981; 41:73–81.