

Elevating Blood Pressure as a Strategy to Increase Tumor-targeted Delivery of Macromolecular Drug SMANCS: Cases of Advanced Solid Tumors

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The purpose of this study is to evaluate the improved method of arterial infusion therapy of SMANCS (SX) with lipiodol under the angiotensin-induced hypertensive state for various difficult-to-treat solid tumors. Most patients were unresectable with no other therapeutic options, recurrence after resection, or patients do not respond to common treatments. The new method utilizes angiotensin II (AT) to induce hypertension (e.g. ~15–30 mmHg above norm) for 15–20 min. This method was successfully applied to metastatic liver cancer, cholangiocarcinoma, massive renal cell carcinoma, pancreatic and other abdominal solid cancers. This AT-induced hypertension resulted in remarkably enhanced tumor delivery accompanied by improved therapeutic response, and a shorter time to achieve 50% regression of tumor size with least toxicity. We demonstrated clinically herein improved therapy for various advanced solid tumors with SX by elevating the tumor blood flow selectively. This is the first clinical proof that modulations of vascular pathophysiology can uniquely accomplish enhanced tumor selective delivery of polymeric drugs and thus yielded better clinical outcome.

Key words: tumor delivery – angiotensin-induced hypertension – SMANCS – intra-arterial infusion – metastatic liver cancer

INTRODUCTION

With the advent of nanomedicine for detection and treatment of cancer, interest is intensifying in sophisticated polymeric and micellar anticancer drugs (1). One of the most well-established anticancer agents along this line is the polymeric drug SMANCS (SX), which is a conjugate of the protein antitumor antibiotic neocarzinostatin (NCS) with hydrophobic copolymer of styrene/maleic acid (SMA). SX shows remarkable activity for treatment of hepatocellular carcinoma (HCC) and approved by the Japanese Ministry of Health and Welfare in 1993. Since that time, the drug has been in regular use in Japan, delivered by intra-arterial (i.a.) infusion, as a solution form in the lipid contrast agent lipiodol (LP). Its remarkable anticancer efficacy against HCC has been confirmed in many medical centers (2–5), although anecdotal reports have suggested that SX also has activity against other tumor types. Since unique and extensive delivery of SX to HCC is thought to exploit the hyperpermeable tumor vasculature, it might be expected to be less effective

against tumors that are less well vascularized and less permeable tumors than HCC, for example, metastatic liver cancer and pancreatic cancer. In this article, we briefly assess clinical effect of SX against HCC, metastatic liver cancer and other solid tumors, and describe a clinical observations relating to exploratory use of SX for treatment of several different tumor types. This novel strategy involves the use of angiotensin II (AT)-induced transient elevation of blood pressure to enhance the delivery of SX into poorly vascularized solid tumor tissues.

In a series of studies spanning more than 25 years, we have found that most experimental solid tumors demonstrated enhanced vascular permeability and retention (EPR) effect, especially in the periphery of the tumor mass. This is normally coupled with poor convective and lymphatic drainage, giving prolonged retention of macromolecular (>40 kDa) or colloidal drugs within the tumor tissue (6–9). In the clinical setting, computed tomography (CT) has demonstrated marked deposition of the lipid contrast agent LP (containing SX) in HCC, renal cell carcinoma (RCC) and other cancers, apparently as a result of this EPR effect (2,3,9–16) (Fig. 1).

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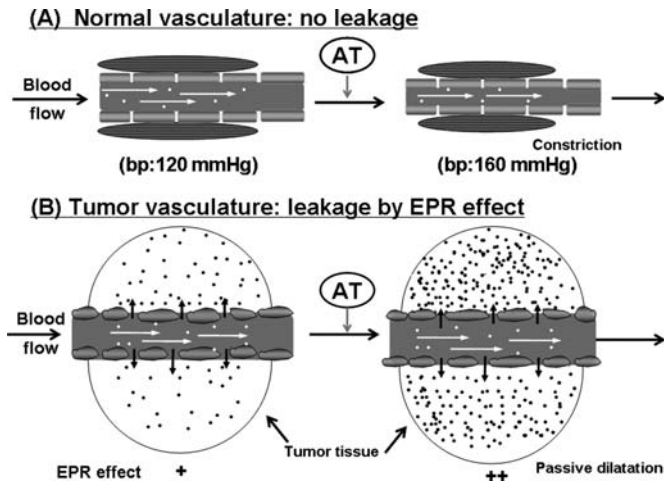


Figure 1. Diagrammatic representation of blood vasculature in normal tissue (A) and tumor tissue (B) under hypertensive condition. In (B), angiotensin II (AT)-induced vasoconstriction and extravasation of macromolecular drugs (dark dots) are shown at the right. The EPR effect occurs clearly in tumor tissue when AT-induced systemic hypertension was applied in (B), which is not seen in normal tissue (A) (no endothelial cell gap opening, etc. see text). A colour version of this figure is available as supplementary data at <http://www.jjco.oxfordjournals.org>.

This EPR phenomenon enabled efficient targeting of the drug to experimental tumors; SX/LP levels in tumors reaching more than 2000-fold higher than drug levels in circulating blood, after injection via the tumor-feeding artery (9). Radioscintigraphy using radioemitting ^{56}Ga citrate can provide a clinical analogy since it also exploits the EPR effect, after intravenous (i.v.) injection of Ga^{2+} , which complexes with plasma transferrin in the circulation and shows a biodistribution similar to macromolecules of ~ 90 kDa, enabling EPR-mediated accumulation of radioactive Ga^{2+} -transferrin to tumor and sensitive detection of solid tumors by radioscintigraphy.

The EPR effect is mediated by many factors including bradykinin, nitric oxide, prostaglandins, vascular endothelial growth factors (12,16–20) and architectural abnormalities including defective vasoconstrictive smooth muscle layers and hypervascular density (12–16,21–27). Vascular mediators, facilitating vascular leakage, are selectively and predominantly produced by tumors and inflammatory tissues in and adjacent to the tumors. In addition, the lymphatic clearance is greatly suppressed in most solid tumors (9–11,21), leading to prolonged retention of macromolecular

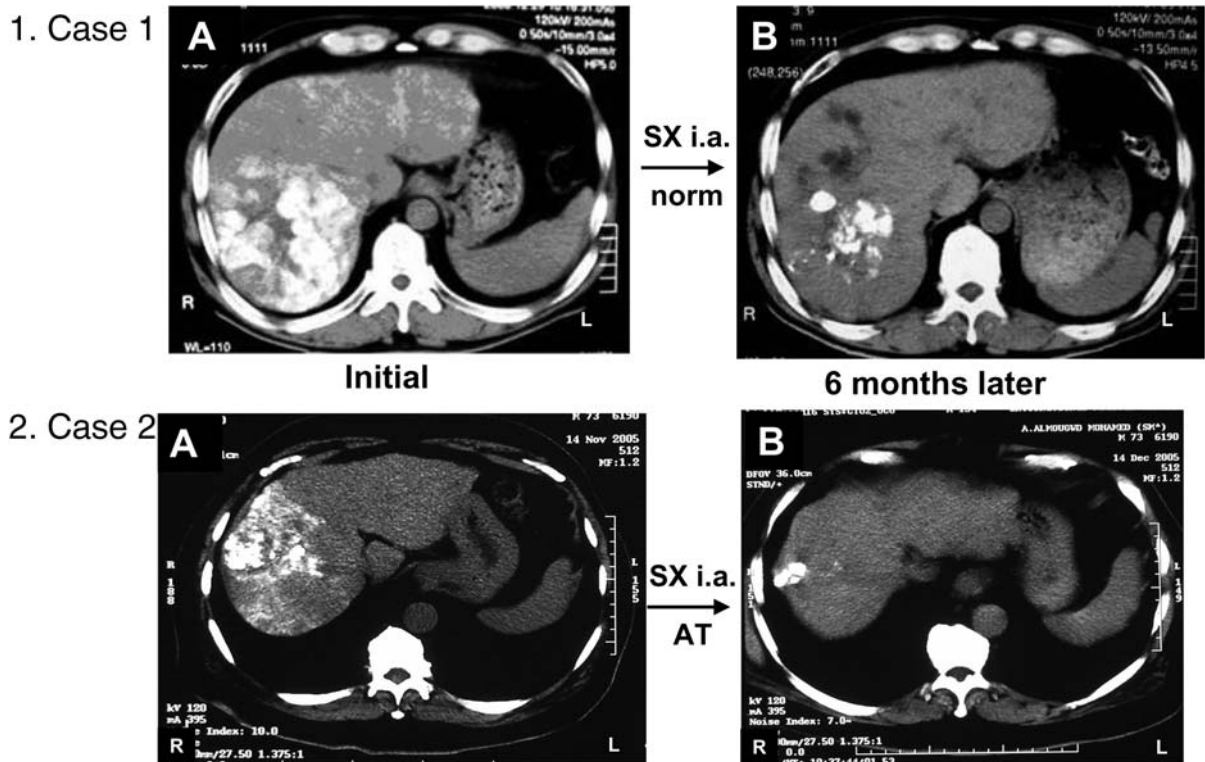


Figure 2. Therapeutic effect of SMANCS (SX)/lipiodol (LP) on hepatocellular carcinoma (HCC) given via the hepatic artery. 1 (Case 1): SX/LP was administered, three times in 6 months, to a patient with a massive HCC under normotensive conditions. The light (white) areas in right lobe (R) indicate tumor uptake of the drug (SX/LP) as revealed by computed tomographic (CT) scan image. A marked reduction in tumor size in 6 months was found by CT (A vs. B). 2 (Case 2): Response of recurrent HCC to SX/LP under AT-induced hypertension (AT/hyper) 3 years after resection. Reduction in the size of the major tumor in 1 month after only one treatment was remarkable (A vs. B). 3 (Case 3): A massive HCC treated with SX/LP (3 ml) under AT/hyper. A considerable tumor size reduction in 1 month was obtained (A vs. B). 4 (Case 4): Another case of recurrent HCC 2.5 years after resection. The patient received i.a. SX/LP under AT/hyper. The arterio-portal shunts are seen in (A and B). In (C) (angiogram), unique feeding artery branching off from the right proper hepatic artery (arrow) extending to left lower part (encircled tumor) is seen in (D). (B) CT after 6 months, which showed a definite reduction in tumor volume from (A). Enhanced tumor stain (drug delivery) in (D), lower left circled, is seen in the angiogram under AT/hyper.

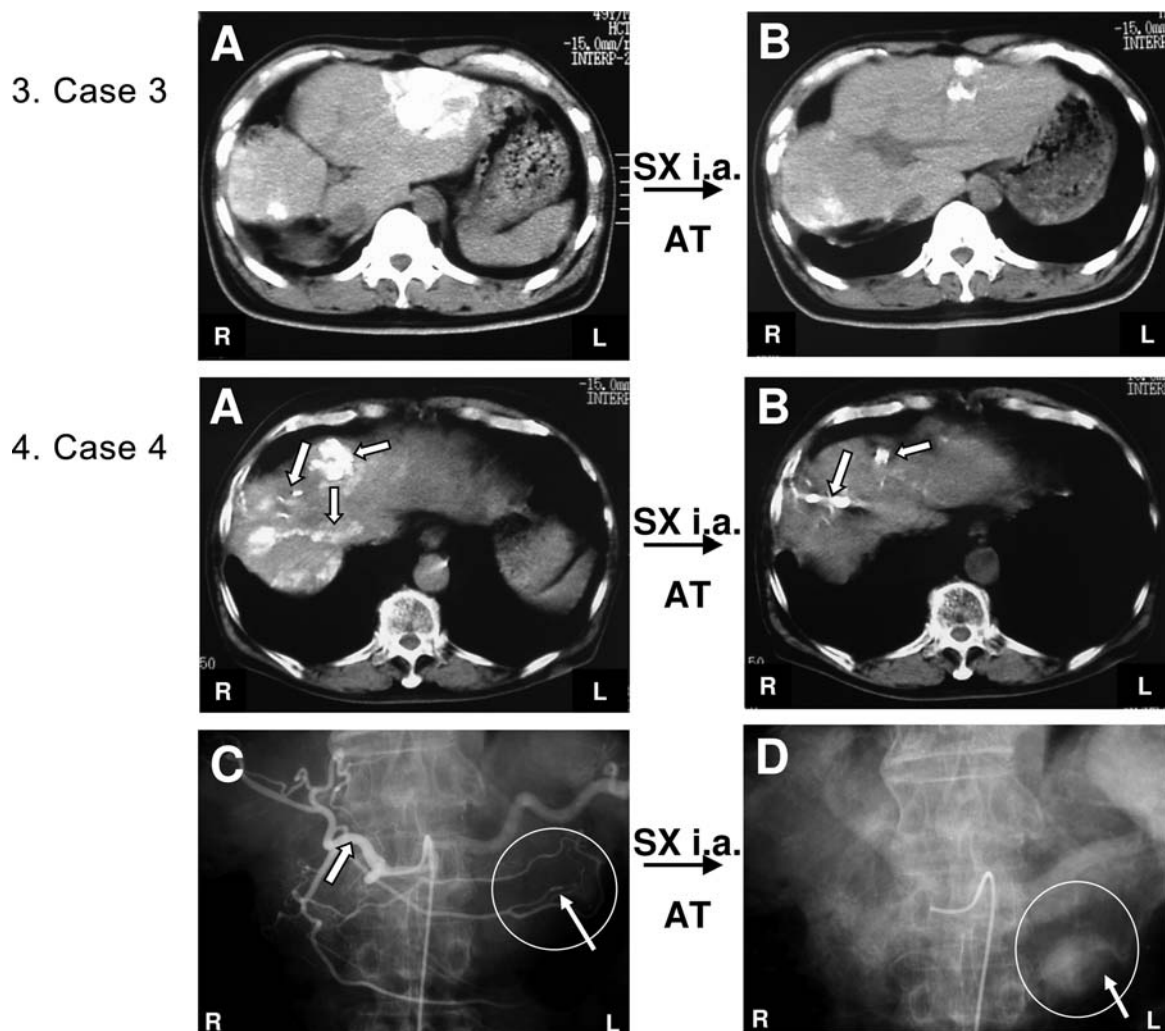


Figure 2. *Continued.*

drugs in the tumor interstitium (2,3,9,11). There are thus two important components of the EPR effect; not only in enhanced drug uptake into tumor tissues but also in prolonged drug retention giving sustained and targeted pharmacological activity.

Induction of systemic hypertension, by i.v. infusion of AT (28,29), leads to a relative increase in tumor blood flow volume, whereas that of all normal tissues and organs remains constant during vasoconstriction. In normal tissues, AT-induced hypertension accelerates the speed of blood flow but reduces the vascular diameter, the result being homeostasis of blood flow volume (28,29). On the contrary, as anticipated, we observed excessively EPR effect for macromolecular drugs in solid tumor under such conditions of induced hypertension (Fig. 1B, right and many CT scan images in Fig. 2-2A, 2-3A and 2-4A), although no increased accumulation was observed for low-molecular-weight drugs in such a manner (29). Therefore, AT-induced hypertension (AT/hyper) chemotherapy is most beneficial for only macromolecular drugs (Fig. 1B, right).

We report here the clinical development of AT/hyper to enhance the drug delivery of SX in LP (SX/LP) (Fig. 1). This is an extension of the use of AT for arterial infusion of SX/LP in the following advanced solid tumor treatment. The AT/hyper therapy for gastric cancer in conjugation with i.v. mitomycin C had been approved by the Ministry of Health and Welfare of Japan in 1990s. The method using AT under the present protocol was approved by our internal review board (IRB) of the hospital. Our standard protocol involved infusion of AT via i.v. route so as to increase mean arterial blood pressure by 20–25% (e.g. systolic blood pressure: 110→150 mmHg) during the i.a. infusion of SX/LP. This method achieves a much higher drug concentration in the tumor tissue than in normal tissue that will persist for more than 4 weeks, as judged by CT scan (see below) and quantification of macromolecular drug concentrations in an experimental and clinical solid tumor models (see CT scans in the text). SX/LP delivered to tumor released the drug SX slowly during a period of weeks. The therapeutic response of metastatic liver cancer, cholangiocarcinoma (CCC) and cancers

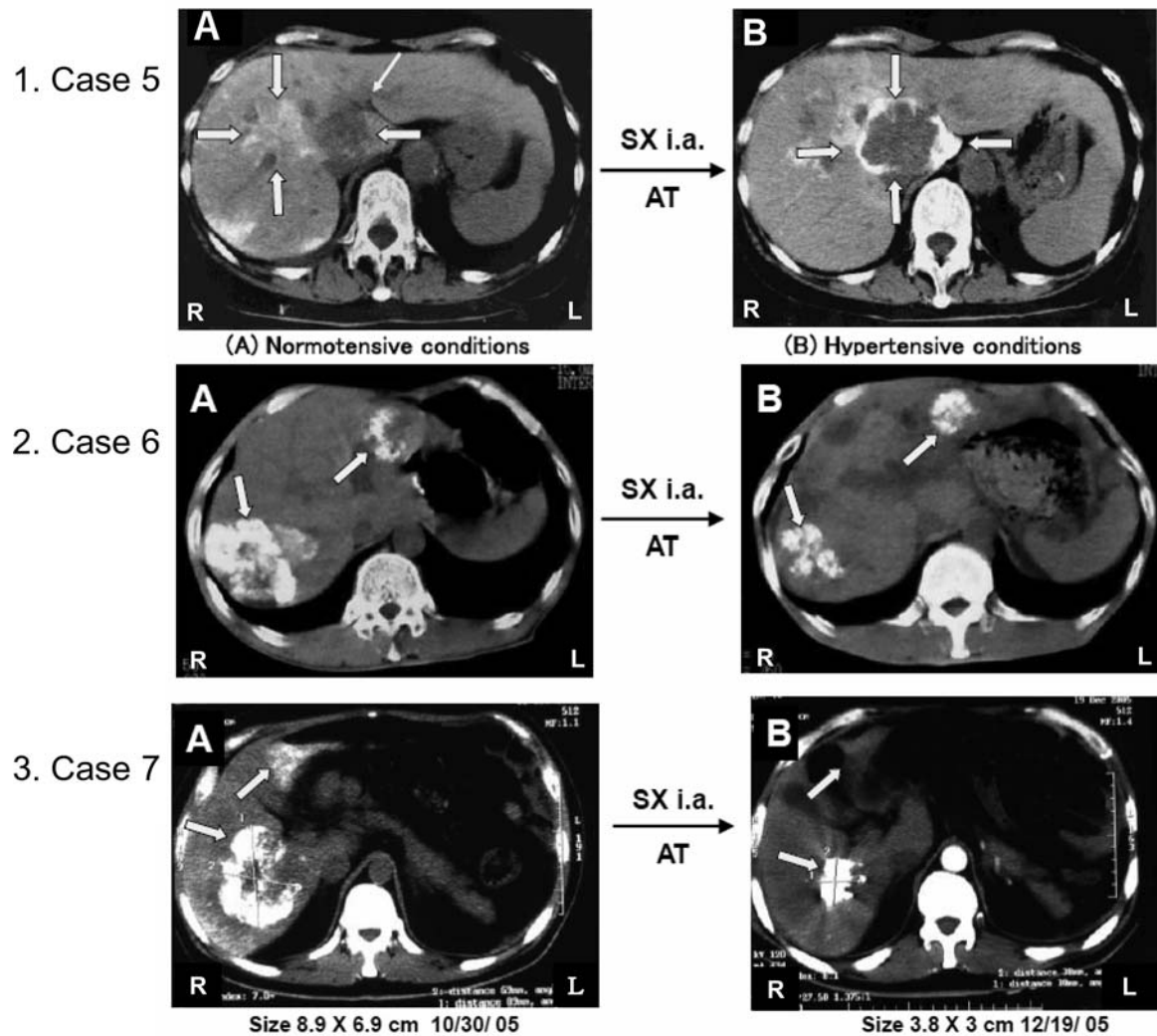


Figure 3. Responses of various metastatic liver cancers to SX/LP under AT/hyper. 1. CT of metastatic liver cancer from colon cancer (Case 5). Clear difference can be seen for normotensive (A) vs. hypertensive (B) conditions in this case. Tumor uptake of SX/LP under hypertensive conditions (B) was greater than that obtained under normotensive conditions (A). 2. CT of Case 6, stomach cancer metastatic to the liver after resection 3 years earlier. Both posterior and anterior metastatic liver tumors showed marked reductions in volume found 8 months after i.a. SX/LP infusion under AT/hyper. 3. A massive metastatic liver cancer originating from stomach cancer regressed considerably in 50 days (Case 7). The B-type staining (peripheral ring shape), usually seen in metastatic tumors by CT (1B), indicates greater drug uptake under AT/hyper (2A and 3A) than under normotensive conditions (data not shown). 4. Massive metastatic liver cancer originating from pancreatic cancer (Case 8). (A) CT of both the metastatic mass in the liver [center front in (A)] and the primary pancreatic cancer (left middle) at the time of the first infusion of SX/LP. A large metastatic tumor mass in the frontal area that regressed considerably (B) in 5 months after one injection. The primary pancreatic cancer taken up the SX/LP also (B). 5. Ovarian cancer (Case 9), which was removed surgically. However, it metastasized to the spleen and SX/LP was infused under AT/hyper (C/D). After 1 month, it showed a good response (B), which corresponded to the decrease of CA125 tumor marker after SX/LP (E). Angiography under AT/hyper shows the splenic artery and tumor in the spleen (C and D, white arrow) that is visible in the initial CT scan (A) and significant reduction after 1 month (B, heavy tumor stain). Clear radiodense area (arrow) indicates high uptake of SX/LP. A colour version of this figure is available as supplementary data at <http://www.jjco.oxfordjournals.org>.

of the kidney and the pancreas were much improved by using this AT/hyper approach, as was that of HCC (Fig. 2-1-4). Also, the high uptake of SX/LP by tumors permits identification of daughter nodules <3 mm, as well as spread and extent of tumors. Present experience has shown that estimation of the degree of drug filling can have important clinical utility. In the following sections, we present clinical observations relating to intra-arterial treatment under present protocol, using these principles, of 11 patients who presented with a range of advanced malignancies.

PATIENTS AND TREATMENT PROCEDURE FOR SX

ARTERIAL INFUSION OF SX/LP

PATIENTS AND ELIGIBILITY

Brief profiles of all patients are described in Table 1. Eligible patients included those with total bilirubin values <3.0 mg/dl; liver functions [glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), alanine aminotransferase

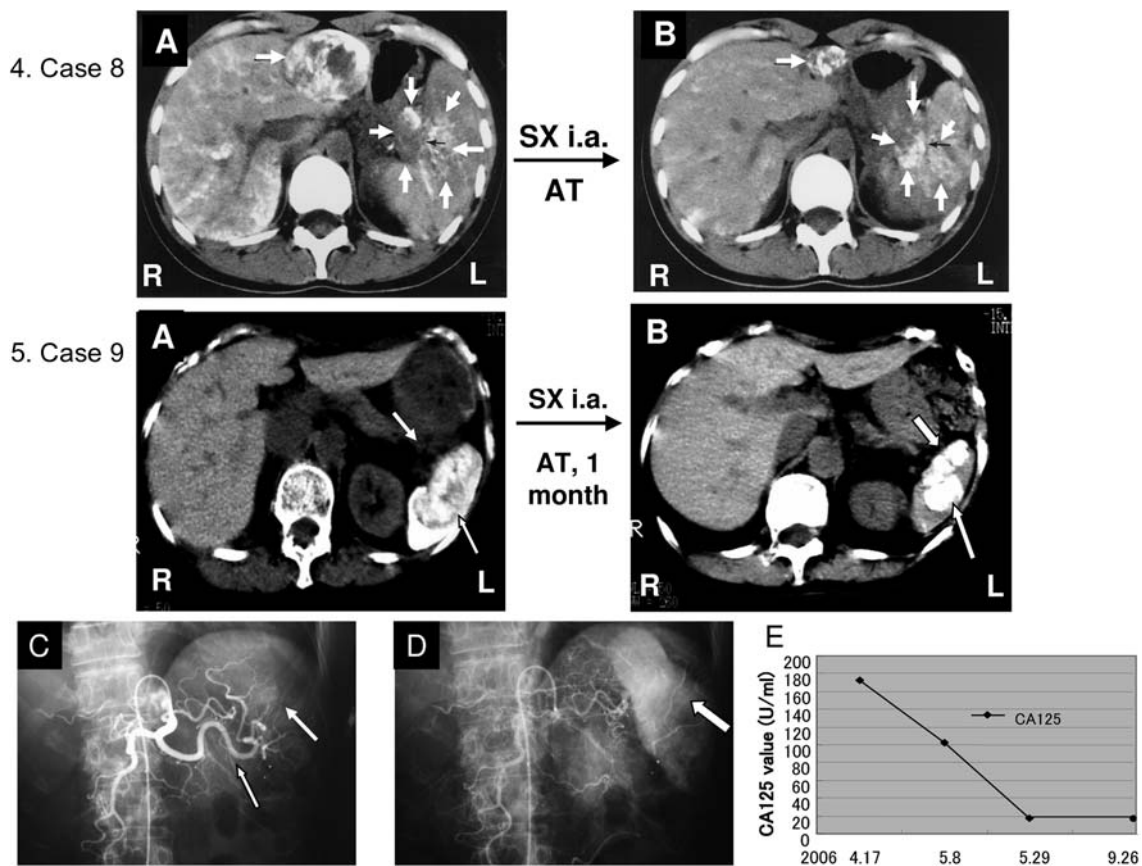


Figure 3. Continued.

(ALT), γ -glutamic-oxaloacetate transaminase (γ -GOT), respectively] and kidney functions (creatinine and blood urea nitrogen) are normal; platelet and white blood cell counts more than 5×10^4 and $4 \times 10^3/\text{mm}^3$, respectively; and no excessive ascitic/pleural fluid. Most patients were referred to our clinic with advanced solid tumors (Stage III or IV) involving, however, no more than three organs including metastatic liver cancers originating from the colon or the stomach, RCC, CCC, pancreatic cancer or recurrent HCC. These patients are age ranged between 40 and 80 years and unfit for the normal randomization study.

GENERATION OF HYPERTENSION BY SLOW I.V. INFUSION OF AT DURING ARTERIAL INJECTION OF SX/LP VIA THE TUMOR-FEEDING ARTERY

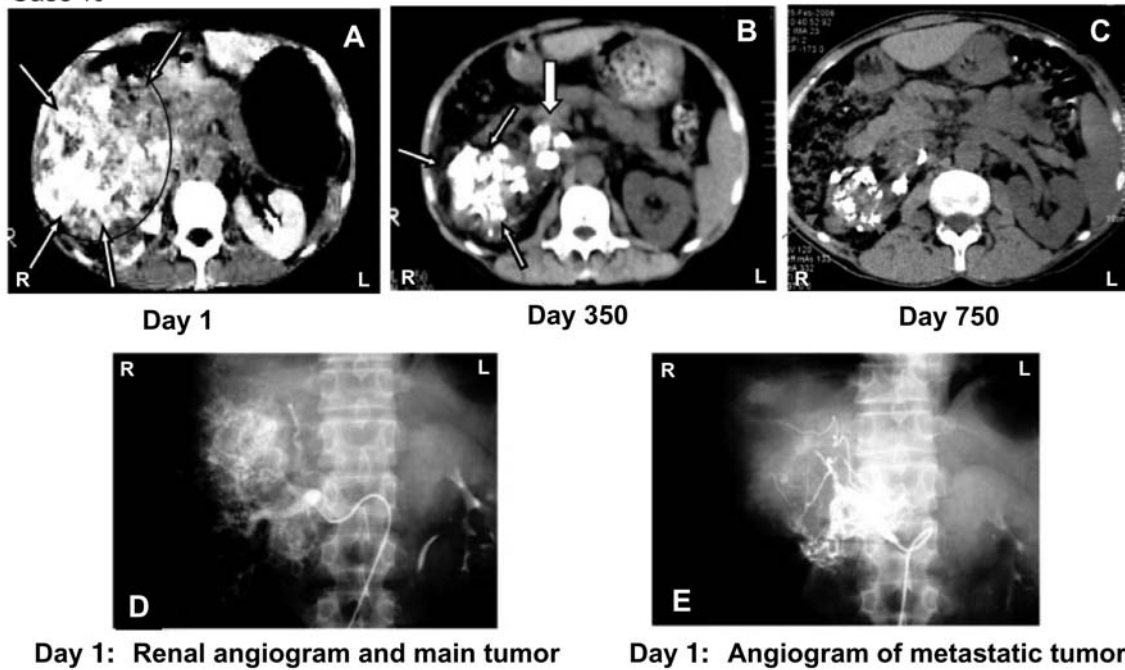
Human AT as lyophilized powder, 50 μg (Toa Eiyo Pharmaceutical Co., Tokyo), was first dissolved in 10 ml of saline, after which 2 ml was diluted 10 times with saline immediately before use. A 20 ml sample of this dilution was placed in an automatic infusion syringe pump (Model STC-525, Terumo Co., Tokyo). Polyethylene tubing from the infusion pump was connected to the vein in the left arm, and blood pressure of the right arm was measured every 2 min. The targeted hypertension value was usually 40–60 mmHg above the normal pressure, but not to exceed 180 mmHg (systolic). Raising the systolic blood pressure by 40–60 mmHg above normal by means of AT infusion usually

took 10–20 min. When the desired pressure was achieved, the arterial infusion of SX/LP would be undertaken via the Seldinger method.

ANGIOGRAPHY AND ARTERIAL INFUSION OF SX/LP BY MEANS OF THE SELDINGER METHOD

Catheterization used during angiography (Seldinger method) was performed through the femoral artery with fluoroscopic X-ray monitoring. Catheterization of the specific tumor-feeding artery varied depending on the individual tumor; e.g. the proper hepatic artery for most hepatomas and CCC and the renal artery for RCCs. Under X-ray guidance with a non-ionic contrast agent, the catheter tip was secured at the entrance of the tumor-feeding artery. In many cases, aberrant feeding arteries were observed in these tumors, e.g. intercostal, adrenal and other arteries for HCCs, metastatic liver tumors and RCCs, as discussed later. Manual SX/LP infusion requires an intermittent push of the syringe; a continuous push of the syringe should be avoided because it may result in complete filling of the vasculature or arterial embolization, thereby causing necrosis of blood vessels, damage to the normal parts of the target organ, hepatic or other organ failure, or shock. It should be emphasized that this method of SX/LP therapy is totally different from embolization, which may cause undesirable adverse effects, and indeed,

1. Case 10



2.

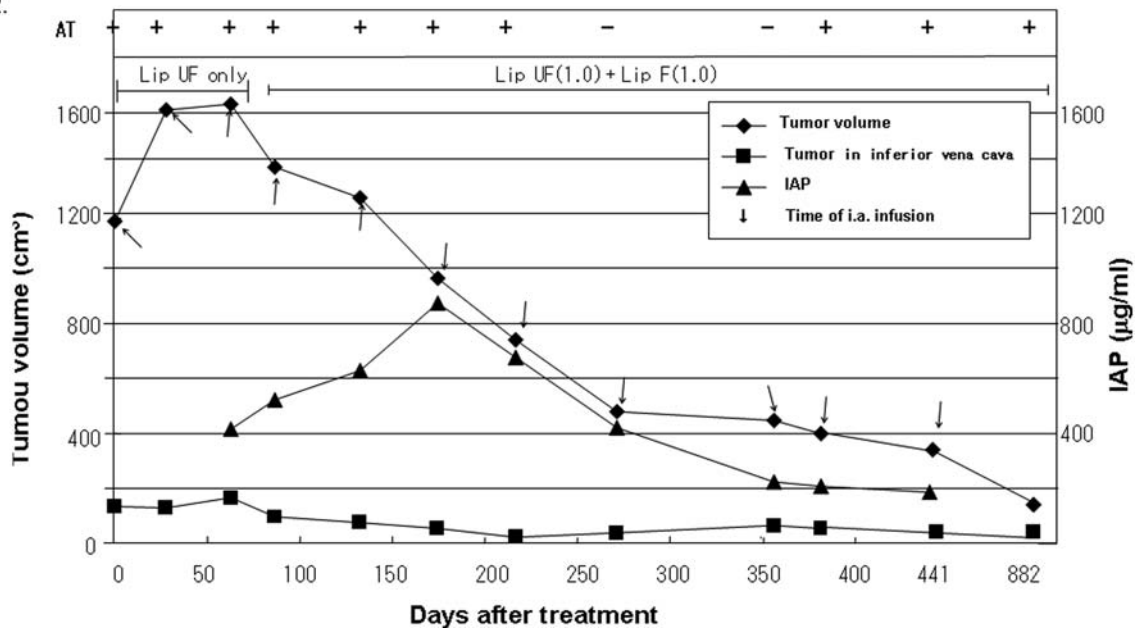


Figure 4. Renal cell carcinoma treated with SX/LP under AT/hyper. 1. (A–C) CT scans of Case 10 on Day 1, Day 350 and Day 750 over time. An initial renal angiogram showing major renal tumor in (D) and also metastatic tumor in the inferior vena cava in (E), both on Day 1. 2. Time course of tumor volume (closed diamond), tumor marker (immunosuppressive acidic glycoprotein, IAP) values (closed triangle) and estimated volume of metastatic tumor nodule (closed square) in the inferior vena cava. The times of i.a. infusions of SX/LP are indicated, as is use of AT/hyper on the top.

many problems associated with SX/LP therapy may be attributed to embolization.

According to the level of tumor uptake of SX/LP, one can semi-quantify as Grade I (<20% filling of tumor) to Grade IV (75–100% filling) for HCC in which LP uptake is predominantly inside of tumor (denoting IA–IVA), whereas metastatic liver cancer shows LP uptake predominantly at the periphery of tumor, thus denoted Grades IB–IVB. These

grading are used to indicate semi-quantitative extent of drug (SX/LP) delivery by CT image (11,13).

AT-induced hypertensive state was maintained during arterial SX/LP infusion, which usually lasted for ~20 min or less. Cessation of AT infusion resulted in a rapid drop in blood pressure and a return to a normal blood pressure within ~5 min. Our patients usually had normal systolic pressures of <160 mmHg; namely a mean systolic/

Table 1. Profiles of patients evaluated, and response to SMANCS i.a. by angiotensin II (AT)/hypertension

Case	Age, M/F	Cancer histology	Previous treatment	Location/type, previous treatments and other comments	Grade of filling of SMANCS ^a	No. of SMANCS injections	Response (+/-) (% reduction to: vol/area in CT ^b), period	Remarks
1	47, M	HCC	None	Liver, solitary massive. HBV(+) (12 × 10.6 cm)	III–IV	3	+ (→ <10% in 6 months)	Remarkable normotension (no AT)
2	73, M	HCC	Recurrence 3 years after partial hepatectomy, lung mets +	Liver, massive; 5-FU/IFN	II→IV	1	+ (→ 4% in 1 month)	Remarkable after AT/hyper ^c . Lung met caused death
3	49, F	HCC; lung met	Partial hepatectomy 2.5 years ago → recurrence	Bilobar mass; left: 7 cm × 5 cm; right: multiple	II–IV; right: I/II; left: IV	1	+ (→ 10% in 1 month)	Remarkable after AT/hyper
4	72, M	HCC	Partial hepatectomy → recurrence at 2.5 year	Bilobar multiple; TEA not possible	IV	2	+ (→ <10% in 6 months); main tumor; reduced A-P shunt	AT/hyper. New tumor appeared in left lobe after previous resection
5	56, M	Liver mets from colon adenocarcinoma	5-FU/leucovorin	Colon → liver	0–I normotensive; III–IVB AT/hyper	normotension 1 hypertension 2	+ (→ 80% in 3 months) (→ 20% in 5 months) (data not shown)	No clear stain under normotension. Typical type B staining after AT/hyper. CEA decreased markedly
6	60, M	Liver mets from stomach adenocarcinoma	Primary resected. Met in the liver after 3 years	Stomach → liver: massive one at right lobe, small egg size at left lobe	IVB	5	+ (main → 26% in 8 months); + (small → 43%)	AT/hyper. Died of peritoneal carcinomatosis
7	47, M	Liver mets from stomach adenocarcinoma	Primary resected UFT	Stomach → liver	IVB	1	+ (→ <10% in 1.5 months)	Remarkable reduction. AT/hyper
8	27, F	Liver mets, and primary in pancreas	Chemo	Massive met in liver and primary in pancreas (~6 cm)	IVB	4	primary: unchanged; + liver met (→ 13% in 5 months)	AT/hyper. Living with good QOL for 6.9 years
9	53, F	Ovarian ca. primary, met in spleen	Primary ovarian ca. resected; Metastasis to spleen	Spleen	IV (via spleen i.e. artery)	2	+ (→ 52% in 1 months)	AT/hyper. CA125: marked reduction (170→20)
10	54, M	Renal cell carcinoma	Also met to IVC	Main in kidney (16 cm × 15 cm); second in IVC (4.5 cm × 6.0 cm)	IV	11	+ (→ 10% in 2.3 years)	AT/hyper. Remarkable response: IAP ^d (840→175). Living 6 years with good QOL
11	70, F	Cholangiocarcinoma	5-FU/leucovorin	Liver	IIIB–IVB	6	+ (→ <10% in 17 months)	AT/hyper. Good QOL for 2.5 years

HBV, hepatitis virus type B; FU, fluorouracil; INF, interferon α ; Met, metastasis (+).

^aSee text for other abbreviations: Grade IV, 90–100% filling. Grade I, being 10–20% filling seen on CT scan image (11).

^bArbitrary area measured by CT image (longitude × cross-section in %) unless specified otherwise.

^cAT/hyper means SX i.a. infusion was conducted under angiotensin II-induced hypertensive condition.

^dImmunosuppressive acidic protein (tumor variant of α 1-acid glycoprotein).

diastolic blood pressure of 135/84 mmHg was observed. Some hypertensive patients with pressures \sim 160 mmHg received oral diazepam, and AT/hyper was performed after the blood pressure decreased. Slow i.v. infusion of AT raised the blood pressure to a mean of 162/97 mmHg. Although the infusions of SX/LP under AT/hyper were usually completed within 20 min, a few exceptional cases took 60 min or longer. One patient in this study experienced a mild headache during one treatment but not at other times.

CONCENTRATION OF SX AND ADMINISTRATION

A concentration of SX at 1.0 mg/ml was usually used for HCC (2,3,5), whereas for metastatic liver cancer of colorectal and pancreatic origin, CCC and RCC, it was 1.3–1.5 mg/ml. For most tumors, the drug (SX) was suspended in LP Ultrafluid UF (Laboratoire Guerbet, Paris), but for the treatment of RCC, LP used was a 1:1 mixture of Ultrafluid UF (viscosity, $\nu = 34$ cSt at 20°C) and F ($\nu = 105$ cSt at 20°C) to increase viscosity to suppress wash out by the rapid renal blood flow. The amount of SX/LP injected was determined based on the size of tumor, which ranged from 0.2 ml for a small nodule to 5.0 ml for a large tumor (e.g. cross-sectional diameter of 5 cm) (4,11,13). Multiple injections are advised for tumors >5 cm in diameter to achieve Grade IV fillings; excessive filling by one injection might cause rupture of the tumor with possible unwanted bleeding or adverse effects. This recommendation may be quite important for lung cancer (3,13,30). Setting of dose regimen based on tumor size is in contrast to that of conventional chemotherapy (4) which is based on the maximum tolerable dose, or a protocol-driven regimen of drug dosage, disregarding tumor size. Overall, an experienced angiographer can usually complete the whole procedure within \sim 20 min after administration of local anesthesia with lidocaine for the arterial puncture.

PREMEDICATION AND PRECAUTION

Premedication with an oral antihistamine at 12 h before the procedure, and/or corticosteroid (500 mg of hydrocortisone sodium phosphate) given i.v. immediately before SX/LP infusion is now a routine part of the procedure to prevent shock or anaphylaxis, which was observed more frequently during a second or subsequent infusion (such an event was very rare at the time of the first injection). No serious adverse effects occurred since adoption of this premedication procedure in our clinic. For rapid hypotension [e.g. 140 \rightarrow 100 mmHg or 100 \rightarrow 80 (or lower) mmHg], a cardio-tonic agent, e.g. etilefrine HCl, or an antihistamine, such as chlorpheniramine maleate, or both were administered, followed by hydrocortisone at 500 mg, i.v. A dose of 15 mg of pentazocine was injected i.v. or i.m. for pain caused by liver cancers.

ETHICAL ISSUES

All patients agree this procedure under the informed consent and it is approved by the IRB of the Hospital. They all sought for the present treatment.

CASE REPORT

CASE 1–4, HEPATOCELLULAR CARCINOMA

Results for four representative cases of HCC treated under either normotensive conditions or AT/hyper with SX/LP are shown in Fig. 2-1–4. Figure 2-1A is a case of 47-year-old male, presents massive HCC in a CT scan, obtained 3 days after the first injection of SX/LP (3.5 ml) under normotensive conditions. The large tumor mass shows Grades IIIA–IVA filling. After the third injection 6 months later, CT showed a $>90\%$ reduction in tumor volume (Fig. 2-1A vs. B). On the basis of more than 25 years of experience of SX/LP via i.a. route, we believe that the marked size reduction to size $<50\%$ of the targeted tumor will be usually observed when Grades III–IV drug filling is achieved. Under normotensive conditions, about 6 months is usually required for a 50% reduction in tumor volume (7,13). Figure 2-2 of Case 2, 73-year-old male, shows results for a patient (Case 2) underwent partial hepatic resection, then recurrence of tumor in the liver was detected 3 years later; massive tumor metastases were also found in the lung as were metastases in vertebral bone (data not shown). In this case, the tumor in the liver was treated under AT/hyper with SX/LP, as described above, and a marked response was obtained after only one injection in 1 month (Fig. 2-2A and B). However, the patient died 4 months later because of respiratory insufficiency caused by the lung tumor.

Figure 2-3 provided CT scans for Case 3 (49-year-old female), with a large HCC in the left lobe. About 3 ml of SX/LP was injected under AT/hyper, and Grade I/II (right lobe) and Grade IV (left lobe) were achieved (Fig. 2-3A). About 1 month later, CT showed regression of the right tumor volume to $<10\%$ (Fig. 2-3B), which indicated an impressive response. This patient was alive after 2.5 years, but we lost contact now at 3 years.

Case 4, 72-year-old male, recurrence of HCC 2.5 years after partial hepatectomy appeared (Fig. 2-4A). Multiple focal HCCs involved both left and right lobes of the liver and the arterio-portal vein (A-P) shunt (Fig. 2-4A, arrows). In this case, transarterial embolization was not possible, so the patient was referred to us. We obtained CT 3 days after i.a. infusion of SX/LP under AT/hyper (Fig. 2-4A). The CT scan in Fig. 2-4B was taken 6 months later, which indicated a good response after two injections of SX/LP in 6 months (compare Fig. 2-4A with B) (see angiograms in Fig. 2-4C and D). A new tumor stain (Fig. 2-4D) in the left lobe (encircled L and arrow) is seen, which is fed by an aberrant feeding at lower abdomen (seen in Fig. 2-4C). This stain is

invisible in CT slice (Fig. 2-4C or D) (located in lower slice).

CASE 5–7, METASTATIC LIVER CANCER

Case 5 of 56-year-old male in Fig. 3-1, involved metastatic liver cancer from colon cancer. This patient first underwent SX/LP infusion via the right hepatic artery under normotensive conditions, and only very faint LP staining if any was noted in the tumor mass in the right mid-lobe (Fig. 3-1A, Case 5), other area (central part in CT) of the tumor remained dark (low density), i.e. no uptake of LP under normotensive conditions. One week later, after SX/LP was administered via the hepatic artery under AT/hyper, it showed a marked uptake of SX/LP at the tumor periphery, a typical pattern of staining for metastatic tumors that is classified as ‘B-type’ staining (Fig. 3-1B) (11), suggesting significant central hypovascularity of the tumor. We classified the staining of peripheral ring as B-type, thus in this case Grades IIIB–IVB filling (75–100%) (Fig. 3-1B). After 3 months of one more infusion of SX/LP with AT/hyper, the patient showed falls in tumor markers (carcinoembryonic antigen and immunosuppressive acidic protein), improved performance status and a reduction of tumor volume to one-fifth of the original that persisted for at least 8 months (data not shown).

Case 6 of 60-year-old male with two metastatic liver cancer, one massive at the right posterior, and one small egg size nodule at middle frontal originating from stomach cancer, showed a striking tumor volume reduction (Fig. 3-2B) after 8 months of treatment with five infusions of SX/LP with AT/hyper (compare Fig. 3-2A vs. B). The patient’s quality of life was very good, and the metastatic liver cancer was stable for 1 year, although the patient died of peritoneal carcinomatosis.

Case 7 of 47-year-old male is shown in Fig. 3-3. It shows a marked reduction in tumor volume (to ~10% of the original) of metastatic liver cancer originating from stomach cancer. This response was achieved in 6 weeks after one injection (3.0 ml) of SX/LP (1.3 mg/ml) under AT/hyper and showing Grade IVB filling.

Case 8 of 27-year-old female is shown in Fig. 3-4. A significant effect of SX/LP under AT/hyper on metastatic liver cancer from pancreatic cancer was obtained. Five months of treatment (four injections) caused reduction of the main metastatic liver tumor to be ~13% in volume. The pancreatic tumor (original, left side with arrows) appeared stable during treatment (Fig. 3-4A). The metastatic pancreatic tumor in the liver (middle frontal) showed Grade IVB filling with good uptake of SX/LP. After subsequent injection, considerable regression was observed in 5 months of treatment (cf. Fig. 3-4B). The patient remains alive 6.5 years after the present protocol of AT/hyper began. Under normotensive conditions, delivery of SX/LP to pancreatic cancer was poor; however, the use of AT/hyper made drug delivery far better (Fig. 3-4A vs. B). A potentially good therapeutic response thus appears possible.

CASE 9, 53-YEAR-OLD FEMALE OF SPLENIC METASTASIS

Figure 3-5 presents results for ovarian tumor that had metastasized to the spleen. She had undergone an ovariectomy to remove the primary cancer. However, a splenic metastasis was detected by ultrasonography 2 years later, and the patient was referred to our hospital. A significant decrease in tumor size was seen after 6 weeks (Fig. 3-5A → B, and the value of the tumor marker CA125 declined to 10% of the initial value in 2 months (Fig. 3-5E). The patient was well, with a good quality of life and without further treatment, until January 2007. In January 2007, when the CA125 value reached 27 U/ml, the patient received another 2.0 ml of SX/LP under AT/hyper and follow-up continued in December 2008.

CASE 10, 54-YEAR-OLD MALE OF RCC

Successive radiological images for Case 10 with a massive unilateral RCC, cross-sectional diameter ~16 cm, are shown in Fig. 4-1. The patient (male, 54 years) was referred to us 5.5 years ago. At his first visit, this patient appeared very weak, with Karnofsky’s performance status of 30. Initial SX/LP under AT/hyper showed Grades III–IV filling of the primary tumor (Fig. 4-1A) and he had only one metastasis, which is clearly seen in the inferior vena cava laden with SX/LP (Fig. 4-1B, D and E). For the first 8 months, the patient received monthly injections of SX/LP under AT/hyper, thereafter the intervals between injections became longer. Both the main tumor and the secondary tumor in the vena cava showed significant regression in volume (Fig. 4-2). After more than 5.5 years of treatment (11 i.a. infusions), he is doing well, with Karnofsky’s performance status of 100 until now. Tumor size, marker and dosing of SX/LP AT/hyper are shown in Fig. 4-2.

Tsuchiya et al. has treated RCC with SX/LP under normotensive conditions in combination with native interferon- α given i.v. followed by nephrectomy. They achieved 75% survival of patients after 13 years for the patients with RCC >11 cm, which was a good response rate for RCC as this regimen (6).

CASE 11, 65-YEAR-OLD MALE OF CCC

Case 11 involved CCC in a 65 years male (Fig. 5A). SX/LP infusions were performed via the hepatic artery under AT/hyper. The patient received eight infusions during 2 years, with the result that tumor volume decreased continuously (Fig. 5C); tumor marker also declined (data not shown). The Karnofsky performance status of the patient became 100, and no recurrence was seen for at least 2.5 years. He died of hepatic failure after 3 years. We have several cases like this with good outcome.

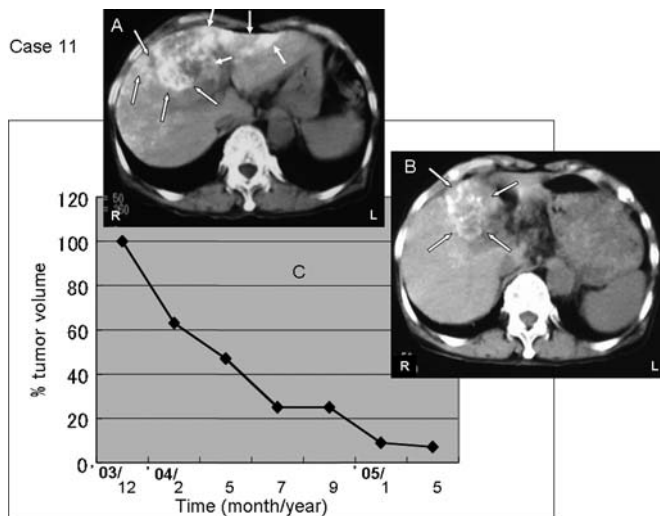


Figure 5. Effects of SX/LP on cholangiocarcinoma. Case 11 showed a steady decrease in tumor volume as shown by CT (A and B) and by tumor size measured in volume (C). Multiple injections (8×) were performed in 2 years.

DISCUSSION

ADVERSE EFFECTS

In general, adverse effects of intra-arterial SX/LP given under AT/hyper are less than those seen under normotensive conditions. Toxicity such as suppression of bone marrow, impaired liver and renal functions, hair loss and loss of appetite usually occurred in <1–5% of patients receiving normotensive SX/LP therapy, according to a post-marketing survey data of the manufacturer based on 3956 patients (data not shown) (30). The major adverse effect was a low-grade transitory fever (temperature 37–39°C), which may be seen between 20% and 30% of subjects during the first week after the infusion and may be attributed partly to the host response including an inflammatory reaction (13). With our present protocol, using SX/LP under AT/hyper, such adverse effects seem to occur less frequently than normal administration, although detailed critical evaluation is still needed. Other adverse effects such as anaphylaxis (shock) were observed infrequently using the normotensive protocol, usually after the second or subsequent injection. The use of medications before angiography eliminated the occurrence of these events in the AT/hyper protocol as described before. Allergic reactions and anaphylaxis (shock), for example, were almost completely eliminated under the present protocol.

CASES WITH POOR RESPONSE TO TREATMENT AND WITH MILD HYPERTENSION

Responses of patients with HCC to SX/LP infusion, as measured by α -fetoprotein (AFP) values, varied according to individual cases, although >90% eventually responded. The response pattern was classified as follows. The best response

was a progressive decrease as seen by AFP; this response occurs most often. At other times, we may observe a slight increase in AFP values, even though Grade II or IV filling of SX/LP is noted on CT scans. Reasons for this may be reflecting (i) shedding of AFP from dead tumor tissue, which may enter the blood circulation; (ii) growth of other tumor nodules at the sites of insufficient drug filling (Grade I or 0), or aberrant feeding arteries may exist but not identified; and (iii) rapid washout of SX/LP and new tumor growth, or continued growth of tumor accompanied by increased AFP. In such cases, additional or more infusions would be needed. The AFP value is then expected to decrease, if the proper tumor-feeding artery is targeted.

Patients with mild hypertension, who were taking antihypertensive medication, were advised to cease taking the medication 2 days before the infusion of SX/LP, although such cases were rare (i.e. at most 1 of 50 in our cases). There was a great variation in the response to AT during its infusion if patients were receiving antihypertensive agents; their response to AT was very slow, so that larger doses of AT (e.g. 30–50 ng/min instead of the usual dose of 10–20 ng/min) were needed to achieve the desired blood pressure. In such cases, abrupt increases in blood pressure during AT infusion should be watched.

ADVANTAGES TO THIS NEW TREATMENT STRATEGY

Uptake of SX/LP into poorly vascularized tumors such as metastatic liver cancer and pancreatic, the use of SX/LP with AT-induced hypertension promises important treatment options for currently untreatable common cancers and has several important features that warrant its clinical use. Most notably, an antitumor effect is invariably seen when tumor drug-filling of Grade III or IV can be achieved. This allows predictive assessment of likely outcome and also enables development of imaging-guided treatment protocols. In addition, the response time is shortened in many cases, with tumors showing significant shrinkage in a period of just a few weeks. Interestingly, this is much faster than is normally seen with conventional normotensive SX/LP protocol and, probably, reflects the greater drug loading in tumor that can be achieved with AT/hyper.

Most importantly, the use of this transient hypertension allows entirely new treatment option for different tumors and with macromolecular drugs including antibody conjugates. Namely, a series of clinical studies by our group in Japan have shown very encouraging responses, including definite regression of most of the advanced tumors which was quite remarkable in the cases of metastatic liver cancer, massive RCC and CCC. In addition, toxicities were easily manageable and almost all patients had a good quality of life. Given the safety and clinical usefulness of this approach, we warrant benefit of large-scale evaluation of this technique for the treatment of various advanced solid tumors to meet the urgent clinical needs.

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Conflict of interest statement

None declared.

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