1.0–1.5 mg/ml appears ideal in this respect; a higher concentration was recommended for metastatic liver cancer and renal cell carcinoma of 1.3–1.5 mg/ml. For cholangiocarcinoma and pancreatic cancer, a concentration of 1.2–1.3 mg/ml can be recommended [15, 27].

3.4.2
Use of NO-Releasing Agents

The second method we developed recently is the use of nitroglycerin ointment [42]. Nitroglycerin has been used for treating angina pectoris or cardiac infarct in humans for more than 100 years. Both tumor tissue and infarct cardiac tissues show low oxygen tension (pO_2). Nitroglycerin is known to be absorbed from the skin rapidly and enter the general circulation effectively within 5 min. In the hypoxic tissue (where low pO_2 is prevalent) NO_2^- is liberated from nitroglycerin and nitrite (NO_2^-) is further reduced to NO• (Figure 3.13a).

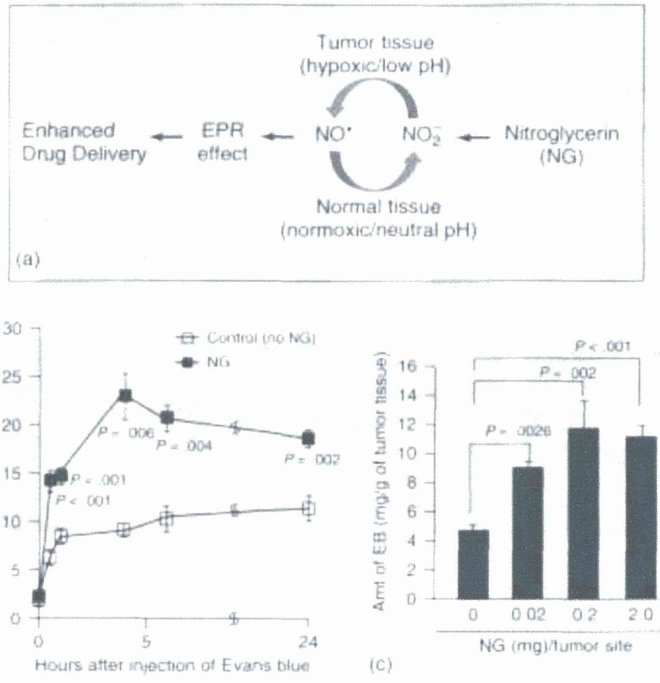

Figure 3.13 Another method to augment the EPR effect in tumor-bearing mice. (a) Conversion of nitroglycerin to nitrite to NO in the tumor. (b) Enhanced drug delivery to the tumor at different timepoints. (c) Effect of the dose of nitroglycerin on the EPR effect measured after 6 h of treatment of glycerin ointment on the skin [42].

It is intriguing that this process occurs more selectively in tumor tissues, such as seen in the infarct cardiac tissue when compared to normal tissues. As stated above, NO is one of the major factors that facilitates the EPR effect [16–20, 29, 42, 43], and hence it will trigger vascular leakage and thus enhance tumor delivery (2- to 3-fold) (Figure 3.13b and c) [42]. Consequently, nitroglycerin application augmented the EPR effect in rodent tumors and hence the therapeutic effect was also augmented in all four experimental tumor models (S-180, colon 38, Meth A, and chemical 7,12-dimethylbenz[*a*]anthracene-induced rat tumors).

More importantly, this account was validated by Yasuda *et al.* and Graham *et al.* even with commonly used anticancer agents in human patients [44–46]. It is also surprising that both mouse and human data showed that nitroglycerin alone has a tumor-suppressive effect that is as good as a single anticancer agent alone without nitroglycerin.

3.4.3
Use of Other Vascular Modulators

In terms of modulation of the EPR effect by use of vascular mediators, we have previously demonstrated enhancement of the EPR effect by angiotensin II-converting enzyme (ACE) inhibitors such as enalapril. As a result of the analogy in the amino acid sequence of angiotensin II and bradykinin, the ACE inhibitor also blocks the degradation of bradykinin. This means that by administrating the ACE inhibitor, the concentration of bradykinin at the tumor site will remain higher because of suppressed degradation of bradykinin. This account is briefly described by Noguchi *et al.* [47], demonstrating that the increased tumor delivery of even a monoclonal antibody was about 2-fold higher when enalapril and angiotensin II were combined.

We also examined the prostaglandin I_2 agonist, sodium beraprost, in order to enhance the EPR effect. Namely, sodium beraprost given orally has a much longer plasma half-life than parental prostaglandin I_2 and can induce tumor-selective enhanced drug delivery [48].

Very recently, we found CO (gas) is a mediator of EPR effect. CO (carbon mono oxide), together with biliverden and Fe^{+}, are generated by heme oxygenase using heme and oxygen as substrates. Therefore, induction of heme oxygenase by such as hemin (49), UV irradiation, reactive oxygen species as well as NO (50) can be used as enhancer of EPR effect (49).

3.5
PEG Dilemma: Stealth Effect and Anti-PEG IgM Antibody

As more PEGylated macromolecular drugs are explored, it has been realized in recent years that cellular uptake of PEGylated nanoparticles is not as efficient as one wished for, although PEGylated particles can reach the tumor site selectively by the EPR effect (e.g., [51, 52]). The reason is that the hydrated barrier of the surface of PEGylated particles impedes contact of the PEGylated particle to the cell surface receptors, which can result in less-efficient cellular uptake of the

PEGylated nanoparticles. This is now referred to as the "PEG dilemma" [53, 54]. To overcome this problem, Harashima and others recently [53, 54] proposed to select a shorter chain of PEG or proteolytically cleavable type of bonds between PEG chains and effector molecules for drug delivery. We also reported that PEG linked via an ester bond was more preferred over PEG chains bound through an amide bond [55–57]. Alternatively, different types of polymers (e.g., SMA) have been proposed that exhibit improved cellular uptake [57].

Another problem related to PEGylated drugs as pointed out by Ishida *et al.* [57] is a rapid clearance from the circulating blood, which becomes apparent when a PEGylated drug is injected, not at the first time, but at subsequent injections after 3–7 days of the first injection. They identified PEG-specific IgM antibodies being formed, which is a cause for the rapid elimination from plasma where the IgM antibody complexed with PEGylated drug is cleared by the liver or macrophages [57].

3.6 Concluding Remarks

It is now well known that solid tumor tissue has extensive angiogenesis with pronounced vascular permeability enhancement (EPR effect), albeit some part of the tumor mass may exhibit hypovascular properties or necrotic mass. Thus, tumors may exhibit an inconsistent EPR effect when tumors become larger in size and exhibit a diminished vascular permeability effect. The biological importance of the enhanced vascular permeability is primarily to support the nutritional and oxygen supply to rapidly growing tumor cells.

Heterogeneity of the EPR effect, however, poses a problem in drug delivery that exploits the EPR effect. In this chapter, I have described basic aspects of the EPR effect and its heterogeneity, followed by methods of augmenting drug delivery in tumors with a decreased EPR effect in order to overcome this drawback in relation to passive targeting. Namely, one method to enhance the EPR effect is to utilize angiotensin II-induced hypertension. Some clinical successes using this method were described. Another method is to use the NO generator, nitroglycerin. It was found that nitroglycerin can affect hypoxic tumor tissue more selectively than normal tissues or organs, similar to the cardiac tissue of pectoris angina. Both these methods exhibit significantly improved drug delivery and therapeutic effects.

Our earlier finding regarding the EPR effect of macromolecular drugs in combination with lipid particles could archieve by far the most tumor-selective delivery using arterial infusion into the tumor-feeding artery. Namely, the drug level of tumor to blood ratio is greater than 2000 [24], and no other method is more universally and selectively unique to tumor tissue. Therefore, there is no reason not to utilize further strategies of augmenting the EPR effect in order to achieve an improved tumor-selective drug delivery. Methods such as the use of ACE inhibitors, nitroglycerin, or sodium beraprost, and HO-1 inducer (hemin) or even angiotensin II-induced hypertension are simple. Another important aspect of the EPR effect is its sustained drug retention and release in the tumor tissue. Thus,

the use of macromolecular drugs and enhancers of the EPR effect undoubtedly warrants further clinical study. Considering the potential benefit and the great numbers of suffering patients, negligence or unwillingness to adapt such safe and inexpensive therapeutic options is a frustrating reality.

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47
Liver Tumor Targeting

Katrin Hochdorffer, Giuseppina Di Stefano, Hiroshi Maeda, and Felix Kratz

47.1
Introduction

Liver cancers or hepatic cancers develop from liver tissue (primary liver cancer), in contrast to liver metastases that are formed by cancer cells migrating from other organs to the liver (secondary liver cancer). There are three types of primary liver cancer: cholangiocarcinoma, hepatoblastoma (which occurs predominantly in childhood), and hepatocellular carcinoma (HCC), which all differ regarding their cause, symptoms, diagnosis, and treatment. Due to the frequency of HCC (approximately 80%), this malignant disease will be discussed in detail in this chapter [1].

47.1.1
Epidemiology and Incidence of HCC

Currently, HCC is the fifth most common malignant tumor in the world. The geographic distribution of the incidence of HCC as shown in Figure 47.1 is variable and increases in developed countries [2]. The HCC incidence varies from less than 10 cases per 100 000 persons per year in Western countries to 50–150 cases per 100 000 people per year in parts of Africa and Asia [3, 4]. The American Cancer Society expected that in the United States the number of new cases of liver cancer would reach around 24 120 and predictable mortalities for liver cancer around 18 910 for both sexes in the year 2010 [5].

Apart from chronic hepatitis B, C, and D virus infections, the highest HCC risk factor in Western countries is alcohol-induced liver disease. Other risk factors include diabetes mellitus, nonalcoholic steatohepatitis, and obesity for males. HCC prevalence is more than twice as high in men as in women. Patients with chronic liver disease, in particular liver cirrhosis, have an increased risk of developing HCC. The HCC risk also correlates with the etiology, duration, and activity of the underlying liver disease. In general, the highest HCC risks pertain to patients with chronic hepatitis B or C virus with hereditary hemochromatosis or alcoholic toxic liver cirrhosis [6]. Patients with liver cirrhosis caused by a primary biliary

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Edited by Felix Kratz, Peter Senter, and Henning Steinhagen.

In summary, L-HSA–DOX is a promising lactosaminated albumin conjugate of DOX that has pronounced antitumor activity in an autochthonous liver tumor model, is effective against all forms of HCCs, and has a very favorable toxicity profile due to low levels in extrahepatic tissues.

47.3.2.3 SMANCS: A Conjugate of Poly(Styrene-co-Maleic Acid) and the Antitumor Agent Neocarzinostatin

Neocarzinostatin (NCS) is a macromolecular chromoprotein of a highly potent bicyclic dienediyne antibiotic (as shown in Figure 47.16) bound tightly and non-covalently with high affinity ($K_d = 10^{-10}$ M) to a 113-amino-acid apoprotein. The chromophore is a very potent and labile DNA-damaging agent, and is protected and released from the apoprotein to interact with its target DNA. Opening of the epoxide under reductive conditions present in cancer cells leads to a diradical intermediate through a Bergman cyclization and eventually double-strand DNA cleavage [148].

The major limitations of NCS are its great toxicity (primarily bone marrow suppression) and its very fast clearance rate. Thus, in order to improve the pharmacokinetic profile, to reduce the systemic toxicity as well as the tumor targeting properties, poly(styrene-co-maleic acid) (SMA) was conjugated to NCS by coupling amino groups of the apoprotein to the maleic anhydride groups of the alternating copolymer of SMA (Figure 47.17) [146, 147].

Due to a considerably increased hydrophilicity, SMANCS exhibits high affinity to a lipid contrast agent (Lipiodol), and thus a lipid formulation, SMANCS/Lipiodol, was used in clinical practice where an intra-arterial route of administration gave the best preclinical and clinical results [146–153].

In preclinical models by infusing a lipid contrast agent, such as Lipiodol, with/without the polymeric anticancer drug SMANCS via the tumor-feeding arterial route, Lipiodol is very effectively taken up by the tumor [149]. As an example, the results of treatment with SMANCS in a liver tumor model in rabbits are shown in

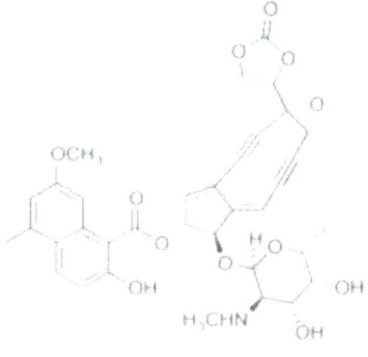

Figure 47.16 Chemical structure of the highly toxic chromophore dienediyne antibiotic of NCS (see ref. 148).

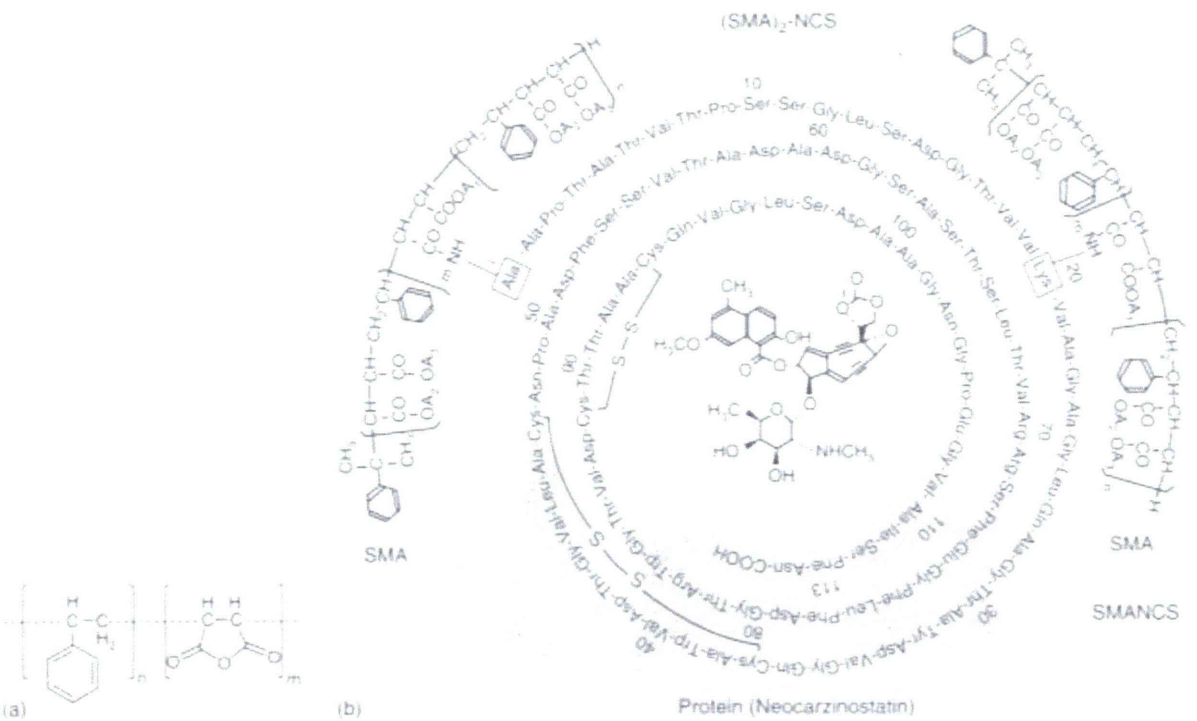

Figure 47.17 (a) Schematic structure of SMA. (b) Structure of SMANCS, which consists of the NCS (protein + chromophore) and SMA

Figure 47.18a–d, in which VX-2 papilloma cells (around 2×10^6) were implanted in subcapsular parenchyma of the left anterior lobe of the rabbit liver [151]. In Figure 47.18a–d, soft X-rays of the liver with large size tumors are shown after SMANCS/Lipiodol (0.1 mg/0.1 ml) was injected into the proper hepatic artery. All liver tumors show significant tumor selective uptake of Lipiodol as white stains that were retained for more than 7 days, whereas no clear uptake in the normal liver parenchyma was noted after day 3 [151]. Quantitation of radioactive Lipiodol indicated that tumor selectivity over other normal organs or tissues was more than 100-fold [149], and the ratio of tissue drug concentration of the tumor/blood was

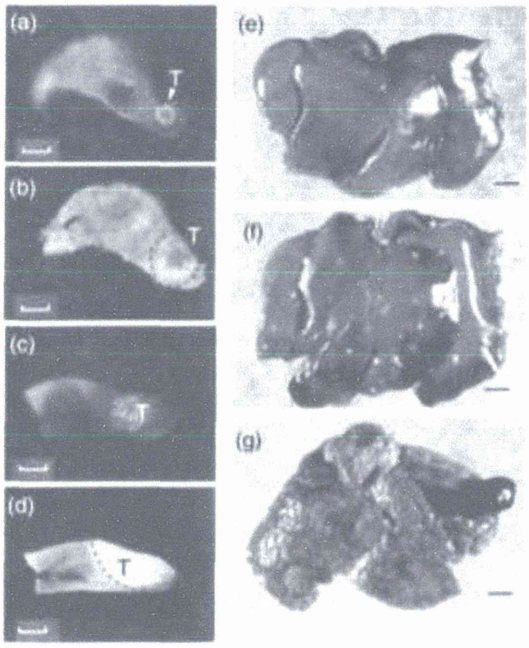

Figure 47.18 (a)–(d) Soft X-ray film images of sliced liver with experimentally implanted VX-2 tumor obtained after arterial injection of SMANCS/Lipiodol(0.1 mg/0.1 ml). (a) 15 min after injection, (b) after 1 day, (c) after 3 days, and (d) after 7 days. Note: at 15 min in (a) and day 1 in (b), Lipiodol is still retained in the vascular bed, which gradually disappeared after a few days, as shown in (c), day 3. One day after the intra-arterial injection, Lipiodol is still retained in normal parenchyma although Lipiodol is more clearly seen in the tumor nodules. By days 3 and 7, tumor staining became more distinct as Lipiodol was cleared by the lymphatic system in the normal tissue in contrast to tumor. (e)–(g) Suppression of metastatic liver tumor (VX-2) by SMANCS/Lipiodol in rabbit. Tumor cells (VX-2) were inoculated via the portal vein of rabbits ($n = 12$ per group) and SMANCS was injected on the same day via the same route. (e) SMANCS/Lipiodol(0.4 mg/0.4 ml/kg), (f) SMANCS in 5% glucose (0.4 mg/0.4 ml/kg), and (g) control, with vehicle 0.4 ml saline only. Bar = 1 cm. All livers were removed 12 days after drug injection. The SMANCS/Lipiodol group showed no tumor nodules in 44% of tested rabbits. In contrast, the majority of the livers of the control group (no drug) showed more than 500 tumor nodules/rabbit in 58%, > 100 nodules in 90% of the rabbits ($n = 12$) [151].

about 2000. When such rabbit livers were examined at later timepoints, remarkable differences of tumor growth compared to the control group without drug were seen (Figure 47.18e–g), where SMANCS/Lipiodol given via the proper hepatic artery resulted in remarkable suppression of tumor growth. Even SMANCS alone in 5% glucose (Figure 47.18f) showed significant effects when compared with the untreated control group (Figure 47.18g).

Due to these promising results and subsequent toxicological studies, SMANCS was investigated in clinical trials for treating patients with HCC [152, 153] (see Section 47.4). SMANCS/Lipiodol was approved in 1993 for the treatment of HCC and marketed by Yamauchi Pharmaceutical (now Astellas Pharma).

47.3.3 Development of Nanoparticles for Treating Liver Tumors

Prominent examples of drug-encapsulated nanoparticles are Doxorubicin Transdrug and a PBCA–mitoxantrone nanoparticle. A DOX-loaded PIHCA nanoparticle, also known as Doxorubicin Transdrug, was determined in *in vitro* and *in vivo* studies, and later in clinical trials. The results of the *in vitro* data were promising due to the high antitumor efficacy on HCC of PIHCA–DOX versus free-DOX as control. These nanoparticles can bypass the multidrug resistance (MDR) phenotype, which is responsible for the chemoresistance of HCC [154]. They showed promising antitumor efficacy in preclinical tumor models and Doxorubicin Transdrug was subsequently studied in clinical trials for regional therapy of liver tumors (see Section 47.4).

A further nanoparticle – a PBCA nanoparticle loaded with mitoxantrone (dihydroxyanthracenedione (DHAD)), an antineoplastic agent used in the treatment of various forms of cancer – showed promising results in a phase II clinical trial in the treatment of patients with unresected HCC (see below).

In contrast, in a phase I clinical trial in patients with refractory solid tumor a nanoparticle with the same polymer (i.e., a DOX-loaded PIHCA nanoparticle) was unsuccessful due to side-effects such as allergic reactions, fever, and bone pain [48].

47.3.3.1 Doxorubicin Transdrug

PIHCA nanoparticles, which are known to bypass MDR, were loaded with DOX (PIHCA–DOX) and tested in *in vitro* and *in vivo* studies. The 50% inhibitory concentration (IC_{50}) of PIHCA–DOX and DOX was determined in different human hepatoma cell lines, and the results showed higher cytotoxicity of PIHCA–DOX versus DOX. Conversely, unloaded PIHCA nanoparticles and DOX that were administered together did not increase the chemosensitivity/antitumor property of free-DOX. Consequently, the antitumor efficacy of PIHCA–DOX was due to the encapsulation of DOX into PIHCA nanoparticles [49].

The antitumor efficacy was determined *in vivo* in a transgenic murine model. In a first study the maximum tolerated dose (MTD) was found to be 9 mg/kg and this value was used for administration to transgenic mice. Four groups of transgenic mice were intravenously administered with one injection of PIHCA–DOX

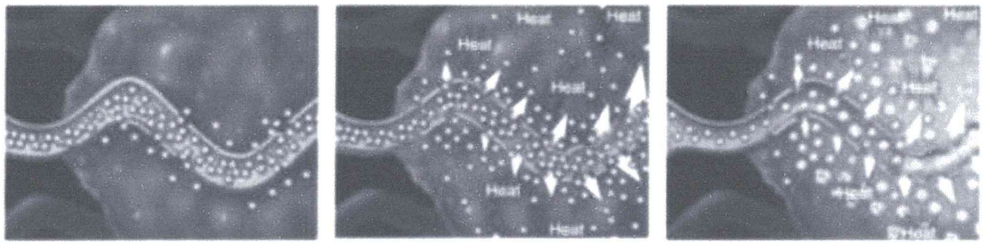

Figure 47.26 (a) Leaky tumor vessels (37 °C), (b) heat adds permeability (39 – 41 – 42 °C), and (c) mechanical release at 39–42 °C. (Reproduced courtesy of Celsion.)

15 patients receiving less than 50 mg/m² DOX had an average time to treatment failure of 80 days. Based on this data, Celsion has initiated a global phase III HEAT study with ThermoDox that is being conducting under a Special Protocol Assessment with the FDA. Six hundred patients are being assessed in this clinical trial in sites in the United States, Hong Kong, Canada, Taiwan, South Korea, China, and Italy. The antitumor efficacy is determined in patients receiving ThermoDox in combination with RFA compared to patients who receive RFA as control. The primary endpoint of this global trial is progression-free survival with a secondary confirmative endpoint of overall survival. Celsion expects an end of the clinical study by the middle of 2011 (for further information, see www.celsion.com).

47.4.5
SMANCS: A Conjugate of SMA and the Antitumor Agent NCS

As early as 1982, Maeda *et al.* reported on the remarkable therapeutic effect of SMANCS on primary hepatoma (HCC), in which SMANCS dissolved at a concentration of 1 mg/ml in the lipid contrast agent Lipiodol was infused via the hepatic artery [152, 153, 159]. The dose with respect to the volume of the SMANCS/Lipiodol solution that is applied may vary depending on the size of the tumor [58, 160, 161]. Usually, for small size tumors with maximum cross sections less than 2 cm, the administered volume may be about 1–1.5 ml; for those with a diameter of 2–3 cm, the administered volume can be increased to about 1.5–3 ml; and for those with a tumor diameter of 4–6 cm, the administered volume can be increased to 4–5 ml. As stated below for larger tumors (greater than 6 cm), the infusion volume should be divided into multiple doses with intervals of about 4 weeks be repeated 2–3 times. Most HCC patients need subsequent treatment after 4 months. As described Chapter 3 in this volume, arterial administration of SMANCS/Lipiodol results in selective drug delivery to cancer tissue with great efficiency (i.e., the tumor/blood plasma ratio of the drug is greater than 2000) [149]. The EPR effect is clearly observed in computed tomography (CT) scan images taken 2–3 days after infusion of SMANCS/Lipiodol, and one can follow the tumor-selective targeting as well as response using this method. This pronounced

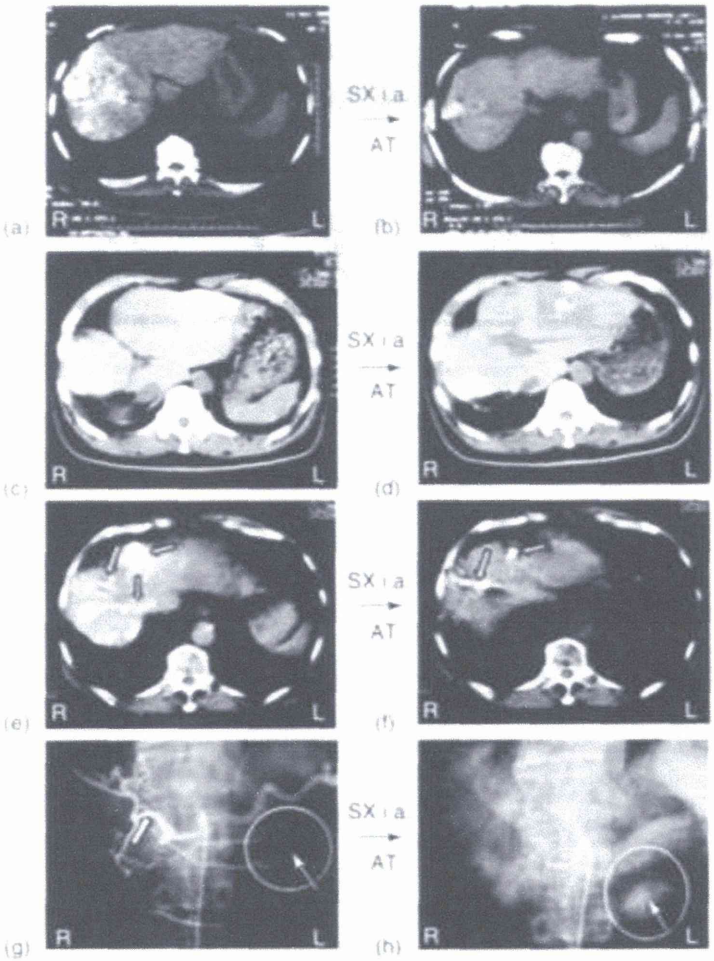

Figure 47.27 X-ray CT scan images of HCC either solitary/massive type (a and c) or recurrent case (e) with arterio-portal shunt. The figures show CT scan images of the malignant liver of the patients before and after arterial infusion of SMANCS/Lipiodol (SX-i.a.) with concomitant angiotensin II (AT)-induced hypertension. In (a)–(f), white areas indicate tumors with SMANCS/Lipiodol retention as well as the spinal and costal bones [162]. All three cases showed rapid tumor regression within 1 month (see text). In (g), metastatic tumor nodule is invisible in the angiography under the normotension. However, it becomes visible under the angiotensin II-induced hypertensive state in the angiogram (h) (see arrow in the circle) indicating enhanced drug delivery effect under hypertensive state.

targeting effect may be due to the EPR effect as well as the first-pass effect (see Figure 3.1, 3.5, 3.8 and others in Chapter 3, and Figures 47.27 and 47.28).

In patients with HCC, the response rate with SMANCS/Lipiodol, when properly infused into the hepatic artery, is more than 90% for Child A and B cirrhotic stage of the liver. White areas demonstrate tumors that have accumulated

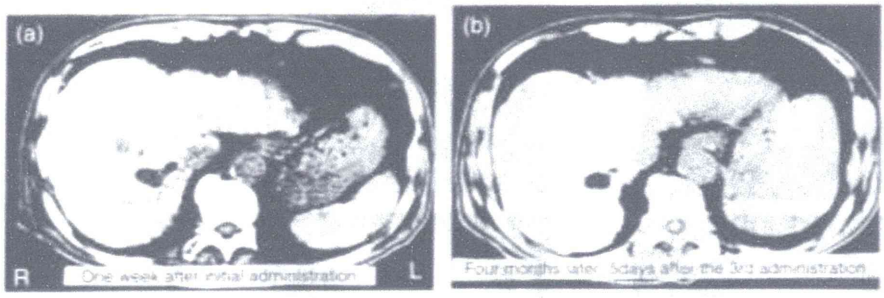

Figure 47.28 X-ray CT scan images of multinodular HCC after arterial infusion of SMANCS/Lipiodol. (a) One week after the infusion under normotensive states. Note numerous tumor nodules in the entire liver have taken up SMANCS/Lipiodol. (b) The same image after 4 months. The patient was treated with three infusions of the drug under normotension over 4 months. Please note disappearance of numerous nodules.

SMANCS/Lipiodol as illustrated in Figure 47.27a and b, which demonstrates the response to treatment with SMANCS/Lipiodol under angiotensin II-induced hypertension after 1 month (see Chapter 3 for this therapeutic method).

Figure 47.27c and d demonstrates the case of a massive HCC treated with SMANCS/Lipiodol similar to Figure 47.27a and b under angiotensin II induced hypertension a remarkable regression of the tumor was obtained during the follow-up period of 1 month. Another case report of recurrent HCC, 2.5 years after tumor resection that was treated similarly as above, is depicted in Figure 47.27e and f. Antitumor activity against HCC with an arterio-portal shunt administration of SMANCS/Lipiodol resulted in a formidable outcome with significant regression of the hepatoma (Figure 47.27e and f), which is usually uncontrollable by conventional treatments including surgical resection. In the angiograms (Figure 47.27g and h), a unique branching off from the right proper hepatic artery is seen that extends to the left lower part (arrow in the circle). Only under hypertension induced by angiotensin II did the metastatic tumor become diagnostically visible (see arrow in Figure 47.27g).

The arterial infusion of the normotensive state is also effective but takes a longer time to achieve 50% tumor reduction (see Chapter 3). The tumor-selective delivery of SMANCS in Lipiodol is not only observed in highly vascularized solitary HCC, but also in multinodular type HCC as seen in Figure 47.28a, in which SMANCS/Lipiodol is taken up effectively into the small micronodules of sizes less than 5 mm. The majority of small nodules disappeared in 4 months (Figure 47.28b).

We have observed this prominent drug uptake in HCC even under normotensive blood pressure. However, when the Seldinger arterial infusion is performed under angiotensin II-induced hypertensive conditions (the Seldinger technique is a well-established procedure in clinical practice used to introduce catheters by puncturing the vessel with a needle, inserting the Seldinger or plastic probe into the vessel thus ensuring a permanent access to the artery), the time that is required for the tumor to decrease to less than 50% of its original size (cross-section) will

be much shorter (less than 1 month) due to a higher and more selective drug accumulation (see Section 3.4, Figure 3.11 and 3.12, and Figure 47.27a, c and e).

A postmarketing survey of SMANCS therapy for HCC in about 4000 cases was published as summarized in Table 47.5 [163]. It is seen that the drug caused very few serious adverse effects even in the advanced stages of HCC and yet a good therapeutic response was documented.

The effect on metastatic liver cancer is also encouraging when SMANCS/Lipiodol is infused into the tumor-feeding artery under angiotensin II-induced high blood pressure (e.g., 110 → 150 mmHg) [162]. The therapeutic efficacy of SMANCS/Lipiodol injected similarly into the tumor-feeding artery is also promising for cancers of the lung and other difficult-to-treat abdominal tumors, such as cancers of the kidney and pancreas [152, 160, 161], bile duct, and gallbladder [162].

Table 47.5 Adverse effects of intra-arterial SMANCS/Lipiodol therapy in hepatoma patients [163].

Symptoms	Parameter	Change (%)
Dermatological (exanthema)	–	0.36
Nausea	–	5.35[a]
Vomiting	–	4.06[a]
Anorexia	–	3.63[a]
Abdominal pain(transitory)	–	5.53
Liver function		
glutamyl oxaloacetic transaminase	increased	2.16[a]
glutamyl pyruvic transaminase	increased	2.12[a]
bilirubin	(> 1.5 mg/dl)	3.45[a]
Hypotension	–	2.22
Blood counts		
white blood cells	decreased	0.38
	increased	0.83[a]
polymorphonuclear leukocytes	decreased	0.04
	increased	0.28
Platelets	decreased	0.83
Renal function	impaired	0.71
blood urea nitrogen	increased	0.41
Anaphylaxis/shock	–	0.14
Rigor (transitory)	–	4.88
Chest pain (transitory)	–	0.20
Fever (low grade, 2–7 days)	–	27.80
C-reactive protein	increased	0.67
Ascites formation	–	1.35[a]

Based on 3956 patients (by Yamauchi Pharmaceutical, PMS, 2003).
[a]These issues are potentially associated with liver disease such as liver cirrhosis per se, not necessary induced by the drug, SMANCS.

Additional comments and precautions for arterial infusion of SMANCS/Lipiodol in the arterial infusion into hepatic artery include:

- Excessive and rapid infusion of SMANCS/Lipiodol will result in backlash flow of injected drug into the gastroduodenal artery, which may cause gastric or duodenal ulcer.
- The feeding artery of a individual tumor may be different from normal feeding artery (e.g., the normal feeding artery for hepatoma is the hepatic artery; for lung cancer, the bronchial artery, etc.); however, frequently there are anomalous vascular-feeding routes that may occur, from, such as, the costal, or even from the renal arteries, or other branching in hepatoma.
- A continuous flow (push) using a syringe connected to the catheter should be avoided; on the contrary, an intermittent push to avoid homeostasis, thrombus formation, or shock should be applied that maintains normal blood flow after the procedure. This method is not the embolization method.
- Do not try to fill a large tumor completely at once, since a large tumor may collapse under this treatment and extensive bleeding may result with a risk of causing complications.
- Angiotensin II-induced hypertension (e.g., 100 → 150 mmHg) will generally result in an improved delivery of SMANCS/Lipiodol and other polymeric drugs in general [162].
- Most adverse side-effects such as shock, which occurs every once in a while in angiography, can be avoided by appropriate use of glucocorticoids (such as betamethasone) and/or antihistamines. Patients with iodine allergy should be desensitized similarly by injection of a glucocorticoid 1 day before the procedure. The prick test using microgram quantity of SMANCS/Lipiodol may be helpful to predict allergic reaction.

47.5 Conclusions and Perspectives

Liver cancer, especially HCC, has become a major global health problem and is the fifth most common cancer worldwide. Since surgical or regional therapy with anticancer agents is restricted to patients at an early tumor stage, there is an urgent need to develop new therapeutic strategies for treating patients with advanced stages of HCC and also multiple liver metastases, which are typically a result of breast, esophageal, lung, stomach, or colorectal cancer. Since the RES, the EPR effect of liver metastases as well as the expression of certain liver-associated receptors, such as ASGPR, are prominent in the liver and liver tumors, tailor-made drug delivery systems relying on passive as well as active targeting can be considered ideal for improving the palliative and curative therapy of primary liver tumors and liver metastases.

Examples of drug–polymer conjugates with HPMA or serum albumin bearing galactose molecules and DOX bound though a cathepsin B-cleavable or acid-sensitive linker have shown impressive preclinical results. In addition, two drug nanoparticles that are taken up by the RES of the liver have advanced to

the clinic: Doxorubicin Transdrug, a nanoparticle comprising PIHCA and DOX, reached phase II studies, but further development is on hold due to lung toxicity. A second nanoparticle with mitoxantrone encapsulated in PBCA showed promising activity in a phase II trial in the treatment of patients with unresected HCC with an overall increase in survival of around 2.2 months compared to the mitoxantrone control arm.

The most successful drug–polymer conjugate for treating HCC to date is SMANCS – a conjugate of two synthetic copolymers of SMA and the highly potent chromoprotein NCS that has been approved for the treatment of HCC in Japan since 1993. SMANCS is administered via the hepatic artery dissolved in Lipiodol, a lipid contrast agent, and has meanwhile demonstrated convincing antitumor activity in thousands of patients. Indeed, because a drug–polymer conjugate is applied combined with a contrast agent Lipiodol, an ethyl ester of iodinated poppy seed oil that allows X-ray detection of liver tumor nodules, SMANCS/Lipiodol can be viewed as a first successful clinical application of a theranostic approach.

For the future, in the era of nanomedicine it can be expected that the development of numerous polymer- or lipid-based nanoparticles with or without targeting ligands will be intensively pursued that target liver tumors with the aim of improving the therapeutic options for treating patients with primary and secondary liver tumors.

In addition, a global phase III HEAT study with ThermoDox, a heat-sensitive liposomal formulation of DOX, is being conducting under a Special Protocol Assessment with the FDA. Six hundred patients will be assessed in this clinical trial worldwide. The antitumor efficacy of ThermoDox in combination with RFA will be compared to patients who receive RFA as a control.

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Running Title: Nanomedicine for EPR effect based tumor targeting

Nanomedicine and cancer drug delivery based on the EPR effect and EPR augmentation

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