were considered to be probable or possible drug-related toxicities, except for the cases of SIRS and AMI in the SM-11355 group. SIRS was judged to have no association with the investigational drug based on the results of blood culture and changes in test values. This patient was treated using a urinary catheter, and urinary tract infection is a cause of SIRS. A similar judgment was made for the case of AMI based on the chronological relationship between drug administration and the onset of disease.

In the subsequent angiographic examination before the second administration of SM-11355 or Zinostatin stimalamer or in postprotocol treatment, hepatic artery damage that was probably due to intra-arterial drug administration was observed in 15/31 (48.4%) patients, shunt occurred in 5/31 (16.1%), and disorders of the hepatobiliary system were observed in 3/39 (7.7%) in the Zinostatin stimalamer group. None of these events were observed in patients in the SM-11355 group. Grade 3 hepatic artery damage and a grade 4 disorder of the hepatobiliary system were observed in 1 case each in the Zinostatin stimalamer group. Hepatobiliary damage that may have been caused by arterial damage was found in 3 patients in the Zinostatin stimalamer group (1 case each of liver atrophy and bile duct dilatation, bile duct necrosis, and liver failure and bile duct stricture), whereas there were no such findings in the SM-11355 group.

In the SM-11355 group, the percentages of patients with an increase in Child-Pugh score of one or more points compared to the pre-administration score were 27.7% (23/83) and 17.9% (10/56) in the 5 weeks after the 1st administration and the 5 weeks after the 2nd administration, respectively. In the Zinostatin stimalamer group, these percentages were 35.9% (14/39) and 50.0% (12/24), respectively (Fig. 4).

Pharmacokinetics

Total plasma platinum concentrations and platinum concentrations in methanol extracts (Table 4) were determined in 30 and 24 patients in the SM-11355 group who were given one and two injections, respectively, and received median doses of 85 (Min-max: 24–120) and 120 (10–120) mg, respectively. The mean total platinum concentrations after the first and second injections were 9.6 and 12.9 ng/mL, respectively, and the mean percentages of the concentration in methanol extracts relative to the total plasma platinum concentration were 12.2% and 9.8% after the first and second injections, respectively. In one patient who underwent surgery 172 days after the second injection, the total platinum concentration was determined in the resected liver tissue. The total dose was 200 mg (first injection: 100 mg; second injection: 100 mg) and the concentration in the tumor region of sample S6, which had a 10% necrotic effect, was 62,000 ng/g tissue and that in the non-tumor region was 22,000 ng/g tissue. In contrast, the concentration in the tumor region of sample S8, which showed 50% necrosis, was 260,000 ng/g tissue and that in the non-tumor region was 67,000 ng/g tissue.

Discussion

Most anticancer agents used in TACE are water-soluble and inappropriate for suspension in iodized oil, and are usually administered as a water-in-oil emulsion. Consequently, these agents have reduced sustained release due to poorer retention in the tumor, leading to a limited antitumor effect and adverse effects caused by diffusion of the agents into the blood [16]. In contrast, lipophilic anticancer agents have a high affinity for iodized oil and those injected into the hepatic artery with iodized oil are retained selectively in tumors and exert continuous antitumor effects. SM-11355 is a structurally modified platinum complex with improved affinity for iodized oil due to increased lipophilicity [3]. In an AH109A-transplanted rat liver tumor model, the platinum concentration in the tumor was sustained for longer following administration of a iodized oil suspension of SM-11355 compared to a suspension of cisplatin, with SM-11355 distributed in tumor tissues more selectively than cisplatin [17]. Phase I and early phase II trials

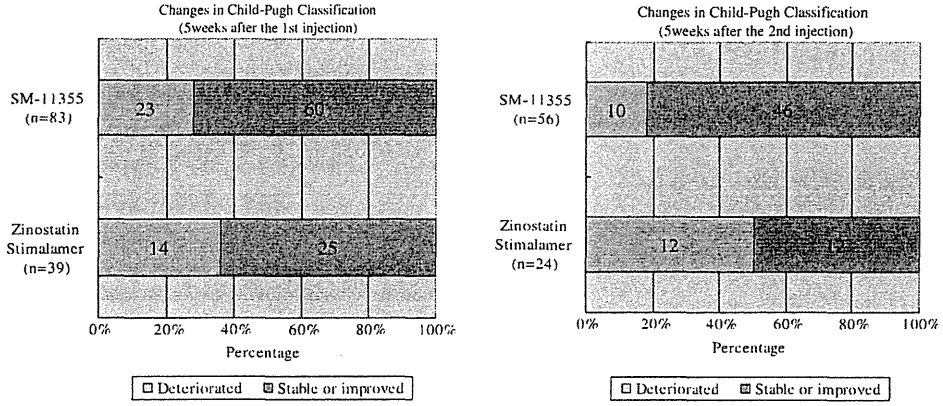

Fig. 4 Changes in Child-Pugh Classification

Table 4 Blood drug concentrations

Administration frequency		Once	Twice
Dose (mg)	Number of patients	30*	24*
	Median (Min-Max)	85.0 (24–120)	120.0 (10–120)
Total plasma platinum concentration (ng/mL)	Number of patients	30	24
	Mean	9.6	12.9
SM-11355 metabolite concentration in methanol extracts (ng/mL)	Number of patients	32	24
	Mean	1.17	1.19
[SM-11355 in methanol-extracted fraction*] / [total plasma platinum concentration] × 100 (%)	Number of patients	30	24
	Mean	12.2	9.8

Number of subjects in whom both the total plasma platinum concentration and SM-11355 metabolite concentration in methanol extracts were measured

* Methanol-extracted fraction: The fraction of SM-11355-derived substances includes components that may exert therapeutic activity as an anticancer agent and excludes components that are irreversibly bound to plasma protein

of SM-11355 have also shown that the total plasma platinum concentration is much lower than that with cisplatin [4, 5, 18]. Our pharmacokinetic data verify these results and suggest that SM-11355 is retained in liver tumors selectively and exerts a continuous effect on the tumor.

In patients in whom the total plasma platinum concentration and the platinum concentration in methanol extracts were determined after the first and second injections, the platinum concentration in methanol extracts 3 weeks after injection (estimated to be the peak of the total plasma platinum concentration) was approximately 10% of the total plasma platinum concentration. Of the platinum components released from the SM-11355 suspension and transferred into the systemic circulation, some are irreversibly bound to plasma proteins and are no longer bioactive. After exclusion of these components, the amount remaining in the plasma is estimated to be up to about 10% of the dose. The total platinum concentrations in several regions of the liver were also determined in one patient. The concentrations in tumors regions were significantly higher than those in non-tumor regions and several thousand-fold higher than the mean total plasma platinum concentration at 3 weeks ±3 days after the second injection (12.9 ng/mL). The total platinum concentration was also higher in tissues in which a higher antitumor effect was observed.

The results of the efficacy re-evaluation suggested that SM-11355 has a similar effect to that of Zinostatin stimalamer following injection of an iodized oil suspension of each drug into the hepatic artery. The primary endpoint (TE V rate based on the Criteria for Evaluation of Direct Effects on Hepatocellular Carcinoma) and the secondary endpoint (response rate based on the Japan Society for Cancer Therapy Criteria and RECIST) in the SM-11355 group were almost the same as those in the Zinostatin stimalamer group. However, the percentage of TE V cases in the SM-11355 group (26.5% [17.4–37.3%]) in this trial was lower than the value of 56% [30–80%] found in the early phase II trial. The discrepancy in the percentage of TE V cases may be due to differences in the tumor burden in the two trials. Eleven (68.8%) of 16 patients in the early phase II study had 3 or less tumors and a longest tumor diameter of 3 cm or less, whereas only 38 (45.8%) of 83 patients in the late phase II study had these characteristics.

The major toxicities of grade 3 or higher involved liver dysfunction, including increases in AST, ALT and bilirubin, and a decrease in platelets in both groups. The incidences were similar in each group and most of the effects were reversible. An increase in eosinophils was found in 84.3% of patients in the SM-11355 group, and was considered to be a SM-11355-specific adverse event. The precise mechanism is unknown, but the finding was not thought to indicate anaphylaxis because the increase in eosinophils showed no marked correlation with an increase in IgE and/or allegic symptoms like wheezing. Renal disorder was transient in patients of the SM-11355 group, except for a patient with sepsis. The incidences and severity of increased blood creatinine and positive urine protein in the SM-11355 group were higher than the respective levels in the Zinostatin stimalamer group (9/83, 10.8% vs. 2/39, 5.1%; and 22/83, 26.5% vs. 2/39, 5.1%, respectively). Based on these data, we consider that the patients were thoroughly followed up.

Injection of SM-11355 did not lead to local vascular damage and had fewer irreversible effects on the hepatobiliary system compared with Zinostatin stimalamer. Zinostatin stimalamer has been reported to have major safety problems, including hepatic arterial damage and effects on the hepatobiliary system that are irreversible and prevent repeated treatment [5, 19, 20] Therefore, SM-11355 may be advantageous for frequent repeated treatment and maintenance of liver function. The changes in Child-Pugh Class indicated a low incidence of treatment-induced hepatic dysfunction in the SM-11355 group.

Based on the results of this trial, we conclude that SM-11355 in iodized oil has similar efficacy to that of Zinostatin stimalamer, which is the only drug currently approved for chemolipiodolization for HCC in Japan. The TE V rate of 26.5% in the SM-11355 group was considered 'favorable'

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based on our assumption of a TE V rate of 15% for conventional TACE before the initiation of this study, and was equivalent or superior to the rate of about 20% found in patients receiving current standard TACE treatment in a recent report [7]. Our results also suggest that repeated dosing of SM-11355 in iodized oil is possible without development of hepatic vascular injury in a case of relapse. We are currently conducting a phase III study of intra-arterial treatment with SM-11355 in comparison with conventional TACE with epirubicin, which is designed to detect the superiority of intra-arterial treatment with SM-11355 in overall survival of TACE-naïve patients with advanced HCC (Appendix).

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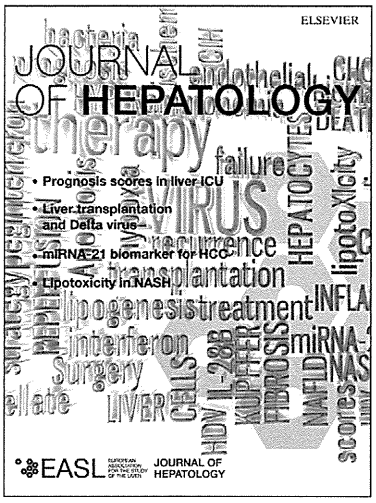

Non-hypervascular Hypointense Nodules Detected by Gd-EOB-DTPA-enhanced MRI is a Risk Factor for Recurrence of HCC after Hepatectomy

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Non-hypervascular Hypointense Nodules Detected by Gd-EOB-DTPA-enhanced MRI is a Risk Factor for Recurrence of HCC after Hepatectomy

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Key words: heparocellular carcinoma, Gd-EOB-DTPA-enhanced MRI, non-hypervascular hypointense nodule, hepatobiliary phase, hepatectomy, recurrence

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List of Abbreviations

Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma; US, ultrasonography; MDCT, multidetector-row computed tomography; TFE, turbo field echo; CTHA, computed tomography during hepatic arteriography.

Conflict of interest

There is no conflict of interest on this study.

Financial support

There is no grant or other financial supports on this study.

Abstract

Background & Aims: The gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) often depicts non-hypervascular hypointense hepatic nodules during the hepatobiliary phase in patients with hepatocellular carcinoma (HCC). It is not unclear whether the presence of these nodules is associated with HCC recurrence after hepatectomy. We conducted prospective observational study to investigate the impact of the presence of non-hypervascular hypointense hepatic nodules on the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI on the recurrence of HCC after hepatectomy. *Methods*: A total of 77 patients who underwent hepatectomy for primary, non-recurrent, hypervascular HCC were prospectively followed up after hepatectomy. Post-operative recurrence rates were compared according to the presence of non-hypervascular hypointense nodules on preoperative Gd-EOB-DTPA-enhanced MRI. *Results*: Recurrence rates after hepatectomy were higher in patients with non-hypervascular hypointense nodules (risk ratio 1.9396 [1.3615-2.7222]) and the presence of non-hypervascular hypointense nodules was an

independent factor associated with postoperative recurrence (risk ratio 2.1767 [1.5089-3.1105]) along with HCC differentiation and portal vein invasion. Whereas no differences were found in the rate of intrahepatic metastasis recurrence based on the preoperative presence of non-hypervascular hypointense hepatic nodules, the rate of multicentric recurrence was significantly higher in patients with preoperative non-hypervascular hypointense hepatic nodules. *Conclusions*: Patients with preoperative non-hypervascular hypointense hepatic nodules detected during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI are at higher risk of HCC recurrence after hepatectomy, mainly due to multicentric recurrence.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of cancer-related death [1,2]. In Japan, HCC is the third and fifth most common causes of death from cancer in men and women, respectively [3]. Tremendous efforts have been made to improve various imaging techniques including ultrasonography (US), multidetector-row computed tomography (MDCT) [4,5], and magnetic resonance imaging (MRI) [6] for the detection of hepatic nodules, including small early-stage HCC tumors in high-risk patients under surveillance.

The liver-specific contrast agent gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), which is taken up by hepatocytes, has been in clinical use for dynamic MRI studies since February 2008 in Japan. Gd-EOB-DTPA provides both dynamic and liver-specific hepatobiliary MR images [7-10]. In the hepatobiliary phase, hepatic lesions that lack normally functioning hepatocytes are imaged as an absence of hepatocyte-selective enhancement as compared with normal parenchyma

[10,11]. The use of Gd-EOB-DTPA-enhanced MRI increases detection of concurrent non-hypervascular hepatic nodules as hypointense nodules during the hepatobiliary phase in patients with HCC. It is controversial whether the presences of these non-hypervascular hepatic nodules detected in patients with typical hypervascular HCC lesions have an impact on the recurrence of HCC after treatment.

In the present study, we attempted to evaluate the impact of concurrent non-hypervascular hepatic nodules detected as hypointense nodules during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI on postoperative recurrence in patients who underwent hepatectomy with curative intent for HCC.

Methods

Patients, Treatment and Follow-up

This prospective study was conducted after the approval by the hospital institutional review board and carried out in compliance with the Helsinki Declaration. Patient enrollment was carried out between February 2008 and December 2011. A total of 102 patients underwent hepatectomy

as a curative treatment for primary, non-recurrent HCC during the study period at Ogaki Municipal Hospital. Gd-EOB-DTPA-enhanced MRI could not be performed prior to hepatectomy in 25 patients, including 11 patients who had been referred from another institution only for hepatectomy and 14 patients who could not receive examination due to metal implants, history of allergy to contrast medium, tattoos, or claustrophobia. The remaining 77 patients who underwent Gd-EOB-DTPA-enhanced MRI within 2 weeks prior to hepatectomy were studied. The initial diagnosis of HCC before treatment was based on appropriate imaging characteristics according to criteria of the guidelines by the American Association for the Study of Liver Diseases (12,13). The final diagnosis of HCC was confirmed by pathologic diagnosis of resected specimens.

Decisions regarding individual treatments were based on Japanese treatment guidelines for HCC [14]. In all patients, HCC tumors were resected with ample margins; enucleation of tumors without margins was not performed.

After hepatectomy, all patients were prospectively followed for 8.5 months to 55.4 months (median follow-up, 34.1 months) until the end of

September 2012 at our institution, with US and either MDCT or MRI every 3 to 6 months. Regular monitoring of serum tumor markers (alpha-fetoprotein, *lens culinaris* agglutinin-reactive alpha-fetoprotein, and des-gamma-carboxy prothrombin) was performed every 3 months. When an elevation in tumor markers was detected, additional imaging (usually MDCT or MRI) was performed to check for HCC recurrence. Recurrence was diagnosed by pathologic examination of resected specimens when patients underwent re-hepatectomy. In the remaining patients, HCC was diagnosed by appropriate imaging characteristics according to criteria of the guidelines by the American Association for the Study of Liver Diseases [12,13]. Recurrent HCC was categorized into two groups prior to the study as intrahepatic metastasis recurrence or multicentric recurrence according to a previous study [15,16]. Intrahepatic metastasis recurrence was defined as recurrent tumors consisting of moderately or poorly differentiated HCC with the same or lower degree of differentiation than the primary tumors on pathologic examination or hypervascular tumor without non-hypervascular peripheral regions in a same hepatic segment on imaging examination. Multicentric recurrence was defined according to previously reported

criteria with some modifications [17,18] as follows: (i) the recurrent tumor consists of well-differentiated HCC occurring in a different hepatic segment, than moderately or poorly differentiated pre-existing HCCs; (ii) both the primary and recurrent tumors are well-differentiated HCCs; and (iii) the recurrent tumor contained regions of dysplastic nodules in peripheral areas based on pathologic examination or contained non-hypervascular regions in peripheral areas of hypervascular tumor on imaging examination.

Preoperative Imaging Examinations of Liver Nodules by Gadolinium-Ethoxybenzyl-Diethylenetriamine Pentaacetic Acid-enhanced MRI and Confirmation of Non-hypervascular Hypointense Hepatic Nodules

All patients underwent Gd-EOB-DTPA-enhanced MRI within 2weeks of hepatectomy. MRI was performed using a 1.5-T whole-body MRI system (Intera Achieva 1.5T NOVA; Philips Medical Systems) with a phased-array body coil as the receiver coil. T1-weighted sequences were acquired with the following parameters: T1-weighted turbo field echo (TFE) in-phase and opposed-phase transverse (TE, opposed-phase 2.3,

in-phase 4.6; flip angle, 12°; matrix size, 256 X 512; scan percentage, 70) with 3.5-mm section thickness, a 0-mm intersection gap, and a 38 cm field of view. After intravenous injection of Gd-EOB-DTPA (Primovist; Bayer Schering Pharma, Osaka, Japan), T1-weighted transverse gradient-echo sequences (high-resolution isotropic volume examination [THRIVE] with spectral presaturation with inversion recovery [SPIR], 4/1.8; flip angle, 12°; matrix size, 256 X 512; scan percentage, 78.54) with 3.5-mm section thickness, a 0-mm intersection gap, and a 38 cm field of view were obtained. Gd-EOB-DTPA was administered intravenously as a bolus at a rate of 2 mL/sec (0.1 mL/kg, maximum dose of 10 mL) through an intravenous cubital line (20–22 gauge), which was flushed with 20 mL of saline using a power injector (Sonic Shot; Nemoto Kyorindo, Tokyo, Japan). The timing for dynamic arterial phase imaging was determined using MR fluoroscopic bolus detection of the descending aorta (Bolus Trak; Philips Medical Systems). The mean delay times (time interval between the start of bolus administration and the start of image acquisition) for the arterial, portal, and delayed phases were 20, 60, and 180 seconds, respectively. Immediately after the dynamic study, a respiration-triggered

single-shot T2-weighted sequence with a reduction factor of 4 (1,200/100; flip angle, 90°; matrix size, 400 X 512) with 7-mm section thickness, a 1-mm intersection gap, and a 38 cm field of view was obtained with SPIR. The 20-min-delayed hepatobiliary phase [19] was obtained with a T1-weighted TFE sequence (TR/TE, 4/1.8; flip angle, 12°; matrix size, 256 X 512) with 3.5-mm section thickness, a 0-mm intersection gap, and a 38 cm field of view. All the sequences were obtained with parallel imaging (SENSE). Hypointense hepatic nodules during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI were nodules greater than 3.5 mm with low-intensity.

Prior to hepatectomy, all patients underwent CT during hepatic arteriography (CTHA) [20-22] to evaluate the intranodular blood supply, and to confirm the hypervascularity of HCC lesions and the lack of hypervascularity of non-hypervascular hepatic nodules.

All imaging findings were evaluated by radiologist (Y.S.) and by hepatologist (H.T.) independently, being blind to the clinical data. When the imaging assessment was discordant between two reviewers, consensus was made through the discussion.

Statistical Analyses

Differences in percentages between groups were analyzed using the chi-square test. Differences in mean quantitative values were analyzed by the Mann-Whitney U test. The date of hepatectomy was defined as time zero for calculations of recurrence rates. In the analysis of the overall recurrence rate, patients in whom HCC did not recur were censored, and those in whom HCC recurred were not censored. In the analysis of the intrahepatic metastasis recurrence rate, patients in whom HCC did not recur or patients with multicentric HCC recurrence were censored, and those in whom HCC recurred as intrahepatic metastases were not censored. In the analysis of the multicentric recurrence rate, patients in whom HCC did not recur were censored and patients with multicentric HCC recurrence were not censored, while those in whom HCC recurred as intrahepatic metastases were excluded from the analysis. The Kaplan-Meier method [23] was used to calculate recurrence rates, and the log-rank test [24] was used to analyze differences.

The Cox proportional hazards model [25] was used for univariate

and multivariate analyses of factors related to recurrence. Variables analyzed included patient age and sex, Child-Pugh class (A/B), tumor size, number of tumors (single/multiple), differentiation of resected HCC (well-differentiated/moderately or poorly differentiated), growth pattern of resected HCC (expansive growth/infiltrative growth), portal vein invasion of resected HCC (absent/present), and presence of non-hypervascular hypointense nodules on the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI (absent/present). Data analyses were performed using JMP statistical software, version 6.0 (Macintosh version; SAS Institute, Cary, NC). All *p* values were derived from 2-tailed tests, with $p<0.05$ accepted as statistically significant.

Results

Patients Characteristics and Imaging Findings

Patients consisted of 56 males and 21 females with a mean age of 68.3 ± 7.6 years (range, 46-82 years). A total of 40 non-hypervascular hypointense hepatic nodules were identified during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI in 28 of 77 patients (36.4%). The size of

non-hypervascular hypointense nodules was 1.17 ± 0.38 cm (range, 0.4-2.1 cm). Two of 40 non-hypervascular hypointense hepatic nodules (5.0%) were identified by T2-weighted sequence as high-intensity nodules. Nodules were not identified both by T1- and T2-weighted sequences in case of the other 38 non-hypervascular hypointense hepatic nodules. Two nodules were located in segment II of the liver, 7 in III, 1 in IV, 10 in V, 6 in VI, 4 in VII, and 10 in VIII, respectively. Among 28 patients with non-htpervascular hypointense nodules, 19 patients had one non-htpervascular hypointense nodule, 6 patients had 2 nodules, and the remaining 3 patients had 3 nodules. Non-hypervascular hypointense nodules were resected along with HCC lesions during hepatectomy in 10 patients because they were included within the intended area of resection. Therefore, we categorized these 10 patients and the 49 patients in whom non-hypervascular hypointense nodules were not detected by preoperative Gd-EOB-DTPA-enhanced MRI as the hypointense nodule (-) group and the remaining 18 patients who had residual hypointense nodules after hepatectomy as the hypointense nodule (+) group. Of 13 hypointense nodules in 10 patients resected along with HCC at hepatectomy, 3 nodules